Confidential

RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	**Chlorhexidine digluconate** **Isopropyl alcohol**
Pharmaco-therapeutic group (ATC Code):	**ANTISEPTICS AND DISINFECTANTS** **ATC code: D08AC52**
Name of Marketing Authorisation Holder or Applicant:	**LABORATOIRES GILBERT**
Number of medicinal products to which this RMP refers:	**1**
Product(s) concerned (brand name(s)):	**Chlorhexidine alcoolique Gilbert Healthcare 2%, solution pour application cutanée**

Data lock point for this RMP	December 2014	Version number	2
Date of final sign off	29/11/2018		

Part I: Product(s) Overview

Administrative information on the RMP

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted/ or Not Applicable**
Part II Safety Specification	SV Post authorisation experience Only required for updates to the RMP	Not applicable	Not applicable
	SVIII Summary of the safety concerns	03-12-2014	Not applicable
Part III Pharmacovigilance Plan	Only needed if reference product has additional PhV activities	03-12-2014	Not applicable
Part IV Plan for post-authorisation efficacy studies	Only needed if reference product has imposed post-authorisation efficacy studies	Not applicable	Not applicable
Part V Risk Minimisation Measures		03-12-2014	Not applicable
Part VI Summary of RMP		03-12-2014	Not applicable
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	30-11-2018	Not applicable
	ANNEX 3 Worldwide marketing status by country	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data	03-12-2014	Not applicable

QPPV name [redacted]

QPPV signature

Contact person for this RMP

E-mail address or telephone

[redacted]

Overview of versions:

Version number of last agreed RMP: NA

Version number	2
Agreed within	<Indicate procedure>

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
1	13-05-2016	Marketing Authorisation Application
2	30-11-2018	Marketing Authorisation Application

For each product in the RMP

Invented name(s) in the European Economic Area (EEA)	CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2 %, Solution pour application cutanée
Authorisation procedure	Purely national
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Chemical class of active substances: - Chlorhexidine digluconate: GUANIDINE DERIVATIVE ATC ranking D DERMATOLOGICALS D08 ANTISEPTICS AND DISINFECTANTS D08A ANTISEPTICS AND DISINFECTANTS D08AC BIGUANIDES AND AMIDINES D08AC02 CHLORHEXIDINE Mechanism of actions are: Combination of two active ingredients, with bactericidal or bacteriostatic activity against Gram +, Gram- and a fungicidal activity for several organisms: • chlorhexidine (bactericidal antiseptic with a broad spectrum from biguanide family), • isopropyl alcohol (bactericidal broad spectrum antiseptic)
Indication(s) in the EEA Current (if applicable)	Not applicable
Proposed (if applicable)	Disinfection of the skin before an invasive medical procedure.
Posology and route of administration in the EEA Current (if applicable)	Not applicable
Proposed (if applicable)	Cutaneous application. Minor surgery: Apply with a sterile dressing. Surgical antisepsis: after cleansing, apply using a sterile dressing and allow to air dry spontaneously.
Pharmaceutical form(s) and strengths Current (if applicable)	Not applicable

Proposed (if applicable)	Solution for cutaneous application Chlorhexidine digluconate: 2.00 g (20% m/v) Isopropyl alcohol: 70% v/v

Country and date of first authorisation worldwide	<Enter a country> <Enter a date>
Country and date of first launch worldwide	<Enter a country> <Enter a date>
Country and date of first authorisation in the EEA	<Enter a country> <Enter a date>

Is the product subject to additional monitoring in the EU? Yes ☐ No ☒

Part II: Module SV - Post-authorisation experience

Not required for RMP associated to marketing authorisation request

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Not Applicable

SV.2 Non-study post-authorisation exposure

Not Applicable

SV.3 Post-authorisation use in special populations

Not Applicable

SV.4 Post-authorisation off-label use

Not Applicable

SV.5 Epidemiological study exposure (if applicable)

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Important identified risks have been identified with CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2 %, Solution pour application cutanée

Table 1. Summary of safety concerns for CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2 %, Solution pour application cutanée

Summary of safety concerns	
Important identified risks	- *Allergic reaction* - *Organ or mucosa damage in case of direct exposure* - *Risk of systemic effect* - *Interference with other antiseptics or soap* - *Risk of burns with the use of electric bistoury*
Important potential risks	-
Missing information	-

Part III: Pharmacovigilance Plan

Laboratoire Gilbert has conducted preclinical testing to support the safety of CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée. Please see Annex 9 for more details of the report.

The tests of tolerance were:

- IC-iso-PH-12/0562: Assessment of primary skin irritation in rabbits,
- ITC-iso-PH-12/0562: Evaluation of local tolerance after 14 days repeated application in the rabbit,
- LLNA-PH-12/0562 : Evaluation of potential skin sensitization in mice (Local lymph node assay, LLNA)

The various studies performed and presented have shown that the specialty tested CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée presented:

- Good local tolerance after acute application (1 day) or sub-chronic (14 days) to healthy skin in rabbits.
- No sensitizing properties (LLNA test) after application (3 days) on the dorsal surface of the ear of mouse

In all studies, treatment was well tolerated. No clinical signs were reported. Based on these findings, the medicinal product CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée has a satisfactory bactericidal and fungicidal activity without sensitization characteristics but with a favourable local tolerability profile.

A pharmacovigilance plan is not required as CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée has no additional pharmacovigilance activities.

III.1 Safety concerns and overview of planned pharmacovigilance actions

Not Applicable

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Not Applicable

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Not Applicable

III.4 Details of outstanding additional pharmacovigilance activities

Not Applicable

III.5 Summary of the Pharmacovigilance Plan

Not Applicable

Part IV: Plans for post-authorisation efficacy studies

Not required as CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée has no additional PhV activities.

IV.1 Tables of post-authorisation efficacy studies

Not Applicable

IV.2 Summary of post authorisation efficacy development plan

Not Applicable

IV.3 Summary of completed post authorisation efficacy studies

Not Applicable

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Safety concern	**Allergic reactions**
Objective(s) of the risk minimisation measures	Inform Health Care Providers and patients of the systemic allergic reaction and hypersensitivity risks to chlorhexidine
Routine risk minimisation measures	Proposed text in SmPC: *Section 4.3: Contraindications* Contraindicated in patients with hypersensitivity to chlorhexidine or isopropyl alcohol. *Section 4.8: Undesirable effects* Allergic reaction or skin irritation to chlorhexidine or isopropyl alcohol. Risk of systemic allergy which can (rarely) lead to anaphylactic shock. At the first signs of local skin reaction, stop applying the product. Proposed text in PL: *Contra-indications* Do not use CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée - if you are allergic to one of active substances. *Possible side effects* Like all medications, CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée , may cause side effects, although not everyone is subject to it: Rarely, systemic allergic accident that can lead up to anaphylactic shock
Additional risk minimisation measure(s) (repeat as necessary)	Not applicable Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable

Safety concern	**Allergic reactions**
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Organ or mucosa damages in case of direct exposure**
Objective(s) of the risk minimisation measures	Inform Health Care Providers and patients of the absence of data on skin absorption
Routine risk minimisation measures	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Reserved to external use in healthy skin. This medication should not be used on mucous membranes, especially genital mucosa, on open skin wounds, on broken skin. In addition, direct contact with nervous tissue or brain, the eyes, the ear canals in case of eardrum puncture or the middle ear should be avoided. Proposed text in PL: *Special Warnings* This product should not be used: - in the ear canal (middle ear), on mucous membranes (nose, throat, genital mucosa) - on open skin wounds, broken skin - in direct contact with neural tissue
Additional risk minimisation measure(s) (repeat as necessary)	Not applicable Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Risk of Systemic effect**
Objective(s) of the risk minimisation measures	Inform Health Care Providers and patients of the absence of data on skin absorption and the risk of systemic effect
Routine risk minimisation measures	<u>Proposed text in SmPC:</u> *Section 4.4 Special warnings and precautions for use* Prolonged skin exposure to alcoholic solutions should be avoided. Even though the transcutaneous absorption of chlorhexidine is very low, , the risk of systemic effects cannot be excluded. More caution should be taken especially when the antiseptic is used on a large area, on damaged skin (especially on burned skin), mucosa, skin of preterm babies or infants (because of surface area / weight ratio and the occlusion effect of layers. <u>Proposed text in PL:</u> *Special Warnings* There is a risk of absorption of the active ingredient into the systemic circulation when used on a large area under occlusion, on damaged skin (especially burned), skin of preterm infants or infants.
Additional risk minimisation measure(s)	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Interference with other antiseptics or soap**
Objective(s) of the risk minimisation measures	Inform Health Care Providers and patients of the interactions with other medicinal products
Routine risk minimisation measures	<u>Proposed text in SmPC:</u> *Section 4.5. Interaction with other medicinal products and other forms of interaction* Given the possible interference (antagonism, inactivation), simultaneous or successive use of antiseptics or soap should be avoided. <u>Proposed text in PL :</u> Interaction with other medicinal product *Using other medicines* This medication should not be used with other local antiseptics (risk of incompatibility or inefficacy). The prior use of soap should be followed by thorough rinsing. Tell your doctor if you are taking or have recently taken any other medications.
Additional risk minimisation measure(s) (repeat as necessary)	Not applicable
	Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

Safety concern	**Risk of burns with the use of electric bistoury**
Objective(s) of the risk minimisation measures	Inform Health Care Providers and patients of the risk of burns
Routine risk minimisation measures	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Cases of burns were reported with the use of electrocautery after application of alcohol-based antiseptics related to the presence of residual product. It is therefore necessary to allow, after skin preparation for minor surgery, the product to dry completely and ensure the absence of residual product that could flow, especially at the skinfolds and the drapes before using electrocautery. Proposed text in PL : Precaution of use ; special warnings Special warnings Allow to dry before using an electrical instrument due to a risk of burn.
Additional risk minimisation measure(s) (repeat as necessary)	Not applicable Not applicable
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

V.2 Risk minimisation measure failure (if applicable)

Not applicable

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Allergic reaction	Proposed text in SmPC: *Section 4.3: Contraindications* Contraindicated in patients with hypersensitivity to chlorhexidine or isopropyl alcohol. *Section 4.8: Undesirable effects* Allergic reaction or skin irritation to chlorhexidine or isopropyl alcohol. Risk of systemic allergy which can (rarely) lead to anaphylactic shock. At the first signs of local skin reaction, stop applying the product. Proposed text in PL: *Contra-indications* Do not use CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée - if you are allergic to one of active substances *Possible side effects* Like all medications, CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée, may cause side effects, although not everyone is subject to it: Rarely, systemic allergic accident that can lead up to anaphylactic shock	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Organ or mucosa damage in case of direct exposure	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Reserved to external use in healthy skin. This medication should not be used on mucous membranes, especially genital mucosa, on open skin wounds, on broken skin. In addition, direct contact with nervous tissue or brain, the eyes, the ear canals in case of eardrum puncture or the middle ear should be avoided. Proposed text in PL: *Special Warnings* This product should not be used: - in the ear canal (middle ear), on mucous membranes (nose, throat, genital mucosa) - on open skin wounds, broken skin - in direct contact with neural tissue	Not applicable
Risk of systemic effect	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Prolonged skin exposure to alcoholic solutions should be avoided. Even though the transcutaneous absorption of chlorhexidine is very low, , the risk of systemic effects cannot be excluded. More caution should be taken especially when the antiseptic is used on a large area, on damaged skin (especially on burned skin), mucosa, skin of preterm babies or infants (because of surface area / weight ratio and the occlusion effect of layers. Proposed text in PL: *Special Warnings* There is a risk of absorption of the active ingredient into the systemic circulation when used on a large area under occlusion, on damaged skin (especially burned), skin of preterm infants or infants.	Not applicable

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Interference with other antiseptics or soap	Proposed text in SmPC: *Section 4.5. Interaction with other medicinal products and other forms of interaction* Given the possible interference (antagonism, inactivation), simultaneous or successive use of antiseptics or soap should be avoided. Proposed text in PL : Interaction with other medicinal product *Using other medicines* This medication should not be used with other local antiseptics (risk of incompatibility or inefficacy). The prior use of soap should be followed by thorough rinsing. Tell your doctor if you are taking or have recently taken any other medications, including medications obtained without a prescription	Not applicable
Risk of burns with the use of electric bistoury	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Cases of burns were reported with the use of electrocautery after application of alcohol-based antiseptics related to the presence of residual product. It is therefore necessary to allow, after skin preparation for minor surgery, the product to dry completely and ensure the absence of residual product that could flow, especially at the skinfolds and the drapes before using electrocautery. Proposed text in PL : Precaution of use ; special warnings Special warnings Allow to dry before using an electrical instrument due to a risk of burn.	Not applicable

Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	- *Allergic reactions* - *Organ or mucosa damage in case of direct exposure* - *Risk of systemic effect* - *Interference with other antiseptics or soap* - *Risk of burns with the use of electric bistoury*
Important potential risks	Not applicable
Missing information	Not applicable

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Allergic reaction	<u>Proposed text in SmPC:</u> *Section 4.3: Contraindications* Contraindicated in patients with hypersensitivity to chlorhexidine or isopropyl alcohol. *Section 4.8: Undesirable effects* Allergic reaction or skin irritation to chlorhexidine or isopropyl alcohol. Risk of systemic allergy which can (rarely) lead to anaphylactic shock. At the first signs of local skin reaction, stop applying the product.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Proposed text in PL: *Contra-indications* Do not use CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée - if you are allergic to one of active substances. *Possible side effects* Like all medications, CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée, may cause side effects, although not everyone is subject to it: Rarely, systemic allergic accident that can lead up to anaphylactic shock	
Organ or mucosa damage in case of direct exposure	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Reserved to external use in healthy skin. This medication should not be used on mucous membranes, especially genital mucosa, on open skin wounds, on broken skin. In addition, direct contact with nervous tissue or brain, the eyes, the ear canals in case of eardrum puncture or the middle ear should be avoided. Proposed text in PL: *Special Warnings* This product should not be used: - in the ear canal (middle ear), on mucous membranes (nose, throat, genital mucosa) - on open skin wounds, broken skin - in direct contact with neural tissue	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of systemic effect	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Prolonged skin exposure to alcoholic solutions should be avoided. Even though the transcutaneous absorption of chlorhexidine is very low, , the risk of systemic effects cannot be excluded. More caution should be taken especially when the antiseptic is used on a large area, on damaged skin (especially on burned skin), mucosa, skin of preterm babies or infants (because of surface area / weight ratio and the occlusion effect of layers. Proposed text in PL: *Special Warnings* There is a risk of absorption of the active ingredient into the systemic circulation when used on a large area under occlusion, on damaged skin (especially burned), skin of preterm infants or infants.	Not applicable
Interference with other antiseptics or soap	Proposed text in SmPC: *Section 4.5. Interaction with other medicinal products and other forms of interaction* Given the possible interference (antagonism, inactivation), simultaneous or successive use of antiseptics or soap should be avoided. Proposed text in PL : Interaction with other medicinal product *Using other medicines* This medication should not be used with other local antiseptics (risk of incompatibility or inefficacy). The prior use of soap should be followed by thorough rinsing. Tell your doctor if you are taking or have recently taken any other medications, including medications obtained without a prescription	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Risk of burns with the use of electric bistoury	Proposed text in SmPC: *Section 4.4 Special warnings and precautions for use* Cases of burns were reported with the use of electrocautery after application of alcohol-based antiseptics related to the presence of residual product. It is therefore necessary to allow, after skin preparation for minor surgery, the product to dry completely and ensure the absence of residual product that could flow, especially at the skinfolds and the drapes before using electrocautery. Proposed text in PL : Precaution of use ; special warnings Special warnings Allow to dry before using an electrical instrument due to a risk of burn.	Not applicable

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

In hospital practice the disinfection of the skin (removal of bacteria from the skin) is desired essentially for two reasons: to prevent cross infection from the hands of nurses and doctors to the susceptible tissues of patients and to prevent self-infection of patients by blocking the transfer of pathogens from the skin to the underlying tissues on a knife blade or a needle.

VI.2.2 Summary of treatment benefits

A preoperative skin antiseptic aims to reduce the microorganisms present on the skin and therefore reduce the risk that the surgical wound will become infected.

CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée is suitable for disinfecting the skin before an invasive medical procedure. As an antiseptic, it is applied to the skin to help eliminate certain microorganisms. It is active on certain bacteria and fungi thanks to its two complementary active ingredients.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions	Contact dermatitis, urticaria, and anaphylaxis have followed repeated skin exposures to chlorhexidine. Generalised allergic reactions to chlorhexidine are extremely rare (Beaudouin, 2004).	Proposed text in PL: *Contra-indications* Do not use CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée - if you are allergic to one of active substances. *Possible side effects* Like all medications, CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée, may cause side effects, although not everyone is subject to it: Rarely, systemic allergic accident that can lead up to anaphylactic shock
Organ or mucosa damage in case of direct exposure	Organ damage has been described from accidental exposures. These cases are extremely rare. Neurotoxic effects of chlorhexidine on rats have been described such as degeneration of peripheral adrenergic nerve terminals – Henschen, 1984). Corneal injuries have been described in several cases after inadvertent exposure of the eyes to the 4% concentration. These injuries have resulted in permanent corneal scarring (Tabor, 1984). Contact with the inner ear has caused deafness (Denton, 1991). The application of chlorhexidine especially to mucous membranes is discouraged as it could cause anaphylaxis (Beaudouin, 2004).	Proposed text in PL: *Special Warnings* This product should not be used: - in the ear canal (middle ear), on mucous membranes (nose, throat, genital mucosa) - on open skin wounds, broken skin - in direct contact with neural tissue

Risk	What is known	Preventability
	Mucosal erosion have been reported after ingestion or enema of Chlorhexidine (Roche, 1991 – Hardin, 1986). Desquamating vaginal mucosa has been observed after vaginal cleansing with chlorhexidine gluconate (Shippey, 2004). Balanitis have been also reported (Barrazza, 2001).	
Risk of systemic effect	Systemic administration of chlorhexidine by oral, intravenous and subcutaneous routes have been performed in rats and mice. Chlorhexidine is poorly absorbed from the gut and is excreted mainly unchanged in the feces. Intravenous route toxicity is due to a stromalytic effect on red blood cells resulting from its surfactant activity (Denton, 1991). Chlorhexidine is poorly absorbed from skin or the gastrointestinal tract. A comprehensive review conducted concluded that some percutaneous absorption occurs at trace levels in preterm infant (Milestone, 2008).	<u>Proposed text in PL:</u> *Special Warnings* There is a risk of absorption of the active ingredient into the systemic circulation when used on a large area under occlusion, on damaged skin (especially burned), skin of preterm infants or infants.
Interference with other antiseptics or soap	Chlorhexidine is a cationic substance inactivated by organic matter, soap and anionic detergents. This can reduce the effect of the antimicrobial agent to a level that may be clinically significant (Denton, 1991).	<u>Proposed text in PL :</u> Interaction with other medicinal product *Using other medicines* This medication should not be used with other local antiseptics (risk of incompatibility or inefficacy). The prior use of soap should be followed by thorough rinsing. Tell your doctor if you are taking or have recently taken any other medications, including medications obtained without a prescription

Risk	What is known	Preventability
Risk of burn with the use of electric bistoury	Cases of burns have been reported with the use of electric bistoury after application of alcohol-based antiseptic solution (Afssaps, 2012).	Proposed text in PL : Precaution of use ; special warnings Special warnings Allow to dry before using an electrical instrument due to a risk of burn.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Not applicable	Not applicable

Missing information

Risk	What is known
Not applicable	Not applicable

VI.2.5 Summary of risk minimisation measures by safety concern

Routine risk minimisation measures for CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée are described below:

CHLORHEXIDINE 2 pour cent ALCOOLIQUE GILBERT, Solution pour application cutanée have a proposed Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them.

An abbreviated version of this in lay language is provided in the form of the proposed package leaflet (PL).

This medicine requires a marketing authorization through national procedure.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not required for national procedure.

Annex 2 - SmPC & Package Leaflet

RESUME DES CARACTERISTIQUES DU PRODUIT

1. DENOMINATION DU MEDICAMENT

CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

2. COMPOSITION QUALITATIVE ET QUANTITATIVE

Solution de Digluconate de chlorhexidine à 20% ..... 10,65 g

Alcool isopropylique..... 70 ml

Pour 100 ml de solution.

Pour la liste complète des excipients, voir rubrique 6.1.

3. FORME PHARMACEUTIQUE

Solution pour application cutanée.

4. DONNEES CLINIQUES

4.1. Indications thérapeutiques

Ce médicament est à utiliser pour désinfecter la peau avant une intervention médicale invasive.

4.2. Posologie et mode d'administration

VOIE CUTANÉE. Ne pas avaler.

Acte de petite chirurgie : appliquer le produit à l'aide d'une compresse stérile.

Antisepsie chirurgicale : après une phase de détersion, appliquer le produit à l'aide d'une compresse stérile et laisser sécher spontanément à l'air.

4.3. Contre-indications

Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1.

4.4. Mises en garde spéciales et précautions d'emploi

Mises en garde

- Réservé à un usage externe sur une peau saine. Cette préparation ne doit pas être utilisée sur les muqueuses, notamment génitales, sur des plaies cutanées ouvertes, sur une peau écorchée. En outre, le contact direct avec du tissu nerveux ou des méninges, l'œil, le conduit auditif en cas de perforation tympanique ou l'oreille moyenne doit être évité.
- Tout contact prolongé de la peau avec des solutions alcooliques doit être évité.
- Cette préparation ne doit pas être utilisée pour la désinfection du matériel médico-chirurgical.
- Bien que la résorption transcutanée de la chlorhexidine soit très faible, le risque d'effets systémiques ne peut être exclu. Ils sont d'autant plus à redouter que l'antiseptique est utilisé sur une grande surface, sur une peau lésée (notamment brûlée) une muqueuse, une peau de prématuré ou de nourrisson (en raison du rapport surface/poids et de l'effet d'occlusion des couches au niveau du siège).
- Des cas de brûlures ont été rapportés lors de l'utilisation de bistouri électrique après application d'antiseptique à base d'alcool, liés à la présence de produit résiduel. Il convient donc de s'assurer, après préparation de la peau pour petite chirurgie, du séchage complet du produit et de l'absence de quantités résiduelles de produit qui auraient pu couler, notamment au niveau des plis cutanés, et du drap de la table avant utilisation d'un bistouri électrique.

Précautions d'emploi

Dès l'ouverture du conditionnement d'une préparation à visée antiseptique, une contamination microbienne est possible.

4.5. Interactions avec d'autres médicaments et autres formes d'interactions

Compte tenu des interférences possibles (antagonisme, inactivation), l'emploi simultané ou successif d'antiseptiques ou de savons est à éviter, sauf avec les autres composés cationiques.

4.6. Fertilité, grossesse et allaitement

Aucun effet durant la grossesse ou l'allaitement n'est à anticiper puisque l'exposition systémique de la chlorhexidine est négligeable.
CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, solution pour application cutanée peut être utilisé durant la grossesse ou l'allaitement.

4.7. Effets sur l'aptitude à conduire des véhicules et à utiliser des machines

Sans objet.

4.8. Effets indésirables

- Réactions allergiques ou d'irritation cutanée à la chlorhexidine, à l'alcool isopropylique.
- Risque d'allergie générale pouvant (rarement) aller jusqu'au choc anaphylactique.
- Dès les premiers signes d'une réaction cutanée locale, arrêter d'appliquer le produit.

Déclaration des effets indésirables suspectés

La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : www.ansm.sante.fr.

4.9. Surdosage

Sans objet.

5. PROPRIETES PHARMACOLOGIQUES

5.1. Propriétés pharmacodynamiques

Classe pharmacothérapeutique : Antiseptiques et désinfectants, code ATC : D08AC02.

Mécanisme d'action

Le Digluconate de chlorhexidine est un bisdiguanide cationique. Son activité antimicrobienne est due à une interaction non spécifique avec les phospholipides acides de la membrane cellulaire et à la précipitation du contenu de la cellule. Il a un effet bactéricide ou bactériostatique sur un grand spectre de bactéries à Gram positif et à Gram négatif. Il est relativement inefficace contre les mycobactéries. Il inhibe certains virus et se révèle actif contre certains champignons. Il est inactif contre les spores bactériennes. Il a un pouvoir résiduel supérieur par rapport aux antiseptiques cutanés actuellement disponibles. Le Digluconate de chlorhexidine a un pouvoir liant fort avec la peau et un pouvoir résiduel cutané documenté à 48 heures. Le Digluconate de chlorhexidine n'est pas neutralisé en présence de substances organiques.

CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, solution pour application cutanée répond aux normes européennes concernant les désinfectants et les produits antiseptiques :

- **Norme EN 1040 :** activité bactéricide de base (phase 1),
- **Norme EN 1275 :** activité levuricide ou fongicide de base (phase 1),
- **Norme EN 1276 :** activité bactéricide (phase 2 étape 1),

- **Norme EN 1650 :** activité fongicide (phase 2 étape 1).
- **Norme EN 13727 :** activité bactéricide en médecine (phase 2, étape 1).

Souche	Temps de mise en contact	Conditions	Résultats	Critère satisfait
Pseudomonas aeruginosa	30 s, 1 min, 5 min	100 %, 50 %, 25 %	Réduction de log > 5.32	EN 1040
Staphylococcus aureus	30 s, 1 min, 5 min	100 %, 50 %, 25 %	Réduction de log > 5.47	
Candida albicans	1 min, 5 min, 15 min	100 %, 50 %, 25 %	Réduction de log > 4.42	EN 1275
Aspergillus brasiliensis	1 min, 5 min, 15 min	100 %, 50 %, 25 %	Réduction de log < 3.76	/
Pseudomonas aeruginosa	30 s, 1 min, 5 min	Pure ou diluée à 50% et 25%	Réduction de log > 5.26	EN 1276
Staphylococcus aureus	30 s, 1 min, 5 min	Pure ou diluée à 50% et 25%	Réduction de log > 5.35	
Escherichia coli	30 s, 1 min, 5 min	Pure ou diluée à 50% et 25%	Réduction de log > 5.34	
Enterococcus hirae	30 s, 1 min, 5 min	Pure ou diluée à 50% et 25%	Réduction de log > 5.23	
Candida albicans	1 min, 5 min, 15 min	Pure ou diluée à 50% et 25%	Réduction de log < 4.42	EN 1650
Pseudomonas aeruginosa	30 secondes	80%, 50%, 1%	Réduction de log > 5.49	EN 13727
		0.005%	Réduction de log < 3.99	
Staphyloccocus aureus	30 secondes	80%, 50%	Réduction de log > 5.42	
		1%	Réduction de log < 4.05	
Enterococcus hirae	30 secondes	80%, 50%, 1%	Réduction de log > 5.44	
		0.005%	Réduction de log < 3.89	
Escherichia coli	30 secondes	80%, 50%	Réduction de log > 5.17	
		0.005%	Réduction de log < 3.80	
Pseudomonas aeruginosa	5 minutes	80%	Réduction de log > 5.42	Pharmacopée Européenne Chapitre 5.1.11
Escherichia coli	5 minutes	80%	Réduction de log > 5.57	
Staphylococcus aureus	5 minutes	80%	Réduction de log > 5.61	
Enterococcus hirae	5 minutes	80%	Réduction de log > 5.37	
Candida albicans	15 minutes	80%	Réduction de log > 4.57	

5.2. Propriétés pharmacocinétiques

L'absorption du gluconate de chlorhexidine est très faible sur une peau saine.

Aucune étude pharmacocinétique n'a été réalisée avec ce produit.

5.3. Données de sécurité préclinique

Les données non cliniques issues des études conventionnelles de pharmacologie de sécurité, toxicologie en administration répétée, n'ont pas révélé de risque particulier pour l'homme.

6. DONNEES PHARMACEUTIQUES

6.1. Liste des excipients

Acide citrique, Eau purifiée.

6.2. Incompatibilités

La chlorhexidine se comporte comme un cationique : elle est donc incompatible avec tous les dérivés anioniques.

6.3. Durée de conservation

3 ans.

6.4. Précautions particulières de conservation

Ce produit ne requière pas de conditions spéciales de conservation.

6.5. Nature et contenu de l'emballage extérieur

125 ml de solution en flacon PE avec capsule inviolable.

250 ml de solution en flacon PE avec capsule inviolable.

500 ml de solution en flacon PE avec capsule inviolable.

6.6. Précautions particulières d'élimination et de manipulation

La solution est inflammable. Ne pas l'utiliser en fumant ou à proximité de flammes nues ou de fortes sources de chaleur. Eviter d'exposer le récipient et son contenu à des flammes nues lors de son utilisation, stockage et élimination.

Tout médicament non utilisé ou déchet doit être éliminé conformément à la réglementation en vigueur.

7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE

LABORATOIRES GILBERT
928 AVENUE DU GENERAL DE GAULLE
14200 HEROUVILLE SAINT-CLAIR

[Tel, fax, e-Mail : à compléter ultérieurement par le titulaire]

8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE

- CIP 34009 XXX XXX X X : flacon de 125 ml.
- CIP 34009 XXX XXX X X : flacon de 250 ml.
- CIP 34009 XXX XXX X X : flacon de 500 ml.

9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION

[à compléter ultérieurement par le titulaire]

10. DATE DE MISE A JOUR DU TEXTE

[à compléter ultérieurement par le titulaire]

11. DOSIMETRIE

Sans objet.

12. INSTRUCTIONS POUR LA PREPARATION DES RADIOPHARMACEUTIQUES

Sans objet.

CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

Médicament non soumis à prescription médicale.

Proposed package leaflet(s) for CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

NOTICE : INFORMATION DE L'UTILISATEUR

Dénomination du médicament

CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

Chlorhexidine Digluconate (Solution de), Alcool isopropylique

Encadré

Veuillez lire attentivement cette notice avant d'utiliser ce médicament car elle contient des informations importantes pour vous.

Vous devez toujours utiliser ce médicament en suivant scrupuleusement les informations fournies dans cette notice ou par votre médecin ou votre pharmacien.

- Gardez cette notice. Vous pourriez avoir besoin de la relire.
- Adressez-vous à votre pharmacien pour tout conseil ou information.
- Si vous ressentez un quelconque effet indésirable, parlez-en à votre médecin ou votre pharmacien. Ceci s'applique aussi à tout effet indésirable qui ne serait pas mentionné dans cette notice. Voir rubrique 4.
- Vous devez vous adresser à votre médecin si vous ne ressentez aucune amélioration ou si vous vous sentez moins bien.

Que contient cette notice ?

1. QU'EST-CE QUE CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée ET DANS QUELS CAS EST-IL UTILISE ?

Classe pharmacothérapeutique : Antiseptique et désinfectant - code ATC : D08AC02

Ce médicament est une solution antiseptique à action rapide, utilisée pour désinfecter la peau et prévenir des infections avant une intervention médicale invasive, comme une injection, l'insertion de cathéters et une intervention chirurgicale mineure ou majeure.

2. QUELLES SONT LES INFORMATIONS A CONNAITRE AVANT D'UTILISER CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée ?

N'utilisez jamais CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée :

- si vous êtes allergique à la chlorhexidine ou à l'un des autres composants contenus dans ce médicament, mentionnés dans la rubrique 6.

Avertissements et précautions

- Ce médicament est réservé à l'usage externe.
- Ce médicament ne doit pas être :
  - appliqué dans le conduit auditif (oreille moyenne), sur les muqueuses (nez, gorge, muqueuses génitales),

- utilisé sur des plaies cutanées ouvertes, sur une peau écorchée,
- en contact direct avec des tissus nerveux.

- Il existe un risque de passage du principe actif dans la circulation générale en cas d'utilisation sur une grande surface, sous pansement occlusif, sur une peau lésée (en particulier brûlée), une peau de prématurée ou de nourrisson.
- Laisser sécher avant utilisation d'un instrument électrique en raison d'un risque de brûlure.
- Utiliser proprement et ne pas garder longtemps un flacon entamé car une contamination microbienne est possible dès l'ouverture, d'autant plus si le volume du flacon est supérieur à 250 ml.

Adressez-vous à votre médecin ou pharmacien avant d'utiliser CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée.

Enfants

Sans objet.

Autres médicaments et CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

Ce médicament ne doit pas être utilisé en même temps que d'autres antiseptiques locaux (risque d'incompatibilité ou d'inefficacité). L'utilisation préalable de savon doit être suivie d'un rinçage soigneux.

Informez votre médecin ou pharmacien si vous utilisez, avez récemment utilisé ou pourriez utiliser tout autre médicament.

CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée avec des aliments et boissons

Sans objet.

Grossesse et allaitement

Ce médicament doit être utilisé avec prudence pendant la grossesse et l'allaitement.

Si vous êtes enceinte ou que vous allaitez, si vous pensez être enceinte ou planifiez une grossesse, demandez conseil à votre médecin ou votre pharmacien avant de prendre ce médicament.

Conduite de véhicules et utilisation de machines

Sans objet.

3. COMMENT UTILISER CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée ?

Veillez à toujours utiliser ce médicament en suivant exactement les indications de votre médecin ou pharmacien. Vérifiez auprès de votre médecin ou pharmacien en cas de doute.

Posologie

Ne pas avaler. Ne pas injecter.

Préparation de la peau saine avant une intervention médicale invasive : appliquer à l'aide d'une compresse stérile sur la zone à désinfecter.

Mode et voie d'administration

VOIE CUTANÉE.

USAGE EXTERNE.

Si vous avez utilisé plus de CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée que vous n'auriez dû

Sans objet.

Si vous oubliez d'utiliser CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

Sans objet.

Si vous arrêtez d'utiliser CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

Sans objet.

Si vous avez d'autres questions sur l'utilisation de ce médicament, demandez plus d'informations à votre médecin ou à votre pharmacien.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS ?

Comme tous les médicaments, ce médicament peut provoquer des effets indésirables, mais ils ne surviennent pas systématiquement chez tout le monde.

- Eczéma allergique au contact du produit, d'autant plus s'il s'agit d'une peau lésée, de muqueuses ou d'ulcérations des membres inférieurs.
- Rarement, accident allergique général pouvant aller jusqu'au choc anaphylactique

Déclaration des effets secondaires

Si vous ressentez un quelconque effet indésirable, parlez-en à votre médecin ou votre pharmacien. Ceci s'applique aussi à tout effet indésirable qui ne serait pas mentionné dans cette notice. Vous pouvez également déclarer les effets indésirables directement via le système national de déclaration : Agence nationale de sécurité du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: www.ansm.sante.fr

En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament.

5. COMMENT CONSERVER CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée ?

Tenir ce médicament hors de la vue et de la portée des enfants.

N'utilisez pas ce médicament après la date de péremption indiquée sur l'étiquette après EXP. La date de péremption fait référence au dernier jour de ce mois.

Ce médicament ne requière pas de conditions spéciales de conservation.

Ne jetez aucun médicament au tout-à-l'égout ou avec les ordures ménagères. Demandez à votre pharmacien d'éliminer les médicaments que vous n'utilisez plus. Ces mesures contribueront à protéger l'environnement.

6. CONTENU DE L'EMBALLAGE ET AUTRES INFORMATIONS

Ce que contient CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée

- Les substances actives sont :
  Solution de Digluconate de chlorhexidine à 20% ..... 10,65 g

  Alcool isopropylique ..... 70 ml

  Pour 100 ml de solution.
- Les autres composants sont : acide citrique, eau purifiée.

Qu'est-ce que CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée et contenu de l'emballage extérieur

Ce médicament se présente sous forme de solution pour application cutanée en flacon de 125, 250 ou 500 ml.

Titulaire de l'autorisation de mise sur le marché

LABORATOIRES GILBERT

928 AVENUE DU GENERAL DE GAULLE
14200 HEROUVILLE SAINT-CLAIR

Exploitant de l'autorisation de mise sur le marché

LABORATOIRES GILBERT
928 AVENUE DU GENERAL DE GAULLE
14200 HEROUVILLE SAINT-CLAIR

Fabricant

LABORATOIRES GILBERT
928 AVENUE DU GENERAL DE GAULLE
14200 HEROUVILLE SAINT-CLAIR

Noms du médicament dans les Etats membres de l'Espace Economique Européen

Sans objet.

La dernière date à laquelle cette notice a été révisée est :

[à compléter ultérieurement par le titulaire]

Autres

Des informations détaillées sur ce médicament sont disponibles sur le site Internet de l'ANSM (France).

Annex 3 - Worldwide marketing authorisation by country (including EEA)

For each product in the RMP provide:

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action [1]	Date first marketed in country	Brand name(s)	Comments
FRANCE	Under review	NA	NA	CHLORHEXIDINE 2 POUR CENT ALCOOLIQUE GILBERT, Solution pour application cutanée.	

A3.2 Licensing status in the rest of the world

Not applicable

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Not applicable

Annex 7 - Specific adverse event follow-up forms

Not applicable

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 9 - Newly available study reports for RMP parts III & IV

La spécialité «Chlorhexidine 2% isopropylique – REF G10096_1.04»

Laboratoire Gilbert has conducted preclinical testing to support the safety of CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée. These studies are detailed in module 2.4 Evaluation Toxico-Pharmacologique et clinique de la spécialité Chlorhexidine 2% isopropylique - REF G10096_1.04 Laboratoires Gilbert. A summary of these studies is presented below :

In accordance with the guideline CPMP/SWP/2145/00 « *note for guidance on non clinical local tolerance testing of medicinal products* », the following studies were conducted:

- IC-iso-PH-12/0562 : Evaluation of primary skin irritation in rabbits,
- ITC-iso-PH-12/0562: Evaluation of local tolerance after 14 days repeated application in the rabbit,
- LLNA-PH-12/0562 : Evaluation of potential skin sensitization in mice (Local lymph node assay, LLNA)

IC-iso-PH-12/0562 report : Evaluation of primary skin irritation in rabbits

One-half (0.5) mL of CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée was applied for 4 hours under semi-occlusive dressing on a surface of healthy skin in 3 female New Zealand rabbits . The study plan was prepared in accordance with OECD No. 404 of 24 April 2002 and NF EN ISO 10993-10 December 2010 (Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization) directives.

This protocol is Good Laboratory Practice (GLP) compliant .

The reaction of the skin was examined 1, 24, 48 and 72 hours after removal of the product .

A very slight or well defined erythema was observed at Time 1 hour of observation on both flanks of the animals (3/3) . This reaction is reversible in nature 1-2 days after application.

The Primary Skin Irritation (PSI) index has been evaluated to 0.06 according to the standard NF EN ISO 10993-10 .

In conclusion, under the experimental conditions of this study, "CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée" presents no risk of skin irritation in accordance with the classification published February 21, 2002 in the Official Journal of the French Republic .

ITC-iso-PH-12/0562 Report : Evaluation of local tolerance after 14 days repeated application in the rabbit

"CHLORHEXIDINE 2 POUR CENT ISOPROPYLIQUE GILBERT, Solution pour application cutanée" was applied daily for 14 consecutive days to healthy skin of 3 rabbits at a dose of 0.5 ml over an area of approximately 6 cm^2. This experimental protocol was established from the official method described in the decree dated 11 May 1993 (Official Journal of the French Republic on 25 May 1993) and NF EN ISO 10993-10 December 2010 (Biological evaluation of medical devices - Part 10: tests for irritation and skin sensitization) directive.

This protocol is GLP compliant.

The degree of irritation was evaluated at regular intervals before each application of the product. A similar area on the opposite flank of the animal was treated in the same experimental conditions, with distilled water and was used as control . The treated areas were not covered.

The change in weight was normal for the duration of the study. No mortality and no clinical signs due to systemic toxicity after possible transdermal absorption were observed.

No skin reaction (erythema , edema) was observed regardless of the duration of the examination . No change in the skin structure (appearance and elasticity) were reported.

In conclusion, under the experimental conditions of this study, "CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée" did not cause skin reactions after application for 14 days on healthy skin in rabbits. The treatment was well tolerated.

LLNA-PH-12/0562 Report: Evaluation of potential skin sensitization in mice (LLNA)
This study was conducted to assess the skin sensitization potential of "CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée" in the CBA/J mice after topical application on the dorsal surface of the ear.
The LLNA test provides an alternative method to identify the potential for skin sensitization. The study plan was prepared in accordance with OECD No. 429 directive and NF EN ISO 10993-10 December 2010 (Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization) guideline.
This protocol was GLP compliant.
The product and the vehicle (25 µL on each ear) were applied to the dorsal surface of the right ear using a micropipette. The deposit zone was not covered. The animals were divided into 4 groups:

- Group 1 (control): 25 µL vehicle (dimethylformamide)
- Group 2 (treated): 25 µL of the appropriate dilution of the product (low concentration, dilution in dimethylformamide at 50%).
- Group 3 (treated): 25 µL of the appropriate dilution of the product (medium concentration, dilution in dimethylformamide at 25%).
- Group 4 (treated): 25 µL of the solution without dilution (high concentration, 100%)

This procedure was repeated on days 2 and 3. No application was performed on days 4 and 5. On day 6, the animals were euthanized. Biopsies of 8 mm of diameter of the apical region of both ears were prepared and weighed to determine the irritation potential.
The thickness of the right ear (local response) was measured with a micrometer on day 1 prior to application, on day 3 prior to application and on day 6 after the sacrifice. The examination consisted in the evaluation of the reaction of the skin exposed to the product or vehicle in comparison with untreated left ear. The irritant reactions (erythema) were recorded in parallel. Lymphocyte proliferation in the auricular draining lymph node was assessed by cell counting.

This study revealed no specific clinical sign. No deaths were reported. Changes in body weight were similar in the groups treated with drug and vehicle.
No skin reaction was recorded during the test and in any group. The thickness and weight of the ears did not changed.
The proliferation index was never greater than 1.4. The stimulation index (SI) was 0.98, 1.08 and 1.37 for the treated with 25, 50 and 100% diluted groups, respectively.
Under the experimental conditions of this study, "CHLORHEXIDINE ALCOOLIQUE GILBERT HEALTHCARE 2%, Solution pour application cutanée" did not show any sensitizing potential.


In conclusion, under the experimental conditions of this study, "CHLORHEXIDINE 2 POUR CENT ALCOOLIQUE GILBERT, Solution pour application cutanée" should not be regarded as a sensitizer according to EU Directives 67/548, 2001/59 and 99/45.
In accordance with CE no 1272/2008 regulation, this medication will not be classified in Category 1. No mention of danger or warning is necessary.

Other preclinical safety data
Sub-chronic studies of general toxicity have been conducted with chlorhexidine diacetate in New Zealand rabbits which received topical doses of 0, 250, 500 or 1000 mg / kg / day for 13 weeks (EPA, United States Environmental Protection Agency, 1996). Mild skin irritation was observed only at the lowest dose tested (erythema, edema, desquamation). At a dose of 500 mg/kg, histological alterations in hepatic levels have been reported in female animals, secondary to systemic exposure. Given the low intensity of the observations made at 250 mg/kg, this dose was selected as NOEL (No Observable Effect Level).
Genotoxicity studies showed no genotoxic or clastogenic potential.

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

Not applicable

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable

Annex 12 - Other supporting data (including referenced material)

A literature search was conducted on key resources including Embase and PubMed and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type.
The search was limited to English and French languages.

12.1 Efficacy and Safety Studies

CHLORHEXIDINE GLUCONATE 2% and ISOPROPYL ALCOHOL 70%

Hibbard JS, Mulberry GK, Brady AR. A clinical study comparing the skin antisepsis and safety of chloraprep, 70% isopropyl alcohol and 2% aqueous chlorhexidine. J Infus Nurs 2002; 25:244-249.
In a controlled open-label trial of 85 healthy volunteers aged 18 to 70 years without dermatosis, inflammation or abdominal or inguinal wounds, Hibbard et al. assessed the immediate and persistent antimicrobial efficacy and safety of 2% chlorhexidine gluconate with 70% isopropyl alcohol compared with 70% isopropyl alcohol or a 2% chlorhexidine aqueous solution alone. Each antiseptic significantly reduced abdominal and inguinal microbial counts from baseline at 10 minutes, 6 hours, and 24 hours (p=0.0001). Two percent chlorhexidine gluconate with 70% isopropyl alcohol provided significantly more persistent antimicrobial activity on abdominal sites than isopropyl alcohol (p=0.003) or chlorhexidine gluconate (p=0.028) at 24 hours. No skin irritations were reported for any of the three antiseptics. In addition, no significant differences in the frequency of erythema, edema, rash or dryness on abdominal or groin treatment sites were reported during the study period.

Small H, Adams D, Casey A et al. Efficacy of Adding 2% (w/v) Chlorhexidine Gluconate to 70% (v/v) Isopropyl Alcohol for Skin Disinfection Prior to Peripheral Venous Cannulation. Infect Control Hosp Epidemiol 2008; 29:963-965
Small et al. undertook a clinical trial to compare the efficacy of 2% (w/v) chlorhexidine gluconate (CHG) in 70% (v/v) isopropyl alcohol (IPA) with the efficacy of 70% (v/v) isopropyl alcohol alone for skin disinfection to prevent peripheral venous catheter colonization and contamination in patients admitted for ablation or pacemaker insertion at a University Hospital in the United Kingdom. Patients were randomly assigned to receive skin preparation prior to peripheral venous catheter (PVC) insertion either with the 2% CHG in IPA solution or with wipes containing 0.6 mL of 70% IPA. Blinding was not achieved because of the physical differences in the antiseptic applicators. The authors analyzed PVCs from 170 patients with a mean age of 61.3 years; there were 91 patients in the 2% CHG with IPA group and 79 patients in the IPA group. The use of 2% CHG in IPA was associated with a reduced number of PVC tips with microorganisms present on their surface, compared with the use of 70% IPA alone. Microorganisms were present on 39 (49.4%) of 79 PVC tips in the 70% IPA group, compared with 18 (19.8%) of 91 PVC tips in the 2% CHG in IPA group ($p<0.001$; odds ratio, 4.0 [95% confidence interval, 2.0–7.8]). This study suggests that the use of 2% CHG in IPA for skin decontamination prior to PVC insertion may reduce the risk of subsequent PVC contamination or colonization, compared with the use of 70% IPA alone.

Darouiche H, Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis. N Engl J Med 2010;362:18-26
Darouiche et al. conducted a randomized double-blind, multicenter study to compare the efficacy of chlorhexidine–alcohol with that of povidone–iodine for preventing surgical-site infections. Adults undergoing clean-contaminated surgery in six hospitals were assigned to preoperative skin preparation with either chlorhexidine-alcohol scrub or povidone-iodine scrub and paint. The primary

outcome was any surgical-site infection within 30 days after surgery and secondary outcomes included individual types of surgical-site infections. A total of 849 subjects (409 in the chlorhexidine-alcohol group and 440 in the povidone-iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection within 30 days after surgery was significantly lower in the chlorhexidine-alcohol group than in the povidone-iodine group (9.5% vs. 16.1%; p=0.004; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine-alcohol was significantly more protective than povidone-iodine against both superficial incisional infections (4.2% vs. 8.6%, p=0.008) and deep incisional infections (1% vs. 3%, p=0.05) but not against organ-space infections (4.4% vs. 4.5%). In the intention-to-treat analysis, adverse events occurred in equal proportions among the patients in the chlorhexidine–alcohol group and the povidone–iodine group (228 of 409 [55.7%] and 256 of 440 [58.2%], respectively), as did serious adverse events (72 of 409 [17.6%] and 70 of 440 [15.9%], respectively). Three patients (0.7%) in each study group had an adverse event (pruritus, erythema, or both around the surgical wound) that was judged to be related to the study drugs; however, no serious adverse events were judged to be related to the study drugs. There were no cases of fire or chemical skin burn in the operating room. Authors concluded that preoperative cleansing of the patient's skin with chlorhexidine-alcohol is superior to cleansing with povidone-iodine for preventing surgical-site infection after clean-contaminated surgery.

Art G. Comparison of the safety and efficacy of two topical antiseptic products: chlorhexidine gluconate + isopropyl alcohol and povidone-iodine + isopropyl alcohol. Journal of the Association for Vascular Access. 2007;12: 156–163.

Art G. reported efficacy results of two studies directly comparing products containing a combination of povidone-iodine (PVP-I) and alcohol with chlorhexidine gluconate (CHG) and alcohol. The first study compared a product containing a combination of 7.5% PVP-I+72% isopropyl alcohol (IPA) with a product containing the combination 2% CHG+70% IPA as patient preoperative and precatheter/catheter site maintenance skin preparations. Healthy human subjects between the ages of 18 and 70 were recruited. Two anatomical sites were used: the inguinal area (groin; 8-9 subjects) and the abdomen (7-10 subjects). For the patient preoperative skin preparation evaluation, inguinal site sampling was performed immediately (within 30 seconds of drying), and at approximately 6 and 24 hours post-product application. For the patient precatheter/catheter site maintenance skin preparation evaluation, abdominal sites were sampled 24 hours, 48 hours, and 7 days post-product application. The product containing a combination 7.5% PVP-I+72% IPA formulation above met the tentative finam monograph (TFM) requirements as a moist site patient preoperative skin preparation (3 log10/cm2 reduction within 10 minutes, not to exceed baseline before six hours). The product containing a combination 2% CHG+70% IPA product failed to achieve the required initial 3 log10/cm2 reduction to be considered an effective moist site patient preoperative skin preparation. Both products maintained microorganism populations below baseline for the entire seven day duration of the study. With one exception, no significant difference ($p \geq 0.05$) was determined between the efficacy of the product containing a combination 7.5% PVP-I+72% IPA formulation and the product containing a combination 2% CHG+70% IPA formulation; the products performed equally. However, a significantly ($p < 0.05$) greater log10/cm2 reduction was achieved by the product containing a combination 7.5% PVP-I+72% IPA formulation on inguinal sites immediately after product application, suggesting the product containing a combination 7.5% PVP-I+72% IPA as being superior to the product containing a combination 2% CHG+70% IPA as a fast-acting antiseptic. The second study compared the antimicrobial efficacy of 7.5% PVP-I+72% IPA formulation with 2% CHG+70% IPA formulation as a patient preinjection skin preparation. Both products met the TFM requirements to validate their use as a patient preinjection skin preparation. No significant difference ($p \geq 0.05$) was determined between the efficacy of the product containing a

combination 7.5% PVP-I+72% IPA formulation applied to the skin for 10 seconds and the product containing a combination 2% CHG+70% IPA formulation applied for 30 seconds; the products performed equally.

CHLORHEXIDINE

Milstone AM, Passaretti C, Perl TM. Chlorhexidine: expanding the armamentarium for infection control and prevention. Clin Infect Dis 2008;46:274-81
Chlorhexidine, an antiseptic solution that has been used worldwide since 1954, is a safe and effective product with broad antiseptic activity. Milestone et al. reviewed some of the many infection control applications of chlorhexidine in the battle against health care associated infections (HAIs), such as general skin cleansing, preoperative showering and bathing, vascular catheter site preparation, impregnated catheter site dressings, impregnated catheters, and oral decontamination. In this review is stated that for decades, chlorhexidine has been a well-tolerated, broadly used, skin and mucous membrane disinfectant. The most frequent adverse reaction to chlorhexidine is contact dermatitis, but rare cases of hypersensitivity and anaphylaxis have been reported. Contact of chlorhexidine with the inner ear may result in permanent hearing loss. Since the 1970s, investigators have studied the efficacy of wiping or bathing neonates with chlorhexidine to reduce neonatal sepsis, and no significant adverse events have been reported. A recent, comprehensive review concluded that some percutaneous absorption occurs at trace levels, particularly in preterm infants; however, there have been no reports of adverse consequences as a result of chlorhexidine absorption in pediatric patients and no data to suggest that trace levels have clinical importance. Authors concluded that chlorhexidine-containing products may provide a vast armamentarium for the control and prevention of HAI.

Karki S, Cheng AC. Impact of non-rinse skin cleansing with chlorhexidine gluconate on prevention of healthcare-associated infections and colonization with multiresistant organisms: a systematic review. J Hosp Infect 2012;82:71-84
Karki et al. conducted a systematic review to assess the impact of body bath or skin cleansing with chlorhexidine gluconate (CHG)-impregnated or CHG-saturated washcloths in preventing healthcare-associated infections and colonization. The use of non-rinse chlorhexidine gluconate application significantly reduced the risk of central-line-associated bloodstream infection (CLABSI) (IRR= 0.43, 05%CI: 0.26-0.71), surgical site infection (RR= 0.29, 95% CI: 0.17-0.49), vancomycin-resistant enterococci (VRE) colonization (IRR=0.43, 95% CI: 0.32-0.59), meticillin-resistant Staphylococcus aureus (MRSA) colonization (IRR= 0.48, 95% CI: 0.24-0.95). There was no statistical significant difference for the risk of VRE and MRSA infections. There was no reduction in acinetobacter infection rates in the three studies where this was reported. Authors concluded that the use of non-rinse CHG application significantly reduces the risk of CLABSI, SSI and colonization with VRE or MRSA, but not infection.

Beaudouin E, Kanny G, Morisset M, Renaudin JM, Mertes M et al. Immediate hypersensitivity to chlorhexdine: literature review. Eur Ann Allergy Clin Immunol 2004;36:123-6.
Beaudouin et al. conducted a literature review and reported that late onset hypersensitivity and eczema occur in 0.1 to 0.8% of cases and are well documented events. Immediate hypersensitivity, sometimes taking the form of acute urticaria that can result in anaphylactic shock, is rarer. These manifestations can occur during contact of the skin or mucosa with chlorhexidine. Out of the fifty case reports of chlorhexidine-related anaphylaxis published worldwide over the past ten years, fifteen occurred during surgery. Signs generally appear from 15 to 45 minutes after the start of anesthesia.

Gavrey LH et al; Acta Anaesthesiol Scand 47 (6): 720-4 (2003)
Gavrey et al. conducted a study in Denmark where chlorhexidine is the standard disinfectant in most hospitals and health care workers are repeatedly exposed to it. The aim of this study was to establish whether there is a risk of sensitization and allergy to chlorhexidine from this type of exposure. Two hundred and forty-eight doctors, nurses and auxiliary staff were invited to participate in the study. One hundred and four individuals took part in the full study including skin tests and a questionnaire and a further 74 individuals filled in the questionnaire giving a total of 178 questionnaires (72%). Patch tests with chlorhexidine gluconate 1% and chlorhexidine acetate 1%

were performed looking for type IV (delayed type) allergy. A prick test with chlorhexidine gluconate 0.5% and an intradermal test with chlorhexidine 0.0002% were performed looking for type I (immediate type) allergy. There were no positive tests in any of the 104 individuals tested (99% confidence interval 0-4.9%). There was a predominance of females in both groups and the overall median age was 42 years (28-63). No one in the group not tested reported to have a verified or suspected allergy to chlorhexidine. In this first study to examine the risk of type I and type IV allergy to chlorhexidine in health care workers with daily exposure to chlorhexidine, we did not identify allergies to chlorhexidine in any of the 104 individuals tested or in the additional 74 individuals who completed the questionnaire.

Stingeni L et al; Contact Dermatitis 33 (3): 172-6 (1995)
Stingeni L et al. conducted a study in Italy where Health care personnel from the 5th category at major occupational risk of skin disease. The aim of this study was to assess the prevalence and clinical relevance of contact dermatitis in a group of 1301 employees of the Perugia Monteluce Hospital (658 females and 643 males; mean age 39.8 years) who answered a self-administered questionnaire. The subjects with anamnestic hand dermatitis and/or atopic mucosal reactions were clinically examined and submitted to skin tests (patch and/or prick tests). Contact dermatitis of the hands and/or forearms occurred in 21.2% and was significantly more frequent ($p<0.001$) in women, subjects under 31 years of age, workers in internistic and surgical fields, cleaners and nurses. In the majority of cases (94.9%), the lesions were irritant in origin and mainly related to disinfectants (especially, chlorhexidine gluconate and glutaraldehyde) and gloves (latex proteins and starch glove powder, rather than accelerators and additives of rubber). Finally, atopy seemed to favor the onset of hand dermatitis.

Andersen BL et al; Contact Dermatitis 13 (5): 307-9 (1985)
Andersen et al conducted a study on skin reactions to chlorhexidine-acetate and chlorhexidine-gluconate among eczema patients. Subjects were tested with 1% chlorhexidine-gluconate and 1% chlorhexidine-acetate by patch test. The patches were applied for 48 hours and read at 72 hours. Subjects with a positive reaction at the initial testing were retested 1 month later. Positive reactions were found in 52 (5.4%) of the 1,063 subjects at the initial test. Of these subjects, 29 were retested, and 21 were still found to have positive reactions. A use test performed on these 29 patients resulted in all of them developing a dermatitis with one or both of the chlorhexidine solutions. Those patients with leg eczema or leg ulcers appeared to be particularly at risk. The authors conclude that patients with eczema, and especially those with leg ulcers or leg eczema, are especially prone to chlorhexidine allergies.

Heinemann C, Sinaiko R, Maibach HI. Immunological contact urticaria and anaphylaxis to chlorhexidine: Overview. Exogenous Dermatology 2002;1:186-94
A literature review of 66 case reports was done by Heinemann et al. Twenty reactions occurred when chlorhexidine was applied to damaged skin surfaces and 27 patients showed an immediate type reaction when chlorhexidine was applied to mucous membranes.

Cowen J et al; Arch Dis Child 54 (5): 379-83 (1979)
Cowen studied data on 34 newborn infants who had been bathed in a standard manner with Hibiscrub to find out whether it was absorbed percutaneously. Low levels of chlorhexidine were found in the blood of all 10 babies sampled by heel prick, and 5 of 24 from whom venous blood was taken.

Rosenberg A, Alatary SD, Peterson AF. Safety and efficacy of the antiseptic chlorhexidine gluconate. Surg Gynecol Obstet. 1976 Nov;143(5):789-92.
Chlorhexidine gluconate, an antiseptic for the skin, has recently been investigated in a series of clinical studies on its safety and efficacy. By using standard methods, Hibiclens, Hibitane tinted tincture and 0.5 per cent aqueous chlorhexidine gluconate were shown to have an extremely low potential for the production of irritation, allergic contact sensitization, photoallergic contact sensitization and phototoxicity. In the glove fluid test for efficacy against resident flora of the hand, Hibiclens produced log10 reductions over the control of 1.9398, 2.5371 and 2.6885 for test days 1, 2 and 5, respectively. Corresponding reductions for Hibitane tinted tincture were 3.6903, 4.0984 and 4.1253 and for the aqueous formulation, 1.5003, 1.5721 and 1.8692. In a transient flora skin contamination study, Serratia marcescens was applied at an average level of 6.8363 log10

organisms per milliliter to persons' hands, after which a 15 second Hibiclens hand wash was performed. Following five of these contaminations and hand washes, there was an over-all log10 reduction in recoverable Serratia of 3.8500. Counts were further determined after ten, 15, 20 and 25 contaminations and hand washes, resulting in corresponding reductions of 4.2649, 4.6661, 4.8501 and 5.1725, respectively. Chlorhexidine gluconate offers an alternative to available antiseptics for the skin. It has been shown to be a fast acting, broad spectrum antimicrobial agent, with an extremely low potential for eliciting dermal reactions.

Clinical trials:

Edmiston C.E., Okoli O., Graham M.B., Sinski S., Seabrook G.R. Evidence for Using Chlorhexidine Gluconate Preoperative Cleansing to Reduce the Risk of Surgical Site Infection. AORN Journal. 92 (5) (pp 509-518), 2010.
Edmiston et al. noted that although older clinical trials question the clinical efficacy of cleansing with CHG, recent evidence-based scientific and clinical studies support two types of CHG application (ie, a 2% CHG-coated cloth or 4% CHG soap) using a standardized, timed process before hospital admission as an effective strategy for reducing the risk of postoperative surgical site infection

CHLORHEXIDINE and ALCOHOL

Maiwald M., Chan E.S.-Y. The Forgotten Role of Alcohol: A Systematic Review and Meta-Analysis of the Clinical Efficacy and Perceived Role of Chlorhexidine in Skin Antisepsis. PLoS ONE. 7(9), 2012.
The efficacy of chlorhexidine is actively discussed in the literature on skin antisepsis. However, study outcomes due to chlorhexidine-alcohol combinations are often attributed to chlorhexidine alone. Maiwald et al. thus, sought to review the efficacy of chlorhexidine for skin antisepsis and the extent of a possible misinterpretation of evidence. A systematic literature review of clinical trials and systematic reviews investigating chlorhexidine compounds for blood culture collection, vascular catheter insertion and surgical skin preparation was performed. Study design, antiseptic composition, and the following outcomes blood culture contamination, catheter colonisation, catheter-related bloodstream infection and surgical site infection data were collected. A meta-analyses of the clinical efficacy of chlorhexidine compounds and reviewed the appropriateness of the authors' attribution were conducted. In all three application areas and for all outcomes, there was good evidence favouring chlorhexidine-alcohol over aqueous competitors, but not over competitors combined with alcohols. For blood cultures and surgery, we found no evidence supporting chlorhexidine alone. For catheters, we found evidence in support of chlorhexidine alone for preventing catheter colonisation, but not for preventing bloodstream infection. A range of 29 to 43% of articles attributed outcomes solely to chlorhexidine when the combination with alcohol was in fact used. Articles with ambiguous attribution were common (8-35%). Unsubstantiated recommendations for chlorhexidine alone instead of chlorhexidine-alcohol were identified in several practice recommendations and evidence-based guidelines. Authors concluded that perceived efficacy of chlorhexidine is often in fact based on evidence for the efficacy of the chlorhexidine-alcohol combination; the role of alcohol has frequently been overlooked in evidence assessments. This has broader implications for knowledge translation as well as potential implications for patient safety.

Nishihara Y. Kajiura T. Yokota K. Kobayashi H. Okubo T. Evaluation with a focus on both the antimicrobial efficacy and cumulative skin irritation potential of chlorhexidine gluconate alcohol-containing preoperative skin preparations. American Journal of Infection Control (2012) 40:10 (973-978).
Nishihara et al. enrolled 55 healthy adult subjects to evaluate the antimicrobial effects of 3 test formulations applied to inguinal, abdominal, and antecubital sites at post-treatment time points of 30 seconds, 72 hours, and 7 days. To investigate skin irritation potential, the 3 formulations were tested in a 21-day repeat-insult patch test conducted on the skin of the backs of 23 healthy subjects. The mean log(10) reduction (MLR) at 7 days post-treatment produced by a 79% vol/vol ethanol containing 1% wt/vol chlorhexidine gluconate (1% CHG-EtOH) applied to abdominal sites was significantly superior to that produced by a 10% povidone-iodine solution (2.45 MLR vs 0.90 MLR; $P < .05$). The 1% CHG-EtOH and a 70% vol/vol isopropanol containing 2% wt/vol CHG (2% CHG-IPA) provided statistically equivalent persistence at 72 hours and 7 days post-treatment. The

1% CHG-EtOH had less skin irritation potential than the 2% CHG-IPA and the 10% povidone-iodine solution, although the differences were not statistically significant (P > .05). Authors concluded that considering its persistent effect and low skin irritation potential, the 1% CHG-EtOH preparation is expected to perform well in surgical site preparation to reduce the risk of surgery- and catheter-related bloodstream infection.

Caldeira D, David C, Sampaio C. Skin antiseptics in venous puncture-site disinfection for prevention of blood culture contamination: systematic review with meta-analysis. J Hosp Infect 2011;77:223-32
Caldeira et al. conducted database search using CENTRAL (Cochrane Library issue April 2010), MEDLINE, EMBASE and mRCT, in June 2010 to systematically review randomised controlled trials with skin antiseptics for prevention of contamination in venous-puncture drawn blood cultures. Six studies were identified. Meta-analysis demonstrated that alcoholic chlorhexidine was better than non-alcoholic povidone-iodine (RR: 0.33; 95% CI: 0.24-0.46) in 4757 blood cultures from two trials. Alcoholic solutions were better than non-alcoholic products (0.53; 0.31-0.90) in 21,300 blood cultures from four studies. Comparison of chlorhexidine versus iodine compounds was not conclusive. Alcoholic chlorhexidine solutions reduced blood culture false positives compared with aqueous povidone-iodine.

Moon K.T. Chlorhexidine-alcohol antiseptic reduces surgical site infections. American Family Physician. 81 (11) (pp 1369), 2010.
Moon et al. prospectively examined the relative merits of 10% povidone-iodine and 2% chlorhexidine gluconate with 70% isopropyl alcohol in reducing surgical site infections. Adult patients were randomized to have their surgical sites preoperatively scrubbed with either agent. All patients were undergoing clean-contaminated surgery (e.g., gastrointestinal, thoracic), and received systemic prophylactic antibiotics within one hour before the initial incision. The primary end point was surgical-site infection within 30 days, with secondary end points reviewing specific types of postsurgical infections. A total of 849 patients were randomized to receive a povidone-iodine or a chlorhexidine with isopropyl alcohol skin scrubbing. Participants in both groups had similar baseline traits, presurgical prophylactic antibiotics, and surgery types. The chlorhexidine group had a significantly lower postsurgical infection rate than persons receiving povidone-iodine (9.5 versus 16.1 percent; relative risk [RR] = 0.59). Fewer superficial (RR = 0.48) and deep incisional (RR = 0.33) infections occurred in the chlorhexidine group, although the incidence of organ-space infection and sepsis were similar between groups. Three patients in each study group reported local reactions at the wound site, such as pruritus or erythema, but no serious adverse events were reported. The authors concluded that using chlorhexidine-alcohol antiseptic before surgery reduced the risk of surgical site infection by 41 percent, compared with povidone-iodine. Although no episodes of fire or chemical skin burn occurred in the study, the authors caution that this is a potential risk when using alcohol-based agents.

12.2 Recommendations and cautions

Guidelines for the prevention of intravascular catheter-related infections, 2011 recommends to prepare clean skin with more than 0.5% chlorhexidine preparation with alcohol before central venous catheter and peripheral arterial catheter insertion and during dressing changes.
GUIDELINE SUMMARY NGC-8683. Guideline Title "Guidelines for the prevention of intravascular catheter-related infections, 2011". US Department of Health and Human Services. Available at: http://f.i-md.com/medinfo/material/80f/4ef3f5002cdc8344ce0d580f/CAB7C70B208380465CEB405F31FEB848.pdf. Accessed 04 November 2013.

The French Society of Hospital Hygiene (Société Française d'Hygiène Hospitalière, SFHH) and the French Health Authority (Haute Autorité de Santé, HAS) recommends the preferential use of antiseptics in alcoholic solution such as the chlorhexidine alcohol for skin preparation of the surgical site, in compliance with the precautions of use (respecting the drying time before electrocautery).
Recommandations pour la pratique clinique, Prévention des infections liées aux cathéters veineux périphériques, SFHH - HAS (Service des recommandations professionnelles) / Novembre 2005

The Danish Health and Medicines Authority is reminding doctors to be aware that chlorhexidine may trigger anaphylaxis in very rare cases. The authority's ADR database contains seven reports of anaphylactic reaction following the use of medicinal products containing chlorhexidine.

Danish authority draws attention to chlorhexidine, ciclosporin safety.
Reactions. vol.1439 16 Feb 2013 page. 4.

12.3 Toxicology (*in vitro* and *in vivo* studies):

Chlorhexidine

McEvoy, GK. American Hospital Formulary Service – Drug Information 2003. Bethesda, MD: American Society of Heath-System Pharmacists, Inc. 2003 (plus supplements p. 2619 Peer reviewed)

- Acute Exposure/ Results of a controlled study in rabbits indicate that marked corneal de-epithelialization, conjunctival chemosis, and anterior stromal edema occur 3 hours after topical application of chlorhexidine gluconate solution to the eye.

- Mutagenic effects were not observed in 2 mammalian in vivo mutagenesis studies evaluating chlorhexidine gluconate. The highest daily dosages of chlorhexidine used in a mouse dominate lethal assay and a hamster cytogenetics test were 1000 and 250 mg/kg respectively. The results of several mutagenicity studies, including an Ames in vitro assay, a chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and an in vivo mouse micronucleus assay, did not show evidence that chlorhexidine has the potential to cause genetic toxicity.

12.4 Data on post marketing authorisation:

Case reports from literature:

CHLORHEXIDINE

Allergic reaction

Chlorhexidine. [Urticaria following occupational exposure: 4 case reports]. IgE-mediated chlorhexidine allergy: a new occupational hazard?
Nagendran V; Wicking J; Ekbote A; Onyekwe T; Garvey LH
Occupational Medicine (Oxford). vol.59 (4), 01 Jun 2009 page. 270-2.
Four healthcare workers developed urticaria after occupational exposure to chlorhexidine [Hydrex] 4% w/v skin cleanser [durations of exposure to reaction onset not stated].
A 31-year-old female nurse developed redness and itching on her wrists and forearms after using chlorhexidine hand wash. Her symptoms progressed to urticaria over the next few months. Skin prick testing with chlorhexidine was positive, and she had a chlorhexidine-specific IgE level of 1.4 kuA/L. She switched to non-chlorhexidine hand wash, and her symptoms resolved within 3 months.
A 51-year-old female nurse developed itching and urticarial rash immediately after using chlorhexidine hand wash. She stopped using chlorhexidine-containing products, and her symptoms resolved. Her chlorhexidine-specific IgE level was 0.27 kuA/L.
A 35-year-old male nurse developed rhinitis and redness and itching on his hands after wearing powdered latex gloves when preceded by hand washing. Despite avoiding latex gloves, his symptoms persisted. Skin prick tests to both chlorhexidine and latex were positive. Chlorhexidine- and latex-specific IgE levels were 0.20 and 0.23 kuA/L, respectively [outcome not stated].
A 43-year-old female hospital worker developed dermatitis on her hands after washing them 15-20 times during a 4-hour shift. She went on to develop a secondary infection, which was treated with clobetasol and flucloxacillin. It was discovered that she had developed urticaria on her forearms after using chlorhexidine hand wash several weeks prior to the onset of dermatitis. Chlorhexidine- and latex-specific IgE levels were 14.8 and 28.5 kuA/L, respectively, and skin prick tests to both chlorhexidine and latex were positive [outcome not stated].

Chlorhexidine. [Hypersensitivity in an elderly patient: case report]. Skin cleansers: The risks of chlorhexidine.
Sivathasan N; Goodfellow PB
Journal of Clinical Pharmacology. vol.51 (5), 01 May 2011 page. 785-786.
A 74-year-old man developed hypersensitivity after receiving topical chlorhexidine [dosage not stated]. The man was hospitalised for laparoscopic anterior resection. His skin was prepared with a chlorhexidine-based solution. During abdominal insufflation, his oxygen saturation and BP decreased acutely, leading to cardiovascular collapse. Cardiopulmonary resuscitation was performed. The man was transferred to the ICU with a rash and hypotension requiring inotropes. He received dexamethasone for a very swollen tongue. After extubation, it was discovered that he

had previous episodes of tingling lips and throat swelling after visiting the dentist. Skin testing showed a repeatable positive response to chlorhexidine. He was readmitted for operation, and a skin-cleansing wipe was used. He promptly developed a rash and breathing difficulties, and was admitted to the high-dependency unit. Residual chlorhexidine was thought to have entered his circulation after skin cleansing. It was later discovered that he had developed facial swelling after using certain toothpastes. [Patient outcome not stated.]

Chlorhexidine. [Allergic contact dermatitis in an infant: case report]. Allergic contact dermatitis to chlorhexidine in a very young child.
Le Corre Y; Barbarot S; Frot AS; Milpied B
Pediatric Dermatology. vol.27 (5), 01 Oct 2010 page. 485-487.
A 23-month-old infant injured his forehead in March 2006 and his wound was treated with topical chlorhexidine-based antiseptic solutions [Biseptine and Diaseptyl; dosages not stated] in addition to antibiotic cream. Two days later, he developed acute facial eczema and allergic contact dermatitis was suspected. All topical medications were discontinued and steroid cream was administered instead; rapid healing ensued. He was patch tested 2 months later with various allergens including the topical agents used previously. He had positive reactions to Biseptine, Diaseptyl and 5% aqueous chlorhexidine. He was subsequently diagnosed with chlorhexidine contact dermatitis. It was later revealed that Biseptine had been used twice daily for more than 11/2 months for umbilical cord care. Author comment: "In this case, the prolonged use of chlorhexidine solution (Biseptine) for umbilical cord care caused early sensitization."

Several recent publications have reported cases of anaphylaxis with the use of chlorhexidine but serious reactions are related to its use on the mucous membranes and not on the skin (preoperative cardiac surgery, multiple exposures). These cases are considered rare but the exact incidence of anaphylactic reactions to chlorhexidine is poorly understood. In the UK, the Public Health Agency MHRA has reported 301 cases of reactions to chlorhexidine between 1963 and 2006. In Japan, 9 cases of anaphylactic shock have been reported in the period from 1967 to 1984, all related to the exposure of chlorhexidine on mucous membranes.

Garvey LH, Roed-Petersen J, Husum B. Case Report, Anaphylactic reactions in anaesthetised patients four cases of chlorhexidine allergy. Acta Anaesthesiol Scand 2001; 45: 1290–1294
Garvey et al describe four cases of anaphylactic reactions in anaesthetised patients, which on subsequent testing in the Danish Anaesthesia Allergy Centre (1) turned out to be attributed to chlorhexidine. All four patients had clinically severe reactions, with the first symptom appearing 20–40 min into the operation. Two patients had serious reactions on more than one occasion, and in retrospect, all four had a history of minor reactions, e.g. itching, rashes or faints on previous contact with chlorhexidine. Authors suggest that chlorhexidine allergy may account for some of the cases where the clinical picture points to an anaphylactoid reaction, but subsequent testing with suspected anaesthetic drugs and latex is negative. They advise that investigation after anaphylactoid reactions under anaesthesia should include testing with chlorhexidine, especially if the history indicates repeated reactions, however minor, in connection with surgical procedures.

Guleri A, Kumar A, Richard J.M. Morgan R, Hartley M, Roberts D H. Anaphylaxis to Chlorhexidine-Coated Central Venous Catheters: A Case Series and Review of the Literature. Surgical Infection. Volume 13, Number 3, 2012
Guleri et al. reported three cases of anaphylaxis to chlorhexidine in patients presenting for cardiac surgery. In each case, anaphylaxis was precipitated by the insertion of a central venous catheter impregnated with chlorhexidine acetate. Subsequent investigations confirmed chlorhexidine as the causal agent. Author concluded that extensive use of chlorhexidine to reduce hospital-acquired infections has the potential to sensitize a small proportion of patients, leading to life-threatening anaphylaxis on subsequent exposure.

Khan R A, Kazi T, O'Donohoe B. Unexpected outcome (positive or negative) including adverse drug reactions. Near fatal intra-operative anaphylaxis to chlorhexidine, is it time to change practice? BMJ Case Reports, 2011;09.2009.2300
Khan et al. reported a case of a near fatal anaphylactic reaction to chlorhexidine. A 49-year-old man presented for cystolithotripsy. He had a history of rheumatoid arthritis with recurrent renal and bladder stones. He was a chronic smoker and had noknown allergies. Previous anaesthetics (general and spinal) were uneventful. Anaesthesia was induced and maintained with propofol and remi fentanil. A laryngeal mask airway (LMA) was used to secure the airway. Intraoperatively he received ciprofl oxacin, gentamicin, diamorphine, hyoscinenbutylbromide (buscopan) and

ondansetron. Fifty minutes from the start of anaesthesia, the patient developed unexplained tachycardia associated with a drop in saturation (89%) and ETCO 2 (2.5 kpa). The LMA was changed to an endotracheal tube. The patient continued to desaturate, which was followed by pulseless electrical activity (PEA). Cardiopulmonary resuscitation was initiated rapidly and the patient received three doses of epinephrine (1 mg each) and one dose of atropine (1 mg). The PEA changed to ventricular fi brillation for which the patient was defi brillated. This was followed by a normal sinus rhythm. An epinephrine infusion was started to maintain the blood pressure. He was ventilated over night. Blood samples were sent for troponin-T and mast cell tryptase assays. He made an uneventful recovery and he was extubated next day. The mast cell tryptase level was elevated to 73 µg/litre (normal <11.4 µg/litre) supporting the diagnosis of anaphylactic reaction. Troponin-T (1.03 ng/ml) was raised, which could have resulted from cardiopulmonary resuscitation. On review, it was noted that the urologist had used Instillagel to the urethra to facilitate passage of cystoscope. Instillagel contained lignocaine hydrochloride 2.0% and chlorhexidine digluconate 0.25%. The patient was advised to avoid exposure to chlorhexidine preparations and he should be treated in a latex-free environment in future as in 20% of cases skin prick test to latex is negative.

Chlorhexidine. [Anaphylaxis: case report]. Chlorhexidine anaphylaxis in Auckland.
Wills A
British Journal of Anaesthesia. vol.102 (5), 01 May 2009 page. 722-723.
A woman of undisclosed age developed anaphylaxis after receiving 1% chlorhexidine in 70% alcohol skin wash [Hibitane; dose, indication and duration of therapy to reaction onset not stated]. A positive result was returned on skin prick testing with 2% chlorhexidine aqueous skin wash [outcome not stated]. Editor Comment: The woman was one of 26 patients who had anaphylaxis to chlorhexidine; however, individual patient details were not provided for the other 25 patients.

Chlorhexidine. [Anaphylaxis: 4 case reports]. IgE-mediated anaphylaxis from chlorhexidine: diagnostic possibilities.
Ebo DG; Bridts CH; Stevens WJ
Contact Dermatitis. vol.55 (5), 01 Nov 2006 page. 301-302.
Four men aged 68, 54, 87 and 22 years underwent skin disinfection or urethral catheterisation with a product containing chlorhexidine [dosages not stated] and developed anaphylaxis [times to onset of reactions and treatments not stated]. Six to 16 weeks after anaphylaxis, they underwent prick tests with 2% chlorhexidine in 70% alcohol. They experienced signs including bronchospasm, hypotension, ventricular fibrillation, angiooedema, urticaria, pruritus and shock. Chlorhexidine-specific IgE antibody levels were 3.5, 0.55, 10.9 and 1.68 kUa/L (positive >= 0.35) for the 68-, 54-, 87- and 22-year-old man, respectively; the corresponding prick test values were 5/10, 7/25, 5/9 and 10/35mm (>= 3/3). Chlorhexidine-induced basophilic CD63 expression was observed in all of the patients. [Patient outcomes not stated.]

Chlorhexidine. [Anaphylaxis: case report]. Chlorhexidine anaphlaxis: case report and review of the literature.
Krautheim AB; Jermann THM; Bircher AJ
Contact Dermatitis. vol.50 (3), 01 Mar 2004 page. 113-116.
A 20-year-old woman experienced anaphylaxis after application of a chlorhexidine-containing disinfectant to a cut on her foot. The woman treated the cut with a disinfectant solution [Merfen blue] containing 0.05% chlorhexidine and 0.01% benzoxonium chloride. Within a few minutes, she developed generalised urticaria, angioedema, wheezing, dizziness, vomiting and diarrhoea.
The woman was hospitalised and treated with corticosteroids and calcium, and her symptoms resolved. Subsequent skin tests were strongly positive to an open application of 1% chlorhexidine after 15-20 minutes, and a sulfidoleukotriene stimulation test resulted in high stimulation with chlorhexidine.

Chlorhexidine. [Anaphylaxis in an elderly patient: case report]. Anaphylactic reactions due to chlorhexidine allergy.
Lockhart AS; Harle CC
British Journal of Anaesthesia. vol.87 01 Dec 2001 page. 940-941.
A 70-year-old man developed anaphylaxis following exposure to chlorhexidine during cardiac surgery. His anaphylaxis was managed with epinephrine [adrenaline], metaraminol, hydrocortisone and chlorphenamine and he recovered without event. Subsequent skin patch testing was positive for chlorhexidine, which had been used to prepare his skin for insertion of a central line. He was rescheduled for his original surgery and chlorhexidine-containing skin preparations were avoided. However, during surgery he again developed anaphylaxis that was successfully treated. The source

of chlorhexidine was found to be the lubricant for insertion of his urethral catheter and he subsequently underwent the original surgery without further event.
Author comment: `We believe that on each occasion the anaphylaxis was unrelated to the insertion of the central venous line and was caused by absorption of chlorhexidine from the urethral mucosa.'

Chlorhexidine. [Anaphylaxis: case report]. Anaphylactic shock after application of chlorhexidine to unbroken skin.
Autegarden JE; Pecquet C; Huet S; Bayrou O; Leynadier F
Contact Dermatitis. vol.40 01 Apr 1999 page. 215.
A 33-year-old man experienced anaphylaxis after he applied the antiseptic chlorhexidine 0.6% to a rash on his buttocks; the skin was unbroken. The patient developed generalised urticaria, dyspnoea and loss of consciousness a few minutes after he used chlorhexidine. He was treated with SC epinephrine [adrenaline] and IV corticosteroids and recovered rapidly. Two months later, prick tests were positive to the antiseptic solution (1/100 in physiological saline) and to an aqueous solution of chlorhexidine 0.2% (1/100 in physiological saline). Author comment: `To our knowledge, this is the 1st report of anaphylaxis after application of chlorhexidine to unbroken skin. In previously reported cases, chlorhexidine was either in contact with the mucosa, or on a wound.'

Chlorhexidine. [Anaphylaxis after topical administration: case report]. Life-threatening anaphylactic shock due to skin application of chlorhexidine.
Torricelli R; Wuthrich B
Clinical and Experimental Allergy. vol.26 01 Jan 1996 page. 112.
Topical chlorhexidine can cause life-threatening anaphylactic shock even when applied to the skin in the recommended concentration of 0.05%, as the following case demonstrates.
A 20-year-old man applied a topical solution containing chlorhexidine 0.05% and benzoxonium chloride 0.01% over a 2cm square area of skin to disinfect a wound. Approximately 2 minutes later he developed generalised urticaria and then became unconscious. He was found with no detectable BP, tachycardia and he was incontinent. He was resuscitated and made a good recovery.
Subsequent skin prick and lymphocyte stimulation tests were positive for chlorhexidine at concentrations as low as 0.005%. There were no reactions to benzoxonium chloride or other components of the solution. Author comment: Although severe anaphylactic reactions have previously been described with topical chlorhexidine, this is the first reported case after topical application of chlorhexidine at a concentration of 0.05% to the skin.

Waclawski ER et al; BMJ 298 (6678): 929-30 (1989)
Occupational asthma in two health care workers, as a result of exposure to chlorhexidine and alcohol aerosols. The first case involved a 54 yr old nursing auxiliary who presented with a 3 month history of increasingly frequent attacks of cough and wheezing occurring within minutes after using a chlorhexidine and alcohol aerosol called Dispray 2 Hard Surface Disinfectant. On challenge with the substance in a work simulation test her forced expiratory volume in 1 second fell by 13% within 10 minutes after challenge, accompanied by chest tightness and cough. There were no late responses. The second case involved a 43 yr old midwife with a 6 month history of chest tightness after exposure to chlorhexidine and alcohol aerosol in the same product. A bronchial provocation test with the aerosol showed a maximum fall in forced expiratory volume in 1 second of 22% two minutes after exposure to the spray. No late responses were observed. Neither woman smoked currently, one had smoked earlier in life, and neither had a history of asthma. No increased airways responsiveness to histamine was demonstrated in either case. The use of this product was stopped in their departments, and both nurses remain free of symptoms. The diagnosis of occupational asthma was confirmed.

Okano M, Nomura M, Hata S, et al. Anaphylactic symptoms due to chlorhexidine gluconate. Arch Dermatol 1989;125:50-2.

A 53 year old man with acromegaly was admitted for transsphenoidal resection of a pituitary adenoma. He was otherwise healthy and gave no history of drug allergy. Anaesthesia was initially uneventful. His nasal mucosa were cleaned with an aqueous solution of chlorhexidine gluconate 0.05%. Shortly after the nasal incision his blood pressure fell to 30/15 mm Hg with a heart rate of 70 beats per minute. One litre of 0.9% saline was infused rapidly, with ephedrine 20 mg and then adrenaline 0.5 mg being given intravenously. This failed to restore his blood pressure, and his systolic pressure fell to below 20 mm Hg. The operation was abandoned and cardiac massage started. Over the next 20 minutes he required a further 3 mg of adrenaline, as well as three direct

current shocks for persistent ventricular fibrillation. A total of 1.5 l of 0.9% saline and 1 l of colloid solution were infused during this initial resuscitation period. He was transferred to intensive care being given an adrenaline infusion, the tube being removed 20 hours later.

At no stage was there any evidence of bronchospasm, erythema, or oedema. He suffered no neurological or cardiac damage. He remembered that a red blotchy skin rash had appeared on his face after chlorhexidine 1% dental gel had been applied to his gums during a visit to a dental hygienist in the previous year. Allergy testing was therefore arranged. Skin prick testing to chlorhexidine gave a strongly positive result at 500 µg/ml, and a leucocyte histamine release test was strongly positive for chlorhexidine. All the other agents used during anaesthesia gave negative results.

Chlorhexidine. [Anaphylaxis: 6 case reports]. Anaphylactic symptoms due to chlorhexidine gluconate.
O Kano M; Nomura M; Itata S; Okada N; Sato K
Archives of Dermatology. vol.125 01 Jan 1989
Two boys, both aged 9 years, 3 men aged 15, 26, and 48 years, respectively, and a woman aged 31 years, were admitted for surgery for right-sided corneal leukoma (case 1), injured upper lip (case 2), wound on the forehead (case 3), circumcision (case 4), excision of a subnasal atheroma (case 5) and conization of the cervix uteri (case 6). All patients were disinfected with 0.05-1% chlorhexidine gluconate applied over the palpebra and urethral orifice (case 1), trauma on lip (case 2), wound on forehead (case 3), penis (case 4), face (case 5) and vagina (case 6). Patients showed the following symptoms after chlorhexidine application generalized urticaria, bronchospasm and atelectasis of the upper right lung (case 1; time to onset of symptoms 40 min); cough, dyspnea, wheezing cyanosis, facial urticaria and edema of the palpebral conjunctiva (case 3; within 10 min); generalized urticaria, fatigue, flushing, cough (case 2; 10 min); facial wheals and flushes, general numbness and dyspnea (case 4; 5 min); generalized urticaria, dyspnea and abdominal pain (case 6; 30 min); urticarial lesions on the eyelids, facial pruritus, erythema of the face, malaise (case 5, within 30 min) All symptoms resolved following therapy with oxygen inhalation, IV aminophylline hydrocortisone and sodium bicarbonate (case 1); IM epinephrine (adrenaline), IV hydrocortisone (case 3); IM diphenhydramine (case 2) ; IV hydrocortisone 500mg (case 4); IV hydrocortisone 500mg + chlorpheniramine 5mg (case 6); betamethasone ointment (case 5). Patients showed a positive skin reaction to a scratch test (cases 1, 3, 5 and 6), epicutaneous test (cases 1 and 5), and intradermal injection test (cases 2 and 4). In all patients chlorhexidine was considered responsible for the various symptoms of immediate hypersensitivity.

Skin burn

Chlorhexidine. [Chemical burns in a preterm neonate: case report]. Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant.
Lashkari HP; Chow P; Godambe S
Archives of Disease in Childhood. Fetal and Neonatal Edition. vol.97 (1), 01 Jan 2012 page. F64.
A neonate, with a gestational age of 25 weeks, required insertion of an umbilical catheter shortly after birth. A solution of chlorhexidine 2.0% w/v aqueous solution [AquiHex 2%] was applied to the skin for antisepsis [volume administered not stated]. Two hours later, the right iliac fossa, periumbilical area, groin, right flank and perineum were erythematous. Over the next 6 hours, the skin became pale with loss of the epithelium, consistent with mixed-depth partial-thickness burns. After conservative management, the injuries resolved over 4 weeks without residual scarring.

Third-degree chemical Burns from chlorhexidine local antisepsis. Ezequiel Palmanovich MD, Yaron S. Brin MD, Lior Laver MD, Meir Nyska MD and Binyamin Kish M case cOmmunicatiOns. 323. IMAJ ● VOL 15 ● June 2013
A healthy 55 year old woman was admitted with a displaced ankle fracture to our department for operative treatment. The patient is a nurse in the emergency department in our hospital and is frequently exposed to chlorhexidine solution during the course of her work. No antecedents of drug, food or animal allergic reactions were reported by the patient. The surgery was performed using the chlorhexidine antiseptic technique. Approximately 48 to 72 hours after the operation, redness and pain in the posterior part of the knee was documented. After a week of complaints of mild pain, the patient returned to the outpatient clinic. On examination, a ci cular third-degree burn was

discovered in the middle/distal third of the thigh and deep second and third-degree burns were observed in the posterior aspect of the same knee [Figures B & C]. No skin lesion was observed near the operative field. After consultation with a plastic surgeon, conservative treatment was recommended. During follow-up, no knee contracture was observed and the skin was regenerated with a mild scar.

Corneal injury

Tabor E, Bostwick DC, and Evans CC. Corneal damage due to eye contact with chlorhexidine gluconate. JAMA 1989;261:557-8.
Use of chlorhexidine gluconate for preparing a patient's facial skin prior to surgical incision has resulted in irreversible corneal damage in at least four patients. Cases 1 and 2 were reported to the Food and Drug Administration; cases 3 and 4 were reported by Hamed et al.[1]
Case 1. A 60-year-old woman was treated with chlorhexidine gluconate on the face prior to transantral ethmoidectomy. Chlorhexidine gluconate got into her eyes, where it remained for one hour. She developed bilateral eye redness, pain, and diminished vision (20/200), due to severe corneal damage. A corneal transplant was performed two months later.

Case 2. A 45-year-old woman was treated with chlorhexidine gluconate for presurgical preparation of the face. The length of time the drug remained in the eyes is not known. Corneal injuries resulted in both eyes and remained present at three months' follow-up. Vision in one.

Anders N et al; J Cataract Refract Surg 23 (6): 959-62 (1997)
In three consecutive cataract operations, chlorhexidine was inadvertently used as an intraocular irrigating solution as a result of inattentiveness of an assistant. In two of the three patients, corneal endothelium damage was so severe that penetrating keratoplasty had to be performed. Further effects included pronounced iris atrophy, anterior chamber applanation, and a retrocorneal membrane. In one case, an increase in intraocular pressure developed. No effects were observed in the retina or optic nerve. Inadvertently using chlorhexidine for intraocular irrigation has far-reaching consequences for the affected eye and is recognizable by streak formation in the anterior chamber when intraocular infusion is initiated.

Systemic reactions following chlorhexidine administration

Massano G, Ciocatto E, Rosabianca C, et al. Striking aminotransferase rise after chlorhexidine
self-poisoning. Lancet 1982;1:289.
Intentional ingestion of 150 mL of chlorhexidine gluconate solution (about 30 g of the drug) caused pharyngeal edema and necrotic lesions of the esophagus and increased serum aminotransferase concentrations to 30 times normal. A liver biopsy, performed at the time of the elevated aminotransferase concentrations, showed diffuse fatty degeneration and lobular hepatitis; aminotransferase concentrations returned to normal 6 months later.

Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. Vet Hum Toxicol 2002; 44:89-91
As ingestion of chlorhexidine gluconate (CHG) usually causes relatively mild symptoms, this chemical has been considered safe. An 80-y-old woman with dementia accidentally ingested approximately 200 ml of Maskin (5% CHG) in a nursing home and then presumably aspirated gastric contents. She was intubated for airway protection in the nearest hospital and referred to our critical care unit because of hypotension and rapid deterioration of consciousness. Despite intensive treatment, the patient died of acute respiratory distress syndrome (ARDS) 12 h after ingestion. The serum concentration of CHG was markedly high, although CHG reportedly has poor enteral absorption. We suspect the CHG was absorbed through the pulmonary alveoli following aspiration, not from the gastrointestinal tract. CHG has the potential for fatal ARDS when aspiration occurs following ingestion.

Chlorhexidine gluconate
Ishigami S et al; J Toxicol Clin Toxicol 39 (1): 77-80 (2001)
A 67-yr-old man undergoing a colectomy for colon cancer was unintentionally administered 0.8 mg of chlorhexidine gluconate intravenously and subsequently developed acute respiratory distress syndrome. The operation was discontinued immediately. Respiratory failure progressed despite three cycles of plasma exchange beginning on day 1. Extracorporeal membrane oxygenation for 72 hr beginning on day 3 was associated with dramatic improvement. The patient showed complete

recovery of intellectual function and subsequently underwent a colectomy with lymph node dissection for colon cancer. For acute respiratory distress syndrome secondary to chlorhexidine gluconate intoxication, consideration should be given to the treatment of initial respiratory distress and subsequent pneumonia. The benefit of extracorporeal membrane oxygenation and plasma exchange may merit further investigation.

Douw CM, Bulstra SK, Vandenbroucke J, Geesink RG, Vermeulen A. Clinical and pathological changes in the knee after accidental chlorhexidine irrigation during arthroscopy. Case reports and review of the literature. J Bone Joint Surg Br 1998; 80:437-440.
We describe six knees in five patients, referred to us after accidental irrigation with chlorhexidine 1% in aqueous solution during arthroscopy. All six knees developed persisting pain, swelling and crepitus with loss of range of movement. Radiographs showed loss of joint space in all three compartments due to extensive chondrolysis, with many loose bodies and synovitis. Histological examination showed partial necrosis of the cartilage, with slight non-specific inflammation and fibrosis of synovial specimens. Care is needed in checking irrigation fluids, and these should have a distinctive colour.

Emerson D et al; Vet Hum Toxicol 30 (6): 583 (1988)
The case history of an 89-yr-old female who ingested 30 mL of Hibiclens (chlorhexidine gluconate) in a single dose is reported. The ingestion was treated with milk to drink. Mild symptoms of intoxication manifested by slight giddiness and unusual laughter were observed. The patient exhibited no other symptoms.

Cetrimide/chlorhexidine.
Oral edema and ulceration in neonates after medication error: 5 case reports]. Accidental feeding of a dilute antiseptic solution (Chlorhexidine 0.05%
Mucklow E S
Human Toxicology. vol.7 01 Nov 1988
A dilute antiseptic solution, cetrimide 1% and chlorhexidine 0.05%, was inadvertently fed to 5 neonates (25-132 hours of age), instead of sterile water. All 5 neonates developed excess mucus and edema of the tongue followed by tongue, cheek and gum ulcers. Pulmonary edema with oral frothing developed in 1 neonate. Routine gastric lavage was performed on all 5 neonates before it was known that they had received dilute antiseptic solution. The author concluded that gastric lavage '.. should be avoided in cases of caustic poisoning due to the risk of perforation consequent to the procedure, and it may embarrass respiration even further where acute pulmonary edema exists as in case 1'

Percutaneous absorption of chlorhexidine in neonatal cord care.
P J Aggett, L V Cooper, S H Ellis, and J McAinsh
Arch Dis Child. 1981 November; 56(11): 878–880.
The percutaneous absorption of chlorhexidine during its routine use in topical antiseptic preparations used in umbilical cord care was investigated by determining plasma chlorhexidine concentrations at ages 5 and 9 days. These showed that percutaneous absorption of chlorhexidine occurred in preterm neonates treated with a 1% solution of chlorhexidine in ethanol, but not in term infants similarly treated, or in preterm infants treated only with a dusting powder containing 1 % chlorhexidine and 3% zinc oxide.

Absorption of chlorhexidine from the intact skin of newborn infants.
J Cowen, S H Ellis, and J McAinsh
Arch Dis Child. 1979 May; 54(5): 379–383.
Cowen studied data on 34 newborn infants who had been bathed in a standard manner with Hibiscrub to find out whether it was absorbed percutaneously. Low levels of chlorhexidine were found in the blood of all 10 babies sampled by heel prick, and 5 of 24 from whom venous blood was taken.

A K Chapman, S W Aucott, M M Gilmore, S Advani, W Clarke & + et al.
Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates.
Journal of Perinatology. 2013.61
Chapman et al assessed chlorhexidine absorption and skin tolerability in premature infants, following skin antisepsis with 2% aqueous chlorhexidine gluconate (CHG) prior to peripherally inserted central catheter (PICC) placement. Neonates less than 32 weeks gestation had skin cleansed with CHG prior to PICC placement. CHG concentrations were measured on serial blood

samples. Skin integrity was evaluated for 2 weeks after CHG exposure. Twenty infants were enrolled; median gestational age was 28 2/7 weeks (range 24 3/7 to 31 4/7). Ten infants had detectable serum chlorhexidine concentrations (range 1.6 to 206 $ng.ml^{-1}$). Seven of these infants had their highest serum concentration 2 to 3 days following exposure. No CHG-related skin irritation occurred in any infant. CHG was detected in the blood of preterm infants receiving CHG skin antisepsis for PICC insertion. Highest serum concentrations occurred 2 to 3 days after exposure. Further investigation is needed to determine the clinical relevance of CHG absorption in preterm infants.

Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. A K Chapman, S W Aucott & A M Milstone.
Journal of Perinatology. 2011, 32, 4-9
CHG has been detected in the blood of preterm infants receiving CHG skin antisepsis. Further investigation is needed to determine the clinical relevance of CHG absorption in preterm infants.

Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, Harris MC. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone - iodine antisepsis for central venous catheter placement in neonates. J Perinatol. 2009;29(12):808–813.
The purpose of this pilot trial was to determine whether rates of contact dermatitis following cutaneous antisepsis for central catheter placement were similar among neonates treated with chlorhexidine gluconate and povidone-iodine. Chlorhexidine gluconate absorption was also evaluated. Infants weighing > or =1500 g and > or =7 days of age were randomized to a 10% povidone-iodine or 2% chlorhexidine gluconate site scrub before catheter placement. Primary outcomes evaluated included dermatitis, catheter colonization and chlorhexidine gluconate absorption.
A total of 48 neonates were enrolled. Colonization rates were similar among treatment groups (P<0.6). Dermatitis did not occur at chlorhexidine gluconate (central catheters, n=24; peripheral catheters, n=29) sites. Seven neonates had measurable chlorhexidine gluconate concentrations (range 13 to 100 ng ml(-1)) during catheterization. Authors concluded that in this small trial chlorhexidine gluconate antisepsis was tolerated by study neonates. Chlorhexidine gluconate was cutaneously absorbed. Larger trials are needed to determine efficacy and tolerance of chlorhexidine gluconate in neonates.

<u>Mucosa damages observed with chlorhexidine</u>

Chlorhexidine-induced gastritis.
S. Roche, R. Chinn, and S. Webb Postgrad Med J. 1991 February; 67(784): 210–211.
A 72 year old man was admitted to Saint Charles'hospital for investigation of palpitations and postural hypotension. He also suffered from Parkinson 'disease but was well controlled on treatment.
The positive findings on examination included the classical features of Parkinson's disease and a postural drop in blood pressure. The latter quickly resolved on withdrawal of his diuretic therapy. Two days after admission he started vomiting, initially four times on one day and the intermittently over the following 10 days. This usually occurred in the mornings. He was not receiving any new medication. Fibreoptic gastroscopy showed multiple erosions in the lower part of his stomach and first part of duodenum. His oesophagus appeared normal. Histology confirmed an active atrophic gastritis with many helicobacter-like organisms present. A full blood count, biochemical screen and liver function tests were all normal. It transpired that every morning he washed himself on the ward with Hydrex. However he also used this preparation as a mouth wash and the swallowed it. He said that he felt nauseated each time he did this. He was advised to discontinue this practice and was given ranitidine. He made a full recovery with no further vomiting and repeat endoscopy after 6 weeks revealed resolution of his mucosal erosions with some mild residual antral gastritis.

Hardin RD and Tedesco FJ. Colitis after hibiclens enema. J Clin Gastroenterol 1986;8:572-5.
Acute colitis occurred after a Hibiclens cleanser enema. Endoscopic and histologic features were not helpful in distinguishing this colitis from an infectious or idiopathic colitis, and a careful history proved invaluable. We review the complications of using soapsuds and various chemical-containing enemas; these complications range from mild colitis to death. Because soap and other chemicals are damaging to colonic mucosa, these enemas should be included as a cause of acute colitis.

Contact Dermatitis. 2001 Jul;45(1):42. Connubial allergic contact balanitis due to chlorhexidine. Barrazza V.
A 40-year-old non-atopic man developed acute pruritic erythema, erosions and oedema of the glans and prepuce less than 24 h after intercourse. Slight balanitis had similarly been noted 3 months before. On questioning, hiswife was found to have used a lubricant gel, containing chlorhexidine gluconate 0.003%, plant mucilages and water, before intercourse. With topical corticosteroids, the balanitis cleared in 10 days. Patch testing with chlorhexidine gluconate (0.5% aq.) and the gel was пп for both at D2 and D3. The patient experienced no recurrence after avoiding topical products containing chlorhexidine, his wife being advised to use an alternative lubrica.

Shippey, Stuart H.; MALAN, Todd K. Desquamating vaginal mucosa from Chlorhexidine gluconate. Obstetrics and gynecology. 2004 vol. 103 (5) : pp. 1048 – 1050.
Shippey et al. presented a case of a healthy premenopausal woman who was taken to the operating room for a planned laparoscopically assisted vaginal hysterectomy. After vaginal, vulvar, perineal, and abdominal cleansing with chlorhexidine gluconate, the patient developed a desquamating vaginal reaction that was treated with intravenous corticosteroids, antihistamine, topical conjugated estrogen, and hydrocortisone cream. The planned surgery was aborted, and the patient recovered uneventfully overnight in the postanesthesia care unit. With continued application of conjugated estrogen cream, the patient's vaginal mucosa was well healed within 2 weeks. Authors concluded that although chlorhexidine gluconate has been used effectively to minimize surgical site infection in vaginal surgery, the possibility for adverse reaction should be considered.

Nervous tissue damages

Henschen A, Olson L. Chlorhexidine-induced dengeneration of adrenergic nerves. *Acta Neuropathol* 1984;63:18-23.
Summary
Possible toxic effects of chlorhexidine (CHX) on the sympathetic adrenergic ground plexus were studied in whole mounts of albino rat irides using Falck-Hillarp fluorescence histochemistry. CHX dissolved in an isotone, buffered sodium-acetate solution or in 70% alcohol was injected into the anterior chamber of eye. CHX caused a marked and dose-dependent degeneration of adrenergic nerves. Two days after the lowest dose, 0,25 µg (5 µl of a 0.05% CHX solution), approximately 30% of the nerves had disappeared. Almost complete degeneration was observed after the same time with higher doses (2.5 µg, 5.0 µg, and 7.5 µg corresponding to 0.5, 1.0, and 1.5% CHX respectively). Two weeks after the lowest dose, the nerves had regenerated almost completely. With the highest dose used, only some 40% of the normal adrenergic nerve plexus had reformed after 51 days. Alcohol as a solvent did not have an additive effect on the neurotoxic action caused by CHX. The results demonstrate yet another aspect of chlorhexidine neurotoxicity, degeneration of peripheral adrenergic nerve terminals. This suggests that neurotoxic actions on thin unmyelinated fiber systems should be looked for also in the central nervous system (CNS).

Inner Ear damages

Denton DW. Chlorhexidine. In: Block SS, ed. Disinfection, sterilization, and preservation. 4th edition. Philadelphia: Lea & Febiger; 1991:274-89.

Denton GW. The use of 0.5% chlorhexidine in 70% alcohol for disinfection of the ear-canal in children with serous otitis media. Int J Pediatr Otorhinolaryngol. 1990 Mar;19(1):80-1

Aursnes, J.,Vestibular damage from chlorhexidine in guinea pigs, Acta Otolaryngol., 92 (1981) 89-100.

Bicknell, P.G., Sensorineural deafness following Myringoplasty operations, J. Laryngol. Otol.. 85 (1971) 957-961. 3

Igarashi, Y. and Suzuki, J.I., Cochlear ototoxicity of chlorhexidine gluconate in cats, Arch. Oto-Rhino-Laryngol., 242 (1985) 167-176.

Morizono, T., Johnstone, B.M. and Hadjar, E., The ototoxicity of antiseptics (preliminary report), J. Otolaryngolog. Sot. Amt., 3 (1973) 550-553.

Others Adverse Drug reactions

Bradycardia in an exposed neonate: case report. Bradycardia associated with chlorhexidine spray.
Quinn M W; Bini R M
Archives of Disease in Childhood. vol.64 01 Jun 1989
A normal delivery produced a girl with Apgar scores of 9 and 10 at 1 and 5 min, respectively. From the age of 12 hours her mother used chlorhexidine spray applied to her breasts prior to breastfeeding to prevent mastitis. From the age of 48 hours the neonate experienced episodes of bradycardia which responded to stimulation. Multiple episodes continued over the next 48 hours and atropine was administered on some occasions. Chlorhexidine spray was withdrawn and the neonate inproved with cessation of bradycardia episodes after 6 days. Follow-up examination 5 weeks later was normal.

Laryngospasm (first report), generalised seizures (first report) and cyanosis in an infant: case report. Laryngospasm with convulsion in an infant. Caution: danger of confusion with the bottles unidoses of chlorhexidine.
Flodrops H; Stoven C; Razafintsalama S; Randrianjafinimpanana H; Feriot JP; Renouil M
Archives de Pediatrie. vol.14 (10), 01 Oct 2007 page. 1248-1249.
A 3.5-month-old male infant developed generalised seizures with cyanosis due to laryngospasm after two accidental administrations of chlorhexidine [dosages not clearly stated], instead of isotonic solution, for clearing rhinopharyngeal obstruction.
The infant presented with sialorrhoea, malaise and a generalised tonic-clonic seizure with cyanosis, which lasted for less than 30 minutes. His symptoms had developed after receiving the contents of a transparent single-dose (5mL) vial for clearing the rhinopharyngeal obstruction.
The infant's seizures stopped after treatment with diazepam and he was hospitalised for further investigation. Laboratory investigations showed a transient hyperglycaemia (18.7 mmol/L), an elevated creatine kinase level (230 IU/l) and a blood lactate level of 1.6 mmol/L. Cerebrospinal fluid investigations revealed a slightly increased lactate level (2.8 mmol/L) with protein and glucose levels of 0.5 g/L and 7.3 mmol/L, respectively. A diagnosis of laryngospasm with seizures secondary to clearing a rhinopharyngeal obstruction was made.
After 10 days, the infant developed another seizure, which lasted for 45 minutes, after receiving the contents of a transparent single-dose (5mL) vial for clearing the rhinopharyngeal obstruction. The convulsion stopped after diazepam treatment. He was hospitalised and had normal EEG, Holter-ECG and blood test values. He was finally diagnosed with tonic seizures of the four limbs with cyanosis, probably because of laryngospasm induced by chlorhexidine 0.2% contained in the single-dose (5mL) vials; a suspicion by the infant's mother about the vial's contents led to the diagnosis. It was later revealed that chlorhexidine was being prescribed to the mother to treat the umbilical cord, whereas the infant was being prescribed isotonic solution for the treatment of his nose and eyes. The accidental administration of chlorhexidine in place of isotonic solution was attributed to the transparency and identical presentation of both solutions. Author comment: A direct systemic effect of chlorhexidine cannot be excluded, but the cyanosis followed by the seizure suggests an irritation leading to laryngospasm.
Editor Comment: A search of AdisBase and Medline did not reveal any previous case reports of laryngospasm or generalised seizures associated with chlorhexidine. The WHO Adverse Drug Reactions database contained nine reports of laryngismus and no reports of grand mal convulsions associated with chlorhexidine.

Chemical compatibility

Denton GW, Chlorhexidine. In Seymour S. Block (Ed.) Disinfection, sterilization, and preservation. 4th Edition, Lea & Febiger, Williams & Wilkins, Media PA, 1991:279.
http://books.google.fr/books?id=3f-kPJ17_TYC&pg=PA321&lpg=PA321&dq=Denton+GW,+Chlorhexidine&source=bl&ots=KlGsEy2RJ5&sig=DKMzKCfdDMB7O5Okz5MA7QkgNJk&hl=en&sa=X&ei=Y140UoaYNtCWhQe5jIDIAQ&ved=0CEEQ6AEwAw#v=onepage&q=Denton%20GW%2C%20Chlorhexidine&f=false
Accessed Nov 25, 2013

Environmental Detection Agency. Chapter 19: Disinfectants. In: Recognition and Management of Pesticide Poisonings, 5th ed. Washington, DC: US Environmental Protection Agency; Available at: http://www.epa.gov/oppfead1/safety/healthcare/handbook/Chap19.pdf Accessed Nov 25, 2013.
ISOPROPYL ALCOHOL

Intoxication

Rich J, Scheife RT, Katz N, et al. Isopropyl alcohol intoxication. Arch Neurol 1990;47:322-4.
Three patients had neurologic signs due to isopropyl alcohol (IPA) intoxication. Over a several-week period, a known alcoholic developed apathy, confusion, ataxia, and hyperreflexia. During this period, there was no ethanol available to him, and he denied use of other intoxicants. He was found stuporous in the hospital after drinking IPA and admitted to IPA abuse during the preceding weeks. Two other men were admitted in a stupor after large ingestions of IPA. Intoxication with IPA has two different presentations: stupor in a known alcoholic and encephalopathy of unknown cause in individuals who hide their addiction. Ethanol, methanol, IPA, and ethylene glycol intoxications are associated with different clinical and laboratory findings.

Vivier PM, Lewander WJ, Martin HF, et al. Isopropyl alcohol intoxication in a neonate through chronic dermal exposure: A complication of a culturally-based umbilical care practice. Pediatr Emerg Care 1994;10:91-3.
A 21-day-old boy presented to our emergency department hypotonic, lethargic, and intermittently unresponsive to pain. A workup for ketoacidosis, sepsis, and central nervous system hemorrhage was negative. A urine drug screen collected eight hours after hospitalization showed 39 mg/dl of isopropyl alcohol and 76 mg/dl of acetone. The first serum drug analysis was not performed until 18 hours after admission, at a time when there had been clinical improvement. The isopropyl alcohol concentration was 8 mg/dl, and the acetone concentration was 203 mg/dl. Management was supportive, and the patient stabilized. He was discharged from the hospital in good health in three days. A further review of the history showed no evidence for an oral exposure to isopropyl alcohol. However, since leaving the maternity hospital the mother had been applying gauze pads or cotton balls soaked with isopropyl alcohol to the umbilicus with every diaper change. We conclude that the child suffered from an isopropyl alcohol intoxication that occurred by absorption through the umbilical area.