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BASE•128 and BASE (Fig. 1) are certified products for the processing of human tissues and cells intended for transplantation.

BASE•128 is a ready-to-use solution to decontaminate different types of human tissues intended for transplantation under different time and temperature conditions. It includes a proprietary antibiotic/antifungal cocktail.

BASE is a rinsing solution to remove both antibiotics and DMSO residues from different types of human tissues intended for transplantation, which can then be subsequently processed without any carryover effect.

BASE•128 and BASE are sterile, pyrogen- and mycoplasma-free according to the current Pharmacopoeias (EP and USP).

BASE•128 and BASE were developed with the aim of offering certified products to Tissue Banks, which allow them to comply with the quality and safety requirements of the European Directives concerning human tissues and cells intended for transplantation. In particular, the antibiotic/antifungal cocktail of BASE•128 was expressly formulated to remove the most commonly found micro-organisms in Tissue Banks, as well as the reference bacterial strains according to Pharmacopoeia; BASE was formulated to remove antibiotics and/or DMSO from tissues, thus increasing patient’s safety with respect to the problem of residue carryover.

<table>
<thead>
<tr>
<th>BASE•128</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INGREDIENTS AND ACTION</strong></td>
<td><strong>INGREDIENTS AND ACTION</strong></td>
</tr>
<tr>
<td>Glucose</td>
<td>Glucose</td>
</tr>
<tr>
<td>Energy source</td>
<td>Energetic source</td>
</tr>
<tr>
<td>Amino acids, Mineral salts, Vitamins</td>
<td>Nutrients</td>
</tr>
<tr>
<td>Gentamicin, Vancomycin, Cefotaxime, Amphotericin B</td>
<td>antibiotic/antifungal mixture</td>
</tr>
<tr>
<td>Hepes and Bicarbonate</td>
<td>buffers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>PHYSICAL PARAMETERS</strong></th>
<th><strong>PHYSICAL PARAMETERS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspect</td>
<td>Clear liquid</td>
</tr>
<tr>
<td>pH</td>
<td>7.20-7.40 pH units</td>
</tr>
<tr>
<td>Osmolality</td>
<td>280-320 mOsm/kg</td>
</tr>
<tr>
<td>Size</td>
<td>250 ml and 500 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MICROBIOLOGICAL PARAMETERS</strong></th>
<th><strong>MICROBIOLOGICAL PARAMETERS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxins</td>
<td>apyrogenic (USP); &lt; 0.03 EU (EP)</td>
</tr>
<tr>
<td>Mycoplasmas</td>
<td>absent (EP, USP)</td>
</tr>
<tr>
<td>Sterilization</td>
<td>sterile (UNI EN 556-2 and UNI EN ISO 13408-1)</td>
</tr>
</tbody>
</table>

**STORAGE AND HANDLING**
- Storage temperature: -20°C
- Shelf-life: 24 months
- Use temperature: 4, 22, 37°C
- Duration of actual use: depending on selected use temperature and tissue
- Duration of actual use: To remove antibiotics
- Duration of actual use: To remove DMSO
- Disposal: Unused and expired products
- After use: According to regulations in force
- As biohazardous products

**STORAGE AND HANDLING**
- Storage temperature: +2°C - 8°C
- Shelf-life: 24 months
- Use temperature: 4°C
- Duration of actual use: depending on selected use temperature and tissue
- Disposal: Unused and expired products
- After use: According to regulations in force
- As biohazardous products

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**INTRODUCTION**

RATIONAL FOR PRODUCT DEVELOPMENT & PRODUCT FORMULAS

**BASE**•128 and **BASE** (Fig. 1) are certified products for the processing of human tissues and cells intended for transplantation.

BASE•128 is a ready-to-use solution to decontaminate different types of human tissues intended for transplantation under different time and temperature conditions. It includes a proprietary antibiotic/antifungal cocktail.

BASE is a rinsing solution to remove both antibiotics and DMSO residues from different types of human tissues intended for transplantation, which can then be subsequently processed without any carryover effect.

BASE•128 and BASE are sterile, pyrogen- and mycoplasma-free according to the current Pharmacopoeias (EP and USP).
The most commonly found contaminating micro-organisms in Tissue Banks are Gram positive bacteria that represent approximately 81% of tissue contaminants. Gram negative bacteria correspond to 14% of tissue contaminants, while approximately 5% of tissue are contaminated by fungi and yeasts.

Our time-kill studies demonstrated that tissue incubation in BASE•128 under different time/temperature conditions reduced contamination, with the most effective condition being incubation at 37°C for 6 hours (Fig. 2).

Tissue rinsing with BASE reduced antibiotic residues of BASE•128 decontaminated tissue as assessed by agar diffusion test (Fig. 3), thus allowing subsequent tissue processing without any carryover effect or antibiotic residue transfer to patient.

Fig. 3 Agar diffusion test detects the presence of antibiotics by formation of inhibition zone on agar plates seeded with Pseudomonas aeruginosa (PA), Staphylococcus aureus (SA), and Candida albicans (CA)

Fig. 4 Effect of post decontamination washing with BASE on antibiotic removal in porcine heart valves decontaminated with BASE•128 either a) at 4°C for 72h or b) at 37°C for 6 hours. (Pseudomonas aeruginosa (PA), Staphylococcus aureus (SA), or Candida albicans (CA) Staphylococcus epidermidis methicillin resistant (SEMR). (Gatto C., Giurgola L., D’Amato Tóthová J.: A suitable and efficient procedure for the removal of decontaminating antibiotics from tissue allografts. Cell and Tissue Banking, 2013 Mar;14(1):107-15)
Tissue rinsing with BASE reduced the DMSO content of cryopreserved skin and amniotic membrane (Fig. 5, 6) thus allowing subsequent tissue processing without any carryover effect or DMSO residue transfer to patient.

Histological analysis of various tissues decontaminated with BASE•128 and rinsed with BASE showed tissue preservation (Fig. 7).

![Fig. 5 Me₂SO content in skin after rinsing with BASE](image1)

![Fig. 6 Me₂SO content in amniotic membrane after rinsing with BASE](image2)

![Fig. 7 Histological analysis of various tissues treated with BASE•128 and BASE](image3)
The decontamination efficacy of BASE•128 on different human tissues intended for transplantation was validated under different time/temperature conditions (Table 3). Similarly, we validated the conditions for an effective removal of antibiotic residues from tissues after decontamination (Table 4) and DMSO after cryopreservation (Table 5).

### Table 3. Validations of tissue decontamination with BASE•128

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>37°C</th>
<th>22°C</th>
<th>4°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR</td>
<td>6 hrs</td>
<td>overnight</td>
<td>24 &amp; 72 hrs</td>
</tr>
<tr>
<td>SKIN</td>
<td>none</td>
<td>overnight</td>
<td>24hrs</td>
</tr>
<tr>
<td>MUSCUOLOSKELETAL</td>
<td>6 hrs</td>
<td>none</td>
<td>72hrs</td>
</tr>
<tr>
<td>AMNIOTIC MEMBRANE</td>
<td>6 hrs</td>
<td>24hrs</td>
<td>24hrs</td>
</tr>
</tbody>
</table>

### Table 4. Validations of antibiotic residue removal with BASE after tissue decontamination with BASE•128

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>TIME&amp;TEMPERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR</td>
<td>overnight at 4°C</td>
</tr>
<tr>
<td>SKIN</td>
<td>overnight at 4°C</td>
</tr>
<tr>
<td>MUSCUOLOSKELETAL</td>
<td>overnight at 4°C</td>
</tr>
<tr>
<td>AMNIOTIC MEMBRANE</td>
<td>overnight at 4°C</td>
</tr>
</tbody>
</table>

### Table 5. Validations of DMSO removal with BASE after tissue cryopreservation

<table>
<thead>
<tr>
<th>TISSUE</th>
<th>TIME&amp;TEMPERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOVASCULAR</td>
<td>15+15min at RT</td>
</tr>
<tr>
<td>SKIN</td>
<td>5+10min at RT</td>
</tr>
<tr>
<td>MUSCUOLOSKELETAL</td>
<td>2X10min at RT</td>
</tr>
<tr>
<td>AMNIOTIC MEMBRANE</td>
<td>2X5min at RT</td>
</tr>
</tbody>
</table>

BASE and BASE•128 comply with the COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices and subsequent modifications and a Quality Management System according to ISO 13485 and ISO 9001.


BASE and BASE•128 comply with the COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices and subsequent modifications and a Quality Management System according to ISO 13485 and ISO 9001.

ORGANISMO NOTIFICATO N° 0546
NOTIFIED BODY N° 0546

APPROVAZIONE DEL SISTEMA DI QUALITÀ ATTUATO DA
APPROVAL OF THE QUALITY SYSTEM OPERATED BY

AL.CHI.MI.A S.R.L.
VIALE AUSTRIA 14 - 20920 PONTE SAN NICOLÒ (FD) - ITALY

UNITA' OPERATIVE
OPERATING SITES
VIALE AUSTRIA 14 - 20920 PONTE SAN NICOLÒ (FD) - ITALY

PER I SEGuentI TIPI/FAMILIgE DI PRODOTTI
FOR THE FOLLOWING TYPES/CLASSES OF PRODUCTS
Endotomoni liquidi o gasosi per la chirurgia visteromorica e relativi accessori. Perfusione cori per la chirurgia visteromorica.
Coloranti tessuali reversibili per evidenziare tessuti da sottoporre nel corso di procedure chirurgiche oftalmiche. Prodotti ed accessori per attività di Banca degli Occhi: dispositivi per il lavaggio, la conservazione ed il trasporto di tessuti destinati alla chirurgia oculare. Dispositivi medici e accessori sanitari per oftalmologia. Prodotti per attività di Banca dei Tessuti: dispositivi per il lavaggio, la conservazione ed il trasporto di tessuti umani e cellule destinate al trapianto.


Certiguality S.r.l., Organismo Notificato n° 0546, certifica che il sistema garanzia qualità
Certiguality S.r.l., Notified Body n°0546, certifies that the quality assurance system
è conforme ai requisiti della Direttiva 93/42 CEE, Allegato II
is in compliance with the requirements of Council Directive 93/42/EEC, Annex II

CERTIFICATO N.
11971/111
CERTIFICATE N.

IL PRESENTE CERTIFICATO NON È DA RITENERSI VALIDO SE NON ACCOMPAGNATO DAL RELATIVO ALLEGATO.
THIS CERTIFICATE IS NOT VALID WITHOUT THE RELEVANT ANNEX

DATA DI SCADENZA
2002/2017
EXPIRY DATE

IL Presidente

CERTIGUALITY S.r.l.
Via Giovanni Giardino 4 - 20121 Milano - tel 02 86062985 - certiguality@certiguality.it - www.certiguality.it
CERTIFICATE

IQNet and its partner
CISQ/CERTIQUALITY s.r.l.

AL.CHI.MI.A. S.R.L.

IT - 35020 PONTE SAN NICOLÒ (PD) - VIALE AUSTRIA 14
has implemented and maintains a
Quality Management System
which fulfills the requirements of the following standard
ISO 13485:2003
for the following activities
Ceda EA 12
Design, manufacturing and sale of medical devices
for ophthalmic applications and for Tissue Banking.

in the following operative units
IT - 35020 PONTE SAN NICOLÒ (PD) - VIALE AUSTRIA 14

Issued on: 2012-12-23
Certified since: 2001-10-25
Expires on: 2015-02-23
Registration number: IT-41225

Michael Dechsel
President of IQNet

Ing. Claudio Provenzi
President of CISQ

IQNet is represented in the USA by: AFNOR Certification, CISQ, DQS Holding GmbH and N SAI Inc.

* The list of IQNet partners is valid at the time of issue of this certificate. Updated information is available under www.iqnet-certification.com
AL.CHI.MI.A. S.R.L.

UNI EN ISO 9001:2008
Certificato n. 4469

IT - 35020 PONTE SAN NICOLÒ (PD) - VAILA AUSTRIA 14

UNI EN ISO 9001:2008
Selection activities: manufacturing and sale of medical devices for ophthalmic applications and for Tissue Banking.
Design and supply of consulting services in the field of product quality and safety.

ISO 9001:2008

Certificate holder:
AL.CHI.MI.A. S.R.L.

IT - 35020 PONTE SAN NICOLÒ (PD) - VAILA AUSTRIA 14

Issued on: 2012-02-21
Certified since: 2010-10-25
Expires on: 2015-02-20
Registration number: IT-21352

IQNet and its partner
CISQ/CERTIQUALITY S.r.l.

President of IQNet

Giancarlo Prioli
President of CISQ

The International Certification Network

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REFERENCES

1. A SUITABLE AND EFFICIENT PROCEDURE FOR THE REMOVAL OF DECONTAMINATING ANTIBIOTICS FROM TISSUE ALLOGRAFTS
Gatto C., Giurgola L, D’Amato Tóthová J.
Cell and Tissue Banking 14(1), 107-115, 2013

2. REMOVAL OF ANTIBIOTIC RESIDUES FROM SAMPLES SUBJECTED STANDARD MICROBIOLOGICAL ANALYSIS IN TISSUE BANKS
EATB, Vienna, Austria, November 21-23, 2012

3. VALIDATION OF TIME AND TEMPERATURE CONDITIONS FOR SKIN DECONTAMINATION
EATB, Vienna, Austria, November 21-23, 2012

4. ESTABLISHING A PROCEDURE FOR DIMETHYL SULFOXIDE REMOVAL FROM CARDIOVASCULAR ALLOGRAFTS: A QUANTITATIVE STUDY.
Gatto C., Dainese L., Buzzi M., Guarino A., Pagliaro P., Polvani G., D’Amato Tóthová J.
Cell and Tissue Banking DOI 10.1007/s10561-012-9331-3, 2012

5. ESTABLISHMENT OF A RINSING PROCEDURE TO ELIMINATE ANTIBIOTIC AND GLYCEROL RESIDUES FROM CRYOPRESERVED SKIN DECONTAMINATION WITH BASE•128
Pianigiani E., Gatto C., Giurgola L., D’Amato Tóthová J.
EATB, Barcelona, Spain, November 9-11, 2011

6. IMPACT OF ANTIBIOTIC RESIDUES ON MICROBIOLOGICAL ANALYSIS: IMPLICATION OF TISSUE BANKING
Gatto C., Giurgola L., Beccaro M., Lipartiti M., D’Amato Tóthová J.
EATB, Barcelona, Spain, November 9-11, 2011

7. TIME-KILL STUDIES OF BASE•128 AGAINST S. EPIDERMIDIS II, S. CAPITIS AND P. ACNES ISOLATED FROM DONOR SKIN
Gatto C., Pianigiani E., Ierardi F., Giurgola L., D’Amato Tóthová J.
EATB, Barcelona, Spain, November 9-11, 2011

8. SKIN DECONTAMINATION AND IMPACT OF ANTIBIOTIC RESIDUES ON MICROBIOLOGICAL TESTS
Vassanelli A., Bosinelli A., Rizzi S., Lucchini E., Gatto C., Giurgola L., D’Amato Tóthová J.
EATB, Barcelona, Spain, November 9-11, 2011

9. OPTIMIZATION OF CARDIOVASCULAR TISSUE DECONTAMINATION AND RINSING WITH BASE•128 AND BASE.
Terzi A., Buzzi M., Guarino A., Dainese L., Vasuri F., D’Amato Tóthová J., Gatto, C.
EATB, Barcelona, Spain, November 9-11, 2011

10. FATE OF ANTIBIOTICS AFTER TISSUE DECONTAMINATION. STUDY ON HEART VALVES, PERICARDIUM, BONE AND SKIN
D’Amato Tóthová J., Gatto C., Cavallaro D., Beccaro M., Lipartiti M.

11. REMOVAL OF ME2SO FROM CRYOPRESERVED SKIN AND HEART VALVE.
Gatto C., Marchiani A., Ruzza P., Beccaro M., D’Amato Tóthová J.
CRYO, Bristol, UK, July 17-20, 2010.
12. REMOVAL OF DMSO FROM CRYOPRESERVED HUMAN SKIN
Vassanelli A., Gatto C., Bosinelli A., Rizzi S., Marchiani A., Ruzza P., D’Amato Tóthová J.,
Aprili G.
EATB, Berlin, Germany, November 3-5, 2010.

13. REMOVAL OF DMSO FROM CARDIOVASCULAR ALLOGRAFTS.
EATB, Berlin, Germany, November 3-5, 2010.

14. COMPARISON AMONG THE MEDICAL DEVICES BASE•128,
BASE, CRYO•ON AND THE SOLUTIONS CURRENTLY USED IN
TWO ITALIAN CARDIOVASCULAR TISSUE BANKS.
Buzzi M., Terzi A., Alviano F., Guarino A., Dainese L., Gatto C., D’Amato Tothova J.,
Polvani G.,
EATB, Berlin, Germany, November 3-5, 2010

15. ELIMINATION OF ANTIBIOTIC CARRY-OVER FROM TISSUES
DECONTAMINATED WITH BASE•128
Gatto C., Beccaro M., Lipartiti M., D’Amato Tothova J.

16. FATE OF ANTIBIOTICS AFTER THE TISSUE
DECONTAMINATION PHASE: STUDY ON PIG HEART VALVES.
D’Amato Tóthová J., Gatto C., Cavallaro C., Beccaro M., Lipartiti M.
EATB, Cracow, Poland, November 4-6, 2009

17. EFFECTS OF TEMPERATURE ON DECONTAMINATION EFFICACY
OF BASE•128 BY IN VITRO TIME-KILL STUDIES
D’Amato Tóthová J., Gatto C., Beccaro M., Candeo L., Bortoluzzi S., Lipartiti M.
EATB, Cracow, Poland, November 4-6, 2009