Suprasorb® X,
a new HydroBalance wound dressing for Modern Wound Management

SUMMARY
Suprasorb® X – prospective clinical evaluation on patients with chronic wounds

Coerper S, Beckert S, Halm-Nill C, Deutschle G, Königsrainer A

Initial experience with Suprasorb® X in the Netherlands

Van Leen MWF

Polihexanide - antimicrobial efficacy and biocompatibility

Kramer A, Roth B, Koburger T, Hipler U-C, Abel M

Experience in US with Suprasorb® X+PHMB – an antimicrobial wound dressing

Cavorsi JP

Suprasorb® X was previously known as XCell® Cellulose Dressings and Suprasorb® X+PHMB was previously known as XCell® Antimicrobial Dressings. The clinical testing described in this document was conducted using XCell® branded products, Xylos® Corporation, Langhorne, PA, USA.
1. Introduction

The Suprasorb® X (SX) Wound Dressing is a sterile product composed of cellulose, water, and 0.085% chlorhexidine gluconate. This wound dressing is capable of significantly hydrating and absorbing fluid to maintain the ideal moisture balance (HydroBalance). We report about the success of the treatment with Suprasorb® X (before under the name of XCell®, Xylos Corporation, Langhorne, PA, USA) on patients with hard to heal ulcers.

2. Methods

Treatment of patients with chronic wounds is performed in an interdisciplinary wound care centre according to a comprehensive wound care protocol. Follow up was documented within a special documentation system. For analysis in patients with multiple ulcers the larger ulcer was defined as a primary ulcer. Pain was defined according to a scale (1-10) and assessed the last visit before and 3 weeks after Suprasorb® X therapy. Data was analysed using SPSS and is given as median and range. Healing rates were calculated with the log rank test because of different observation periods.

3. Patient population

In the last 3 years the healing course according to a standardized protocol was documented for 603 patients (wound duration: 143 days) with 272 diabetic, 113 with venous, 92 with ischemic and 126 patients with ulcers of other diseases. Here the overall healing rate was 81% within a treatment time of 96 days. Within these patients there were 96 patients with 134 hard to heal ulcers. These patients were treated unsuccessfully before and than switched to Suprasorb® X therapy:

4. Purpose

The purpose of this analysis was to evaluate the effect of Suprasorb® X exclusively on hard to heal ulcers.
5. Discussion

There were 96 patients with severe hard-to-heal ulcers. This is demonstrated by baseline characteristics. However, there was an overall healing rate of the primary ulcers of more than 50%. Ischemic ulcers did not respond to Suprasorb® X therapy. In more than 40% of the patients, pain reduction was evident already one visit after start of Suprasorb® X therapy. In contrast to other wound dressings Suprasorb® X was well tolerated in all patients and no allergy or skin irritation was found. Prospective studies are underway to evaluate the impact of Suprasorb® X.

![Hard to heal leg ulcer](image1)

![Treatment with Suprasorb® X](image2)

![Dressing change 3 days after](image3)

![Ulcer after removal of Suprasorb® X](image4)

**Fig. 2:** Suprasorb® X for the treatment of a hard to heal ulcer

![Wound etiology of 96 patients with hard to heal ulcers and treated with Suprasorb® X](image5)

![Healing rates within the time of treatment](image6)

**Fig. 3:** Wound etiology of 96 patients with hard to heal ulcers and treated with Suprasorb® X

**Fig. 4:** Healing rates within the time of treatment
Fig. 5: Wound area and pain reduction with Suprasorb® X therapy
Initial experience with Suprasorb® X in the Netherlands

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At the moment most physicians are using modern wound dressings for wound healing based on healing in a moist environment. The most used products in The Netherlands are alginates, foam dressings and hydrocolloids. All these products are used after sharp or enzymatic debridement or for stimulation of autolytic debridement. At the moment we still see that the products available on the Dutch market do not cover the whole spectrum of wound healing.

This is a reason that we are still looking for new products on the market which can support us to provide good wound healing in the types of wounds that do not heal with normal dressings. Suprasorb® X (available in the Netherlands as XCell®, Xylos Corporation, Langhome, PA, USA) is a product made of biosynthesized cellulose and is the only one available in The Netherlands. Biosynthesized cellulose is a novel material for use in wound care. It has unique moisture absorbing and donating properties (HydroBalance) and is patient friendly. This type of cellulose is also used for other medical purposes.

1. Skin tears

From September 2003 until now I used the product for chronic wounds existing longer than 6 months or for skin-tear wounds caused by injury. In total, 9 patients with skin tears were treated, most wounds were situated on the lower arm or the lower leg. 8 patients were female and 1 male. They all stayed in my nursing home. Most of the patients had a very thin and fragile skin. Six patients had problems of the skin as a result of prolonged use of corticosteroids ('parchmentlike skin').

The way of treatment for these ten patients was application of Suprasorb® X for one week, covered with an absorbing bandage which was changed daily. Full wound closure was seen in 80% of the skin lesions within 6 weeks (see table ‘skin tears’). One patient died before full skin closure.

Table skin tears

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Prolonged use of corticosteroids</th>
<th>Location</th>
<th>Healing time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr 1</td>
<td>female</td>
<td>81 years</td>
<td>Yes</td>
<td>Forearm</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Nr 2</td>
<td>female</td>
<td>85 years</td>
<td>Yes</td>
<td>Forearm</td>
<td>9 weeks</td>
</tr>
<tr>
<td>Nr 3</td>
<td>female</td>
<td>81 years</td>
<td>No</td>
<td>Forearm</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Nr 4</td>
<td>male</td>
<td>87 years</td>
<td>No</td>
<td>Forearm</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Nr 5</td>
<td>female</td>
<td>82 years</td>
<td>Yes</td>
<td>Lower leg</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Nr 6</td>
<td>female</td>
<td>83 years</td>
<td>Yes</td>
<td>Forearm</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Nr 7</td>
<td>female</td>
<td>82 years</td>
<td>No</td>
<td>Lower leg</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Nr 8</td>
<td>female</td>
<td>82 years</td>
<td>Yes</td>
<td>Forearm</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Nr 9</td>
<td>female</td>
<td>81 years</td>
<td>No</td>
<td>Forearm</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

2. Ulcers by rheumatic vasculitis

Another experience with the product was using it for several leg ulcers caused by rheumatic vasculitis. The most remarkable patient had multiple ulcers for more than 3 years on her leg with a diameter of 3 cm. A lot of dressings were used in those three years without any result. We did the same treatment as mentioned above with a very fast result, without the need for oral medication at all. Total time of wound healing was three weeks.
3. Pyoderma gangrenosum

Two patients with Pyoderma gangrenosum at the under leg were also treated with Suprasorb® X. The first patient was a man of 51 years old with diabetes and hypertension. The pyoderma was treated with cyclosporine (Neoral®). In the period from September 2004 until January 2005 he was treated once weekly with Suprasorb® X and his oral medication was continued. The end result was full skin closure and in the three months afterwards there were no signs of recurrence.

Another patient, lady 65 years old, with pyoderma on her lower leg was also treated with cyclosporine but continuation of cyclosporine during wound healing was not possible. She received the same wound treatment but there was no effect, probably caused by failure of oral medication.

4. Abdominal surgery

We treated one male patient of 70 years old with problems of wound healing after abdominal surgery. A few days after the operation a large wound was formed due to dehiscence. He was treated with Suprasorb® X for two weeks and the bandages were changes twice weekly. After two weeks of treatment we changed from Suprasorb® X to Mepilex® because there was too much wound fluid below the Suprasorb® X. In the period after using the Suprasorb® X there were no signs of necrotic tissue or inflammation and the epithelialisation was started (pictures below).

5. Donor sites

We also used Suprasorb® X for covering donor sites and this showed an instant relief of pain and normal wound healing. Our experience is that using the normal way of treatment in The Netherlands with paraffin gauzes / iodine gauzes do not relief the pain for the patient. All the patients we treated with Suprasorb® X did not complain of pain during change of the dressings.
6. Waving / washing effect of Suprasorb® X

Maceration of the wound borders during treatment was not seen. We found some whitening of the skin around the ulcers (may be a disfunctioning of the melanocytes deep in the skin), but there was no enlargement of the ulcers, just closure. After removing of the white, dead cell layers a new epithelized intact skin was visible (waving / washing effect). Looking at the dressing from the outside, when changing the absorbing dressing on top, we noticed that the Suprasorb® X was slightly transparent, enabling us to look at the bottom of the wound through the dressing. When we changed the Suprasorb® X we did not see large amounts of wound fluid at the wound borders, only once when we treated the large abdominal wound. From the outside it is not possible to make conclusions about exchange of fluid between the bandage and the wound.

Looking at the dressing at the moment of change, we saw, in the case of using an absorbing dressing on top of it, that only above the ulcer there was a gel like bandage to see; the part in contact with normal skin was totally dry after two days. Some times we saw that there was adherence between the bandage and the wound edges, but during changing of the bandage we did not see any bleeding of the wound at all. Probably we removed some dead skin when we change the dressing. This phenomenon we see only when we cover the Suprasorb® X with absorbing bandages. When we fixate the Suprasorb® X with a transparent film the whole dressing was jelly at the moment of change.

7. General conclusion

Based on the experience with other types of bandages, we think there is place for Suprasorb® X, especially thinking of superficial wounds which need epithelialization. At the moment we do not have any experience with Suprasorb® X in deeper wounds.

8. Acknowledgement

I thank Harm Jaap Smit, BioMedServ BV, Amersfoort / The Netherlands, for his kind support during the tests with Suprasorb® X.

Suprasorb® X was previously known as XCell® Cellulose Dressings. The clinical testing described in this article was conducted using XCell® Dressings.
Polihexanide - antimicrobial efficacy and biocompatibility

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³ Hygiene North GmbH, 17489 Greifswald, Germany
⁴ Department of Dermatology, Friedrich Schiller University of Jena, Germany
⁵ Medical & Regulatory Affairs, Lohmann & Rauscher GmbH & Co. KG, 56579 Rengsdorf, Germany

Polihexamethylene biguanide [PHMB, polihexanide] is a broad spectrum antimicrobial agent. PHMB is odorless, clear and colorless, and is heat stable to > 140°C. It is safe and biocompatible. PHMB is reliable, fast acting and has a proven history in a diverse range of cosmetic and personal care products including: skin creams and lotions, impregnated wet wipes, wound care and contact lens cleaning solutions (1).

A rapid electrostatic attraction occurs between the positively charged PHMB and the negatively charged bacterial cell surface. The PHMB fights for the negative sites on the cell wall, thereby displacing metallic cations essential to the integrity of the cell outer membrane. This breakdown yields the bacterial cell vulnerable to the action of the remaining PHMB in solution. The cytoplasmic membrane of the bacterial cell is composed of a small number of acidic phospholipids. These phospholipids are essential for expanding the membrane structure and preventing collapse of the two bi-layers of the planes of the membrane. In addition, the functional proteins embedded in the membrane depend on the boundary phospholipids for activity. Any disruption in the organization of the membrane structure will lead to loss of protein function. PHMB destabilizes the cytoplasmic membrane rendering it permeable (1).

The phospholipids of the membrane form aggregates of PHMB surrounding essential proteins leading to loss of protein function. At this point, there is an extensive disruption of the membrane with leakage of macromolecular components from the cell, such as nucleotides. These actions eventually lead to the precipitation of the majority of cell contents and the effects of the PHMB become bactericidal (1).

In the following we will reflect on the micobicidal effects and biocompatibility of polihexanide and Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing (containing 0.3% polihexanide).

1. Microbicidal efficacy of Polihexanide in vitro

1.1 AATCC Test Method 100:

Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing were incubated with approximately $10^6$ CFU/ml of the challenge organism. After 24 hours, a second count was made to determine the reduction in the number of organisms present (1).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Type</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>Yeast</td>
<td>99.9</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Gram negative bacteria</td>
<td>99.9</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Gram positive bacteria</td>
<td>99.5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Gram negative bacteria</td>
<td>99.2</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>Gram positive bacteria</td>
<td>99.9</td>
</tr>
</tbody>
</table>

1.2 AATCC Test Method 30:

Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing was incubated with Aspergillus niger on Sabouraud Dextrose Agar for 7 days. Results are reported as the amount of growth of the organism characterized by 0 (no growth), 1 (microscopic growth) or 2 (macroscopic growth) and the size of the growth zone (1).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Type</th>
<th>Growth/Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus niger</td>
<td>Mold</td>
<td>0/no zone</td>
</tr>
</tbody>
</table>
1.3 Antimicrobial Activity Against Anaerobic Organisms

**AATCC Test Method 100:**
Suprasorb® X +PHMB antimicrobial Hydro-Balance Wound Dressing was incubated under anaerobic conditions with approximately $10^5 - 10^6$ CFU/ml of the challenge organism. After 24 hours, a second count was made to determine the reduction in the number of organisms present (1).

* CFU: colony-forming units

<table>
<thead>
<tr>
<th>Organism</th>
<th>Source</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium perfringens</td>
<td>Wound Infection</td>
<td>99.9</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>Blood</td>
<td>99.9</td>
</tr>
<tr>
<td>Peptostreptococcus prevoti</td>
<td>Human skin</td>
<td>99.9</td>
</tr>
</tbody>
</table>

1.4 Quantitative suspension test according to EN 1040

In the quantitative suspension test according to EN 12353 polihexanide fulfills the requested efficacy for an antiseptic with reduction factor (RF) > 5 lg without load resp. >3 lg with different organic challenges (table 1).

* EN: European Norm

**Microbicidal efficacy of polihexanide**

<table>
<thead>
<tr>
<th>Microbicidal efficacy of polihexanide</th>
<th>concentration (%) for RF** (lg)</th>
<th>without load</th>
<th>with organic challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2 % BSA</td>
</tr>
<tr>
<td>S. aureus 0,5 min</td>
<td>0,02/&gt;5</td>
<td>0,005/3,8</td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>0,02/&gt;6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>0,02/&gt;7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>0,005/&gt;8</td>
<td>0,02/&gt;4</td>
<td>0,02/&gt;3,6</td>
</tr>
<tr>
<td>E. coli 0,5 min</td>
<td>0,02/&gt;6</td>
<td>0,005/&gt;8</td>
<td>0,02/&gt;6</td>
</tr>
<tr>
<td>10 min</td>
<td>0,005/&gt;9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>0,02/&gt;6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. faecium 5 min</td>
<td>0,02/&gt;5</td>
<td>0,02/&gt;4,5</td>
<td>nt*</td>
</tr>
<tr>
<td>60 min</td>
<td>0,02/&gt;6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa 5 min</td>
<td>0,02/&gt;6</td>
<td>0,02/&gt;6</td>
<td>nt*</td>
</tr>
<tr>
<td>60 min</td>
<td>0,02/&gt;6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans 0,5 min</td>
<td>0,02/&gt;5</td>
<td>0,02/&gt;5</td>
<td>nt*</td>
</tr>
<tr>
<td>10 min</td>
<td>0,02/&gt;6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* not tested    ** lg control – lg test sample

BSA: Bovine Serum Albumin

1.5 Sustained Antimicrobial Activity

**AATCC Test Method 100:**
Samples with Suprasorb® X +PHMB were incubated with approximately $10^6$ CFU/ml of the challenge organism. After various times, a second count was made to determine the reduction in the number of organisms present (1).

**Percent Reduction Over Time**

<table>
<thead>
<tr>
<th>Time</th>
<th>MRSA</th>
<th>E. coli</th>
<th>E faecalis</th>
<th>B. subtilis</th>
<th>C. albicans</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hours</td>
<td>99,5</td>
<td>99,9</td>
<td>99,8</td>
<td>99,9</td>
<td>99,9</td>
</tr>
<tr>
<td>8 hours</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
</tr>
<tr>
<td>1 day</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
</tr>
<tr>
<td>3 days</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
</tr>
<tr>
<td>5 days</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
</tr>
<tr>
<td>7 days</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
<td>99,9</td>
</tr>
</tbody>
</table>
1.6 Two Hour MRSA Survival Curve

Method:
The following testing was performed according to modified methods of the Assessment of Antibacterial Finishes on Textile Materials. Testing performed at North American Science Associates (NAmSA).

AATCC Test Method 100:
The figure illustrates the time it takes to bring the MRSA concentration from $10^5$ CFU/ml to less than $10^2$ CFU/ml with various antimicrobial dressings (1).

1.7 Two Hour VRE Survival Curve

Method:
The following testing was performed according to the methods of the Assessment of Antibacterial Finishes on Textile Materials at NAmSA.

AATCC Test Method 100:
The following figure illustrates the time it takes to bring the VRE concentration from $10^6$ CFU/ml to less than $10^2$ CFU/ml with various antimicrobial dressings (1).

1.8 Seven Day MRSA Survival Curve

Method:
The following testing was performed according to modified methods of the Assessment of Antibacterial Finishes on Textile Materials. Testing performed at North American Science Associates (NAmSA).

AATCC Test Method 100:
The figure illustrates the MRSA reduction over 7 days for Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing and Acticoat (1).
2. Local tolerance and biocompatibility of Polihexanide and Suprasorb X+PHMB and in vivo

2.1 Eye irritation test (HETCAM-Test)

The local tolerability was tested in the well-known HETCAM* test on the chorioallantoic membrane with polihexanid + macrogol (Lavasept®). Polihexanide in macrogol (Lavasept®) was significantly better tolerable as the launched used antibiotic eyedrops.

**HETCAM test**: hen’s egg test on the chorioallantoic membrane

Irritant effect after 5 min exposure on chorioallantoic membrane of polihexanide compared with antibiotic commercial eyedrops (2)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reaction (n)</th>
<th>Hyperemia (n)</th>
<th>single hemorrhage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polihexanide 0.02</td>
<td>13</td>
<td>minimal</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin 0.3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gentamycin 0.5</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Azidamphenicol 1.0</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

In comparison to the other antiseptics, the irritant effects of polihexanide 0.1% in the HETCAM test were significantly lower and the tolerability was superior.

**Comparison of irritative effect of selected substances in the HETCAM test**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Use concentration</th>
<th>quotient threshold conc. (%) in HETCAM/ use conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polihexanide</td>
<td>0,1</td>
<td>1,0</td>
</tr>
<tr>
<td>Octenidin</td>
<td>0,1</td>
<td>0,125</td>
</tr>
<tr>
<td>PVP-Iod</td>
<td>10</td>
<td>0,03</td>
</tr>
</tbody>
</table>

The safety and local tolerance for 0.1% polihexanide demonstrated by the electron microscopy results on enucleated porcine eye were the basis for the successful launch of the pre-operative antiseptic on the eye in the medicine (3).

2.2 Hemolysis Study

Performed by NAmSA Laboratories, Northwood, OH

**Description**: An in vitro study was conducted, based on the requirements of the International Organisation of Standardization (ISO 10993-4), to determine whether extract of Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing would cause red blood cell hemolysis (1).

**Method**: Blood was collected from 3 rabbits, pooled, diluted and added to duplicate tubes of the dressing extract (in saline). The tubes were gently mixed and then maintained stationary for 4 hours at 37°C. The suspensions were then centrifuged and the supernatant was tested for mean hemolytic index.

**Results**: The Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing is non-hemolytic.

2.3 Irritation Study

Performed by NAmSA Laboratories, Northwood, OH

**Description**: An intracutaneous reactivity study was conducted, based on the requirements of the ISO 10993-10, to determine the potential for irritation (1).

**Method**: The dressing was extracted in saline and cottonseed oil. Each extract, and appropriate controls, were injected by the intracutaneous route into five separate sites on the back of each of 3 rabbits. The injection sites were observed for erythema and edema immediately and 24, 48 and 72 hours after injection.

**Results**: Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing passed the standard irritation test.

2.4 Cytotoxicity

After exposition of 1 x 1 mm explants on neonatal rat peritoneum polihexanide 0.04% showed a significant better local tolerance and biocompatibility in comparison to other tested antiseptics (4).
Results of the explant test on neonatal rat peritoneum

<table>
<thead>
<tr>
<th>Agent (%)</th>
<th>Exposure</th>
<th>Explants (n)</th>
<th>Explantation rate (%)*</th>
<th>Growth rate (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polihexanide 0.04</td>
<td>5 min</td>
<td>120</td>
<td>99.2</td>
<td>63</td>
</tr>
<tr>
<td>PVP-iod 10</td>
<td></td>
<td>96</td>
<td>98.9</td>
<td>42*</td>
</tr>
<tr>
<td>Polymyxin B 1</td>
<td>24</td>
<td>25</td>
<td>3.7*</td>
<td></td>
</tr>
<tr>
<td>Octenidine 0.1</td>
<td>48</td>
<td>16.7</td>
<td></td>
<td>single cells*</td>
</tr>
<tr>
<td>Chlorhexidine 1.5</td>
<td>28</td>
<td>0</td>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>Polihexanide 0.02</td>
<td>1 min</td>
<td>120</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>PVP-iod 10</td>
<td></td>
<td>120</td>
<td>100</td>
<td>62.5*</td>
</tr>
<tr>
<td>Polymyxin B 1</td>
<td>24</td>
<td>100</td>
<td>35.5*</td>
<td></td>
</tr>
<tr>
<td>Octenidine 0.1</td>
<td>24</td>
<td>0</td>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>Chlorhexidine 1.5</td>
<td>28</td>
<td>35.9</td>
<td></td>
<td>3.2*</td>
</tr>
<tr>
<td>Octenidine 0.05</td>
<td>47</td>
<td>91.5</td>
<td></td>
<td>59.1*</td>
</tr>
</tbody>
</table>

* significant difference to polihexanide (p < 0.05 resp. 0.01)

Cytotoxicity Study of Suprasorb® X+PHMB
Performed by NAmSA Laboratories, Northwood, OH
Description: An in vitro study was conducted, based on the requirements of the ISO, 10993-5, to determine the potential for cytotoxicity (1).
Method: A portion of Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing, a negative control, and a positive control were each placed on triplicate agarose surfaces directly overlaying confluent monolayers of L-929 mouse fibroblast cells. After incubating at 37°C in 5% CO₂ for 24 hours, the cell culture was examined for cell decolonization around the dressing to determine the zone of cell lysis (if any) and cell morphology in proximity to the dressing.
Results: The Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing is non-cytotoxic.

2.5 Sensitization Study
Performed by NAmSA Laboratories, Northwood, OH
Description: A guinea pig maximization test was conducted, based on the requirements of the ISO 10993-10, to evaluate the potential for delayed dermal contact sensitization (1).
Method: The dressing was extracted in saline (SC) and cottonseed oil (CSO). Each extract, and appropriate controls, were intradermally, injected and occlusively patched to ten test guinea pigs in an attempt to induce sensitization. In addition, the dressing and a control were placed in direct contact with the skin. All sites were scored at 24, 48 and 72 hours after patch removal.
Results: The SC and CSO dressing extracts of Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing showed no evidence of causing delayed dermal contact sensitization in the guinea pig.

2.6 Systemic Toxicity Study
Performed by NAmSA Laboratories, Northwood, OH
Description: A study was conducted, in accordance with the guidelines of the United States Pharmacopoeia (USP) and the ISO 10993-11, to evaluate the potential of the Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing for systemic toxicity (1).
Method: The dressing was extracted in saline and cottonseed oil. A single dose of the dressing or control extract was injected into each of 5 mice per extract by either intravenous or intraperitoneal route. The animals were observed immediately and at 4, 24, 48 and 72 hours after systemic injection.
Results: There was no mortality or evidence of systemic toxicity from Suprasorb® X+PHMB antimicrobial HydroBalance Wound Dressing.

2.7 Influence on cartilage metabolism
Antiseptic treatment of bovine sesamoid bone with 0.005 % polihexanide did not increase the catabolism of proteoglycans, whereas octenidine in the same concentration was toxic (5).
3. Stimulation of wound healing and cell metabolism

In a double-blind, randomised, stratified, controlled parallel-group design with experimental superficial aseptic wounds in piglets by computerised planimetry the following results were obtained: The octenidine-based antiseptic retarded wound contraction on day 9 compared with polihexanide 0.04 % and Ringer, whereas in the later phase polihexanide promoted the wound healing (6).

### Influence on healing of experimental superficial aseptic wounds in piglets [6]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Wound area (mm²) on day after exp. Wounding</th>
<th>Duration to wound closure (d)</th>
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</thead>
<tbody>
<tr>
<td>Polihexanide</td>
<td>0.04</td>
<td>338</td>
</tr>
<tr>
<td>Octenidine</td>
<td>0.1</td>
<td>357</td>
</tr>
<tr>
<td>Ringer (placebo)</td>
<td>353</td>
<td>163*</td>
</tr>
</tbody>
</table>

* = difference to polihexanide p < 0.05  ** = difference to ringer

In the proliferation test the PicoGreen® dsDNA quantitation kit was used to determine the double-stranded DNA (dsDNA). The Quant-IT™ PicoGreen® DNA reagent (molecular probes, Eugene, Oregon, USA) is an ultrasensitive fluorescent nucleic acid stain for quantification of dsDNA. A significant increase of the proliferation of fibroblasts and keratinocytes by polihexanide+ macrogulum (Lavasept®) in a concentration of 1-2 μg/ml was found. The results could also confirmed by polihexanide alone in a concentration range of 0.2-2 µg/ml for keratinocytes. The further evaluation on other cell lines is ongoing (personal communication of Hipler UC, Department of Dermatology, Friedrich Schiller University of Jena, Germany, according to [7]).

In Suprasorb® X+PHMB a higher concentration of polihexanide (0.3%) is used. This concentration of polihexanide is needed due to the high absorption of this compound to overcome the permeability barriers to reach the cell layers of the wound – especially the deeper. Therefore higher start concentrations of polihexanide may be clinically necessary for this proliferating effect which was also seen clinically before (8).
4. Conclusion

The compound polihexanide is a highly potent antiseptic, which, in microbicidal concentrations, not only surpasses equivalent effective antiseptic agents like Chlorhexidin, Octenidin, PVP-Iod concerning tolerability, but even induces proliferation in vitro as well as in animals. This is possibly due to the specific mode of action, belonging exclusively to polihexanide. It reacts predominantly with acidic lipid bacterial cell membranes while only slightly affecting neutral lipids of human cell membranes [9].

Polihexanide in the tested concentrations 0,01-0,3 % is safe and biocompatible. Suprasorb® X+PHMB antimicrobial Hydro-Balance Wound Dressing fulfill the testing requirements of the USP and ISO.

5. References

Experience in US with Suprasorb® X+PHMB – an antimicrobial wound dressing

Cavorsi, JP
Wound Care Center and Hyperbaric Medicine, St. Joseph's Medical Center, Reading Pennsylvania, USA

1. Introduction
The Suprasorb® X+PHMB (SX+P) Wound Dressing is a sterile product composed of cellulose, water, and 0.3% polyhexamethylene biguanide (polihexanide). This wound dressing is capable of significant bioburden reduction (1), reduced pain (2), promotion of wound closure (3) and hydrating and absorbing fluid to maintain the ideal moisture balance (HydroBalance) (1,4). We report about the success of the treatment and economic improvements with Suprasorb® X+PHMB (provided as XCell® Antimicrobial in the United States (XAM), Xylos® Corporation, Langhorne, PA, USA) on patients with hard to heal ulcers.

2. Methods
50 patients with 79 wounds of varying etiologies were treated in a multi-center evaluation of XAM until healed or for up-to 7 weeks. In a subset of 8 patients (21 wounds) the XAM treatment was specifically focused on wounds that were non-responsive to silver dressings for at least 3 weeks. Bioburden measurements were performed using a variety of methods including swabs, biopsies and tissue culture.

3. Patient population
Wounds including venous, arterial, pressure, diabetic, trauma, spider bites, pyoderma gangrenosum and vasculitic ulcers, among others. Patients were determined to be clinically infected or had bioburden using semi-quantitative (1+ to 4+) or qualitative (heavy, moderate, light, scant) methods.

4. Results
Suprasorb® X+PHMB either healed or achieved clinical improvement in >80% of the patients evaluated over the course of the study. In the subset of wounds that were not responsive to prior treatment with silver dressings, a decrease in wound size of 33% was observed after 3 weeks.

5. Discussion
Suprasorb® X+PHMB demonstrated very effective results when used on chronic wounds, including wounds that were not responding to silver dressings. Similar to Suprasorb® X (without PHMB), this products demonstrated its ability to achieve continuous autolytic debridement, pain reduction and significant economic savings.
6. Further clinical experiences

Case Study I

Objective: To demonstrate the clinical safety and effectiveness of a cellulose dressing that contains polyhexamethylene biguanide (PHMB).

Design: A case study of a patient with a chronic ulcer of the right lower extremity.

Setting: Wound Care Clinic

Patients: A case series of eight patients with chronic wounds were studied. A representative single case is presented. The patient had lower extremity deep venous thrombosis (DVT) and a chemical burn that progressed into a chronic wound measuring 14.5 cm².

Interventions: The patient received the chemical burn in August 2002 and was treated with hydrogen peroxide and Silvadene® for four months. On January 17, 2003 the patient was first seen at the clinic with a wound that measured 14.4 cm². Henceforth the patient received various treatments including compression therapy, enrolment into a clinical trial where the patient was randomized to the control and lastly, four weeks of a silver containing dressing. After 56 weeks, the wound remained unresponsive and had increased in size to 14.5 cm². On September 2, 2003, the patient was placed on a treatment of a biosynthesized cellulose dressing that contained PHMB and compression therapy.

Main Outcome Measures: Wound size and bioburden were the two measurable outcomes. Autolytic debridement, granulation tissue and epithelialization were also subjectively measured.

Main Results: One week after initial treatment with antimicrobial biosynthesized cellulose the wound began to respond and the size had decreased to 12.1 cm². After 7 weeks it measured 8.4 cm² and eventually it went on to heal at 26 weeks. The initial bioburden consisted of three types of bacteria, two of which were eliminated after 24 hours of treatment with antimicrobial biosynthesized cellulose and one that was highly reduced.

Conclusion: Biosynthesized cellulose with PHMB was very effective at reducing bioburden and healing a chronic wound that was non-responsive to conventional therapy that included silver impregnated dressings. The dressing was effective over the changing stages of the wound from presentation to healing.

Case Study II

Introduction
Unlike acute wounds that follow a well-defined process of healing, chronic wounds are often characterized by a defective process leading to prolonged healing. Often these wounds are non-progressive and are stuck in the one or more phases. It is important that proper wound bed preparation is achieved in order to provide for ongoing debridement, manage the wound exudate, and resolve any bacterial imbalance (5).

Various wound dressings have been used to address each of these aspects separately. Debridement is achieved by various methods of which dressings provide either enzymatic or autolytic debridement. Moisture management of a wound is critical. Dressings, like alginates or foams, often absorb high quantities of exudate that can leave the wound too dry. Moist dressings, that hydrate a wound, do not absorb enough of the exudate and can result in maceration. Lastly various antimicrobial dressings address the bacterial load when present. The primary antimicrobial components currently available are silver in various forms, iodine and polyhexamethylene biguanide (PHMB). PHMB is a common antimicrobial agent used in contact lens solutions, swimming pools and wound dressings.

A dressing that could address more than one of the needs for wound bed preparation would be beneficial.

A biosynthesized cellulose wound dressing (XCell® Cellulose Wound Dressing, Xylos® Corporation, Langhorne, PA, USA) was tested in a forty-nine patient multi-center, controlled, randomized clinical study. It demonstrated effectiveness of the dressing compared to a standard of care on venous stasis ulcers. Results of a single site demonstrated significantly faster autolytic debridement, reduced pain and cleaner wound margins after a 12-week study period (2).

The antimicrobial version containing PHMB was developed for use on infected and non-infected wounds and was used in a forty-nine patient clinical evaluation of various types of wounds. The following case study is a non-progressive chronic wound from a case series of eight patients with 21 wounds.

Methods
Patient History
A 37-year-old obese female patient presented on January 17, 2003 at the Center for Advanced Wound Care (Reading, PA). This patient had sustained a chemical burn on the anterior portion of her right lower extremity four months previously, in August, 2002. Except for a history of deep vein thrombosis, she had no significant medical history. She was treated with coumadin, peroxide and silver sulfadiazine containing cream (Silvadene®, HoechstMarion-Roussel, Kansas City, MO).
As presented the wound measured 4.8 cm x 3.0 cm or 14.4 cm² (Figure 1). She was treated with a gradient, sequential pneumatic pump (Chattanooga Corp, Chattanooga, TN) absorptive foam primary dressing (Allevyn™, Smith & Nephew, Hull, UK), and a compression bandage (Profore™, Smith & Nephew, Hull, UK). After being unresponsive for three weeks, the patient was entered into a 13-week clinical trial for venous leg ulcers and was randomized to the control. Control consisted of sharp debridement, absorptive foam dressing and compression. After the clinical trial the wound remained and standard compression with a variety of primary dressings was used. For four weeks prior to receiving antimicrobial biosynthesized cellulose the patient received weekly applications of a silver dressing (Acticoat™, Smith and Nephew, Hull, UK) with no response.

Treatment
On August 12, 2003, following 56 weeks of treatment for the initial injury, the wound measured 4.4 cm x 3.3 cm (14.5 cm²) which was 3.8% larger than when the patient presented 7 months earlier (Figure 2). Patient was started on antimicrobial biosynthesized cellulose (Suprasorb® X+PHMB = XCell® Antimicrobial, Xylos Corp, Langhorne, PA) and a compression wrap. The patient was followed weekly or as needed until healing. At each dressing change the length and width of the wound was measured and the wound examined.

Results
After 1 week, the wound began to respond and measured 3.9 cm x 3.1, a decrease in wound size of 16.7%. There was evidence of autolytic debridement and the wound remained moist and without maceration. At 7 weeks the wound measured 3.0 cm x 2.8, a 57.4% decrease (Figure 3). Granulation tissue was dark red and epithelialization was observed. This continued until the patient healed at 26 weeks.

The wound was cultured prior to application of antimicrobial biosynthesized cellulose. The wound contained a high level of *Staphylococcus aureus* (3+), *Beta hemolytic Streptococcus B* (3+), and *Pseudomonas aeruginosa* (4+). Suprasorb® X+PHMB was applied and 24 hours later the wound was recultured. Results demonstrated elimination of *Beta hemolytic Streptococcus B* and *Pseudomonas aeruginosa* and a decrease in *Staphylococcus aureus* to 1+.

Discussion
Biosynthesized cellulose has demonstrated efficacy in a multi-center randomized controlled study on venous stasis ulcers. In that study single site statistics have demonstrated significant pain reduction, autolytic debridement and cleaner wound margins than standard care (2). The dressing demonstrated two of the three aspects of the wound bed preparation paradigm: ongoing autolytic debridement and management of exudate.

Development of an antimicrobial version has resulted in a product that not only has all the qualities of the regular biosynthesized cellulose, but also demonstrates antimicrobial efficacy and therefore the third aspect of the wound bed preparation philosophy. Clinically, in this study as in other evaluations (6), the antimicrobial biosynthesized cellulose demonstrated that it resolved the bacterial imbalance and was effective at managing the moisture to heal a chronic wound that had been non-responsive to a variety of therapies.
Conclusions
In this case study, antimicrobial biosynthesized cellulose demonstrated that it is safe and very effective when used on a non-responsive chronic wound. Similar to biosynthesized cellulose without PHMB, antimicrobial biosynthesized cellulose has demonstrated its ability to aid in autolytic debridement, cleansing of wound margins, and managing wound moisture. Additionally, results of this study clearly demonstrate a decrease in bioburden after antimicrobial biosynthesized cellulose use, up to and including elimination of some species of wound bacteria. After 56 weeks of non-responding on a variety of other dressings, the wound healed in 24 weeks when antimicrobial biosynthesized cellulose was used. Unlike other dressings that are specific to the phase of the wound biosynthesized cellulose wound dressing can be used throughout the various stages of healing to provide a continuum of care.

7. References