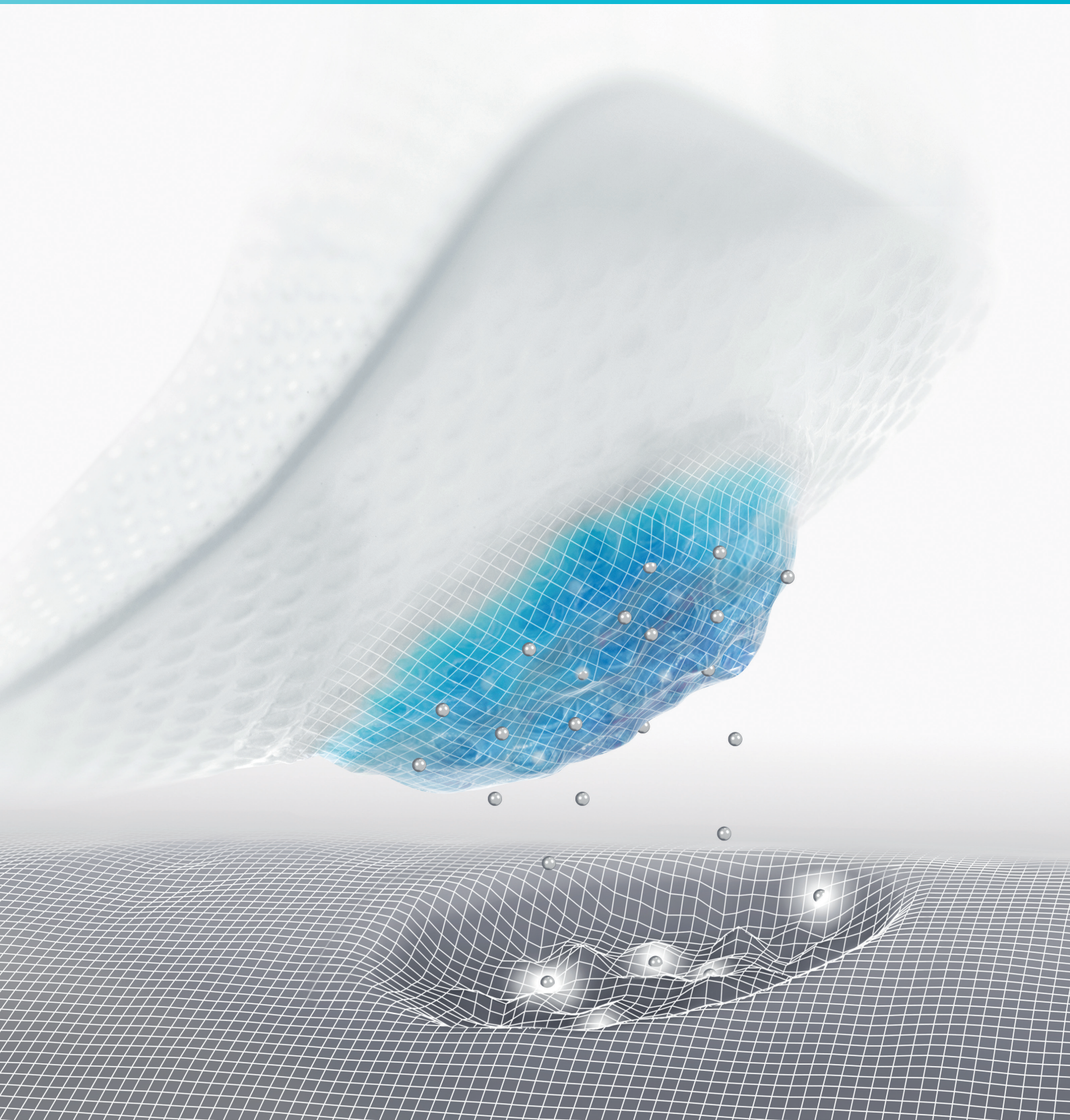
Biatain® Silicone Ag & Biatain® Ag

Monograph

Coloplast



Preface

At Coloplast, our mission is to make life easier for people with intimate health care needs. As our CEO, Lars Rasmussen puts it: 'Ideally, we would like to have people forget they have a medical condition. It's all about people just living the life they want.'

Caring for wounds and skin can be a complex and uncertain process so we are dedicated to sharing deeper knowledge and guidance through our internationally endorsed education programs with the goal of raising the global standard of care. Through close collaboration with health care professionals we build strong and fruitful partnerships. As a present and competent partner, we provide tailored solutions that are sensitive to individual needs and can provide optimised treatment outcomes.

Wound infection is one of the key challenges in managing non-healing wounds. As infected wounds are often highly exuding, may emit an unpleasant odour and can be very painful, the quality of life for the patient can be quite heavily impacted. Furthermore, treatment time, cost increase and wound management practices become more resource demanding. However, with proper diagnosis and early intervention many problems can be avoided, and clinical outcomes improved.

Effective treatment of infected acute and chronic wounds involves cleansing and debridement and requires certain properties from applied dressings, including effective antimicrobial performance. Biatain® Silicone Ag and Biatain Ag, with 3DFit Technology, conform to the wound bed to reduce exudate pooling, absorb exudate vertically and deliver silver at the wound bed. Exudate is locked away and retained even under compression, reducing the risk of maceration and spreading of infection to the wound edges and periwound skin.

Moist wound healing dressings with silver have become widely used as topical antimicrobials. This Monograph addresses the use of silver in wound care and describes mode of action of silver. *In vitro* data on efficacy of Biatain Silicone Ag and Biatain Ag against a broad range of bacteria and fungi, against mature biofilms and for prevention of biofilm formation are reviewed. Furthermore, clinical studies supporting the use of Biatain Silicone Ag and Biatain Ag for infected wounds are presented.

This Monograph has been written by our medical and scientific team and has gone through a thorough review process to ensure high quality content. We hope that you will enjoy reading the Monograph and will find it useful in your daily clinical practice.

Together, we are united by a shared purpose and passion to achieve ***fewer days with wounds.***

Nicolai Buhl Andersen
Senior Vice President, Coloplast Wound & Skin Care

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Introduction

Wound infection is a common complication leading to delayed wound healing and increased risk of amputation[1]. An international anthropological study found that 71% of health care professionals see infection management as the biggest challenge in wound treatment[2]. Implementation of effective strategies to prevent, diagnose and manage wound infection, is important in reducing mortality and morbidity rates[1]. The International Wound Infection Institute defines wound infection as the presence of microorganisms in sufficient number or virulence to cause a host response locally and/or systemically. In their recent update of the wound infection continuum, describing the stages in the wound infection (Figure 1), presence of biofilms has been added[1]. There is increasing evidence that biofilms are present in most, if not all, chronic non-healing wounds[3].

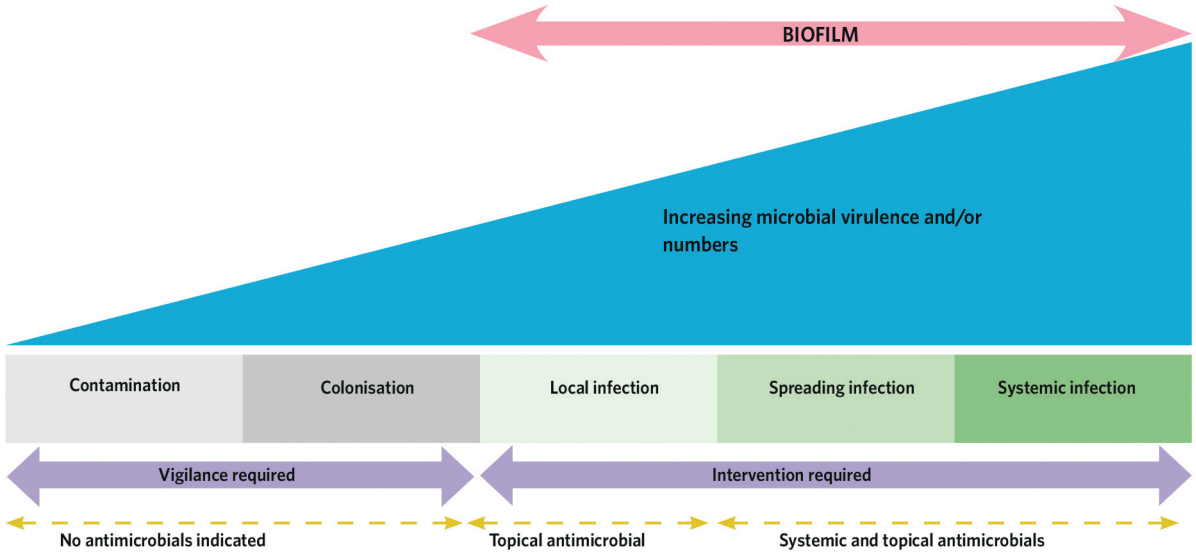


Figure 1. IWII wound infection continuum. Reproduced from the International Wound Infection Institute (IWII) Wound infection in clinical practice document 2016.

New insights in managing infection and biofilms

Infected wounds are often characterised by the presence of increased exudate, slough and non-viable tissue including high bacterial load. Increased exudate may result in exudate pooling and create a favourable environment for microbial growth and biofilm formation. Biofilms are clusters of bacteria and fungi embedded in the wound environment, which can form within 24 hours. New research shows that biofilms can be found both in the wound bed surface and in the tissue below the wound bed. Biofilms are difficult for the immune system and antibiotics to eradicate and may lead to persistent infection, inflammation and delayed healing[3].

Reducing the level of biofilms can support optimal healing conditions in a wound. International best practice for promoting optimal healing conditions for infected wounds recommends to first cleanse and debride the wound creating a window of opportunity for antimicrobials to act effectively[1, 4]. Methods of debridement include autolytic, surgical, sharp, enzymatic, larval therapy, and mechanical debridement. Cleansing and debridement of infected wounds remove slough and non-viable tissue including some, but not all, biofilms[1, 3, 4].

Following cleansing and debridement, appropriate antimicrobial treatment such as antimicrobial dressings should be applied[4]. The dressing should fill the gap between the wound bed and the dressing, as well as absorb and retain exudate, thereby creating a less favourable environment for biofilm development.

Silver dressings are widely used to manage wound infection and there is consensus that topical silver treatment in combination with good wound bed preparation can help resolve wound infection[1, 4, 5].

This Monograph addresses the use of silver in wound care and describes mode of action of silver and mechanisms of silver release. *In vitro* data on efficacy of Biatain® Silicone Ag and Biatain Ag against a broad range of bacteria and fungi, against mature biofilms and for prevention of biofilm formation are reviewed. Finally, clinical studies supporting the use of Biatain Silicone Ag and Biatain Ag for infected wounds are presented.

Clinical relevance of silver in wound care

Silver has been used as a topical antimicrobial agent for hundreds of years in wound care[6] and there is consensus that topical silver treatment in combination with good wound bed preparation can help resolve wound infection[1, 4, 5]. Furthermore, silver dressings can be used as a barrier to micro-organisms in wounds at risk of infection or re-infection, e.g. burns, surgical wounds, pressure ulcers near the anus, or wounds in patients who are immunocompromised, have poor circulation, or unstable diabetes[5].

Appropriate use of silver

It has been recommended to do a '2-week challenge' to determine the clinical efficacy of silver dressings. Thereafter, the wound, the patient and the management approach should be re-evaluated[5]. If there is improvement in the wound, but continuing signs of infection, treatment with silver dressing can be continued with regular reviews. If the wound has improved and the signs and symptoms of wound infection are no longer present, the silver dressing can be discontinued. If there is no improvement after 2 weeks, the silver dressing should be discontinued and consideration given to changing to a different antimicrobial agent, using a systemic antibiotic and/or re-evaluate possible untreated comorbidities[5].

Reviews of the efficacy of silver in wound management

Published reviews of the clinical efficacy of silver-containing topical wound treatments have yielded heterogeneous results, which have created some confusion and debate. To understand these differences in outcomes, a scoping literature review was performed by Rodriguez-Arguello et al. (2018)[7]. It included recent research (until 2016) and closely examined the study details. Although there was some inconsistency, in the majority of controlled clinical studies, silver-containing dressings were indeed effective. Another recent literature review of clinical evidence for silver in wound care similarly found that silver-containing dressings are effective and can improve wound healing, as well as quality of life and cost-effectiveness of treatment[8]. It was concluded that the evidence base for silver in wound management is significantly better than perceived in the current scientific debate. Difficulties in interpreting and comparing studies arise mainly from some studies including a small number of patients and the use of a wide range of different inclusion criteria, study protocols and endpoints[5]. Differences in products, interventions, study designs, and protocols hamper the ability to draw firm conclusions about the effectiveness across all silver-containing treatments[7]. A Cochrane review published in 2018 looks at dressings and topical agents for treating venous leg ulcers and concludes that silver dressings may increase the probability of venous leg ulcer healing compared with nonadherent dressings[9].

Not all silver dressings are the same

Clinical studies on Biatain® Silicone Ag and Biatain Ag have consistently shown positive clinical results in non-healing wounds with signs of infection[10-14]. In the Cochrane review, a subgroup analysis of silver dressings vs. foam comparators shows statistically significant benefit for silver dressings[9]. All studies included in this subgroup analysis are studies on Biatain Ag. The efficacy for Biatain Ag in the treatment of non-healing, venous leg ulcers was previously presented in a meta-analysis[15] and the health economic perspectives were subsequently analysed and published[16]. These data will be presented in detail in a later chapter along with a new study on Biatain Silicone Ag for infected diabetic foot ulcers looking at both microbiological and clinical measures[14].

Biatain® Silicone Ag and Biatain® Ag with 3DFit Technology

Silver dressings can vary in several parameters, e.g. dressing material, silver release profile, absorption and retention capacity, and ability to conform to the wound bed.

Conventional foam dressings leave a gap, or dead space, between the wound bed and dressing, allowing exudate to pool. Pools of exudate promote bacterial growth leading to increased risk of infection and subsequent development of biofilms. An optimal wound dressing should conform to the wound bed to fill the gap and reduce exudate pooling, thus creating a less favourable environment for biofilms to grow in[17-19].

3DFit Technology addresses the challenge of the gap between wound bed and dressing. Upon contact with wound exudate, Biatain Silicone Ag and Biatain Ag, with 3DFit Technology, conform to the wound bed, to fill the gap and reduce exudate pooling for optimal healing conditions (Figure 2). Microcapillaries within the foam absorb the exudate vertically, triggering the release of silver. Due to the conformability of the dressings, silver is delivered at the wound bed. The exudate is locked away and retained even under compression, reducing risk of leakage and maceration of the wound edges and periwound skin.

Kill 99.99% of mature biofilms

Biatain Silicone Ag and Biatain Ag have been shown to kill 99.99% of mature biofilms* (*P. aeruginosa*) and to prevent biofilm formation (shown *in vitro*). Both dressings are also effective against a broad spectrum of bacteria and fungi for up to 7 days[20].

Conform to the wound bed

Biatain Silicone Ag and Biatain Ag conform to the wound bed to reduce exudate pooling and deliver silver at the wound bed.

Absorb vertically

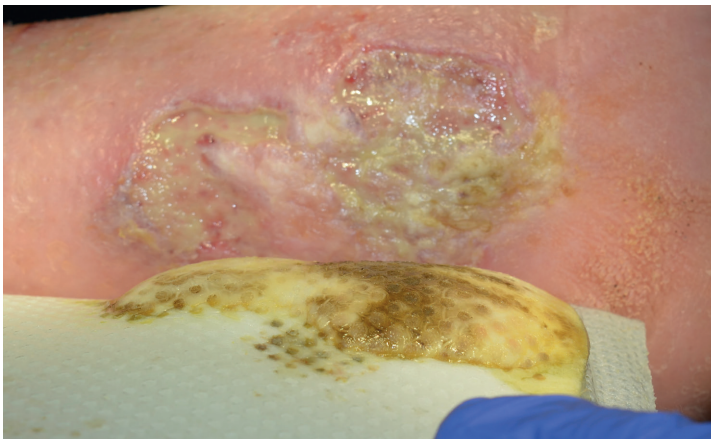
The microcapillaries within the foam absorb exudate vertically, triggering the release of silver.

Retain exudate

Exudate is absorbed and locked away and retained even under compression, reducing the risk of maceration and spreading infection to the wound edges and periwound skin.

*Mature biofilms are defined as minimum 24 hours old

A



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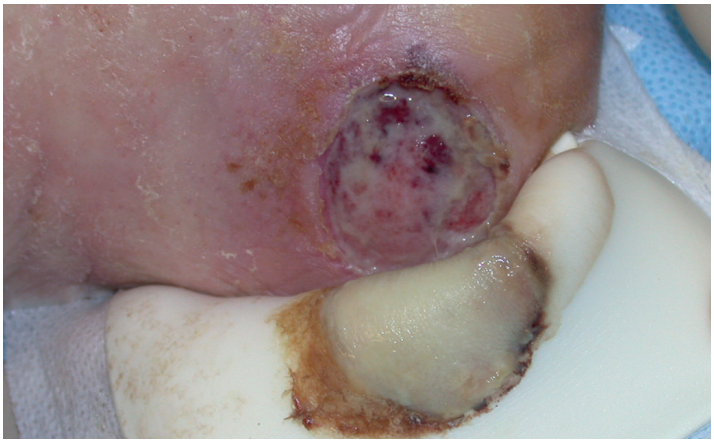


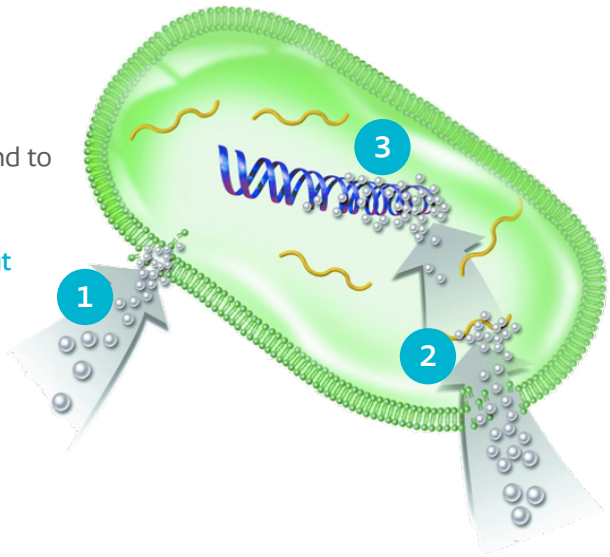
Figure 2: *Conformability of the dressings to the wound bed. A. Biatain® Silicone Ag on a malleolus leg ulcer and B. Biatain Ag Non-Adhesive on a heel pressure ulcer.*

Clinical studies on Biatain Silicone Ag and Biatain Ag have consistently shown positive results in non-healing wounds with clinical signs of infection, e.g. venous leg ulcers[10, 11, 13, 15] and diabetic foot ulcers[10, 12, 14]. A 4-week, 619-patient, randomised, controlled trial (RCT) evaluated clinical outcomes of using Biatain Ag for a range of aetiologies. Mean wound area reduction after 4 weeks was 56% in the treatment group and 34% in the local best practice comparator group (p=0.002). Odour, ease of use, and wear time were also significantly improved with Biatain Ag[10].

Silver. A powerful weapon against microbes

Silver is a well-documented antimicrobial, that has been shown to kill bacteria, fungi and certain viruses. It is the positively charged silver ions (Ag^+) that possess the antimicrobial effect[21, 22]. Silver ions target microorganisms through several different modes of action. For example, silver ions are incorporated into the bacterial cell membranes and bind to membrane proteins responsible for transport of substances in and out of the bacterial cells (Figure 3). Silver ions are also transported into the cells and will block cell division by binding to the DNA. Furthermore, silver ions will block the bacterial respiratory system and thereby destroy the energy production of the cell. In the end, the bacterial cell membrane will burst, and the bacteria will be destroyed[5, 21].

1. Silver ions (Ag^+) bind to the bacterial cell wall blocking transport of substances in and out of the cell.



3. In the bacterial cell silver ions interact with DNA and inhibit bacterial cell division stopping replication.

2. Silver ions are transported into the bacterial cell where they block the respiratory system destroying energy production.

Figure 3: Effects of silver ions on bacteria.

Silver has a long history of use in wound care and the safety record of the modern silver-containing wound dressings has been excellent. Several mechanisms exist by which the body removes excess silver. These mechanisms include natural tissue turnover that occurs particularly in the epidermis, and the host metal detoxification mechanisms involving metallothioneins and glutathione occurring in the liver and kidney, where the silver is excreted ultimately in faeces and urine. While some permanent retention of silver from exposure to silver containing dressings cannot be ruled out, there is good biological basis to suggest that the retained silver will ultimately be in the forms of extremely stable silver selenide and silver sulphide complexes which are effectively not bioavailable. The conversion of silver to these stable forms can be considered as forms of detoxification, even though the silver is not physically eliminated from the body[21].

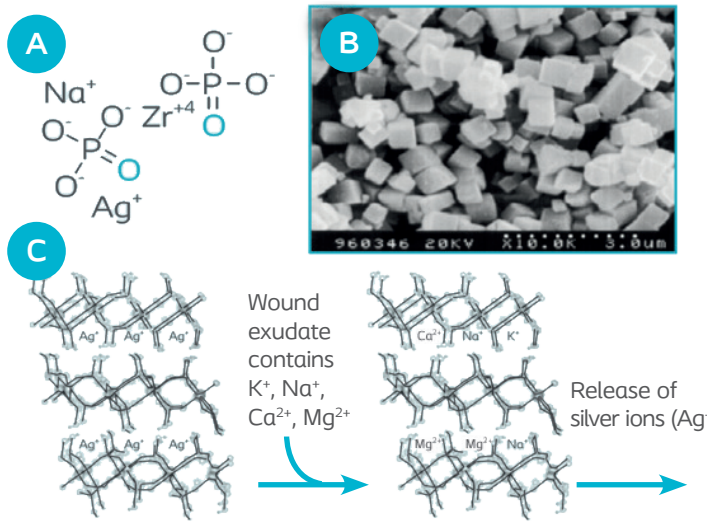
Due to the increasing focus on bacterial resistance to antibiotics, microbial resistance towards antiseptics is also a debated topic. Topical antiseptics, such as silver, differ from antibiotics as they have multiple sites of antimicrobial action on target cells (Figure 3) and therefore a low risk of bacterial resistance[5]. There is a lack of substantial evidence linking bacterial resistance to silver identified in simple laboratory studies to clinical settings. This suggests that while bacterial resistance to silver in wound care should be monitored, the threat of widespread resistance is low and silver-containing dressings remain an extremely important tool in managing wound infection[5, 23, 24].

Mechanisms of silver release

Silver ions can be obtained from various donor systems such as salts, chelated structures, ion exchange systems or even metallic silver. Although they all present the same antimicrobial silver ion, Ag^+, each of these donor mechanisms for silver ions have a unique activation mechanism and release profile[21]. The donor system may impact the amount of silver ions released and the rate of release, which in turn is significant for the antimicrobial effect. It is therefore important to select the right donor system and optimise the conditions for the system to obtain an optimal release profile for antimicrobial efficacy within the infected wound.

An *in vitro* experiment has illustrated the need for a sustained silver release exposing bacteria to a constant suppression during wear time to avoid regrowth[25]. A bacterial biofilm assay simulating wound bed conditions was used. A small volume of protein solution was added every day to imitate inactivation of silver by slough. Products with sustained silver release (high or low silver concentration) or no sustained release (high concentration) were compared. Products with high concentrations had the best eradication effect at day 1. However, if there was not a sustained release of silver, the bacteria re-colonised the wound bed at day 7, while products with sustained silver release (high and low) continued decreasing the bacterial load at day 7. This illustrates the need for a constant suppression of bacteria, by sustained release of silver, throughout the dressing wear time to avoid regrowth.

The sustained silver release system of Biatain® Silicone Ag and Biatain Ag is based on an ion-exchange system, where silver is bound to a zirconium phosphate crystal by ionic interaction with the ortho-phosphate groups in the zirconium phosphate molecule (Figure 4). The zirconium phosphate forms a sheet-like crystal with an average size of 1.3 µm wherein the silver binds in the grid structure at a loading concentration of approximately 10%.



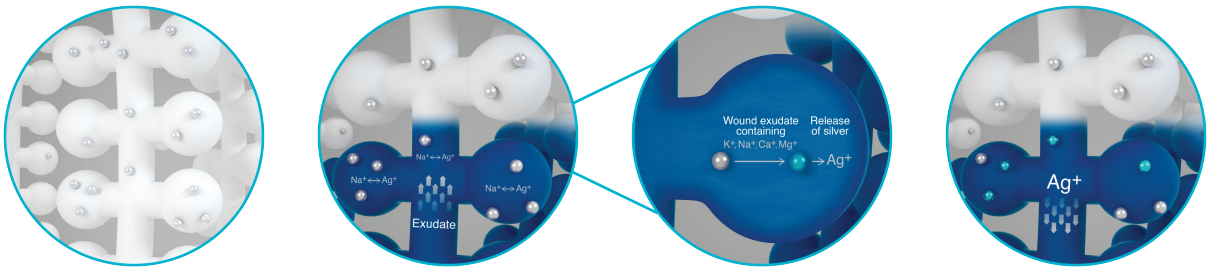
A. The zirconium phosphate molecule illustrating the ionic interaction between the ortho-phosphate and the silver ion.

B. Microscopic picture of the zirconium phosphate crystals.

C. The zirconium crystal structure with silver associated, ready for exchange with cations from the wound exudate.

Figure 4: *Illustration of the zirconium phosphate crystal and its mechanism of silver ion donation. Photo supplied courtesy of Milliken.*

The zirconium crystals are homogeneously incorporated into the foam during the foam manufacturing process as inert particles. The silver ion binds to the ortho-phosphate by ionic interactions and is only released when exchanged with other cations. Since the wound exudate has a high concentration of cations (K^+, Na^+, Ca^{2+}, Mg^{2+}), the exudate triggers the release of silver from Biatain® Silicone Ag and Biatain Ag. When Biatain Silicone Ag or Biatain Ag is placed on an exuding wound, the sustained silver release is carried out in response to the level of exudate (Figure 5).



Biatain Silicone Ag / Biatain Ag - silver impregnated foam.

Exudate absorbed into dressing.

Ion exchange and silver released.

Silver released which diffuses along a concentration gradient to the wound bed.

Figure 5: *Mechanism of silver ion release from Biatain Silicone Ag and Biatain Ag.*

Sustained release of silver

The release rate of silver ions varies between existing dressings on the market. Some dressings release the silver ions rapidly in either small or large amounts. Others, like Biatain® Silicone Ag and Biatain Ag, have a sustained release of silver ions over several days. *In vitro* release profiles from different silver dressings are shown in Figure 6. As described in the previous section, sustained release of silver ions ensures a constant, unfavourable environment for bacteria[25]. The sustained silver release profile of Biatain Silicone Ag and Biatain Ag is controlled by several factors, including the volume of exudate absorbed by the dressing, the rate of cation diffusion into the zirconium crystals, the silver exchange rate and the rate of silver diffusing out into the wound bed. Biatain Silicone Ag and Biatain Ag have sustained release of silver up to 7 days (Figure 6)[26].

The release of silver from a wound dressing can be investigated in a Franz cell setup where the wound dressing is mounted in a cup exposing a specified area of the wound contact side of the dressing to a continuous flow of imitated wound fluid. The silver ions will then be released into the fluid and the release rate can be determined by measuring the silver ion concentration in the fluid by atomic absorption spectroscopy. In a study published in 2015[26], Biatain Silicone Ag and Biatain Ag and other well-known silver dressings on the market were tested. Figure 6A shows release curves over 7 days. Biatain Silicone Ag and Biatain Ag showed a significantly greater, sustained release of silver over the 7-day period than any of the other dressings tested[26]. Figure 6B illustrates how Biatain Silicone Ag and Biatain Ag with their sustained silver release profiles had the highest accumulated silver release over 7 days[26].

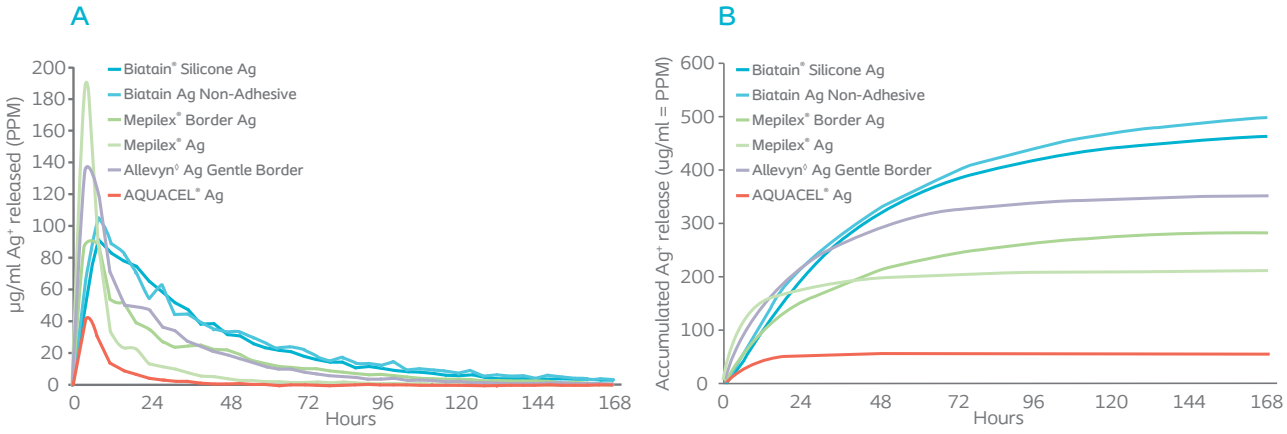


Figure 6: *Silver release profiles for Biatain Silicone Ag, Biatain Ag and other silver dressings.* ***A:*** *Release of silver, measured in 4-hour intervals for 7 days* ***B:*** *Accumulated release of silver over 7 days showing the total amount release from the dressing over time[26]. The Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) has previously been reported to be 12.5µg/ml for Staphylococcus aureus and 7.5µg/ml for Pseudomonas aeruginosa[32].*

The sustained release of silver by Biatain Silicone Ag and Biatain Ag is reflected in the results from a published *in vitro* study demonstrating antimicrobial efficacy against a wide range of pathogenic microorganisms commonly found in non-healing and infected wounds. The antimicrobial effect was continuous for the full 7-day test period[20].

Biofilms in wounds

Wound infection is defined by the presence of microorganisms in sufficient number or virulence to cause a host response locally and/or systemically[1]. Wound infection thus is a complex interplay between the infecting microorganism and the host immune response. Implementation of effective strategies to prevent, diagnose and manage wound infection, is important in reducing patient morbidity and mortality[1].

Recent studies indicate that biofilms can be found in 60-100% of non-healing wounds. Biofilms are known to cause infection, inflammation and delayed wound healing[4, 27]. The exact definition of a biofilm has been extensively debated within the scientific community for some time, but most scientists now agree that biofilms can be described as clusters of bacteria and fungi in a matrix, self-produced or of host origin[4]. Biofilms can be both surface attached and non-surface attached as for instance those found embedded in the wound environment.

Biofilms are microscopic structures that are currently only identified by specialised microscopy (CLSM, SEM) (Figure 7). These techniques are both time consuming and expensive, so diagnosis of biofilms in a non-healing wound currently relies solely on the common signs of wound infection[3].

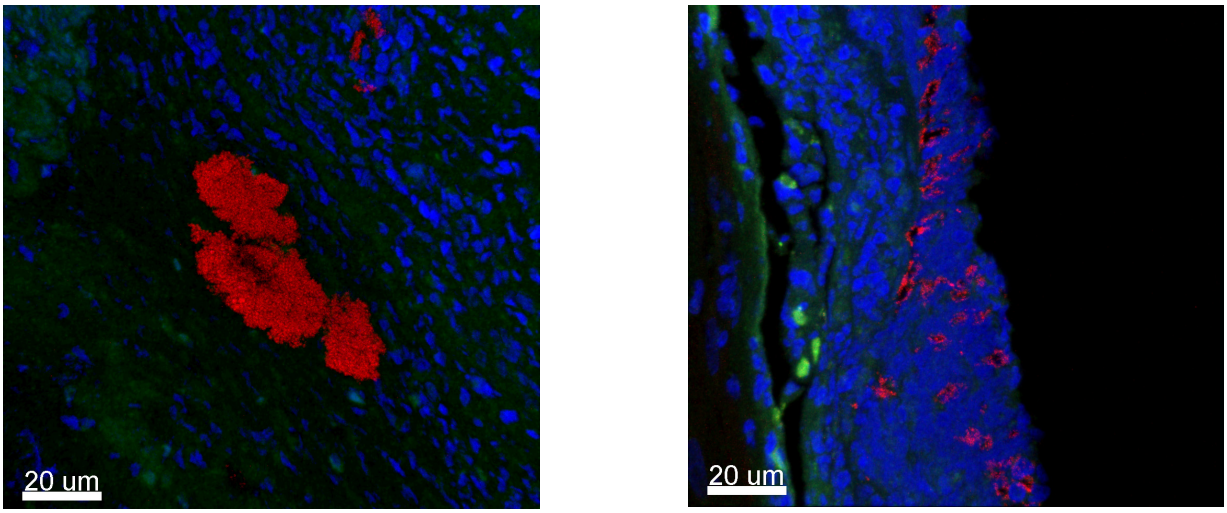


Figure 7. *Confocal laser scanning microscopy (CLSM) on biopsies from an infected porcine wound model (P. aeruginosa). Pig tissue (eukaryotic cells) is stained with DAPI (blue) and the microorganisms/ biofilms are stained with a specific PNA-FISH for bacteria only (red).*

Biofilms are characterised by increased tolerance towards antimicrobials, antibiotics and the host immune cells compared to planktonic microorganisms. Planktonic and biofilms are two different microbial growth forms, each with different characteristics and susceptibility towards treatment. Planktonic microorganisms are free-floating, single cells that are generally easier to kill with antibiotics and antimicrobials and for the immune cells[28, 29]. In the past, most knowledge of microorganisms and treatment strategies were based on studies of these planktonic microorganisms grown in laboratory flask cultures. Recent studies and knowledge of the presence and importance of biofilms in non-healing wounds require the implementation of biofilm strategies into antimicrobial product development and evaluation.

Key evidence

Biatain® Silicone Ag
Biatain® Ag

In vitro evaluation of Biatain® Silicone Ag and Biatain® Ag against biofilms and a broad range of microorganism

Christiansen C, Huniche GB, Allesen-Holm M. EWMA; 2018[20]

Introduction

Clinically, implementation of biofilm based wound management has recently gained increasing attention[4] and ideally, evaluation of antimicrobial wound dressings should include biofilm models as well as standard antimicrobial tests.

Biatain Silicone Ag and Biatain Ag were tested in two different *in vitro* test methods, a wound biofilm model and a standard antimicrobial test over time. As biofilms in non-healing wounds are heterogeneously distributed in the wound, including in the tissue below the wound bed[3], Biatain Silicone Ag and Biatain Ag were evaluated in an *in vitro* wound biofilm model that specifically addresses the problematic biofilms heterogeneously embedded in the wound environment. The study was published at EWMA 2018[20].

Wound biofilm model

The aim of this test was to evaluate the efficacy of Biatain Silicone Ag and Biatain Ag against mature biofilms and in the prevention of biofilm formation in a biofilm model simulating biofilms embedded in the wound environment.

Methods

The *in vitro* wound biofilm model (WBM) is based on a study by S. Crone et al. and was developed at Costerton Biofilm Center, University of Copenhagen[30]. The model consists of biofilm aggregates (either *P. aeruginosa* or *S. aureus*) embedded and grown in semi-solid agar. *S. aureus* and *P. aeruginosa* are both keen biofilm formers and will form mature biofilms within 24 hours *in vitro*. The microorganisms were inoculated into the semi-solid agar containing nutrients and either grown to mature biofilms for 24 hours or treated shortly after inoculation to demonstrate biofilm prevention. In both test setups, the microorganisms/biofilms were subsequently exposed for 24 hours to samples of Biatain Silicone Ag, Biatain Ag or control dressings without silver (Figure 8).

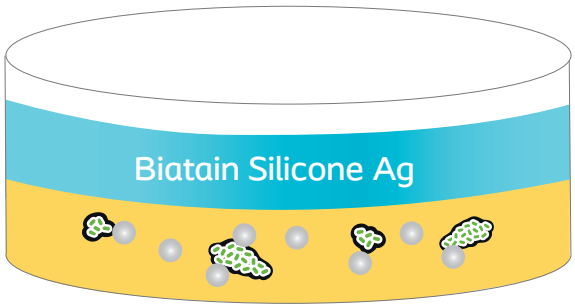


Figure 8. *Model drawing of the WBM illustrating biofilms embedded in the agar. The figure illustrates one well in a 48-well microtiter plate. In the well is the semi-solid agar (yellow), the biofilms as independent aggregates (green), Biatain Silicone Ag or Biatain Ag (blue) and the released silver ions (grey).*

Results

Both Biatain® Silicone Ag and Biatain Ag showed statistically significant effect against mature biofilms of *S. aureus* and *P. aeruginosa*, compared to control dressings without silver (Figure 9A & B). Both test dressings reduced mature *P. aeruginosa* biofilms by more than 99.99% and mature *S. aureus* biofilms by 99.3% (Biatain Silicone Ag) and 99.93% (Biatain Ag), ($p<0.001$ vs. control for all, Students T-test). The variation in results between different bacterial strains is expected and caused by the differences in susceptibility of microorganisms to silver.

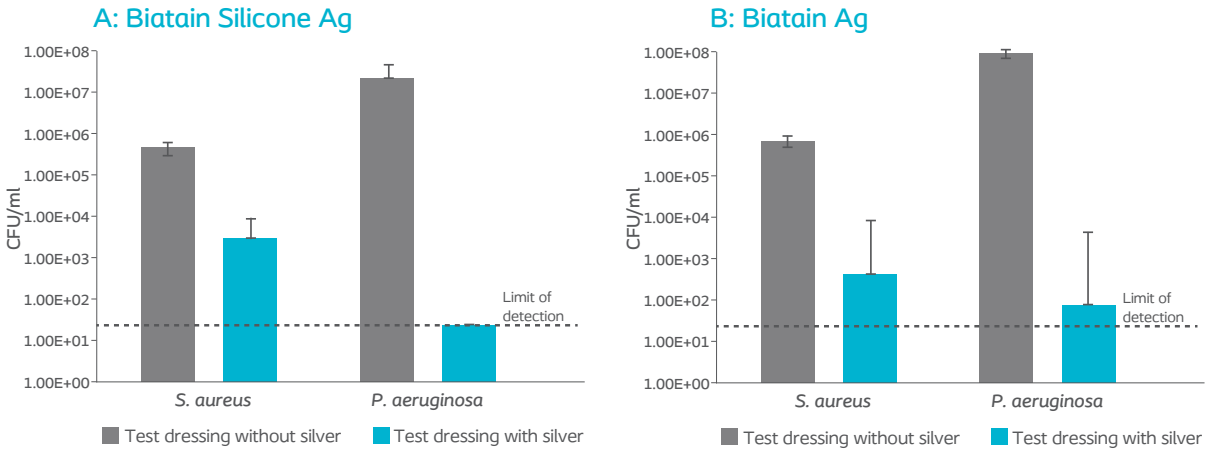


Figure 9. Killing of mature biofilms tested in the WBM. The results are shown as geometrical mean of CFU/ml ± standard deviation (SD). N=20 samples. The horizontal line represents limit of detection at 25 CFU/ml (CFU=Colony Forming Unit).

Biatain Silicone Ag and Biatain Ag equally prevented growth of biofilms of *S. aureus* and *P. aeruginosa* ($p<0.001$ vs. control for all, Students T-test) to the limit of detection which was set to 25 CFU/ml (Figure 10A & B).

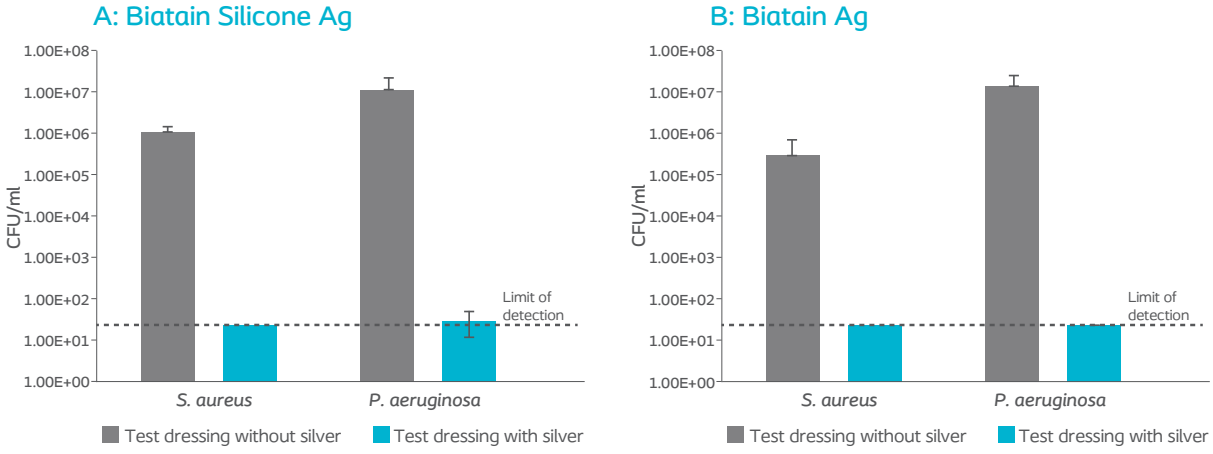


Figure 10. Prevention of biofilm formation tested in the WBM. The results are shown as geometrical mean of CFU/ml ± SD. N=20 samples. The horizontal line represents limit of detection at 25 CFU/ml.

Discussion

Biatain® Silicone Ag and Biatain Ag were effective against mature biofilms and in prevention of biofilm formation. Both treatment of mature biofilms and prevention of biofilm formation are essential strategies in the framework for the treatment of wounds with biofilms[4]. The differences in the efficacy against mature *S. aureus* and *P. aeruginosa* biofilms were expected and most likely caused by differences in susceptibility of the two microorganisms to silver. A generally accepted explanation to this, is the structural differences in the cell walls of Gram-positive and Gram-negative bacteria. Gram-positive bacteria such as *S. aureus* have thicker cell walls that are more difficult for silver ions to penetrate[31, 32]. Additionally, microbiological variation also cause some variation in test results, e.g. as the difference seen for *S. aureus* and the two tested products.

Standard antimicrobial testing over 7 days

The "Standard test method for determining the antimicrobial activity of antimicrobial agents under dynamic contact conditions", ASTM E2149-13a[33], enables a simple, standard evaluation of antimicrobial wound dressings against a wide range of pathogenic microorganisms normally found in non-healing wounds at time points representing relevant wear times.

Method description

Tests of Biatain Silicone Ag and Biatain Ag were performed over a 7-day period. Dressing samples were submerged in separate Erlenmeyer flasks containing a microbial monoculture with a starting concentration of 10^5-10^6 CFU/ml. The samples were incubated for 24 hours and then moved to new flasks, every day for 7 days. This challenges the samples as it is repeatedly exposed to excessive liquid containing high concentration of microorganisms (Figure 11).

Figure 11. *Illustration of the E2149-13a test methods. The dressing samples were exposed to fresh microorganisms every 24 hours for 7 days.*

Samples were taken from the flasks at day 1 and 7, and the number of surviving microorganisms, CFU/ml, were quantified by standard microbial cultivation techniques. Log reduction in CFU/ml was calculated as the difference from the start inoculum to the samples taken after incubation. The antimicrobial activity was evaluated based on the log reduction results. The current log reduction requirements for antimicrobial wound dressings is defined as a log 3 reduction compared with the start concentration of microorganisms (prEN16756)[34].

Six microorganisms were tested in the model, representing some of the most prevalent and pathogenic microorganisms found in infected wounds[35-37], including antibiotic resistant bacteria, and broadly covering the microbial differences between Gram-positive bacteria, Gram-negative bacteria and fungi:

- *Staphylococcus aureus* (Gram-positive bacteria)
- *Pseudomonas aeruginosa* (Gram-negative bacteria)
- Methicillin-resistant *Staphylococcus aureus* (MRSA) (Gram-positive bacteria)
- Vancomycin-resistant Enterococci (VRE) (Gram-positive bacteria)
- *Candida albicans* (yeast)
- *Aspergillus brasiliensis* (mold)

Results

Both dressings reduced all six tested microorganisms, including the antibiotic resistant strains, by more than log 3. The antimicrobial activity was similar on day 1 and 7 (Figure 12A & B) indicating a sustained and effective release of silver up to 7 days. The variation in results between different microorganisms is expected and caused by the differences in susceptibility of microorganisms to silver and general microbiological variation.

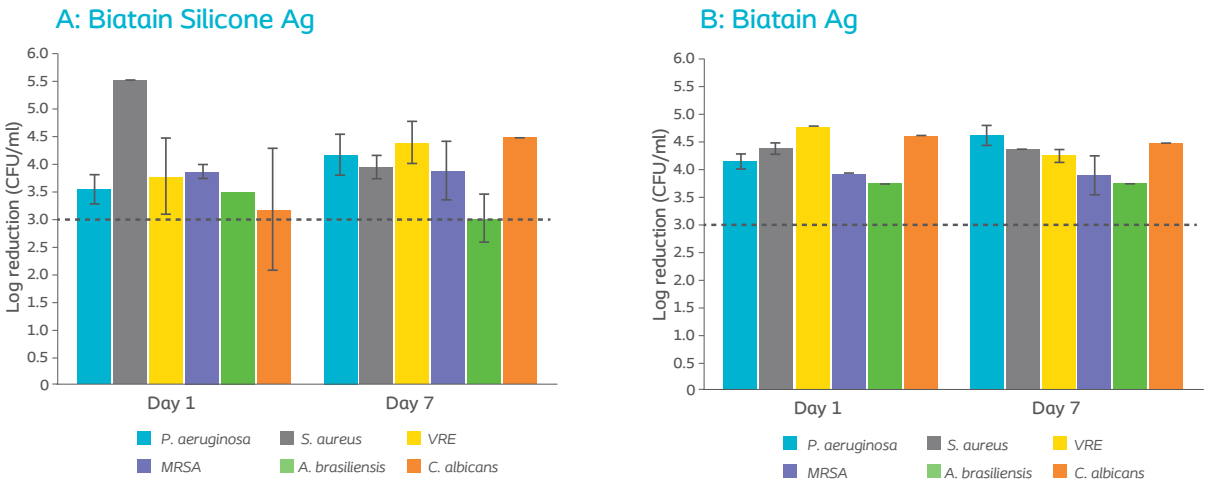


Figure 12. Antimicrobial efficacy tested according to ASTM E2149-13a against a broad range of microorganisms. The results are shown as mean log reduction ± SD. N=3 samples. Log reduction was calculated based on start inoculum. All log reductions were ≥ log 3.

Discussion

The ASTM E2149-13a test provides information about antimicrobial efficacy of a wound dressing against a broad range of planktonic microorganisms over time. The antimicrobial efficacy of both Biatain® Silicone Ag and Biatain Ag was sustained for 7 days with the daily challenge of new freshly cultured microorganisms.

The test represents a worst-case scenario. In non-healing wounds, new microorganisms would not be supplied every day and the amount of released silver would accumulate in the wound bed, resulting in a higher concentration of silver over time and a potentially greater antimicrobial effect than in the *in vitro* situation. On the other hand, this standard test does not consider the presence and complexity of microbial biofilms and only provides information about the basic antimicrobial activity. Therefore, the test results should not be the sole basis for an antimicrobial product evaluation.

Conclusion on *in vitro* tests

Biatain Silicone Ag and Biatain Ag dressings are modern wound dressings containing the antimicrobial agent silver with an intended use for infected wounds and wounds at risk of infection. Biatain Silicone Ag and Biatain Ag demonstrated antimicrobial efficacy against a wide range of pathogenic micro-organisms commonly found in non-healing and infected wounds. The antimicrobial effect was continuous for 7 days with daily challenge of freshly cultured microorganisms. Biatain Silicone Ag and Biatain Ag also demonstrated statistically significant efficacy against mature biofilms of both *S. aureus* and *P. aeruginosa*, and in prevention of biofilm formation in an embedded wound biofilm model. Both treatment of mature biofilms and prevention of biofilm formation are essential strategies in the framework for the treatment of wound infection[4].

Comparison of 24-hour fluid handling and absorption under pressure between four wound dressings with Ag and silicone adhesive

Andersen MB. EWMA; 2016[41]

Introduction

One of the most important performance parameters of a modern wound dressing is the effective management of exudate[38]. A dressing must be able to rapidly remove excess exudate from the wound bed and periwound skin while maintaining a moist wound bed[19]. This will reduce exudate related problems such as periwound skin damage and infection and reduce time to healing[39, 40]. Therefore, evaluation of fluid handling parameters is crucial for the performance of wound dressings. As dressings are commonly used under compression therapy, evaluation of fluid handling capacity, with as well as without compression, is relevant. The next section presents an *in vitro* investigation of fluid handling parameters published at EWMA 2016[41].

Aim

The aim of this study was to compare 24-hour fluid handling as well as absorption under pressure of Biatain® Silicone Ag with three other silver foam dressings with silicone adhesive (Mepilex® Border Ag, Allevyn® Gentle Border Ag and AQUACEL® Ag Foam).

Methods

All tests were performed by an independent laboratory (DB Lab, Denmark). The four Ag dressings with silicone adhesive were tested for 24-hour fluid handling capacity, according to the method described in EN 13726-1; Test methods for primary wounds dressings – Part 1: Aspects of absorbency, section 3.3. Ten samples of each dressing were tested. The dressing samples were mounted in Paddington cups that were weighed before and after addition of 20 ml Solution A. The cups were placed in a climate controlled cabinet (temperature: 37±1°C, relative humidity: 15±5%) for 24 hours. Hereafter the dressings were removed from the cabinet and weighed to register permeability. The leftover fluid was removed from the cups, which were subsequently weighed to register absorption. Total fluid handling was measured by adding absorption and permeability. For test of absorption under pressure, 10 samples of each dressing (Ø = 30 mm) were weighed and placed on ceramic filter plates in Petri dishes and pressed down to the clinical conditions of 40 mmHg. 45 ml Solution A was added without direct contact with the foam. After 90 minutes the remaining liquid was removed and the wet samples were weighed to register absorption under pressure. Comparison of means were performed using a Dunnett's comparison of means with control (JMP10, SAS Institute).

Results

Biatain Silicone Ag had significantly higher 24-hour absorption (0.53 g/cm^2) than Allevyn Gentle Border Ag and AQUACEL Ag Foam ($p<0.001$), while Mepilex Border Ag had the highest absorption value (0.63 g/cm^2, $p<0.0001$). Biatain Silicone Ag had significantly higher 24-hour permeability (0.72 g/cm^2) than all three comparators ($p<0.0001$ for all). Likewise, Biatain Silicone Ag had significantly higher total fluid handling capacity (1.24 g/cm^2) than all three comparators ($p<0.0001$ for all) (Figure 13A). Finally, Biatain Silicone Ag had significantly higher absorption under pressure (0.56 g/cm^2) than Allevyn Gentle Border Ag and AQUACEL Ag Foam ($p<0.0001$ for both) while Mepilex Border Ag had similar absorption under pressure as Biatain Silicone Ag (Figure 13B).

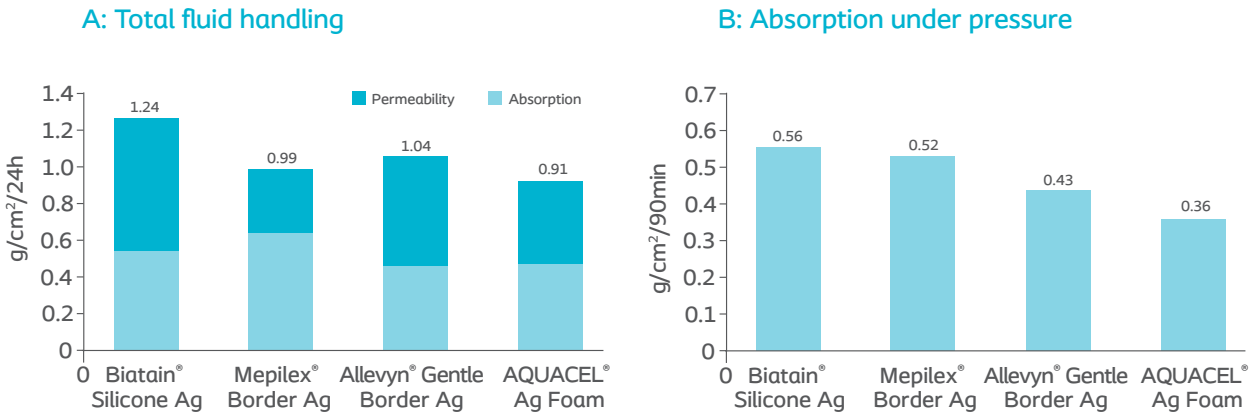


Figure 13. A. Total fluid handling (consisting of Permeability and Absorption) and B. Absorption under pressure of four foam dressings with silver.

Conclusion

In this *in vitro* study Biatain Silicone Ag showed excellent results on fluid handling capacity, with statistically significant higher 24-hour total fluid handling capacity and permeability in comparison with the three comparator dressings. In addition, Biatain Silicone Ag showed statistically significant higher 24-hour absorption as well as absorption under pressure than Allevyn Gentle Border Ag and AQUACEL Ag Foam.

Fluid handling parameters are crucial for the performance of modern wound dressings. As these are commonly used under compression therapy, evaluation of fluid handling capacity with as well as without compression is relevant. In this study, Biatain Silicone Ag demonstrated a high performance on all fluid handling parameters, including absorption under pressure.

Clinical and microbiological effectiveness of a dressing with ionic silver complex and silicone adhesive (Biatain® Silicone Ag)

Lázaro-Martínez JL, Álvaro-Afonso FJ, García-Álvarez Y et al. EWMA; 2018[14]

Introduction

A new clinical study on Biatain Silicone Ag was presented at EWMA 2018[14]. The study is unique because it evaluates both bioburden and clinical parameters. The results show reduction in bioburden as well as improvement in clinical parameters.

Aim

To evaluate the clinical and microbiological effects of Biatain Silicone Ag in diabetic foot ulcers with mild infection.

Design

This was a prospective case series of 16 outpatients with diabetic foot ulcers with mild infection according to IDSA guideline and the European Wound Management Association. Patients with critical limb ischemia were excluded. Patients did not receive systemic antibiotic treatment. Soft tissue punch biopsies (2mm) were taken weeks 0, 3 and 6 during a 6-week treatment period. Wound bed tissue was evaluated for presence, quality and consistency of granulation tissue using the Wollina Wound Score (Table 1).
Bota Optima Diab® were used for offloading.

Wound Quality	Finding	Score Points
Granulation	Absent	0
	¼ of ulcer area	1
	½ of ulcer area	2
	¾ ulcer area	3
	Complete	4
Color	Pale	0
	Pink	1
	Bright red	2
Consistency	Spongy	0
	Solid	1
Maximum total score		**7**

Table 1. Wollina Wound Score.

Results

Fifteen patients completed the 6-week treatment period. Six ulcers healed, one patient discontinued treatment due to an adverse event (not device related). According to the Texas classification, 11 ulcers (68.7%) were type IIB and 5 ulcers (31.3%) were type IID with mean wound duration of 18.6±21.7 weeks. The Wollina score improved from 3.5±1.90 to 5.9±1.40 (p=0.0039) in 6 weeks and the bacterial load decreased from 5.49 to 3.71 Log CFU/ml (p=0.004).

Conclusion

The use of Biatain Silicone Ag markedly improved the clinical and microbiological parameters in this case series of patients with diabetic foot ulcer with mild infection.

Case 1 from the study

The patient was an 80-year-old man with type 2 diabetes mellitus for 20 years, current smoker, hypertension and dyslipidaemia.

Neurological examination was undertaken using Semmes-Weinstein (SWM) 5.07/10-g monofilament and Horwell's Biothesiometer. The patient could not feel SWM 5.07/10-g in 6 sites of the left foot. No vibratory sensation was felt during the examination of both feet. Doppler examination was carried out revealing an ankle/brachial index (ABI) of 1.27 in the left foot. Both distal pulses were present. Texas Classification was IIB. The wound was located at the first metatarsal head (plantar) on the left foot and infected with *S. aureus* and *Corynebacterium*. Duration of the wound was 8 weeks prior to treatment with Biatain® Silicone Ag.

Wound size:
1.68 cm^2

Bacterial load:
19,500 (4.29 log(CFU/ml))

Wound bed: Increased exudate, delayed healing, friable granulation tissue, pocketing

Wound edge: Undermined

Periwound skin: Hyperkeratosis

Figure 14 shows the progress of the wound over the 6 weeks of treatment with Biatain Silicone Ag. The wound healed completely in 6 weeks and the bacterial load decreased from 19,500 CFU/ml to 20 CFU/ml.

Week 0

Bacterial load:
19,500 CFU/ml
Wound at inclusion: 1.68 cm^2

Week 3

Bacterial load:
280 CFU/ml
Week 3: 0.14 cm^2

Week 6

Bacterial load:
20 CFU/ml
Week 6: Complete healing

Figure 14. *Wound at week 0, week 3 and week 6.*

The use of Biatain® Ag in hard-to-heal venous leg ulcers: Meta-analysis of randomised controlled trials

Leaper D, Münter C, Meaume S et al. PLOS ONE. 2013;8(7):e67083[15]

Introduction

Biatain Ag has been on the market for more than 15 years and has been investigated in a number of clinical studies. These studies have consistently shown positive results in non-healing wounds with signs of infection, e.g. in diabetic foot ulcers[10, 12], venous and mixed leg ulcers[10, 11, 13, 42, 43], pressure ulcers[10, 42] and traumatic wounds[10, 42].

This is a meta-analysis of four published RCTs of Biatain Ag vs. non-active foams and other non-active moist wound healing dressings for the treatment of pure and mixed venous leg ulcers with clinical signs of infection and/or delayed healing[10, 11, 13, 43]. The meta-analysis provides statistical significant evidence to support the use of Biatain Ag for treatment of venous leg ulcers, showing faster healing compared with non-active foams and other non-active moist wound healing dressings. 685 patients were included in the analysis and data evaluated at 4 weeks after the start of treatment.

Results

The mean age within the four studies was 72.8 years and the average ulcer area in three of the four studies were in the range of 10–15 cm^2, whereas it was 38 cm^2 in the fourth study.

Relative reduction in ulcer area

Biatain Ag showed 17% greater relative reduction of ulcer area at week 4 compared to the non-active comparators (43.5% vs. 26.3%, $p<0.0001$).

The treatment effects of Biatain Ag versus the comparator were estimated by least square means and the results are visualised in a forest plot (Figure 15).

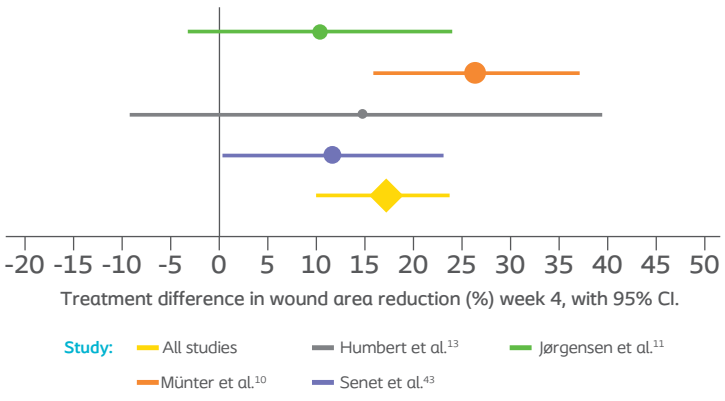


Figure 15. *Forest plot showing the estimated treatment differences defined by percentage relative reduction. The vertical line represents a treatment difference of zero. The confidence intervals (95%) are illustrated by the length of the horizontal lines. The sizes of the filled circles are adjusted to the size of the corresponding study. The result is statistically significant in favour to the treatment with Biatain Ag.*

Proportion of responders

If the ulcer area is reduced by at least 40% after 4 weeks it is indicative of a favourable healing prognosis[44]. In the meta-analysis, patients with a relative reduction in ulcer area >40% were termed 'responders' and the 'responder rate' was evaluated for each study separately and for the compiled dataset.

The proportion of responders was 52% in the Biatain® Ag group and 37% in the comparator group with a significant treatment effect in favour of Biatain Ag ($p<0.001$).

Complete healing

Complete healing was defined as the proportion of subjects with a healed ulcer at 4 weeks. Twice as many wounds healed during 4 weeks when treated with Biatain Ag (12%) compared with the comparator group (6%; $p<0.002$).

Conclusion

This meta-analysis of four published RCTs of Biatain Ag vs. non-active foams and other non-active moist wound healing dressings provides statistically significant evidence to support the use of Biatain Ag as an antibacterial dressing in the treatment of hard to heal venous leg ulcers.

This conclusion is supported by a recent Cochrane review[9], where a subgroup analysis of silver dressings vs. foam comparators shows a statistically significant benefit for silver dressings for treating venous leg ulcers. All studies included in this subgroup analysis were studies of Biatain Ag.

Cost-effective use of silver dressings for the treatment of hard-to-heal chronic venous leg ulcers

Jemec GB, Kerihuel JC, Ousey K et al. PLOS ONE. 2014;9(6):e100582[16]

Introduction

Chronic venous ulceration affects 1–3% of the adult population and typically has a protracted course of healing, resulting in considerable costs to the health care system. The pathogenesis of venous leg ulcers includes excessive and prolonged inflammation which is often related to critical colonisation and early infection. Here is presented an analysis of the cost-effectiveness of Biatain® Ag using a health economic model based on time-to-wound-healing in hard-to-heal chronic venous leg ulcers[16].

Methods

A decision tree was constructed to evaluate the cost-effectiveness of treatment with silver dressings compared with non-silver dressings for four weeks in a primary care setting. The outcomes: 'Healed ulcer', 'Healing ulcer' or 'No improvement' were developed, reflecting the relative reduction in ulcer area from baseline to four weeks of treatment. If ulcers did not improve during the four-week period, the patients were assumed to be referred to specialist care (Figure 16). To estimate the cost of wound management, data was sourced from the clinical trial data in the published meta-analysis of four RCTs on Biatain Ag, described in the previous section[15].

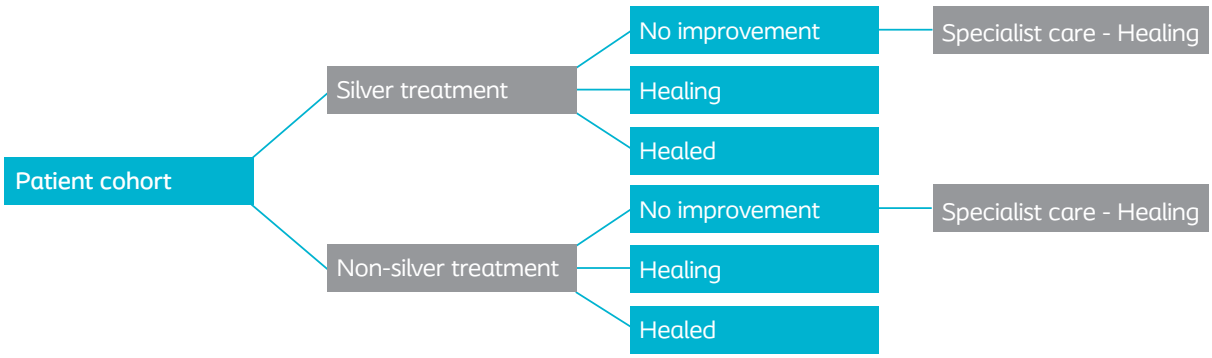


Figure 16. *Framework for health economic model. The patient cohort consisted of 659 hard-to-heal venous leg ulcers.*

Clinical outcomes

As shown in Table 2, a higher proportion of ulcers treated with the silver dressing healed during the four-week period compared with ulcers treated with non-silver dressings (7.6% compared with 3.4%). The proportion of healing ulcers was also higher in the group treated with silver dressings compared with non-silver dressings (79.4% compared with 72.1%). A lower proportion of patients treated with silver dressings had no improvement in ulcer area during the four weeks than patients treated with non-silver dressings (13.0% compared with 24.5%).

		Response classification (%)			Additional weeks to healed ulcer*			Cost per patient (£)**
	N	Healed ulcer†	Healing ulcer†	No improve-ment†	N	Average	Median	
Group								
Silver	369	7.6	79.4	13.0	293	10.1	4.9	1,326.57
Non-silver	290	3.4	72.1	24.5	209	12.8	6.4	1,468.14
Incremental cost								-141.57

Table 2. Patient outcome after four weeks of treatment with Biatain® Ag compared with non-silver dressings in pooled data set from four clinical trials.
**Applies to 'Healing ulcer' only. Number of weeks after week 4. Estimates truncated at 1 year.*
*†Data from Leaper et al. 2016[15]. **Estimated from model.*

Economic results

The economic evaluation of four weeks of silver treatment in primary care compared with non-silver treatment estimated the group treated with silver to be more expensive (£623.52) than non-silver treatment (£533.60). However, a higher proportion of patients treated with silver had ulcers with complete healing or healing ulcers, and therefore the estimated average time-to-healed ulcer was lower (13.8 weeks) compared with non-silver treatment (16.7 weeks). Hence, the average total treatment cost per patient was lower for the silver dressing (£1,326.57) compared with non-silver treatment (£1468.14) with a total cost saving of £141.57 (Table 2).

Conclusion

Based on a health economic model, where clinical data was sourced from a published meta-analysis, it was shown that when patients with hard-to-heal venous leg ulcers are allocated to an initial four-week treatment using silver dressings there can be associated cost savings (£141.57) compared with patients who are treated with non-silver dressings. In addition, patients treated with silver dressings had wound closure approximately 3 weeks before. Thus, the use of silver dressings improves healing time and can lead to overall cost-savings. These results can be used to guide health care decision makers in evaluating the economic aspects of treatment with silver dressings in hard-to-heal chronic venous leg ulcers.

Summary

Wound infection is one of the key challenges in managing non-healing wounds. As infected wounds are often highly exuding, may emit an unpleasant odour and can be very painful, the quality of life for patients can be heavily impacted. Also, treatment time, cost increase and wound management practices become more resource demanding. With proper diagnosis and early intervention many problems can be avoided, and clinical outcomes improved.

Effective treatment of infected acute and chronic wounds involves cleansing and debridement and requires certain properties from applied dressings, including effective antimicrobial performance. Biatain® Silicone Ag and Biatain Ag, with 3DFit Technology, conform to the wound bed to reduce exudate pooling, absorb exudate vertically and deliver silver at the wound bed. Exudate is locked away and retained even under compression, reducing the risk of maceration and spreading of infection to the wound edges and periwound skin. Silver is a well-documented antimicrobial, that has been shown to kill bacteria, fungi and certain viruses and silver dressings are widely used as topical antimicrobials to manage wound infection. Biatain Silicone Ag and Biatain Ag have a sustained silver release system, based on ion-exchange, that secures delivery of antibacterial silver ions in response to uptake of exudate during the entire wear time of the dressings[26].

There is increasing evidence that biofilms are present in most, if not all, chronic non-healing wounds[3]. As biofilms can cause infection, inflammation and delayed wound healing[4, 27], implementation of biofilm based wound management has gained increasing attention. Ideally, evaluation of antimicrobial wound dressings should include biofilm models as well as standard antimicrobial tests. Biatain Silicone Ag and Biatain Ag have been tested in two different *in vitro* test methods, a wound biofilm model and a standard antimicrobial test over time[20]. As biofilms in non-healing wounds are heterogeneously distributed, including in the tissue below the wound bed[3], Biatain Silicone Ag and Biatain Ag were evaluated in an *in vitro* wound biofilm model that specifically addresses the problematic biofilms heterogeneously embedded in the wound environment[20]. The dressings were effective against mature biofilms as well as for prevention of biofilm formation; both treatment of mature biofilms and prevention of biofilm formation are essential strategies in the framework for the treatment of wounds with biofilms. Furthermore, in a standard test against a broad range of planktonic microorganisms over time, the antimicrobial efficacy of both Biatain Silicone Ag and Biatain Ag was sustained for at least 7 days with the daily challenge of new freshly cultured microorganisms.

Clinical studies on Biatain Silicone Ag and Biatain Ag have consistently shown positive clinical results in non-healing wounds with signs of infection[10-14]. A meta-analysis of four RCTs of Biatain Ag vs. non-active foams provides statistically significant evidence to support the use of Biatain Ag as an antibacterial dressing in the treatment of hard to heal venous leg ulcers[15]. A subsequent health economic analysis, based on a published meta-analysis of four RCTs on Biatain Ag, has provided evidence that the use of silver dressings improves healing time and can lead to significant overall cost-savings[16].

In conclusion, *in vitro* evidence on efficacy against biofilms and planktonic bacteria along with a significant amount of clinical evidence support the use Biatain Silicone Ag and Biatain Ag for the treatment of non-healing wounds with signs of infection and biofilms.

We hope that you have enjoyed reading this monograph and will find it useful in your daily clinical practice.

Together, we are united by a shared purpose and passion to achieve ***fewer days with wounds.***

www.coloplast.com/products/wound/biatain-silicone-ag/

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Biatain® Ag portfolio. Combat infection and biofilms where it matters

Biatain Silicone Ag

	Item no.	Size in cm	Foam size	Pcs.
	39636	7.5 x 7.5	4.5 x 4.5	5
	39637	10 x 10	6.5 x 6.5	5
	39638	12.5 x 12.5	8.5 x 8.5	5
	39639	15 x 15	10.5 x 10.5	5
	39640	17.5 x 17.5	13 x 13	5
NEW	39644	10 x 20	5.5 x 15.5	5
NEW	39645	10 x 30	5.5 x 25.5	5

Biatain Silicone Ag Sacral

	Item no.	Size in cm	Foam size	Pcs.
NEW	39650	15 x 19	10.9 x 14	5
NEW	39651	25 x 25	17 x 17.2	5

Biatain Silicone Ag Heel

	Item no.	Size in cm	Foam size	Pcs.
NEW	39652	18 x 18	14 x 13.2	5

Biatain Ag Non-Adhesive

Item no.	Size in cm	Pcs.
5105	5 x 7	5
9622	10 x 10	5
9623	10 x 20	5
9625	15 x 15	5
9626	20 x 20	5
9628	5 x 8 Cavity	5

Biatain Ag Adhesive

Item no.	Size in cm	Pcs.
9631	7.5 x 7.5	5
9632	12.5 x 12.5	5
3464	15 x 25	5
9635	18 x 18	5
9641	23 x 23 Sacral	5
9643	19 x 20 Heel	5

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Coloplast

Coloplast develops products and services that make life easier for people with very personal and private medical conditions. Working closely with the people who use our products, we create solutions that are sensitive to their special needs. We call this intimate healthcare. Our business includes Ostomy Care, Continence Care, Wound and Skin Care and Urology Care. We operate globally and employ about 11,000 employees.

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