medinsight
DECISIONS IN HEALTH CARE

March | 13

0.1% Polihexanide + 0.1% Betaine (Prontosan® Solution) for Cleaning and Irrigation of Chronic Wound Beds - Literature Review & Economic Evaluation

Client: B.Braun

Version: March 20th , 2013

Contents

Executive Summary

Technology: Prontosan®

Request for incorporation in cleaning, decontamination and humidification of chronic wounds.

Characterization of technology: Prontosan® is a solution to irrigate wounds made of purified water (99.8%), undecylaminopropyl betaine (0.1%) and polihexanide (0.1%). Polihexanide has a broad spectrum of action against bacteria, viruses and fungi. Betaine is a surfactant which acts by reducing the surface tension between the biofilm and the wound bed and then repeling wounds debris leading them to float in the irrigating fluid to be removed through the cleaning process.

Question: Is the use of the polihexanide 0.1% + 0.1% betaine solution efficient, safe and cost-effective for the cleaning, decontaminating and humidificating of chronic wounds beds by improving outcomes associated when compared to both saline 0.9% and Ringer's solutions?

Search and analysis of scientific evidence: Searches were conducted using references in PubMed/MEDLINE, EMBASE and Cochrane Library electronic medical literature databases. Furthermore, searches using Google search engine and Internet search manuals in session references of selected articles were also performed. As a result, 14 references were included in the literature review.

Summary of the results from selected studies:

Although various treatment guidelines of chronic wounds such as GENAUPP Spanish group suggest the use of saline as the best alternative for the preparation of the wound bed, recent evidence has shown that the combination of betaine and polihexanide (Prontosan®) is more capable of penetrating wounds hard to remove debris, bacteria and biofilm from the lesions. Furthermore, the use of polihexanide and betaine is simpler and does not require complicated technical procedures like those required for potable water and saline, for example.

Back in 2004, Möller and colleagues conducted a retrospective study that evaluated the treatment of 953 patients (62% with diabetic foot). The effects of cleaning wounds using the irrigation solution containing a combination of betaine and polihexanide (Prontosan® solution) and the removal of non-vital tissue promoted by Prontosan® gel were evaluated. The infection rate fell from 40% to 3% and 80% of the wounds healed. The large number of patients in this study provides relevance to the research, since real-world data are important to assess efficacy and safety of a product outside of the strict control of prospective controlled trials. Retrospective studies have the strong power to gather large numbers of patients and sometimes represent real-life situations in a best way. From a therapeutic standpoint, randomized controlled trials and observational studies complement the training of medical knowledge based on evidence.

In 2006, Horrocks's observational study showed that the use of Prontosan® is a suitable alternative for the management of patients with chronic wounds (e.g., chronic venous ulcers and pressure ulcers) with over a year of evolution. Additionally, Adriessen and colleagues (2008) showed that after six months of treatment, 97% of patients with chronic venous ulcers treated with Prontosan® had their wounds completely healed compared to 89% of patients treated with saline or Ringer's, with significant difference in efficacy between the two treatment groups ($p < 0.0001$). Furthermore, the mean time to healing was significantly lower in the group treated with Prontosan® (3.31 months) than in the group treated with saline or Ringer (4.42 months), $p < 0.0001$. Thus, the irrigation of wounds with Prontosan® was effective and safe, preventing secondary infections and reducing complications, thereby shorten total lenght of treatment.

More recently, in 2010, Romanelli et. al. showed an improvement in the surface of wounds in patients treated with Prontosan®, associated with the decrease in the pH values measured in the wounds bed, which decreased significantly ($p < 0.05$) from 8.9 in the beginning of treatment to 7.0 after four weeks of treatment. The acidification of the pH values in the wound bed is considered a surrogate marker of clinical improvement, thus confirming the beneficial effects of the association of polihexanide and betaine.

In 2011, Santos and da Silva showed through a systematic literature review that the association of polihexanide and betaine is effective in treating colonized/infected wounds, verifying significant reduction in the time of healing, inflammatory signs of infection/colonization and pain upon its use.

Additionally, the editorial written by Roth and Brill in 2010, published in the prestigious journal *Skin Pharmacology and Physiology* provides information about more than 10 000 patients that received prophylactic or curative treatment for chronic wounds for over 20 years and confirms the high degree of efficacy and minimal adverse effects rates of polihexanide. In addition to the reduced rates of infection compared to povidone iodine and hydrogen peroxide, this huge clinical experience also shows the excellent tolerability of polihexanide. The tolerance to polihexanide use is excellent, even in patients with painful sores, which can positively influence their recovery process. All evidence evaluated in this report allow us to conclude that the use of polihexanide associated with betaine gives a safe practice in treating colonized/infected wounds. The irrigation of wounds with Prontosan® solution was effective and safe even when used continuously and in long term, preventing secondary infections, reducing complications and thereby shorthen the length of treatment. The prevention of complications in chronic wounds, such as infections, increases the healing rates, as Moeller and colleagues have shown in their treatment with real-world data.

Based on all the scientific information available until today, the association of polihexanide with betaine can be clearly recognized as safe and effective for the treatment of chronic

wounds.

Results of the economic evaluation:

An evaluation of economic and budget impact was performed in order to analyze the strategies of chronic wounds treatment in the setting of the Suplementary Health System (Brazilian Private Health System), assessing if the additional costs provided by the use of Prontosan Solution® compared to treatment using saline is justified by the expected clinical benefit in terms of completely healed wounds.Results on efficacy were gathered from a non-concurrent cohort study on the treatment of patients with chronic wounds framework compared to a control group receiving saline, with the goal of determining how treatment impacts the number of wounds completely healed and its healing time. Treatment with Prontosan® solution showed a significant reduction in the healing time and increase the number of wounds healed completely within 6 months. There was also a favorable result for the reduction of infections resulting from unhealed wounds.

A cost-effectiveness analysis showed that treatment with Prontosan® Solution has a greater benefit at a lower cost when compared to treatment using saline solution, featuring a *cost-saving* scenario (lower cost and greater effectiveness). Although there are uncertainties about the parameters of cost and effectiveness considered in the analysis, all these parameters were tested in sensitivity analysis. The results of the probabilistic sensitivity analysis performed showed that the results remain favorable (*cost-saving* or cost-effective: ICER <1 time per capita GDP Brazil) to Prontosan® Solution in 99.3% of cases.

The estimated budget impact analysis has shown the maximum commitment of resources to enable the incorporation of Prontosan® Solution in the Supplementary Health System. We estimated a savings in the budget of approximately BRL 75.8 million in the first year of treatment after the incorporation, considering a hypothetical scenario in which all eligible patients were treated with Prontosan® Solution.

1 Description of the health condition related to the use of technology

1.1 Epidemiological and physiopathological aspects

Chronic wounds are those which do not heal in the expected time and present complications. Such injuries can cause chronic pain, depression, inability to work, decrease of movement, loss of self-esteem and social isolation, or severe disorders, both individual and collective. It is a long lasting, high cost treatment and it has a high chance of recurrence which can be unpleasant for patients and families[1].

The presence of biofilms in chronic wounds as a cause of delay in healing times is now more and more accepted[2,3,4]. Biofilms are complex communities of micro-organisms (e.g. bacteria) living in a three-dimensional extracellular matrix of polysaccharide embedded in a viscous mixture of sugars and proteins. The matrix acts as a barrier, protecting the micro-organisms from a cellular and chemical attack.[5].

1.1.1 Most common types of chronic wounds

1.1.1.1 Pressure ulcers

The pressure ulcer is an area of localized cell necrosis, which results from compression of the soft tissue between a bony prominence and a hard surface for an extended period of time, usually due to immobility (e.g., prolonged stay in bed, use of wheel chairs). The most common occurrences are: the sacrum, heels, elbows, lateral malleolus, greater trochanter and the ischium.[6,7].

A pressure ulcer increases the length of hospital stay, morbidity and mortality, and reduces the life quality of patients. The possibility of developing a pressure ulcer increases with the length of hospitalization, older age and years after a spinal cord injury. According to the World Health Organization, the prevalence of patients with pressure ulcers receiving home care in the U.S. ranges from 3% to 10%. In the UK, the annual prevalence of pressure ulcers in patients with at least 65 years old ranges from 0.31% to 0.70%, with the prevalence increasing sharply for patients older than 85, reaching 3.3% among patients over 95. The prevalence, incidence and the methods of evaluation of cost of pressure ulcers vary widely, as do the components of costs between different health systems, making it difficult to estimate the global burden caused by pressure ulcers.[8].

In Brazil, Ferreira and colleagues[9] found a 5% prevalence of pressure ulcers in patients admitted to the Central Institute of HCFMUSP.

1.1.1.2 Vascular ulcers

The vascular ulcers, better known as leg ulcers, can be defined as the loss of continuity of the skin in the lower limbs below the knees. Their healing process continues for more than six weeks and they are mostly of venous origin. They are highly recurrent, affect mainly older people and are often associated with other diseases such as diabetes mellitus, arthritis, hypertension, leprosy, among others. These wounds are a major reason why people seek health units, for about 80% of them can be treated as outpatients. They can cause pain, depression, decrease movement, inability to work, loss of self-esteem and social isolation, or severe disorders (individual and collective).1,7.

The World Health Organization estimates that venous ulcers affect between 0.2% and 1% of the population and between 1% and 3% of the population over 60, accounting for 60% to 70% of lower limb ulcers, with increasing prevalence in Western countries with aging population.8. A Brazilian study showed occurrence of venous ulcers in 67.6% of the population above 60.[10]

1.1.1.3 Neuropathic ulcers

These ulcers are caused by peripheral neuropathy as a result of some underlying diseases, e.g., leprosy, diabetes mellitus and alcoholism. People with diseases affecting peripheral nerves have increased risk of developing lesions of the autonomic, sensory and motor nerves, which can result in primary (e.g., claw hand, foot drop and ankylosis) and secondary lesions (e.g., muscle paralysis, fissures, plantar ulcers and traumatic injuries). The autonomic nerves are responsible for maintaining the sebaceous and sweat glands and lead to a decreased production of secretions if affected. The skin becomes dry, inelastic and can easily crack which, if not addressed, will undermine the structures of hands and feet, increasing the risk of infection.1,7.

According to the World Health Organization, the annual incidence of neuropathic ulcers among diabetic patients goes from 5% to over 7% and it is likely that the cumulative incidence throughout life is as high as 25%.8.

If we take into account the incidence data from the World Health Organization, the amount of patients who developed chronic ulcers in 2012 was higher than 917,000, just among the population with private health insurance (Table 1).

Table 1. Estimated new cases of ulcers in Brazil

Age range	Brazilian population 2012[i]	Population with private health insurance 2012[ii]	% of population with health insurance	% of chronic wound[iii]	Population with health insurance and chronic wound

Up to 1	2,762,262	486,563	17.6%		
1 to 4	11,282,294	2,760,511	24.5%		
5 to 9	15,233,132	3,146,321	20.7%		
10 to 14	17,463,157	2,951,513	16.9%		
15 to 19	17,282,071	2,991,082	17.3%		
20 to 29	34,955,799	9,400,107	26.9%	2.50%	235,003
30 to 39	30,147,083	9,579,203	31.8%	2.50%	239,480
40 to 49	25,253,910	6,905,104	27.3%	2.50%	172,628
50 to 59	18,706,936	5,053,483	27.0%	2.50%	126,337
60 to 69	11,519,233	2,837,036	24.6%	2.50%	70,926
70 to 79	6,394,682	1,616,637	25.3%	2.50%	40,416
80 and over	2,975,971	923,004	31.0%	3.50%	32,305
Overall	**193,976,530**	**48,650,564**	**25.1%**		**917,094**

[i] Health Department – DATASUS.. Available at: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?ibge/cnv/popuf.def - accessed November 6, 2012

[ii] The National Agency of Supplementary Health – ANS. Available at: http://www.ans.gov.br/anstabnet/anstabnet/deftohtm.exe?anstabnet/dados/TABNET_BR.DEF - accessed November 6, 2012

[iii] World Health Organization. Wound and lymphedema management. 2010. http://whqlibdoc.who.int/publications/2010/9789241599139_eng.pdf - accessed November 6, 2012

1.2 Therapeutic approach

Although tissue repair is a systemic process, it is necessary to encourage local conditions through appropriate topical therapy to enable the physiological process. The topical therapy of wounds is based on scientific studies on the physiology of wound healing and is guided by the following principles: removal of necrotic tissue and foreign bodies from the wound bed, identification and elimination of the infectious processes, obliterateration of dead space, absorption of excess exudate, keeping the wound moist to promote insulation and protection of the wound from trauma and bacterial invasion. Cleaning and covering the wound are steps of topical therapy.[11,12].

1.2.1 Preparation of the wound bed

The preparation of the wound bed is not a static but rather a dynamic and rapidly evolving concept that encompasses four key components: **tissue management** (T), **infection and inflammation control** (I), **moisture balance** (M) and **non- advancing edges** (E). The four letters T, I, M and E, form the English acronym *TIME*, meaning Tissue, Infection, Moisture and Edge. Each of these components identifies one factor that determines the healing of a wound, and for each of them it is necessary to define specific goals with its therapeutic interventions. In order to achieve good healing results, it is necessary to observe these four elements. It is mandatory that each of them evolves to make the progression of the healing process possible. However, there are wounds that may need focus on a particular single model. Undesirable

findings in each of the four components require corrective measures in order to reach a new state consistent with healing.[13,14,15].

Thus, for the component ***Tissue*** zones of necrotic or nonviable tissue require removal in order to restore the normal function and the extracellular matrix protein to obtain a clean and viable bed.[13,14,15].

Infection indicates the need to reduce the bacterial counts (less than one million bacteria per gram of tissue) and, consequently, the inflammatory reaction that leads to an increase in the activity of proteases and other substances preventing healing. The removal of pathogens and reduction of the destructive action of proteases is mandatory to achieve balance in terms of bacteriological wound, allowing increased activity of growth factors.[13-15].

Moisture is the need to maintain an appropriate moisture/fluid balance, preventing excessive dryness in the wound or removing excess exudate. In this sense, reduction of edema, moisturization of the wound and elimination of excessive draining, especially in chronic wounds due to the harmful action of MMPs (matrix metalloproteinases, enzymes related to healing and tissue remodeling, and also the process of cellular metastasis in cancers) allows the restoring of the epithelial migration, for instance.[13-15].

Edges refers to the convenient state of the wound edges to allow migration of keratinocytes from the edges via the matrix, allowing its epithelialization. The debridement of non-viable tissue may be sufficient at times to restore cell migration, but in other cases it is necessary to use other products. The prolonged tissue hypoxia is also a barrier to fibroblast proliferation.[13-15].

A thorough cleaning allows adequate preparation of the wound bed so that it can receive covering, another important component of the treatment.**1**,[16,11]. Although tap water may be used for cleaning the wounds and although it doesn't increase the risk of infection or the length of the healing time, the use of specifically designed cleaning agents may have the potential to improve clinical treatment outcomes.**1**,[16,11]. Furthermore, the decision to use tap water for the purpose of cleaning the wounds must take into consideration the quality of tap water, the nature of the wound and the general conditions of the patient[17].

According to Yamada, hydraulic power for irrigation should be below 15 psi (pound/inch), and 8 psi is the adequate pressure for removal, and it can be obtained with the use of 35ml syringe and 19 gauge needle, according to U.S. Standards. A pressure higher than 15 psi may cause trauma to the viable tissue and lower than 8 psi may not perform an effective cleaning. Since 35ml syringes are not found in the Brazilian market, the irrigation of the wound bed is performed differently, with a 20 ml syringe connected to a 12 gauge needle, or to a 250 or 125

ml bottle of vial isotonic saline solution (0.9%) pierced with needles of several gauges. Hence, the pressure reached by such mechanisms is unknown and publications that refer to the fact are not available.[18].

Para For Oliveira et al, cleaning the wound should be undertaken with a saline jet, using a 250 ml saline bottle punched with a 25/8 needle, promoting enough pressure to remove wound exudate and any strange bodies.[19].

The irrigation of the wound with saline must be exhaustive until complete removal of debris and exudate on the wound bed. The volume of required isotonic saline (0.9%) will depend on the extent and depth of the wound and the amount of debris in the bed. The pressure of the saline jet should be efficient without causing trauma to the wound bed. Please note that the whole process aims at controlling the concentration of bacteria.[20].

Recent evidence has shown that the combination of polyhexamethylene (polihexanide), an antimicrobial agent and the surfactant betaine has increased ability to penetrate wounds with covers difficult to remove by promoting the removal of debris, bacteria and biofilm.**[21].** Furthermore, the use of polihexanide and betaine is simpler and does not require complicated technical procedures similar to those required for potable water and saline, for example.**[18-20].**

1.3 Treatment recommended by national and international guidelines

The Manual for Operation of Neurotropic and Traumatic Ulcers from the Health Department recommends performing the wound cleaning with a saline solution (sodium chloride 0.9%) that does not damage the tissues and adequately cleans the lesions without traumatizing the bed, accelerating the healing process. Cleaning can be performed with varying pressure, several times until complete removal of debris and microorganisms.1. Please note that the hydraulic force must be below 15 psi (pound/inch), and 8 psi is the adequate pressure for removal, and it can be obtained with the use of 35ml syringe and 19 gauge needles, according to U.S. Standards. A pressure higher than 15 psi may cause trauma to the viable tissue and lower than 8 psi may not perform an effective cleaning. Since 35ml syringes are not found in the Brazilian market, the irrigation of the wound bed is performed differently, with a 20 ml syringe connected to a 12 gauge needle, or to a 250 ml or 125 ml bottle of isotonic saline solution (0.9%) pierced with needles of several gauges. Hence, the pressure reached by such mechanisms is unknown and publications that refer to the fact are not available.**[18].**

Guimarães Barbosa and Nogueira Campos in their "Guidelines for the Treatment of Venous Ulcers", recommend the use of saline (sodium chloride 0.9%) as the most suitable substance for cleaning wounds for it is an isotonic solution and it has the same plasma pH and does not

interfere with the normal healing process. Furthermore, the solution won't cause hypersensitive reactions and doesn't alter the skin flora. Tap water is also a solution commonly used for this purpose by the community and is accessible, cheap and effective. The problem with the use of tap water is the uncertainty about its actual quality.[22]

Irish Guidelines for the management of wounds recommend the use of tap water for cleaning chronic wounds and acute lacerations in adults[23].

International guidelines for the treatment of diabetic foot developed by the *International Working Group on Diabetic Foot* recommend cleaning chronic ulcers regularly with clean water or saline (0.9% saline).[24]

Two meetings of European consensus on the treatment of wounds (conducted in 2004 *[Consensus paper on wound antisepsis*[25]*]*) and in 2008 *[Practice-oriented expert recommendation for the treatment of critically colonized and infected wounds using location polihexanide* [26]*]*) recommended the consideration of polihexanide (polyhexamethylene biguanide /PHMB) as a choice for the treatment of chronic wounds for it has a good tolerability rate and beneficial effect on wound healing.[27].

The guidelines of the Spanish team *Grupo Nacional para el Estudio y en Asesoramiento Ulcers by Presión y Heridas Chronicles* (GNEAUPP) recommend cleaning thoroughly the lesions before each dressing change. The use of saline should be mandatory. The cleaning and drying of wounds should be performed with as little physical force as possible. The pressure should be effective enough to remove debris, bacteria and remaining dressings without producing trauma to the healthy tissue. The most effective washing pressure is the one provided by gravity or the one achieved by the use of a 35 ml syringe with a needle or catheter projecting 0.9 mm saline over the wound with 2 kg/cm2 pressure. The range of pressure for washing wounds is safer and more effective between 1 kg/cm2 and 4 kg/cm2. GENAUPP guidelines do not recommend the use of local antiseptics (e.g., povidone iodine, chlorhexidine, hydrogen peroxide, acetic acid and hypochlorite solution) or skin cleansers, for their chemicals are cytotoxic for new tissue formation and in some cases their continued use and absorption by the body may cause systemic problems. [28]. GENEAUPP defines antiseptic as *"a chemical applied to living tissues aims at eliminating pathogenic micro-organisms or inactivating viruses. It does not have selective activity since it eliminates all types of germs. The high concentration can be toxic to living tissues. Some may interfere with the action of other topical products used in wound care (collagenase, lidocaine, etc.). Its spectrum of activity, time of onset of action, uptime, residual effects, toxicity, and potential ability to penetrate materials that activate or circumstances may vary from one product to another."*[29]

1.4 Description of the evaluated product

Prontosan® Wound Irrigation Solution is a product composed of purified water (99.8%), undecylaminopropyl betaine (0.1%) and polihexanide (0.1%) and is used for cleaning chronic wounds with proven efficacy and safety in continuous and repeated use. Prontosan® is classified as a *medical device* in its country of origin and as a class III medical device in Brazil. Prontosan® is not an antiseptic drug.

Mechanism of action

Polihexanide (or polyhexamethylene biguanide/PHMB) is structurally similar to the natural antimicrobial peptides produced by many organisms and has a broad spectrum of action against bacteria, viruses and fungi. These positively charged molecules bind to the bacterial cell membrane and induce cell lysis through the destruction of the integrity of the cell membrane caused by the breakdown of the lipopolysaccharide layer, leading the microorganism to death.[30,31,32].

Betaine is a surfactant. Its molecule has a hydrophilic portion which repels dirt and debris in the wound, making it float in the irrigating fluid and thus removing it through the cleaning process.[21]. Betaine also interferes with the production of homoserine lactone, a signaling molecule used for cell-cell communication biofilms which plays an important role in the pathogenicity of biofilms. The ability of betaine to disrupt the biofilm is especially beneficial since biofilms are notoriously resistant to isotonic saline solution (0.9% saline), thereby remaining in the wound bed after the cleaning process.[33].

Unlike antiseptics, polihexanide stimulates the proliferation of keratinocytes (i.e. granulation tissue and wound healing).[56] Antiseptics are contraindicated in the treatment of chronic wounds, for they suppress cell proliferation[34].

Dosage and administration

Continuous and repeated use**Erro! Indicador não definido.**.

Prontosan ® is a product composed of purified water (99.8%), undecylaminopropyl betaine (0.1%) and polihexanide (0.1%) used to clean chronic wounds with proven efficacy and safety in repeated and continuous use.[21]

Side effects

polihexanide has unknown toxic effects [30], and a low risk of inducing hypersensitivity to touch.[35,36].

1.5 Preclinical studies

Kramer 2004[37]

The study aimed to compare the efficacy of octenidine, polihexanide and placebo (Ringer solution) in healing cutaneous wounds in aseptic surface on an animal model. Researchers noted that, in the early stages of the healing process, octenidine retarded the wound contraction, while in the final stage polihexanide promoted wound closure. Complete wound closure was achieved in 22.9 days in the polihexanide group, in 24.1 days in the placebo group and in 28.3 days in the octenidine group ($p < 0.05$ versus octenidine; there was no significant difference versus placebo).

Seipp 2005[38]

The study compared the efficacy of Prontosan®, saline and Ringer's solution against *Pseudomonas aeruginosa* biofilms grown on silicon plates. Prontosan ® only reduced the biofilm (reduction of 87%) after 24 hours of irrigation.

Kaehn e Eberlein 2009[33]

The study aimed to compare the efficacy of an octenidine plus phenoxyethanol solution with a solution of polihexanide plus polyethylene glycol in Ringer's solution and placebo (Ringer's solution) to solubilize and remove wound crusts using an animal model. The solution containing polihexanide was the only one able to remove the crusts and solubilize the denatured proteins.

Hirsch 2010[39]

The *in vitro* study compared five solutions used in clinical practice (Prontosan®, Lavasept®, Braunol®, Octenisept® and Betaisodona®). The minimum inhibitory concentration was determined against *S. aureus, E. faecalis, P. aeruginosa* and *E. coli.* The cytotoxic effects on keratinocytes and fibroblasts cell line HaCaT in a wide variety of concentrations were also evaluated. Lavasept® and Prontosan® showed the best results when it comes to antibacterial efficacy and low cellular toxicity.

Perez 2010[40]

The irrigation solution consisting of the combination of betaine and Polihexanide was compared with Ringer's solution and with saline in terms of effectiveness in removing a biofilm penicillin-resistant *S. aureus* in porcine model. The biofilm removal has only been demonstrated with the use of a solution containing betaine and Polihexanide. Saline and Ringer's solutions failed in reducing the bacterial count of penicillin-resistant *S. aureus.*

Hübner 2010[41]

The study aimed to compare the efficacy of chlorhexidine, polihexanide and PTT (plasma tolerated by tissue) against *Pseudomonas aeruginosa* biofilms growing on polystyrene materials and silicone. The authors concluded that the antimicrobial activity of polihexanide is comparable to that of chlorhexidine. The PTT also led to a significant reduction in the amount of colonies, which could make it an interesting alternative to the use of physical chemical antiseptics in the future.

Goertz 2011[42]

The study aimed to evaluate the effects of antimicrobial agents on the microcirculation in a model of cremaster muscle of rats (n=60). The arteriolar diameter and functional capillary density were investigated after application of the following antimicrobial agents: alcohol, hydrogen peroxide, imipenem, octenidine, and polihexanide ethacridine. The authors observed that polihexanide has a positive effect on the diameter of the vessels and on capillary density, whilst alcohol reduces both parameters.

Minnich 2012[43]

An in vitro study was conducted to evaluate the antimicrobial activity of a solution containing 0.1% polihexanide and 0.1% betaine surfactant. Results of 13 microorganism cultures *(S. epidermidis, P. aeruginosa, S. marcescens, C. albicans, S. aureus, E. faecalis* resistant to vancomycin, *P.mirabilis, E. coli, S. aureus* resistant to methicillin, *A. baumannii, E. cloacae* and *A. brasiliensis)* were evaluated after 7, 14 and 28 days of product use. The results showed inhibition of the activity of 12 of the 13 microorganisms (except *A. brasiliensis)* exposed to the 0.1% polihexanide plus 0.1% betaine solution. The authors stated that the clinical implications of these observations need further research.

2 Literature Review

2.1 Question

The objective of this report is to analyze the best available scientific evidence on the efficacy, safety and cost-effectiveness of combinations of 0.1% polihexanide + 0.1% betaine for the cleaning, decontamination and humidification of the bed of chronic wounds in order to request the incorporation of the medical solution Prontosan® (polihexanide 0.1% + 0.1% betaine) in the Supplementary Health System.

In order to prepare the opinion, a question was settled. The structure can be found in Table 2.

Question:

Is the use of the polihexanide 0.1% + 0.1% betaine solution efficient, safe and cost-effective for the cleaning, decontaminating and humidificating of chronic wounds beds by improving outcomes associated when compared to both saline 0.9% and Ringer's solutions?

Table 2. Question Settled for Preparation of Opinion (PICOT).

Population	Patients with chronic wounds of several etiologies
Intervention (technology)	Prontosan® Solution
Comparison	0.9% saline solution; Ringer's solution
Parameters	Efficacy Safety
Type of study	Systematic reviews of randomized controlled trials, randomized controlled trials, narrative reviews, economic evaluations, retrospective studies (cohort), case reports, records of controlled trials in progress

2.2 Criteria for inclusion and exclusion of articles

In order to evaluate the efficacy of a technology (health product, drug, device) in the treatment of a particular disease or medical condition, the best evidence is obtained from systematic reviews of randomized controlled trials followed by randomized controlled trials, according to the classification of the level of scientific evidence of the *Oxford University*[44]. The criteria of inclusion of studies in this opinion were: systematic reviews of randomized controlled trials, randomized controlled trials, narrative reviews, economic evaluations, retrospective studies (cohort), case reports and records of controlled trials in progress.

Some criteria of exclusion were established: molecular biology studies or pre-clinical (animal models). The pre-clinical trials have already been presented in section **Erro! Fonte de referência não encontrada.** in this report.

There were no restrictions regarding the publication of articles and language of publication.

2.3 Databases and search strategy

For the literature review, we conducted a literature search until November 6, 2012 in PubMed/MEDLINE, Cochrane Library, EMBASE and clinicaltrials.gov (registration of clinical trials) that evaluated the use of the combination of 0.1% polihexanide + 0.1% betaine in the form of solution for cleaning, decontaminating and humidificating the bed of chronic wounds. The bibliographic searches were targeted for systematic reviews of randomized controlled trials, randomized controlled trials, narrative reviews, economic evaluations, retrospective studies (cohort), case reports.

The search strategy in PubMed database/MEDLINE used the keywords "polihexanide wound" without the use of filters to enhance the search scope .

The search details in PubMed/MEDLINE are shown in Table 3.

Table 3. Search strategy at PubMed/MEDLINE

Keywords: polihexanide wound
Search details: ("Vantocil"[Supplementary Concept] OR "Vantocil"[All Fields] OR "polihexanide"[All Fields]) AND ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "wound"[All Fields])

The search strategy in the Cochrane Library database also used the keywords “polihexanide wound”.

In order to perform the search on the database EMBASE we used the terms “polihexanide wound”. Search details are shown in Table 4.

Table 4. Search strategy at EMBASE

Keywords: polihexanide wound
#8 **#3** AND **'controlled study'**/de AND (**'clinical trial'**/de OR **'controlled clinical trial'**/de OR **'controlled study'**/de OR **'human'**/de OR **'randomized controlled trial'**/de) AND (**2004**:py OR **2011**:py) AND **'article'**/it Results = **3**
#7 **#3** AND **'controlled study'**/de AND **'article'**/it AND (**'clinical trial'**/de OR **'controlled clinical trial'**/de OR **'controlled study'**/de OR **'human'**/de OR **'randomized controlled trial'**/de) AND (**2004**:py OR **2011**:py)

Results = **3**

#6

#3 AND **'controlled study'**/de AND **'article'**/it AND (**'clinical trial'**/de OR **'controlled clinical trial'**/de OR **'controlled study'**/de OR **'human'**/de OR **'randomized controlled trial'**/de) Results = **3**

#5

#3 AND **'controlled study'**/de AND **'article'**/it Results = **3**

#4

#3 AND **'controlled study'**/de Results = **3**

#3

polyhexamethylene AND **wounds** AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim) AND [2000-2012]/py Results = **0**

#2

'polyhexamethylenebiguanide'/exp AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim) AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND ([animal model]/lim OR [animal tissue]/lim) AND [2000-2012]/py Results = **0**

#1

polyhexanide AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim) AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND ([animal model]/lim OR [animal tissue]/lim) AND [2000-2012]/py Results = 0

At www.clinicaltrials.gov database, we used the term “Prontosan” five studies are reported, two of which are already closed (no results available), two were in progress and one was not yet recruiting patients, namely:

:

- NCT01048307 - *Effect of Prontosan Wound Irrigation Solution on Venous Ulcers* (study finished, results not available)[45];
- NCT01153633 - *Trial on the Efficacy of Prontosan Wound Irrigation Solution and Prontosan Wound Gel* (study finished, results not available)[46];
- NCT01554644 - *Prontosan Versus Saline in the Cleansing of Chronic Leg Ulcers in Diabetic Patients* (study under recruitment)[47];
- NCT01534858 - *A Prospective, Descriptive Cohort Study With Prontosan Wound Gel X in Partial and Full Thickness Burns Requiring Split Thickness Skin Grafts* (study under recruitment)[48];

- NCT01333670 - *Efficacy of Prontosan Solution on Chronic Ulcers* (this study is not yet recruiting patients)[49].

The search results are summarized in Table 5.

Table 5. Results of searches for references

	Citations found	Citations excluded	Citations included
PubMed/MEDLINE	44	35	9
Cochrane Library	12	12	0
EMBASE	3	3	0
clinicaltrials.gov	5	5	0

The 9 references included from MEDLINE are: Horrocks 2006[58], Andriessen 2008[21], Valenzuela 2008[50], González 2008[51], Romanelli 2010[52], Eberlein 2010[53], Hübner 2010[54], Kaehn 2010[55] and Roth 2010[56].

Another strategy was used to gather more information: searching for a possible product website on the Internet, searching for product manufacturer websites that could contain scientific information and referrals to non-indexed Internet-based journals. Google was used for this purpose. As a result, we located the website www.prontosan.co.uk which has an area with information about scientific evidence related to Prontosan[57]. In this area 13 publications were listed, 2 of which were already included in 9 selected references by the literature review (Andriessen 2008[21] e Horrocks 2006[58]); the study by Möller 2004[59] was selected for inclusion in the literature review. The preclinical studies were included in section **Erro! Fonte de referência não encontrada.** of this report in order to track the development of polihexanide.

The search done via Google also tracked three articles published in journals not indexed in Medline: Santos 2011[60] (review article), Gilliver 2009[27] (review article) and Forma 2006[61] (case report).

The area of international documents on the product manufacturer website contained a 2011 scientific publication *(Wounds International)* evaluated in search for other references[62]. The publication listed 48 references. Among them a preclinical study (Perez 2010) was selected for the description in section **Erro! Fonte de referência não encontrada.** of this report. This list also contained references to Horrocks 2006 and Romanelli 2010 clinical studies, which had been previously selected for inclusion in the literature review. The other studies did not meet the inclusion criteria or had already been included in previous searches.

The manual search in the reference section of the editorial written by Kramer et al[63] led to another review article on the use of polihexanide in treating wounds (Dissemond et al.), which was included in literature review.

At the end of the literature review, 14 references were included: Möller 2004[59], Forma 2006[61], Horrocks 2006[58], Andriessen 2008[21], Valenzuela 2008[50], González 2008[51], Gilliver 2009[27], Romanelli 2010[52], Eberlein 2010[53], Hübner 2010[54], Kaehn 2010[55], Dissemond 2010[64], Roth 2010[56] and Santos 2011[60].

2.4 Evaluation of the quality of evidence and results of the selected studies

Based on the inclusion and exclusion criteria described in the search strategy, we included 14 publications on the efficacy and safety of using Prontosan ® in the treatment of patients with chronic wounds.

To assess the quality of evidence presented by randomized studies, we used a model of quality assessment based on the GRADE system (*Grading of Recommendations Assessment, Development, and Evaluation*)[65]. Publications by Valenzuela 2008[50] and Romanelli 2010[52] were evaluated.

Quality assessment of evidence of randomized trials is shown in Table 6.

Table 6. Quality Assessment of evidence and results of the selected studies

Valenzuela 2008[50]		
Question related to the study	**Yes/No/Not clear/Not Applicable**	**How was the question addressed in the study?**
Randomization was appropriate?	Yes	Randomization of patients in both groups was performed using a table of random numbers. There is no information in the published study. The patient demographics are not described in the publication.
The concealment of allocation was adequate for treatment?	Not clear	
The demographic and clinical characteristics of patients were similar?	Not clear	
The caregivers, participants and assessors of outcomes were blinded to treatment allocation? If	No	The study was not blinded.

any of these people were not blind, what would be the impact on the risk of bias assessment?		
Were there any unexpected imbalances in terms of dropout among treatment groups? If so, this fact was explained or adjusted?	No	All enrolled patients completed treatment two weeks.
Is there some evidence to suggest that the authors have evaluated more outcomes than those reported?	No	The publication provides enough information about the study purposes, it does not seem like other data was evaluated.
Data evaluation included an analysis ITT (intention-to-treat)? If so, the analysis was appropriate? The methods used to deal with the information available were not suitable?	No	Although the document does not mention the results of the ITT analysis, all patients were evaluated.
Romanelli 2010[52]		
Question related to the study	**Yes/No/Not clear/Not applicable**	**How was the question addressed in the study?**
Randomization was appropriate?	Sim	Randomization of patients in both groups was performed by a computerized system.
The concealment of allocation was adequate for treatment?	Not clear	There is no information in the published study.
The demographic and clinical characteristics of patients were similar?	Not clear	The patient demographics are not described in the publication.
The caregivers, participants and assessors of outcomes were blinded to treatment allocation? If any of these people were not blind, what would be the impact on the risk of bias assessment?	Not clear	The authors do not report if parts of the study were blinded (the study was single blind), which increases the risk of bias in interpreting the information.
Were there any unexpected imbalances in terms of dropout among treatment groups? If so, this fact was explained or adjusted?	No	Only 2 patients in the control group discontinued the study.
Is there some evidence to suggest that the authors have evaluated more outcomes than those reported?	No	The publication provides enough information about the study purposes, it does not seem like other data was evaluated.
Data evaluation included an analysis ITT (intention-to-treat)? If so, the analysis was appropriate? The methods used to deal with the information available were not suitable?	Não	There is more information on the two control patients who did not complete the study.

We can draw some comments on the two publications:

1. Valenzuela, Perucho 2008[50]: it is an open, randomized study. Randomization of patients in

both groups was performed using a table of random numbers and seems appropriate, but information is not supplied so that one can judge whether the concealment of allocation of patients to the treatment groups is adequate. The demographic characteristics of patients included in the study is not described, making it impossible to assess whether the two groups of patients allocated to the two treatments had similar characteristics and thus were balanced. The length of treatment (2 weeks) was too short considering the chronic nature of the health condition evaluated. Since there is not enough information, it is not clear if the evaluation of the study results was performed by means of the ITT analysis *(intent-to-treat analysis,* a method that allows biases comparisons between the treatment groups analyzed). Thus, Valenzuela, Perucho 2008[50] is a randomized trial with high risk of bias in the interpretation of the results.

2. Romanelli 2010[52].. It is a single-blind, randomized study. The randomization of patients in both groups was performed using a computer system and seems appropriate but information is not supplied so that one can judge whether the concealment of allocation of patients to the treatment groups is adequate. The demographic characteristics of patients included in the study is not described, making it impossible to assess whether the two groups of patients allocated to the two treatments had similar characteristics and thus were balanced. There is no information as to which population involved in the study was "blind", researchers or patients. There is no information about the analysis following the systematic ITT. Thus, Romanelli 2010[52] is a randomized trial with high risk of bias in the interpretation of the results. However, the single-blind design of the study makes it more consistent than the Valenzuela, Perucho[50] trial, which had an open drawing.

The evaluation of other studies included in this review (Möller 2004, Horrocks 2006, Form 2006, Andriessen 2008, González 2008, Eberlein 2010, Hübner 2010, Kaehn 2010 and Roth 2010), which were not randomized controlled trials, as with basic levels of scientific evidence following the classification of the *Oxford Centre for Evidence-based Medicine (EMBC, University of Oxford),* 2009 version, when publications fit the types of evidence discussed by *EMBC*[66]. The levels of evidence are reproduced below in Table 7 and the assessment of levels of evidence relevant to the observational studies included in the review are described in Table 8.

Table 7. Levels of evidence EMBC, Oxford University*

Level	*Therapy/Prevention, Aetiology/Harm*	*Prognosis*	*Diagnosis*	*Differential diagnosis/symptom prevalence study*	*Economic and decision analyses*

1a	*SR (with homogeneity*) of RCTs*	*SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations*	*SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres*	*SR (with homogeneity*) of prospective cohort studies*	*SR (with homogeneity*) of Level 1 economic studies*
1b	*Individual RCT (with narrow Confidence Interval‡)*	*Individual inception cohort study with > 80% follow-up; CDR† validated in a single population*	*Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre*	*Prospective cohort study with good follow-up****	*Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses*
1c	*All or none§*	*All or none case-series*	*Absolute SpPins and SnNouts††*	*All or none case-series*	*Absolute better-value or worse-value analyses ††††*
2a	*SR (with homogeneity*) of cohort studies*	*SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs*	*SR (with homogeneity*) of Level >2 diagnostic studies*	*SR (with homogeneity*) of 2b and better studies*	*SR (with homogeneity*) of Level >2 economic studies*
2b	*Individual cohort study (including low quality RCT; e.g., <80% follow-up)*	*Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only*	*Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases*	*Retrospective cohort study, or poor follow-up*	*Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses*
2c	*"Outcomes" Research; Ecological studies*	*"Outcomes" Research*		*Ecological studies*	*Audit or outcomes research*
3a	*SR (with homogeneity*) of case-control studies*		*SR (with homogeneity*) of 3b and better studies*	*SR (with homogeneity*) of 3b and better studies*	*SR (with homogeneity*) of 3b and better studies*
3b	*Individual Case-Control Study*		*Non-consecutive study; or without consistently applied reference standards*	*Non-consecutive cohort study, or very limited population*	*Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible*

					variations.
4	*Case-series (and poor quality cohort and case-control studies§§)*	*Case-series (and poor quality prognostic cohort studies***)*	*Case-control study, poor or non-independent reference standard*	*Case-series or superseded reference standards*	*Analysis with no sensitivity analysis*
5	*Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"*	*Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"*	*Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"*	*Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"*	*Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"*

* For definitions of terms used in the table, see the glossary in http://www.cebm.net/?o=1116

It is noteworthy that in an era increasingly dominated by evidence-based medicine, the observational studies, be it cross-sectional, retrospective or chart review, apparently lose value in face of randomized controlled trials (RCTs). However, despite the need for RCTs to be applicable to new therapies or methods, restrictions on patient selection, sometimes the results deviate from what "real life" provides. Please note that there are still limitations in the assessment of adverse events observed, sometimes only in post-market studies.

Thus, observational studies have power to gather large amounts of patients and sometimes represent real-life situations in a better way. From a therapeutic standpoint, randomized controlled trials and observational studies complement the training of medical knowledge based on evidence[66]. However, disagreement persists regarding the possibility of making causal inferences strong enough to support clinical decisions or policies based on observational studies[67].

Table 8. Summary of results of studies with Prontosan®

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Möller A et al. 2004[59] [Experience with the use of polihexanide-containing wound products in the management of chronic wounds – results of a methodical and retrospective analysis of 953 patients]	Non-concurrent cohort study (retrospective)	953 patients with chronic wounds (62% with diabetic foot)	Not applicable	The effects of cleaning the wound with the irrigation solution containing polihexanide + betaine (Prontosan®) and of the removal of non-vital tissue promoted by Prontosan® gel were evaluated. The infection rate fell from 40% to 3% and 80% of wounds healed.	2c (outcomes research).	The large amount of patients studied provides relevance to the work of researchers, since real-world data are important to the assessment of the efficacy and safety of a product outside of the strict control of randomized controlled trials.

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Horrocks et al. 2006[58] *Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation.*	Observational	10 patients with chronic wounds that lasting longer than 12 months.	Not applicable	Seven out of ten patients showed dramatic improvement after 3 weeks of treatment with Prontosan®. As the biofilm was eliminated, the exudated in the wounds decreased. The photographs of injuries and the monitoring of patients showed a decrease in the wound size. Also the odor of wounds improved over treatment. Six out of seven patients showed improvement and no longer needed to be treated with silver salt dressings or antibiotics. One out of seven patients needed silver salt dressings daily for 2 weeks, but did not require antibiotics. Among the remaining 3 patients enrolled in the study, one quit due to lack of cooperation with the treatment and the other two were removed from the study after 3 weeks since there was no notice of significant change in their clinical situation (patients agreed with their withdrawal).	2c (outcomes research)	Observational, predominantly analytical, with a very small number of evaluated patients.

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Forma O. 2006[61] *Valutazione dell'utilizzo di una soluzione detergente "Prontosan®" come coadiuvante nel trattamento delle ulcere.*	Observational	18 patients with chronic skin ulcers: 10 male patients with average age of 69.5 (4 with venous ulcers, 4 mixed ulcers with arterial component, 2 sacral decubitus ulcers), 8 female patients with average age of 71.6 (5 venous ulcers, 1 mixed ulcer, 1 arterial ulcer and 1 sacral decubitus ulcer).	Not applicable	The use of Prontosan® as irrigation solution enables the removal of biofilm and enables the dressing to act directly on the wound bed. Side effects were not observed in any patient enrolled in the study.	2c (outcome research)	Observational, predominantly descriptive, with a very small amount of evaluated patients. The important detail is the chronicity of the ulcers, ranging from 2 to 44 years, with an average length of 23.4 years.

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Andriessen, Eberlein. 2008[21] *Assessment of a wound cleansing solution in the treatment of problem wounds.*	Non-concurrent cohort study (retrospective)	Patients with chronic venous leg ulcers.	Saline solution and Ringer's solution	Study Group (Prontosan ® solution), n = 59, control group (saline / Ringer), n = 53. In the study group (Prontosan ®), 57 out of 59 (97%) patients had wounds completely healed after 6 months of treatment, versus 47 out of 53 (89%) patients in the control group, p = 0.0001. The average time to healing of wounds in the study group was 3.31 months (SE = 0.17) and 4.42 (SE = 0.19) months in the control group, p = 0.0001.	2b (retrospective cohort study)	Non-concurrent cohort study (retrospective). The non-concurrent problems of the studies are: information bias and inability to control confounding variables (lack of information).

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Valenzuela, Perucho. 2008[50] [The effectiveness of a 0.1% polihexanide gel]. [Article in Spanish]	Randomized clinical study	Patients with chronic wounds	0.9% saline	78 patients were treated with betaine + polihexanide gel and 64 with 0.9% saline for two weeks. The study lasted two weeks. The use of polihexanide + betaine promoted statistically significant results in terms of removal of undesirable crusts in the wound bed, bacterial growth control, reduction of biofilm and local infection control. Stimulation of granulation favored the healing process of stagnant wounds.	1A	The randomization of patients in two groups seems appropriate, but there is not enough information to assess whether the concealment of patient allocation to treatment groups was adequate. There is no description of the demographic characteristics of patients, making it impossible to know whether the two groups were balanced. The treatment time was too short in face of the chronic nature of the health conditions under evaluation. Not clear if the results evaluation was performed by analysis of ITT.

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
González et al. 2008[51] *[Effective cleansing and decontamination of the base of an injury; reduction in time for cicatrization]. [Article in Spanish]*	Observational	14 patients (6 men, 8 women) with average age of 67.5, with acute and chronic skin lesions of any etiology	Not applicable	Patients were treated with Prontosan® Wound Irrigation Solution and Prontosan® Gel to cover the wound before dressings were applied. The 14 patients included in the study had their wounds healed completely over a period of time ranging from 15 to 98 days, which according to the author's experience was shorter than the time observed with the use of saline. As a conclusion, the author recommends the use of Prontosan® as first choice in the treatment of wounds, for it promotes a qualitative improvement in the conditions for a better and faster healing process.	2c (outcome research)	Observational, predominantly analytical, with a very small amount of patients evaluated
Gilliver S. 2009[27] *PHMB: a well-tolerated antiseptic with no reported toxic effects.*	Narrative review	Patients with chronic wounds of various etiologies.	Not applicable	Polihexanide has proven antimicrobial activity against common pathogens in chronic wounds and is recommended as first-line treatment for locally infected wounds, as well as for critically colonized wounds.	Not applicable	------

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Romanelli et al. 2010[52] *Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation.*	Randomized controlled trial	Patients with chronic venous leg ulcers.	Saline solution	Group A (Prontosan ® solution), n = 20; Group B (Saline), n = 20. The decrease in pH on the wound surface is associated with the improvement of the healing process. The pH at the wound surface treatment group (median variations) was 8.9 ± 0.6 at baseline. After 4 weeks of treatment -- washing the wound with Prontosan® solution and using moist dressings -- was reduced and stabilized at 7.0. Measurement of pH was significantly lower in the treatment group than in the control group after 4 weeks of treatment ($p < 0.05$).	1A	The randomization of patients in two groups seems appropriate, but there is not enough information to assess whether the concealment of patient allocation to treatment groups was adequate. There is no description of the demographic characteristics of patients, making it impossible to know whether the two groups were balanced. The treatment time was too short in face of the chronic nature of the health conditions under evaluation. Not clear if the results evaluation was performed by analysis of ITT.

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Eberlein, Assadian 2010[53] *Clinical use of polihexanide on acute and chronic wounds for antisepsis and decontamination.*	Narrative review	Patients with chronic wounds of various etiologies.	Not applicable	Polihexanide is an antimicrobial substance suitable for use in critically colonized wounds or acute or chronic infected wounds. The positive evaluation of polihexanide is attributed particularly to its broad spectrum of antimicrobial activity, its good tolerability and cellular tissue, its ability to bind to the organic matrix, with its low risk of contact sensitization and its healing effect. Moreover, until now, the development of bacterial resistance to the use of polihexanide is unknown, and the risk does not seem imminent.	Not applicable	-------
Hübner, Kramer2010[54] *Review on the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic.*	Narrative review	Patients with chronic wounds of various etiologies.	Not applicable	Polihexanide biguanide, better known as PHMB or polihexanide, is one of the modern products that combines a broad spectrum of antimicrobial activity with low toxicity, high tissue compatibility, lack of adsorption and good applicability in various pharmaceutical forms, including solutions.	Not applicable	-------

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Kaehn K. 2010[55] polihexanide: a safe and highly effective biocide.	Narrative review	Not applicable	Not applicable	Polihexanide is a broad spectrum antimicrobial substance that has an excellent tolerability profile and low risk profile of use. The physico-chemical action on the bacterial envelope prevents or hinders the development of resistant strains of bacteria. Thus, polihexanide is particularly useful to combat multiresistant bacteria. The spectrum of ction is not yet fully defined. There is some evidence that the biodegradation of polihexanide requires the adsorption to inert surfaces and only a small number of species of bacteria would be able to utilize polihexanide metabolically.	Not applicable	--------

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Dissemond et al. 2010[64] *A practice-oriented recommendation for treatment of critically colonised and locally infected wounds using polihexanide.*	Narrative review	Patients with chronic wounds of various etiologies.	Not applicable	Polihexanide is an antimicrobial substance extremely suitable for use in the treatment of acute and chronic wounds critically colonized and also in acute and loccaly infected chronic wounds. The broad spectrum and antimicrobial action, the excellent tolerability profile and cellular tissue, the ability to link to the organic matrix, the low risk of contact sensitization and adjuvant effects on the healing demonstrate the usefulness of polihexanide. Moreover, to date, there was no development of microbial resistance to polihexanide.	Not applicable	---------

Study	*Type of study*	*Population*	*Comparators*	*Results*	*Evidence Level*	*Comments on the quality of the studies*
Roth, Brill. 2010[56] *polihexanide for wound treatment - how it began.*	Narrative review	Patients with chronic wounds of various etiologies.	Not applicable	The rating of more than 10 000 cases of patients clinically documented for over 20 years of prophylactic or curative treatment of wounds confirms the high degree of effectiveness and minimum adverse effect rate of polihexanide. In addition to reduced rates of infection compared with povidone iodine and hydrogen peroxide, this huge clinical experience also shows an excellent tolerability profile of polihexanide. The use of polihexanide tolerance is excellent, even in patients with painful sores, which can positively influence the recovery process of patients.	Not applicable	----------
Santos, da Silva. 2011[60] *Treating infected/colonized wounds with polihexanide.*	Review	Patients with chronic wounds of various etiologies.	Not applicable	Studies indicate that polihexanide is effective in treating colonized/infected wounds, showing significant reduction in healing time, inflammation, infection / colonization and pain when used. This evidence allows the conclusion that the use of polihexanide is a safe practice in the treatment of colonized/infected wounds.	Not applicable	----------

2.5 Discussion

From all lower limbs ulcers, approximately 70 to 80% are caused by chronic venous insufficiency[68,69,70]. The first episode of venous stasis ulcer occurs approximately five years after the diagnosis of chronic venous insufficiency.[71] Regarding patients with venous ulcers, 47% had two or more episodes of ulceration, whilst 21% of them already have had six or more episodes.[70]

The lower limbs venous ulcerations represent a significant portion of public spending on health, affecting 1% of all public health expenditures in developed countries [72]. It is estimated that the absolute cost of care for a patient with venous ulcer is 40,000,00, for total annual expenditures of approximately 3 billion in the U.S. and £ 400 million to £ 600 million in the UK [73,74], £ 100 million just in dressings [75], which exposes the fact that the dressings and nursing services are the main components of these values[76]. These numbers are even higher when we refer to ulcers of long duration (> 6 months) of larger sizes (> 10 cm ²) and with complications such as deep skin infections, osteomyelitis and amputations.[77].

In Brazil the prevalence of chronic venous insufficiency is estimated at 47.6%, being the 14th cause of absenteeism [78] and frequent cause of hospitalization - in the year 2011, admissions for procedure # 0303060301 in the public health system (treatment lower limb varicose veins C / ulcer) totaled 8,719, representing 80,913 days of hospitalization at a cost of R$ 3,722,400.31[79]. In the case of procedure 0415040035 (debridement of ulcer / devitalized tissues) 65,509 hospitalizations were performed in the public health system in 2011, totaling 465,048 days of hospitalization at a cost of R$ 61,657,346.68[79].

Although tissue repair is a systemic process, it is necessary to encourage local conditions through appropriate topical therapy to enable the physiological process. Topical therapy of wounds is based on scientific studies on the physiology of wound healing and guided by the following principles: removing necrotic tissue and foreign bodies from the wound bed, identify and eliminate infectious processes, obliterate dead space, absorb excess exudate, maintain the wound moist to promote insulation and protect the wound from trauma and bacterial invasion[11].

The presence of biofilms in chronic wounds as a cause of the delay of the healing process has gained increasing acceptance 2,3,4. Biofilms are complex communities of micro-organisms (e.g., bacteria) living in a three-dimensional extracellular matrix of polysaccharide embedded in a viscous mixture of sugars and proteins. The extracellular matrix acts as a barrier, protecting the microorganisms from chemical and cellular attack 5. Many bacteria grow only in

an environment with a narrow pH range, but when they are present as a biofilm community environment in the wound, these bacteria are able to survive facing a pH variation which would be inhibitory to cells grown in pure culture[80]. The pH of the environment for chronic wounds varies within a range from 7.15 to 8.9. This variability is representative of the process of healing and not healing. The acute and chronic wounds with a high alkaline pH showed healing rates lower than those wounds with pH closer to neutral[81].

Several guidelines, national and international, point to solutions such as saline or Ringer as gold standards for cleaning chronic wounds. The irrigation of the wound with saline must be exhaustive until complete removal of debris and exudate on the wound bed. The volume of required isotonic saline (0.9%) will depend on the extent and depth of the wound and the amount of debris in the bed. The pressure of the saline jet should be efficient without causing trauma to the wound bed. Please note that the whole process aims at controlling the concentration of bacteria.[82]

For example, the guidelines of the Spanish team *Grupo Nacional para el Estudio y en Asesoramiento Ulcers by Presión y Heridas Chronicles* (GNEAUPP) recommend that injuries are thoroughly cleaned before each dressing change and should be used for cleaning, as a rule, the saline. Indicate that the most effective washing pressure that is provided by gravity or, for example, that which is achieved by use of a 35 ml syringe with a needle or catheter projecting 0.9 mm saline on wound at a pressure of 2 kg/cm2. The pressures for washing wounds safer and more effective range between 1 kg/cm2 and 4 kg/cm2. Furthermore, it recommends the use of local antiseptics such as povidone iodine, chlorhexidine, hydrogen peroxide, acetic acid and hypochlorite solution, since these chemicals are cytotoxic for new tissue formation in and in some cases their continued use can cause systemic problems caused by its absorption by the body[28].

Although various treatment guidelines of chronic wounds, such as that of Spanish group GENAUPP [28], suggest the use of saline as the best alternative to the wound bed preparation, recent evidence have shown that the combination of betaine and polihexanide (Prontosan®) is capable of penetrating wounds increased with covers were difficult to remove by promoting the removal of debris, bacteria and biofilm installed in lesions[21,50,52,59,60,56]. Furthermore, the use of polihexanide and betaine is simpler, not requiring complicated technical procedures similar to those required for the use of potable water and saline, for example. [19,20]. Since 35ml syringes are not found in the Brazilian market, the irrigation of the wound bed is performed differently, with a 20 ml syringe connected to a 12 gauge needle, or to a 250 or 125 ml bottle of vial isotonic saline solution (0.9%) pierced with needles of several gauges. Hence, the

pressure reached by such mechanisms is unknown and publications that refer to the fact are not available.[18].

A series of publications made evident over the years, the safety and efficacy of the combination of polihexanide with betaine for cleaning and irrigation of chronic wounds, preventing complications arising from secondary infections.

In 2004, Möller et. al. [59] conducted a retrospective study that evaluated the treatment of 953 patients (62% with diabetic foot). The effects of cleaning wounds with Prontosan Solution and removing non-vital tissue promoted by Prontosan® gel were evaluated. The infection rate fell from 40% to 3% and 80% of wounds healed. The great amount of patients studied provides relevance to the work of researchers, since real-world data shows the efficacy and safety of a product outside of the strict control of prospective controlled trials. Retrospective studies have power to gather a large amount of patients and sometimes represent real-life situations in a better way. From a therapeutic standpoint, randomized controlled trials and observational studies complement the training of medical knowledge based on evidence.[66].

Horrocks' observational study[58] from 2006 showed that Prontosan® is an appropriate alternative for the management of patients with chronic wounds (e.g., chronic venous ulcers and pressure ulcers) with over a year of evolution.

Moreover, Adriessen et al[21], in 2008 showed that after six months of treatment, 97% of patients with chronic venous ulcers treated with Prontosan ® had their wounds completely healed compared to 89% of patients treated with Saline or Ringer's Solution, with a significant difference in efficacy between the two treatment groups ($p < 0.0001$). Furthermore, the average time of healing was significantly shorter in the group treated with Prontosan® (3.31 months) than the group treated with Saline or Ringer's Solution (4.42 months), $p < 0.0001$. The irrigation of wounds with Prontosan® proved to be an effective and safe method by preventing secondary infections, which can reduce complications and thereby reduce the total length of treatment.

Romanelli et all[52], in 2010, demonstrated an improvement of the surface of the wounds of patients treated with Prontosan® with significant decreases ($p < 0.05$) in the wound bed pH, from 8.9 at the baseline to 7.0 after four weeks of treatment. The acidification of the wound bed pH is considered a surrogate marker of clinical improvement.

The editorial written by Roth e Brill[56] published in the prestigious journal *Skin Pharmacology and Physiology* provides information about more than 10 000 patients that received prophylactic or curative treatment for chronic wounds for over 20 years and confirms the high

degree of efficacy and minimal adverse effects rates of polihexanide. In addition to the reduced rates of infection compared to povidone iodine and hydrogen peroxide, this huge clinical experience also shows the excellent tolerability of polihexanide. The tolerance to the use of polihexanide is excellent, even in patients with painful sores, which can positively influence their recovery process.

In 2011, Santos and da Silva [60], showed through a systematic literature review that the association of polihexanide and betaine is effective in treating colonized/infected wounds, verifying significant reduction in the time of healing, inflammatory signs of infection/colonization and pain upon its use. These evidences allow the conclusion that the use of polihexanide is a safe practice in treating infected/colonized wounds.

Thus, the irrigation of chronic wounds with Prontosan® is proved to be effective and safe, even in continued and long term use. It prevents secondary infection, which can reduce complications and thereby reduce length of treatment for it increases the healing of tissues[21,60].

3 Cost-effectiveness analysis

3.1 Purpose

To develop a cost-effectiveness analysis to assess the use of 0.1% polihexanide + 0.1% betaine (Prontosan® Solution) for cleaning, decontamination and humidification of chronic wounds bed.

3.2 Target population

Patients with chronic wounds treated by the supplementary health system.

3.3 Horizon of analysis

It was analyzed the time horizon *Life time*, in order to reflect the horizon for the treatment of patients treated according to the model.

3.4 Perspective

Supplementary Health System.

3.5 Comparators

Prontosan® Solution 350 ml versus Saline Solution (0.9%) 100/250 ml.

3.6 Discount rate

It was applied na annual discount rate of 5% for costs and clinical outcomes, according to methodologic guidelines from Brazilian Ministry of Health. [83].

3.7 Considered outcomes

The **health outcomes** considered are:

- Time free of wounds (months).

The **economic outcomes** considered were direct medical costs, including medical resources used directly for patient care, such as costs of drugs and monitoring tests for patients under treatment of chronic wounds.

Indirect costs and direct non-medical costs were not included in the analysis.

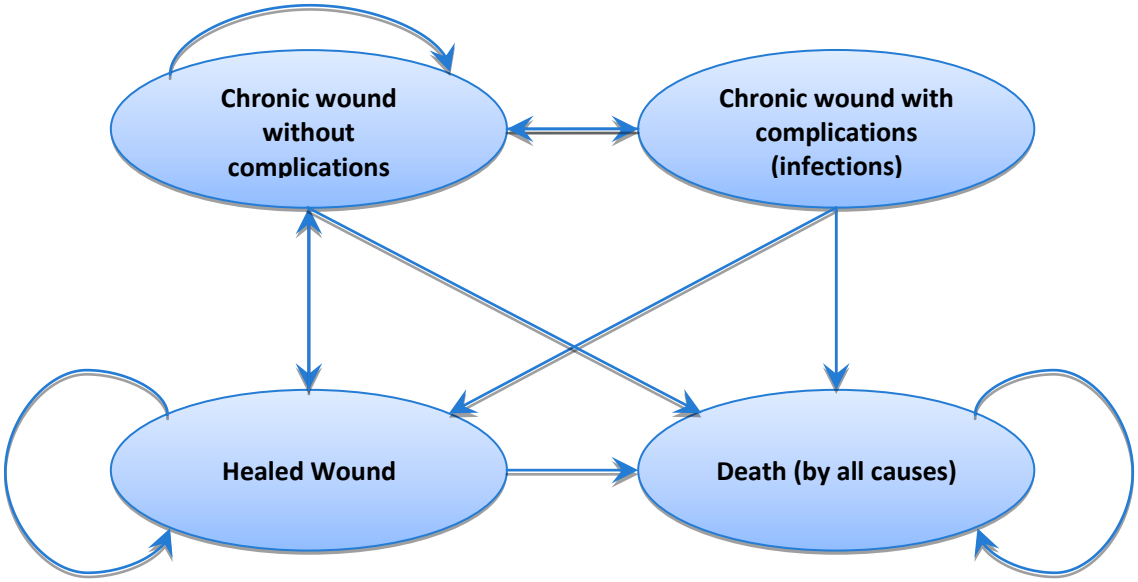
3.8 Model Structure

The type of analysis selected was the cost-effectiveness analysis , since the model aims to compare the direct medical costs and health outcomes involved in the treatment of chronic wounds with Prontosan® Solution versus Saline Solution.

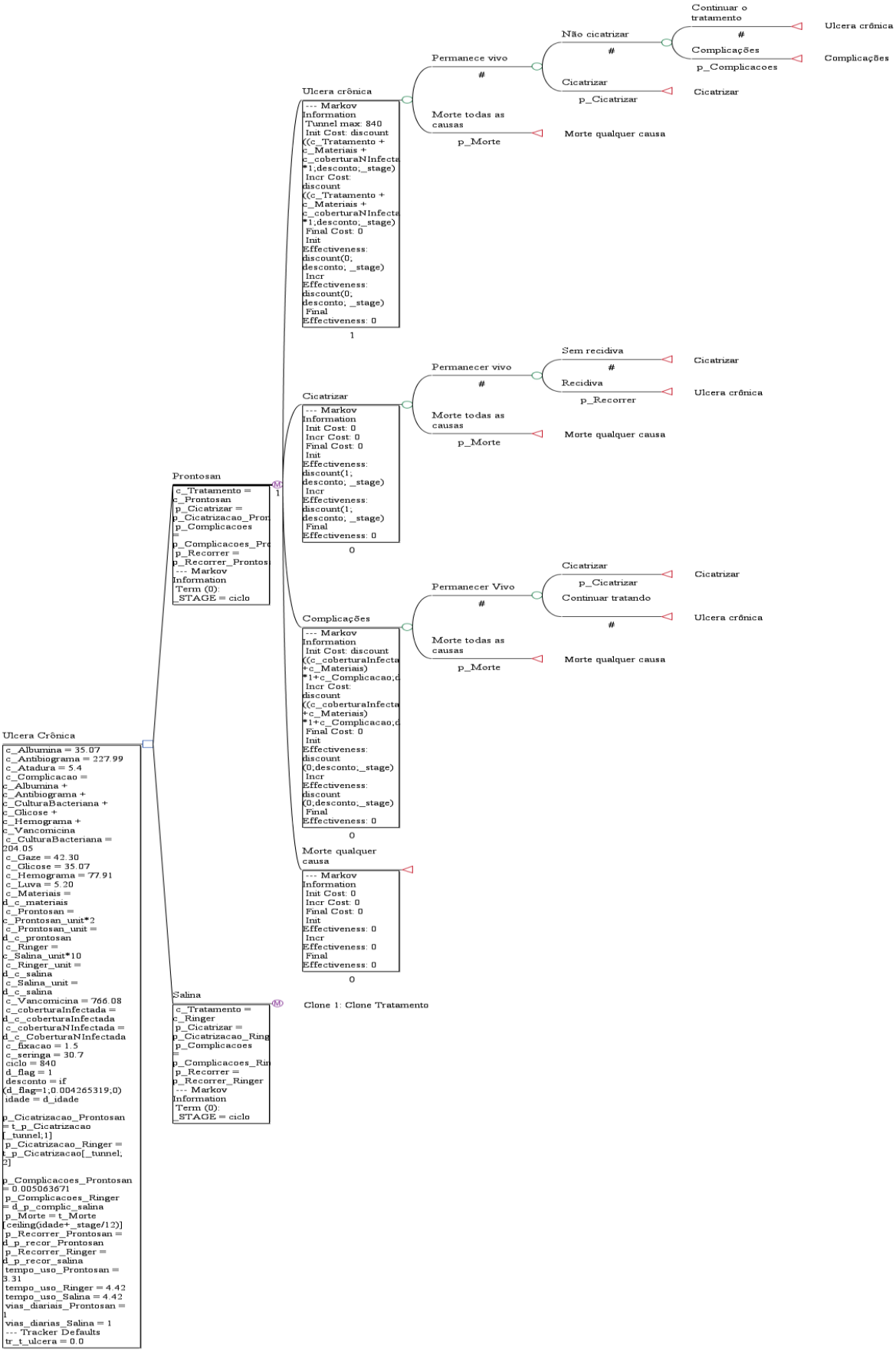
In order to estimate the costs and outcomes of treatments a Markov model was developed to follow each patients with chronic wounds until the end of their lives, considering transitions through different health states. The health states considered in the Markov model were: wound healed, chronic wound treatment without complications, treatment of chronic wounds under complications (bacterial infections) and death by any cause.

The analysis assume monthly cycles, ie patients transitions among all health states listed above were considered every month. Picture 1 represents graphically the Markov model structure , whilst Picture 2 represents the model as seen in software Treeage[84], the electronic system used to perform the analyzes contained herein.

Picture 1. Markov Model Structure



Picture 2. Structure of the model developed with Treeage software



The patient starts treatment with Prontosan® Solution or Saline Solution in the "chronic wound without complication" stage. Over the Markov cycles patients can remain in this state, have the wound healed, suffer some infectious complication or death by any cause. Patients whose wound heals can remain without relapse, relapse or death by any cause. In case of complications, patients can either be cured of the infection and continue treatment, the infection can be cured and the wound be healed or they may die by any cause. The transition probability for the state of death by any cause was adjusted to reflect the increased chance of death inherent in the framework of population with chronic wounds.

3.9 Efficacy data

Efficacy data were taken from two studies[21,22], with the results presented for the group of patients treated with 0.1% polihexanide + 0.1% betaine or saline solution, as shown in Table 9. The outcomes presented were directly used in the economic model.

Table 9. Efficacy data used in the economic model

Outcomes	Prontosan®	Saline	*p-value*
% patients with wound completely healed at the time of analysis[21]			
1st month	7%	2%	-
2nd month	29%	9%	-
3rd month	60%	28%	-
4th month	82%	51%	-
5th month	94%	68%	-
6th month +	97%	89%	< 0.01
Patients treated without complications (6 months)[21]	97%	87%	< 0.01
Recurrence (48 months)[22]	70%	70%	-

Andriessen et al.[21] followed the patients for a period of 6 months and reported the outcomes of the study and the statistical analysis of the results at the end of this monitoring period (Table 9). The outcomes selected to input the economic evaluation were:% of patients with wound healed over time and% of patients treated without complication. In both cases the results were statistically significant (p <0.01). For the percentage of healed wounds the author presented the results on a monthly basis and not just at the end of the 6 month follow-up. Thus, this data could be used to input the model without using any statistical technique to transform the given semester in a given month, mainly because the odds inputted in the model need to reflect the chance of occurrence for each outcome over a month, once it has

been defined the monthly cycle in the model. The recurrence probabilities and probabilities of complications were reported in the clinical studies considering different time intervals. [21,22]Thus, the conversion of these probabilities for a monthly period was necessary and the following equation was used for such conversion.

Equation 1. Calculation of rates for different periods of time

$$Rate\ n = 1 - (1 - Overall\ rate)\ \frac{Time\ n}{Overall\ time}$$

So Equation 1 can be rewritten as below to represent converting the probabilities of complications and recurrence of studies for annual rates, respectively.

Table 10 shows the results of these conversions.

Monthly_probability = 1 - (1-6month_probability) (1/6)

Monthly_probability = 1 - (1-48month_probability) (1/48)

Table 10. Original and converted probabilities for monthly probabilities

Outcomes	Probability in the time of the study		Monthly probability	
Completely healed wounds	Prontosan®	Saline	Prontosan®	Saline
1st month	7%	2%	7%	2%
2nd month	29%	9%	29%	9%
3rd month	60%	28%	60%	28%
4th month	82%	51%	82%	51%
5th month	94%	68%	94%	68%
6th month +	97%	89%	97%	89%
Patients treated with complications (6 months)	3%	13%	0.51%	2.29%
Recurrence (48 months)	70%	70%	4.89%	4.89%

Transition probabilities for each health states were calculated for the first month of the analysis. Table 11 presents such probabilities considering the use of Prontosan ® Solution and Table 12 considers the use of saline solution.

Table 11. Matrix of transition probabilities considered for the model's first month for treatment with Prontosan® Solution

Initial Stage \ Final Stage	Under treatment of chronic wounds without complications	Healed wounds	Under treatment of chronic wounds with complications	Death by any cause
Under treatment of chronic wounds without complications	92.46%	7%	0.5%	0.04%
Healed wounds	4.89%	95.07%	0%	0.04%
Under treatment of chronic wound with complications	92.96%	7%	0%	0.04%
Death by any cause	0%	0%	0%	100%

Table 12. Matrix of transition probabilities considered for the model's first month for treatment with Saline Solution

Initial Stage \ Final Stage	Under treatment of chronic wounds without complications	Healed wounds	Under treatment of chronic wounds with complications	Death by any cause
Under treatment of chronic wounds without complications	95.71%	2%	2.25%	0.04%
Healed wounds	4.89%	95.07%	0%	0.04%
Under treatment of chronic wound with complications	97.96%	2%	0%	0.04%
Death by any cause	0%	0%	0%	100%

Data on mortality by any cause were extracted from IBGE[85]. Mortality by any cause presented in Table 11 and Table 12 considers patients from 20 years-old on. This probability increases with aging of patients throughout the model.

Table 14 presents the average mortality rate adjusted by age group.

The odds of mortality segmented by year are available in the IBGE for ages up to 80 years. From this point onward, the annual probabilities are designed considering a linear projection of the natural logarithm of the mortality probability from 45 years.

The annual probabilities were adjusted in months according to the formula given below and based on Equation 1:

Monthly_probability = 1 - (1 - Probability_12months)^(1/12)

Moreover, it was necessary to adjust mortality rates to reflect the higher probability of death in patients under chronic wounds signs. According to Escandon J. et al[86], the probability of death in patients with 75 years-old in average, in a context of chronic wounds, is 28% in 2 years. This was converted to a monthly probability by Equation 1. Then, relative risk of death

for 75 year old patients with chronic wounds regarding the mortality rate of the population was calculated. The relative risk calculated was higher than those of all other age groups, and thus the monthly mortality rate of patients with manifestations of chronic wounds was also calculated. The details of the calculation of the relative risk is presented in Table 13.

Table 13. Calculating the relative risk of death in patients with chronic wounds

Age	Monthly mortality rate	Mortality of patients with chronic wounds in 2 years	Mortality of patients with chronic wounds adjusted to monthly cycle	RR
75	0.36%	28%	1.36%	3.78

Table 14. Monthly adjusted mortality rate for patients with chronic wounds

Age Range	Average Rate of Mortality
20 - 25 years	0.05%
26 - 30 years	0.06%
31 - 35 years	0.07%
36 - 40 years	0.09%
41 - 45 years	0.12%
46 - 50 years	0.17%
51 - 55 years	0.25%
56 - 60 years	0.36%
61 - 65 years	0.52%
66 - 70 years	0.76%
71 - 75 years	1.16%
76 - 80 years	1.73%
81 - 85 years	2.48%
86 - 90 years	3.69%
91 - 95 years	5.53%
96 - 100 years	8.43%
101 - 105 years	13.17%
106 - 110 years	21.66%

3.10 Use of resources and costs

The health resources considered refer to the costs associated with medical treatment, material and exams required for the treatment of chronic wounds.

The dressing system considered one change every 3 days. For each change a differentiated system of use of solutions was used due to the possibility of reuse of the bottle of Prontosan® Solution. Table 15 shows such systems with more detail.

Table 15. Conditions of use of solutions

	Prontosan®	Saline
Presentation (mL)	350	100/250
Exchanges / month	10	10
Dose (mL) / exchange	70	100/250
Bottles / month	2	10

In the case of complications, the use of vancomycin IV 2 g / day for 7 days was recommended, as well as the following additional tests: complete blood count, serum albumin, fasting glucose and culture with antibiogram daily for 7 days, in order to monitor the progress of patients. The unitary cost of exams was extracted based on the value proposed by the Brazilian Medical Association (AMB)[87]. The unitary cost of saline solution was extracted from the price list of the Board of Market of Medication Regulation (CMED)[88]. Price used was "Factory price" with 19% VAT, through simple average unitary costs of various manufacturers as shown in Appendix I. The Unitary Cost of Prontosan® Solution was considered according the price suggested by the manufacturer.

Besides the cost of solutions, medications and laboratory tests, the cost of materials needed to carry out the correct dressing change and preparation of a chronic wound was also considered. To determine the materials needed for the proper management of a chronic wound, reference protocols[89,90,91] in use in hospitals in Brazil as well as determinations of ANVISA for sanitizing hands were considered. The cost of materials were obtained from reference lists for Brazilian Private Market, such as BRASÍNDICE[92] and SIMPRO[93].

Table 16 shows the unit costs involved in the treatment.

Table 16. Costs per Unit

Treatment	Presentation	Cost	Source
Solutions			
Prontosan® Solution	350 mL	R$ 229.80	Suggested price
Saline Solution	100/250 mL	R$ 383	Appendix I
Medicamentos			
Vancomycin	500 mg - IV	R$ 27.36	CMED – PF 19% - 01/2013
Exams			
CBC	-	R$11.13	CBHPM – 11/2010
Fasting Glucose	-	R$ 5.01	CBHPM – 11/2010

Serum Albumin	-	R$ 5.01	CBHPM – 11/2010
Antibiogram	-	R$ 32.57	CBHPM – 11/2010
Bacterial Culture	-	R$ 29.15	CBHPM – 11/2010
Materials			
Sterile Glove (pair)	1 unit	R$ 0.52	Neve – 12/12 – C50001 – page 129
Sterile gauze (10 x 10 cm)	10 units	R$ 4.23	Neve – 12/12 – C22313 – page 129
Device for fixing	40 cm	R$ 0.15	BRASÍNDICE – Eletronic Ed. N° 637
Syringe 20 mL	01 unit	R$ 3.07	SIMPRO – Eletronic Ed.
Bandage (0.4 m x 1.2 m)	01 unit	R$ 0.54	BRASÍNDICE – Eletronic Ed. N° 637
Dressings			
Infected wounds	01 unit	R$ 420.92	Appendix II
Non-infected wounds	01 unit	R$ 100.12	Appendix II

Prices obtained in 31/01/2013

The cost of dressings were obtained through the simple average unitary costs of different dressings from different manufacturers, in the system Simpro, according to Appendix II.

There are other items also required to conduct the correct dressing change and preparation of a chronic wound bed, however, as resources are not disposable, ie, can be reused for more than one activity, they were not included in the present analysis to avoid an over estimate cost of treatment, for example:

- Sterile dressing kit (scissors, forceps, tray and tub)
- Disposable PPE kit (mask, cap, cloak) + goggles
- Collector box for drill cutting material
- Disposable garbage bag
- Liquid soap for healthy skin

The details of the calculation of treatment costs per monthly cycle is presented in Table 17, for patients with no complications, and in Table 18, for patients with complications.

Table 17. Cost of treatment (monthly) - Patient with no complications

Treatment	Protocol	Cost/ dose	Doses/ Month	Total Cost
Solutions				
Prontosan® Solution	0.2 bottle / 3 days	R$ 45.96	10	R$ 459.60
Saline Solution	1 bottle / 3 days	R$ 3.83	10	R$ 38.30
Materials				
Sterile Glove (pair)	1 unit / 3 days	R$ 0.52	10	R$ 5.20

Sterile gauze (10 x 10 cm)	1 unit / 3 days	R$ 4.23	10	R$ 42.30
Device for fixing	1 unit / 3 days	R$ 0.15	10	R$ 1.50
Syringe 20 mL	1 unit / 3 days	R$ 3.07	10	R$ 30.70
Bandage (0.4 m x 1.2 m)	1 unit / 3 days	R$ 0.54	10	R$ 5.40
Dressings				
Non-infected wounds	1 unit / 3 days	R$ 100.12	10	R$1.001.20
Total				
Prontosan® Solution				R$ 1.545.90
Saline Solution				R$ 1.124.60

Table 18. Cost of treatment (monthly) - Patient with complications

Treatment	Protocol	Cost/ dose	Doses/ Month	Total Cost
Solution				
Prontosan® Solution	0.2 bottle / 3 days	R$ 45.96	10	R$ 459.60
Saline Solution	1 bottle / 3 days	R$ 3.83	10	R$ 38.30
Medication				
Vancomycin	2 g / day	R$ 27.36	28	R$ 766.08
Exams				
Hemogram	1 unit / day	R$ 11.13	7	R$ 77.91
Fasting glucose	1 unit / day	R$ 5.01	7	R$ 35.07
Serum albumin	1 unit / day	R$ 5.01	7	R$ 35.07
Antibiogram	1 unit / day	R$ 32.57	7	R$ 227.99
Bacterial Culture	1 unit / day	R$ 29.15	7	R$ 204.05
Materials				
Sterile Glove (pair)	1 unit / 3 days	R$ 0.52	10	R$ 5.20
Sterile gauze (10 x 10 cm)	1 unit / 3 days	R$ 4.23	10	R$ 42.30
Device for fixing	1 unit / 3 days	R$ 0.15	10	R$ 1.50
Syringe 20 mL	1 unit / 3 days	R$ 3.07	10	R$ 30.70
Bandage (0.4 m x 1.2 m)	1 unit / 3 days	R$ 0.54	10	R$ 5.40
Dressings				
Infected wounds	1 unit / 3 days	R$ 420.92	10	R$ 4.209.20
Total				
Prontosan® Solution				R$ 6.100.07
Saline Solution				R$ 5.678.77

The costs of treating chronic wounds and complications were weighted by the percentage of patients in each health state at each cycle analysis.

3.11 Methodology

A Markov model is a stochastic process that has the Markov property. In general terms, a stochastic process may be defined as a vector of random variables which progress with time. If a property that determines the Markov stochastic process in question does not have memory, ie, to determine the state of the model in the next instant of time, we need to know only its current state, without knowing the events that happened previously.

In a pharmacoeconomic model, the states are determined by the health states of interest and the transition probabilities between them determine the state of the model in the next instant of time.

Taking as an example the economic model of Prontosan ® Solution presented in this report, 100% of patients begin their evolution in health status "Chronic wounds without complication." The distribution of patients by various health states (state model) is then updated for the next instant of time in accordance with the defined transition probability. This process goes on during the defined time horizon until it reaches the final state of the model.

At each iteration defined above variable costs and effectiveness are weighted according to the state vector of the model, which is set the percentage of patients in each health state, thus obtaining the cost of each state of health, Overall Cost of the stage (time) of the model and values of effectiveness. The costs and effectiveness values are then summed by stage and reached the Overall Cost of each treatment and their respective effectiveness.

From this information, it is possible to perform the calculation of the ratio of incremental cost-effectiveness ratio (ICER) relative to the technologies evaluated. To calculate the ICER need to define:

- **Incremental cost:** $\Delta C = Cost_{Prontosan} - Cost_{Saline}$
- **Incremental effectiveness:** ΔE = Effectiveness - Effectiveness

Given these definitions, the ICER is calculated from

Equation 2:

Equation 2. Incremental cost-effectiveness ratio

$$ICER = \frac{\Delta C}{\Delta E}$$

The calculation of this information enables the manager to decide whether the gain in effectiveness of the new treatment is sufficient to justify its increased cost and then decide whether or not the incorporation of a new technology.

All analyzes undertaken in this report were performed using the software Treeage Pro, version 2012.

3.12 Outcomes

3.12.1 Baseline Scenario

The comparative results of alternative treatment strategies were measured by the ratio of incremental cost-effectiveness ratio (ICER). This is defined, for two specific treatment alternatives, such as the additional cost provided by the treatment under analysis divided by the additional health gains achieved by the same treatment.

The outcome of this analysis was:

- Time free of ulcers (months)

The results of the cost comparison of Prontosan ® Solution treatment and Saline Solution are shown in Table 19. The comparative results are shown in Table 20.

Table 19. Cost results for alternative treatment (Saline Solution)

Cost types	Prontosan® Solution	Saline	Incremental
Overall	R$ 92,326.52	R$ 95,321.80	R$ 2,995.28
Overall (Discounted[i])	**R$ 40,335.90**	**R$ 41,576.37**	**(R$ 1,240.47)**

Table 20. Efectiveness results (Saline Solution)

Types of outcome	Prontosan® Solution	Saline	Incremental
Time free of chronic wounds in months	395.46	375.30	20.16
Time free of chronic wounds in months **(discounted i)**	**162.38**	**153.63**	**8.75**

[i] When the scanning goes beyond the period of a year, cost values and effectiveness must be discounted to their values at the present time according to a standard rate. The use of the rate of 5% per year follows the recommendations of the Methodological Guidelines for Economic Evaluation Studies on Health Technology.[83]

As shown in Table 20 a longer time free of chronic wounds is expected when using Prontosan ® Solution compared to the use of Saline Solution.

The results of cost-effectiveness, expressed as incremental cost per months free ofchronic wounds, are presented in

Table 21.

Table 21 Results of cost-effectiveness discounted in the time horizon *Life time* - Saline Solution

	Prontosan® Solution	Saline	Incremental
Total Cost	**R$ 40,335.90**	**R$ 41,576.37**	**(R$ 1,240.47)**
Time free of chronic wounds in months	**162.38**	**153.63**	**8.75**
ICER (R$ / Time free of chronic wounds in months)			***Cost-saving***

It can be observed that the overall treatment costs with Prontosan® Solution is lower than treatment costs with conventional solution in the life time horizon.. Despite the fact that the unitary cost is superior with Prontosan® Solution, this difference is offset by the greater effectiveness of the product, reducing the healing time and complication cases.

Regarding efficacy, treatment with Prontosan ® Solution showed superior results when compared to the group treated with Saline Solution, significantly increasing the time free of chronic wounds. In a sense, therefore, it is a result with lower cost and higher effectiveness. Considering that there was a lower cost with greater effectiveness we can state that treatment with Prontosan® Solution is *cost-saving*[ii] when compared to the treatment with Saline Solution.

3.12.2 Alternative Scenario – Worst Case Scenario

In the previous scenario, it was considered a regime of dressing change where the cleaning of wound beds occurs every 3 days, with the use of one bottle Prontosan® Solution every 15 days vs. a full bottle of Saline Solution in every change. In this scenario, called worst case scenario, solutions will be compared bottle to bottle, with indexing cycles of 3 days. The monthly cost of

[ii] A technology can be considered as *cost-saving*, ie, hás lower costs and higher effectiveness, when its incremental cost-effectiveness ratio (ICER) is negative.. This indicates the referred technology achieves the proposed objectives with saving of financial resources.

treatment considered in this new scenario is detailed in Table 22, for non-infected wounds, and in

Table 23, for infected wounds.

Table 22. Monthly cost of treatment for non-infected wounds - Alternative Scenario

Treatment	Protocol	Cost/ dose	Doses/ month	Total Cost
Solution				
Prontosan® Solution	1 bottle / 3 days	R$ 229.80	10	R$ 2,298.00
Saline Solution	1 bottle / 3 days	R$ 3.83	10	R$ 38.30
Materials				
Sterile Glove (pair)	1 unit / 3 days	R$ 0.52	10	R$ 5.20
Sterile gauze (10 x 10 cm)	1 unit / 3 days	R$ 4.23	10	R$ 42.30
Device for fixing	1 unit / 3 days	R$ 0.15	10	R$ 1.50
Syringe 20 mL	1 unit / 3 days	R$ 3.07	10	R$ 30.70
Bandage (0.4 m x 1.2 m)	1 unit / 3 days	R$ 0.54	10	R$ 5.40
Dressings				
Non-infected wounds	1 unit / 3 days	R$ 100.12	10	R$ 1,001.20
Total				
Prontosan® Solution				R$ 3,384.30
Saline Solution				R$ 1,124.60

Table 23. Monthly cost of treatment for infected wounds – Alternative Scenario

Treatment	Protocol	Cost/ dose	Doses/ month	Total Cost
Solution				
Prontosan ® Solution	1 bottle / 3 days	R$ 229.80	10	R$ 2,298.00
Saline	1 bottle / 3 days	R$ 3.83	10	R$ 38.30
Medication				
Vancomycin	2 g / day	R$ 27.36	28	R$ 766.08
Exams				
Hemogram	1 unit / day	R$ 11.13	7	R$ 77.91
Fasting glucose	1 unit / day	R$ 5.01	7	R$ 35.07
Serum albumin	1 unit / day	R$ 5.01	7	R$ 35.07
Antibiogram	1 unit / day	R$ 32.57	7	R$ 227.99
Bacterial Culture	1 unit / day	R$ 29.15	7	R$ 204.05

Materials				
Sterile Glove (pair)	1 unit / 3 days	R$ 0.52	10	R$ 5.20
Sterile gauze (10 x 10 cm)	1 unit / 3 days	R$ 4.23	10	R$ 42.30
Device for fixing	1 unit / 3 days	R$ 0.15	10	R$ 1.50
Syringe 20 mL	1 unit / 3 days	R$ 3.07	10	R$ 30.70
Bandage (0.4 m x 1.2 m)	1 unit / 3 days	R$ 0.54	10	R$ 5.40
Dressings				
infected wounds	1 unit / 3 days	R$ 420.92	10	R$ 4,209.20
Total				
Prontosan ® Solution				R$ 7,938.47
Saline				R$ 5,678.77

The analysis results considering the treatment costs mentioned above are given in Table 24.

Table 24. Results of cost-effectiveness discounted in the time horizon *Life Time* - Saline (Alternative Scenario)

	Prontosan® Solution	Saline	Incremental
Total Cost	**R$ 87,730.14**	**R$ 41,576.37**	**R$ 46,153.77**
Completely healed wounds	**162.38**	**153.63**	**8.75**
ICER (R$ / Time free of chronic wounds in months)			**R$ 5,273.20**

It can be observed that the total treatment costs with Prontosan® Solution compared bottle to bottle, is higher than the cost of conventional treatment in the life time horizon. This result is mainly driven by the cost of Prontosan® and partially offset by the lower cost of complications. Regarding efficacy, treatment with Prontosan® Solution showed a superior result compared to the group treated with Saline Solution, increasing significantly the time free of chronic wounds. In a sense, therefore, one result of higher cost and higher effectiveness.

The incremental cost-effectiveness ratio (ICER) calculated resulted in R$ 5,273.20 per month free of wounds. Considering that the additional cost calculated per month free of chronic wounds is below the limit of one time per capita GDP in Brazil, equal to R$ 21,252 in 2011, it

can be stated that treatment with Prontosan® Solution, compared bottle to bottle, is cost-effective[iii] when compared to treatment with Saline Solution.

3.13 Univariate sensitivity analysis

An important element in an economic study for decision making is the quantification of uncertainty involved in its results and identifying the variables that most affect this uncertainty.

Sensitivity analysis consider variations of a single parameter at a time, keeping the other parameters constant. In this case, the parameters considered critical had several values in the baseline scenario to limit values and the result obtained for the cost of free time for chronic wounds in months was documented to assess the robustness of the results found in the baseline scenario analysis .

The parameters varied in the univariate sensitivity analysis and their relevant values in the baseline scenario and the scenarios tested are described in Table 25.

Table 25. Varied parameters in the univariate sensitivity analysis

Evaluated parameters	Baseline Scenario	Minimum	Maximum
Initial average age	20.00	20.00	70.00
Prob. recurrence – Prontosan	4.89%	4.40%	5.38%
Prob. recurrence – Saline	4.89%	4.40%	5.38%
Prob. complications – Prontosan	0.51%	0.46%	0.56%
Prob. complications – Saline	2.29%	2.06%	2.52%
Discount for monetary update[83]	5%	0%	10%
Unitary Cost – Prontosan 350 mL	R$ 229.80	R$ 206.82	R$ 252.78
Unitary Cost – Saline 100/250 mL	R$ 3.83	R$ 3.45	R$ 4.21
Total Cost - IV Vancomycin 2 g / day	R$ 766.08	R$ 689.47	R$ 842.69
Total Cost - Hemogram 1x day	R$ 77.91	R$ 70.12	R$ 85.70
Total Cost - Fasting glucose	R$ 35.07	R$ 31.56	R$ 38.58
Total Cost - Serum Albumin	R$ 35.07	R$ 31.56	R$ 38.58

[iii] It is said that a technology is cost-effective, ie, has a higher cost with greater effectiveness, when their ratio for incremental cost-effectiveness is within a predetermined limit. Usually, it happens once the value of the GDP per capita of a nation is used as a high threshold for determining cost-effectiveness of a new technology.

Total Cost - Antibiogram	R$ 227.99	R$ 205.19	R$ 250.79
Total Cost - Bacterial Culture	R$ 204.05	R$ 183.65	R$ 224.46
Total Cost – Materiais	R$ 85.10	R$ 68.08	R$ 102.12
Dressing Cost – Infected wounds	R$ 420.92	R$ 378.83	R$ 463.01
Dressing Cost – Non infected wounds	R$ 100.12	R$ 90.11	R$ 110.13

In the baseline scenario, the incremental cost per completely healed wound using Prontosan® Solution in relation to treatment with Saline Solution was R$ 141.73. The results of the univariate sensitivity analyzes showed that the variables with the greatest impact on the results were:

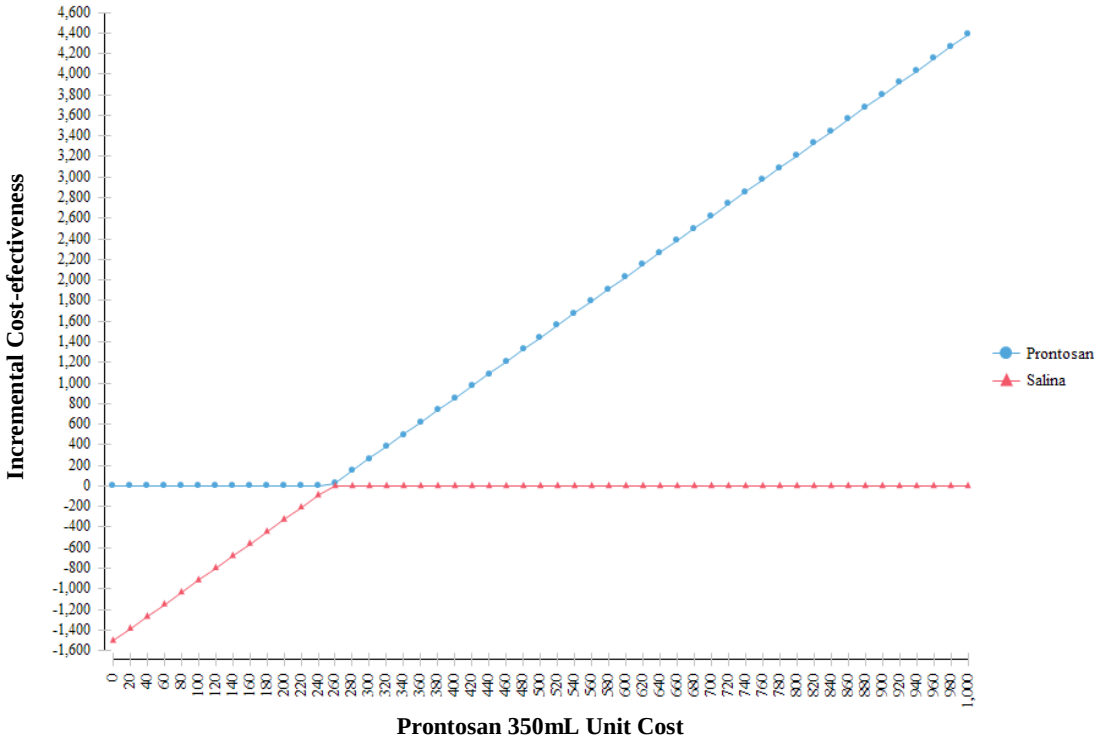
- ***Probability of recurrence - Prontosan®:*** in Prontosan® Solution's best case scenario, considering the monthly probability of 4.40%, using the solution would remain cost-saving, saving R$ 409.79 every month free of chronic wounds; considering the upper limit wherein the monthly probability would be 5.38%, the result would be a R$ 275.67 ICER per month free of chronic wounds using Prontosan ® Solution.
- ***Probability of recurrence – Saline:*** in Prontosan® Solution's best case scenario, considering the monthly probability of 5.38%, using the solution would remain cost-saving, saving R$ 377.82 every month free of chronic wounds; considering the case less favorable to the product, in which the probability would be 4.40% every month, and this would result in a ratio of incremental cost-effectiveness of R$ 304.70 per month free of chronic wounds using Prontosan® Solution.
- ***Probability of complications – Saline:*** in Prontosan® Solution's best case scenario, considering the monthly probability of 2.52%, using the solution would remain cost-saving, saving R$ 187.85 every month free of chronic wounds; considering the case less favorable to the product, in which the monthly probability was 2.06%, the result would remain cost-saving, saving 96.22 every month free of chronic wounds with the use of Prontosan Solution.
- ***Cost of Materials:*** considering a cost of R$ 68.08 for materials, using the solution would remain cost-saving, with an economy of R$ 158.75 per month free of chronic wounds; considering that the upper limit on the cost of materials is R$ 102.12, the result would remain cost-saving with savings of R$ 124.71 per month free of chronic wounds.
- ***Cost of Prontosan® Solution 350 mL:*** in Prontosan® Solution's best case scenario, which was considered a cost of R$ 206.82, a value lower than the baseline scenario,

using the solution would remain cost-saving, with an economy of R$ 277.10 per month free of chronic wounds; considering the upper limit, considered a value of R$ 252.78, the result would remain cost-saving with a cost-effectiveness incremental negative ratio of R$ 6.35 per month free of wounds chronic using Prontosan® Solution. Since the Unit Cost of the product significantly influences the outcome of the model, a detailed analysis of the influence on the ICER cost was performed and the results are shown in Picture 3. The graph shows that at a cost of approximately R$ 260.00 per bottle of 350 mL, the test result would still be cost-saving, ie, provide greater effectiveness at lower cost, bringing thus a monthly saving per month free of chronic wounds to the payer.

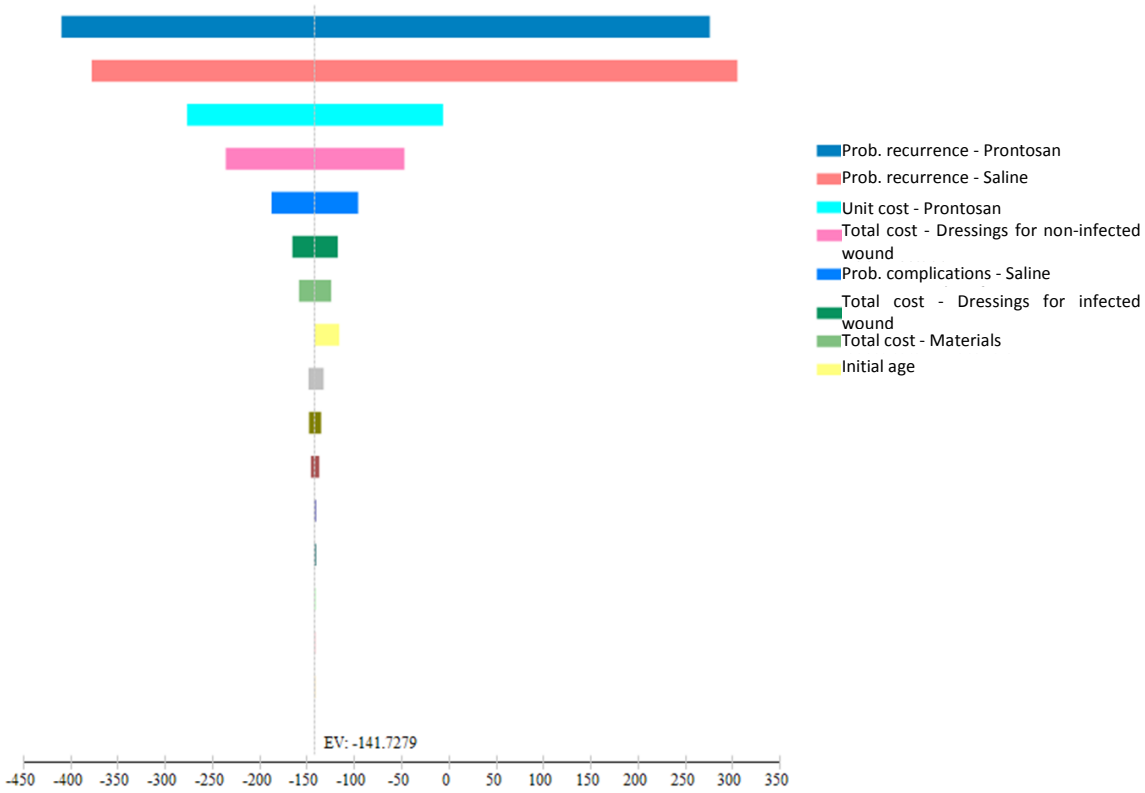
- ***Total Cost – Dressings for non-infected wounds:*** in Prontosan® Solution's best case scenario, a monthly cost of R$ 901.1 was considered, which is a lower value than the one in the baseline scenario, and the use of the solution remains cost-saving, with a savings of R$ 236.11 per month free of chronic wounds; considering the limit, in which it a monthly amount of R$ 1,101.30 was considered, the result would be a reason for negative incremental cost-effectiveness of R$ 47.35 per month free of chronic wounds using Prontosan ® Solution.
- ***Total Cost – Dressings for infected wounds:*** in Prontosan® Solution's best case scenario, a monthly cost of R$ 4,630.10 was considered, which is a higher amound than the one in the baseline scenario, and the use of the solution would remain cost-saving, with a savings of R$ 165.78 per month free of chronic wounds; considering the lower limit, in which a monthly amount of R$ 3,788.30 was considered, the result would remain cost-saving, with savings of R$ 117.68 per month free of chronic wounds using Prontosan® Solution.

The other parameters had little impact on the results, as shown graphically in the tornado chart in Picture 4. In all other scenarios the incremental cost-effectiveness ratio remained below the limit of GDP per capita.

Picture 3. Relationship ICER x Prontosan ® 350 mL Unit Cost



Picture 4. Tornado Chart - Univariate sensitivity analysis - Saline (Comparator)



3.13.1 Costs x Dressing Exchange Regimen

We performed a sensitivity analysis in order to evaluate the influence of dressing exchange arrangements in the final results of the model. For this, the cost of both solutions under comparison and the dressing materials had to be adjusted so that the monthly charge was appropriate to the considered period of dressing change. The time between exchanges varied between 1 and 7 days and the values of cost, effectiveness and ICER were evaluated. Table 26 shows the results of this analysis.

Table 26. Results according to the variation of the period between changes

Prontosan	Saline

Change (days)	Cost	Effectiveness	Cost	Effectiveness	ICER
1	R$ 120,777.46	162.38	R$ 123,152.32	153.63	(R$ 271,34)
2	R$60,446.29	162.38	R$ 61,970.36	153.63	(R$ 174.13)
3	R$ 40,335.90	162.38	R$ 41,576.37	153.63	(R$ 141.73)
4	R$ 30,280.70	162.38	R$ 31,379.38	153.63	(R$ 125.53)
5	R$ 24,247.59	162.38	R$ 25,261.18	153.63	(R$ 115.81)
6	R$ 20,225.51	162.38	R$ 21,182.39	153.63	(R$ 109.33)
7	R$ 17,410.05	162.38	R$ 18,327.23	153.63	(R$ 104.79)

According to the model results, less frequent exchanges improves ICER. This occurrence is explained since the greater the number of exchange times more economic benefit of Prontosan is observed. Independent to the frequency of exchanges adopted, the results remain cost-saving.

3.14 Probabilistic sensitivity analysis

The sensitivity analysis considers probabilistic variation of several parameters at a time, and were performed by assigning a probability distribution suitable for each of the parameters. For the efficacy parameters a beta probability distribution was assigned, to the cost parameters a probability distribution range and to the initial age of the patients a normal distribution was given. The values considered for calculating the parameters of the probability distributions are detailed in Table 27.

Table 27. Distribution Probabilities considered in the probabilistic sensitivity analysis

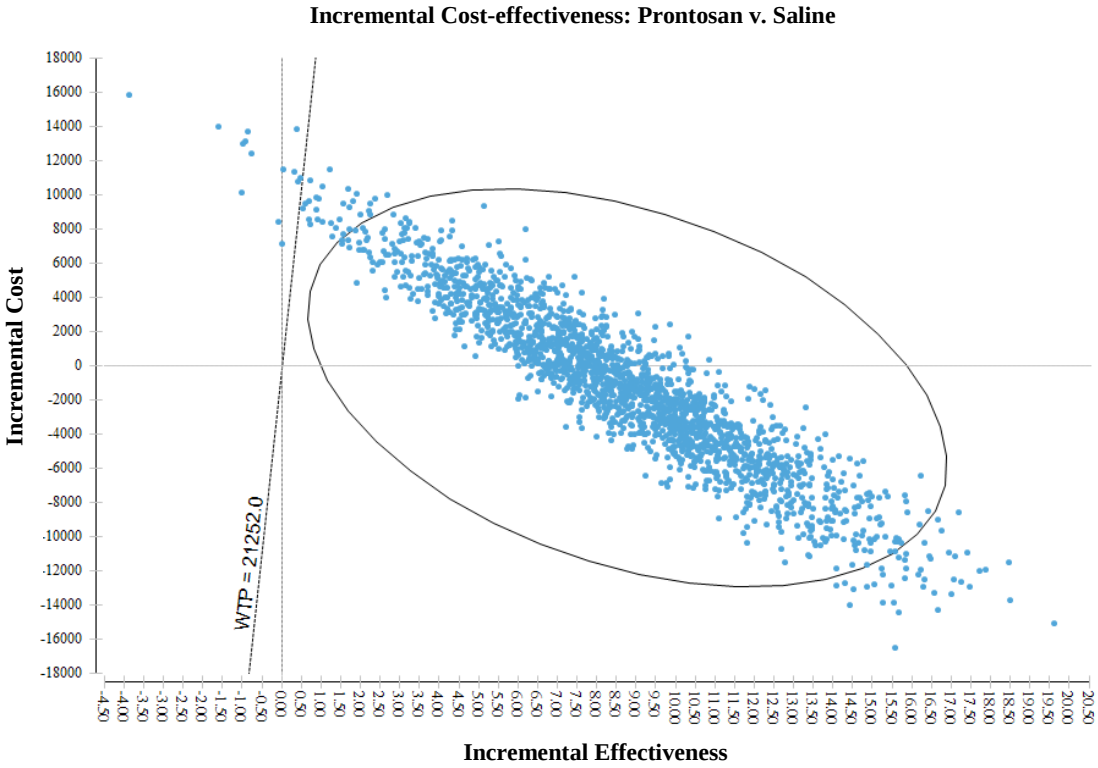
Parameters	Distribution	Average	DP
Initial average age	Normal	20	2.00
Prob. recurrence – Prontosan 350 mL	Beta	4.89%	0.489%
Prob. recurrence – Saline 500 mL	Beta	4.89%	0.489%
Prob. Complications – Saline	Beta	2.29%	0.229%
Unitary cost – Prontosan 350 mL	Gama	229.80	22.98
Unitary cost – Saline 100/250 mL	Gama	3.83	0.383
Total Cost – Materials	Gama	85.01	8.501
Total Cost – Dressings for infected wounds	Gama	420.92	42.092
Total Cost – Dressings for non-infected wounds	Gama	100.12	10.012

Probabilistic sensitivity analysis was calculated with 2000 iterations. The results were evaluated and classified into: Quadrant 1 (incremental effectiveness> 0 and incremental cost> 0); Quadrant 2 (incremental effectiveness <0 and incremental cost> 0); Quadrant 3 (incremental effectiveness <0 and incremental cost <0) and quadrant 4 (incremental effectiveness> 0 and incremental cost <0).

The results of the probabilistic sensitivity analysis are shown in

Picture 5.

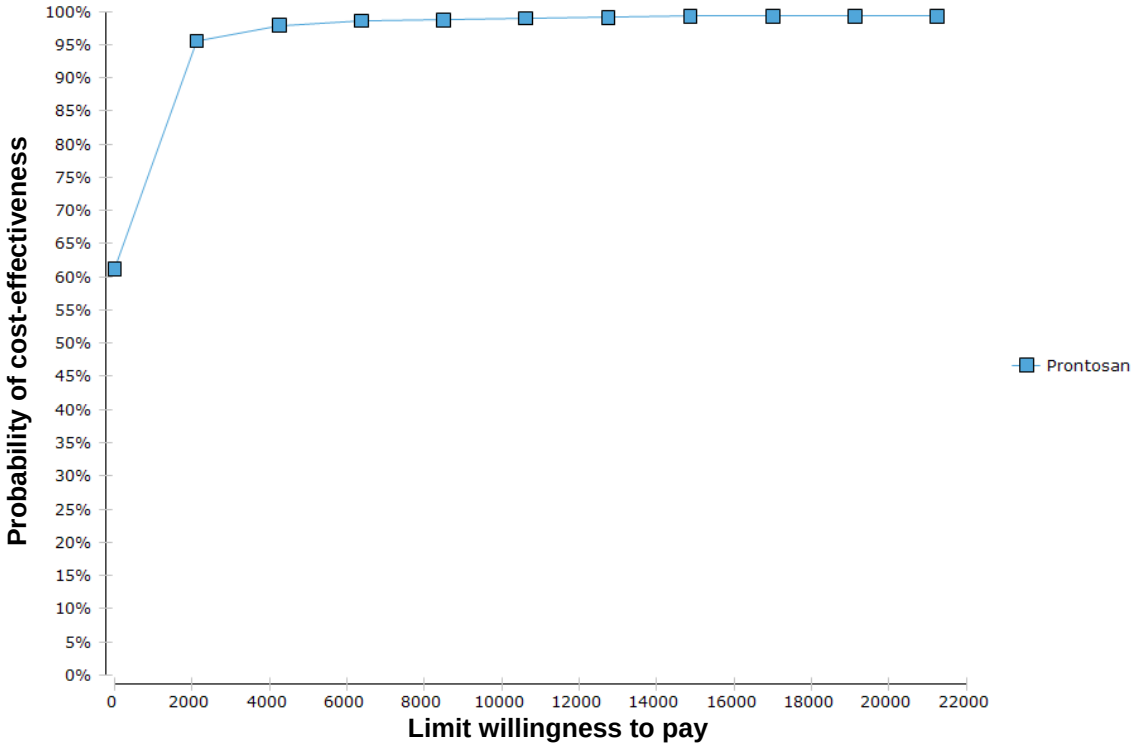
Picture 5. Results of the probabilistic sensitivity analysis - Saline



The results of the probabilistic sensitivity analysis showed that 38.4% of the results remained in quadrant 1, representing incremental results with greater effectiveness (Prontosan® Solution brings greater benefit in face of its comparators) and an also higher incremental cost (Prontosan® Solution has higher cost in face of to its comparators). In 61.2% of cases we obtained a result in quadrant 4, which represents greater incremental effectiveness and incremental cost lower than zero, leading to a cost-saving scenario. So, the result obtained in 99.3% of cases the reason of incremental cost-effectiveness was less than one time the GDP per capita in Brazil (R$ 21,252.00).

The probability of Prontosan ® Solution being cost-effective depends on the threshold willingness to pay per month free of wounds and it is shown in the cost-effectiveness acceptance curve, in Picture 6. It can be observed that, with a limit of willingness to pay equal to zero, cost-effectiveness can be reached inapproximately 61% of cases. This indicates that with a probability close to 61% there will be no need of investment by the payer. With a willingness to pay threshold of approximately R$ 13,000.00 per month free of chronic wounds, more than 99% of cases reached within the limits of cost-effectiveness (Picture 7).

Picture 6. Cost-effectiveness Acceptance Curve – Saline solution



Picture 7. Cost-effectiveness acceptance curve (values between 95 and 100%)

4 Budget impact analysis

Health economic analysis, such as cost-effectiveness analysis, are powerful tools used by policymakers and health funders of health resource allocation as selection of the best investments for limited financial resources. However, they are not able to respond to specific funding issues for the object of analysis. Therefore, we created a budget impact analysis, where the lender can estimate (observing the amount of patients who present chronic wounds in the health system) the financial resources needed to enable the incorporation of treatment Prontosan® Solution by the supplementary health system. The estimated budg impact requires the definition of the population eligible to treatment. According to the IBGE [94], the projection of the Brazilian population aged over 20 years, in 2012, was 129,953,614. Of these, an average of 25.1% is covered by the health system, resulting in a population of 36,314,574 people. The incidence of chronic wounds in this age group varies between 2.5% and 3.5%. Table 28 presents the detailed calculation of the eligible population to treatment with Prontosan ® Solution in the year 2012.

Table 28. Population eligible for treatment – Baseline Scenario

Age range	Brazilian population 2012[i]	Population with private health insurance 2012[ii]	% of population with health insurance	% of chronic wound[iii]	Population with health insurance and chronic wound

20 to 29	34,955,799	9,400,107	26.9%	2.50%	235,003
30 to 39	30,147,083	9,579,203	31.8%	2.50%	239,480
40 to 49	25,253,910	6,905,104	27.3%	2.50%	172,628
50 to 59	18,706,936	5,053,483	27.0%	2.50%	126,337
60 to 69	11,519,233	2,837,036	24.6%	2.50%	70,926
70 to 79	6,394,682	1,616,637	25.3%	2.50%	40,416
80 and over	2,975,971	923,004	31.0%	3.50%	32,305
Overall	**129,953,614**	**36,314,574**	**25.1%**		**917,094**

[i] Health Department– DATASUS. Available at: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?ibge/cnv/popuf.def - Acessed November 6, 2012

[ii] Supplementary National Health Agency – ANS. Available at: http://www.ans.gov.br/anstabnet/anstabnet/deftohtm.exe?anstabnet/dados/TABNET_BR.DEF - Acessed November 6, 2012

[iii] World Health Organization. Wound and lymphoedema management. 2010. http://whqlibdoc.who.int/publications/2010/9789241599139_eng.pdf - Acessed November 6, 2012

Since the treatment of patients with chronic wounds extending throughout its life horizon, the budget impact was calculated only for the first years of treating patients with this health situation. Table 29 presents the total annual cost of the first year of treatment for all comparators involved in the analysis.

Table 29. Total Annual Cost per Patient

Time	Prontosan® Solution	Saline Solution
1 year	R$ 5,889.67	R$ 5,972.35

From the results found in the model of cost-effectiveness and the estimated eligible population, a budget impact of the incorporation of Prontosan ® Solution to the private health system was estimated. This budget impact considers a hypothetical scenario in which all eligible patients would be treated immediately with Prontosan ® Solution.

Table 30. Budgetary impact projected in 2012

Total Cost	Eligible Population	Cost (3 years treatment)	Budget Impact (3 years treatment)
Prontosan® Solution	**917,094**	**R$ 5,889.67**	**R$ 5,401,381,018.98**
Saline	917,094	R$ 5,972.35	R$ 5,477,206,350.90
Incremental			**(R$ 75,825,331.92)**

Thus, a negative budget impact of approximately R$ 75.8 million, i.e., the first year of treatment, incorporating Prontosan® solution to health system represent a saving of R$ 75.8 million.

5 Conclusion

Prontosan® Solution is a solution made of 0.1% polihexanide and 0.1% betaine, duly registered in the country as a Class III medical device since 2008. It has shown over the years differential benefits in the management of chronic wounds, especially in the prevention of complications such as secondary infections, given the best cleaning and debridement when compared to saline and Ringer's solutions.

The solution made from polihexanide and betaine can be used between dressing changes and still be combined with the dressing, making a better preparation of the wound bed to receive coverage, composing, thus, one of the primary steps of the topical treatment of chronic wounds.

Based on all the scientific information available these days, Prontosan® Solution is clearly recognized as a safe and effective health product for the treatment of chronic wounds.

An economic evaluation and budget impact was performed in order to analyze the strategies of treatment of chronic wounds in the setting of the health system by assessing whether the additional cost provided by the use of Prontosan® Solution is justified when compared to the treatment with saline given the expected clinical gain in terms of months free of chronic wounds.

Efficacy results were gathered from a non-concurrent cohort study on the treatment of patients with chronic wounds compared to a control group receiving treatment with saline or Ringer's, with the goal of determining how treatment impacts the percentage of wounds completely healed and its healing time. Treatment with Prontosan® showed a significant reduction in the healing time and increased the percentage of wounds healed completely within 6 months. There was also a favorable result for the reduction of infections resulting from unhealed wounds.

A cost-effectiveness analysis conducted showed that treatment with Prontosan® Solution has greater benefit at lower cost, and is considered cost-saving when compared to treatment using saline. Although there are uncertainties about the parameters of cost and effectiveness considered in the analysis, all these parameters were tested in sensitivity analysis. The results of the probabilistic sensitivity analysis performed showed that the results are favorable to the use of Prontosan® Solution in 99.3% of cases (ICER results that have less than 1 time per capita GDP of Brazil).

The estimated budget impact analysis will need maximum commitment of resources to enable the incorporation of treatment with Prontosan® Solution in the Supplementary Health System.

We estimated savings of approximately R$ 75.8 million in the first year of treatment after the merger, considering a hypothetical scenario in which all eligible patients were treated with Prontosan ® Solution.

6 References

1. Brazilian Health Department 2002. Manual de Condutas para Úlceras Neurotróficas e Traumáticas *(Manual for Operation of Neurotrophic and Traumatic Ulcers)* http://bvsms.saude.gov.br/bvs/publicacoes/manual_Wounds_final.pdf - Acessed November 6, 2012

2. Phillips PL, Wolcott RD, Fletcher J, Schultz GS. Biofilms Made Easy. Wounds International 2010; 1(3). http://www.woundsinternational.com/pdf/content_8851.pdf - Acessed November 15, 2012

3. Cooper R, Okhiria O. Biofilms, infection and the issue of control. Wounds UK 2006;2:48-57.

4. Schierle CF, De la Garza M, Mustoe TA Galiano RD. Staphylococcal biofilms impair wound healing by delayed reepithelialisation in a murine cutaneous wound model. Wound Rep Regen 2009; 17:354-9.

5. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999; 284(5418):1318-22.

6. Rocha JA et al. Abordagem terapêutica das úlceras de pressão - Intervenções baseadas na evidência. *(Therapeutic approach of pressure ulcers - evidence-based interventions.)*Acta Med Port 2006; 19:29-38.

7. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):35S-41S.

8. World Health Organization. Wound and lymphoedema management. 2010. http://whqlibdoc.who.int/publications/2010/9789241599139_eng.pdf - Acessed November 6, 2012

9. Ferreira MC, Tuma P Jr, Carvalho VF. Complex wounds. Clinics. 2006;61(6):571-8.

10. SANT'ANA SMSC. ÚLCERAS VENOSAS: CARACTERIZAÇÃO E TRATAMENTO EM USUÁRIOS ATENDIDOS NAS SALAS DE DRESSINGS DA REDE MUNICIPAL DE SAÚDE DE GOÂNIA/GO. (*VENOUS ULCERS: CHARACTERIZATION AND TREATMENT IN USERS SERVED IN DRESSING ROOMS OF MUNICIPAL HEALTH NETWORK OF GOÂNIA / GO.*)Dissertation submitted to the Post Graduation Program in Nursing, School of Nursing, Federal University of Goiás in order to obtain the title of Master of Nursing. http://mestrado.fen.ufg.br/uploads/127/original_silvia-santana.pdf - Acessed October 10, 2012

11. Yamada BFA. Terapia tópica de Wounds: limpeza e Debridamento. *Topical therapy of wounds: cleaning and debridement*.Rev Esc Enf USP 1999;33:133-40.

12. Hess CT, Kirsner RS. Orchestrating wound healing: assessing and preparing the wound bed. Adv Skin Wound Care. 2003 Sep-Oct;16(5):246-57; quiz 258-9.

13. European Wound Management Association (EWMA). Position Document: Wound Bed Preparation in Practice. London: MEP Ltd, 2004. http://www.woundsinternational.com/pdf/content_49.pdf - Acessed October 15, 2012

14. Sibbald RG et al. Best Practice Recommendations for Preparing the Wound Bed: Update 2006. http://cawc.net/images/uploads/wcc/4-1-vol4no1-BP-WBP.pdf - Acessed October 15, 2012

15. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, Stacey MC, Teot L, Vanscheidt W. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003 Mar;11 Suppl 1:S1-28.

16. Cutting KF. Addressing the challenge of wound cleansing in the modern era. Br J Nurs, 2010; 19(11Suppl) S24-S29.

17. Fernandez R, Griffiths R, Ussia C. Water for wound cleansing. Cochrane Database Syst Rev. 2012 Feb 15;2:CD003861.

18. Yamada BFA. Úlceras Venosas.(*Venous Ulcers)* In: Jorge AS, Dantas SRPE. *Multidisciplinary approach to the treatment of wounds.* São Paulo: Atheneu; 2003. p 247-59.

19. Oliveira AC, Martinho GH, Nunes AA. Wounds e Dressings (*Wounds and Dressings)*. In: Martins AP. Manual de Infecção Hospitalar. Epidemiologia, Prevenção, Controle. *(Manual of Hospital Infection. Epidemiology, Prevention and Control)* 2a ed. CCIH-Hospital das Clínicas-UFMG. Belo Horizonte: MDSI; 2001. p. 325-35.

20. Borges EL. Limpeza e Debridamento. *(Cleansing and Debridement) In*: Borges EL. Wounds; como tratar. (*Wounds: How to treat)* Belo Horizonte: COOPMED, 2001. 130p.

21. Andriessen AE, Eberlein T. Assessment of a wound cleansing solution in the treatment of problem wounds. Wounds 2008; 20(6):171-5.

22. Guimarães Barbosa JA, Nogueira Campos LM. Diretrizes para o Tratamento da Úlcera Venosa. *(Guidelines for the Treatment of Venous Ulcers)* Enfermería Global,2010;9(3):1-13. http://revistas.um.es/eglobal/article/view/111001 - Acessed October 17, 2012

23. Health Service Executive. National best practice and evidence based guidelines for wound management. Ireland. 2009. http://www.hse.ie/eng/services/Publications/services/Primary/woundguidelines.pdf - Acessed October 17, 2012

24. International Working Group on the Diabetic Foot. Specific guidelines on wound and wound bed management 2007. http://www.iwgdf.org/index.php?option=com_content&task=view&id=80&Itemid=125 - Acessed October 17, 2012

25. Kramer, A., Daeschlein, G., Kammerlander, G. et al. Consensus paper on wound antisepsis. JOURNAL OF WOUND CARE;13(4), APRIL 2004. http://www.werner-

sellmer.de/Downloads/Leitlinien/Konsensusempfehlung%20Wundantiseptik%202004%20Englisch.pdf - Acessed October 30, 2012.

26. Dissemond, J., Gerber, V., Kramer, A. et al. Practice-oriented expert recommendation for the treatment of critically colonised and local infected wounds using polihexanide. Zeitschrift für Wundheilung 2009;14: 1, 20-26.

27. Gilliver S. PHMB: a well-tolerated antiseptic with no reported toxic effects. 2009; J Wound Care;9-14. http://www.activahealthcare.co.uk/casestudies-files/SXP025-S-Gilliver-PHMB-a-well-tolerated-antiseptic-with-.pdf - Acessed November 6, 2012

28. Grupo Nacional para el Estudio y Asesoramiento en Ulceras por Presión y Heridas Crónicas (GNEAUPP). Directrices Generales sobre Tratamiento de las Úlceras por Presión. Logroño. 2003 http://www.gneaupp.es/app/adm/documentos-guias/archivos/5_pdf.pdf - Acessed November 26, 2012

29. Documento GNEAUPP Nº VIII - Recomendações sobre a utilização de antissépticos no cuidado de Wounds crónicas *(Recommendations on the use of antiseptics in the care of chronic wounds)* - http://www.gneaupp.es/app/adm/documentos-guias/archivos/80_pdf.pdf - Acessed November 26, 2012

30. Moore K, Gray D. Using PHMB antimicrobial to prevent wound infection. Wounds UK 2007; 3(2):96-102.

31. Gray D, Barrett S, Battacharyya M et al. PHMB and its potential contribution to wound management. Wounds UK 2010;6(2):40-46.

32. Yasuda K, Ohmizo C, Katsu T. Potassium and tetraphenylphosphonium ion-selective electrodes for monitoring changes in the permeability of bacterial outer and cytoplasmic membranes. J Microbiol Methods 2003;54(1):111-15.

33. Kaehn K, Eberlein T. In-vitro test for comparing the efficacy of wound rinsing solutions. Br J Nurs 2009;18(11):S4-S10.

34. Thomas GW, Rael LT, Bar-Or R, et al. Mechanisms of Delayed Wound Healing by Commonly Used Antiseptics. J TRAUMA 2009;66:82-91.

35. Schnuch A, Geier J, Uter W, et al. Polyhexamethylene biguanide: a relevant contact allergen? Contact Dermatitis 2000; 42(5):302-3.

36. Schnuch A, Geier J, Uter W, et al. The biocide polyhexamethyline biguanide remains an uncommon contact allergen. Contact Dermatitis 2007; 56(4):235-59.

37. Kramer A, Roth B, Müller G, Rudolph P, Klöcker N. Influence of the Antiseptic Agents polihexanide and Octenidine on FL Cells and on Healing of Experimental Superficial Aseptic Wounds in Piglets - A Double-Blind, Randomised, Stratified, Controlled, Parallel-Group Study. Skin Pharmacol Physiol. 2004 May-Jun;17(3):141-6.

38. Seipp HM et al. Wirksamkeit verschiedener wundspüllösungen gegenüber Biofilmen [Efficacy of various wound irrigation solutions against biofilm]. Zeitschrift für Wundheilung; 4(5):160-4, 2005.

39. Hirsch T, Koerber A, Jacobsen F, Dissemond J, Steinau HU, Gatermann S, Al-Benna S, Kesting M, Seipp HM, Steinstraesser L. Evaluation of toxic side effects of clinically used skin antiseptics in vitro. J Surg Res. 2010 Dec;164(2):344-50.

40. Perez R, Davies SC, Kaehn K. Effect of different wound rinsing solutions on MRSA biofilm in a porcine wound model. Wund Management 2010;4(2);44-8.

41. Hübner NO, Matthes R, Koban I, Rändler C, Müller G, Bender C, Kindel E, Kocher T, Kramer A. Efficacy of chlorhexidine, polihexanide and tissue-tolerable plasma against Pseudomonas aeruginosa biofilms grown on polystyrene and silicone materials. Skin Pharmacol Physiol. 2010;23 Suppl:28-34.

42. Goertz O, Hirsch T, Ring A, Steinau HU, Daigeler A, Lehnhardt M, Homann HH. Influence of topically applied antimicrobial agents on muscular microcirculation. Ann Plast Surg. 2011 Oct;67(4):407-12.

43. Minnich KE, Stolarick R, Wilkins RG, Chilson G, Pritt SL, Unverdorben M. The Effect of a Wound Care Solution Containing polihexanide and Betaine on Bacterial Counts: Results of an In vitro Study . Ostomy Wound Manage. 2012 Oct;58(10):32-6.

44. BRASIL. Health Department. Secretariat of Science, Technology and Strategic Inputs. Department of Science and Technology. Methodological Guidelines: preparation of technical-scientific opinions. 2nd edition revised and enlarged. Brasília: Health Department, 2009. Available at: http://bvsms.saude.gov.br/bvs/publicacoes/elaboracao_pareceres_tecnico_cientifico.pdf - Acessed October 17, 2012

45. NCT01048307 - Effect of Prontosan Wound Irrigation Solution on Venous Ulcers. http://www.clinicaltrials.gov/ct2/show/NCT01048307?term=Prontosan&rank=1 - Acessed November 7, 2012

46. NCT01153633 - Trial on the Efficacy of Prontosan Wound Irrigation Solution and Prontosan Wound Gel. http://www.clinicaltrials.gov/ct2/show/NCT01153633?term=Prontosan&rank=2 - Acessed November 7, 2012

47. NCT01554644 - Prontosan Versus Saline in the Cleansing of Chronic Leg Ulcers in Diabetic Patients. http://www.clinicaltrials.gov/ct2/show/NCT01554644?term=Prontosan&rank=3 - Acessed November 7, 2012

48. NCT01534858 - A Prospective, Descriptive Cohort Study With Prontosan® Wound Gel X in Partial and Full Thickness Burns Requiring Split Thickness Skin Grafts. http://www.clinicaltrials.gov/ct2/show/NCT01534858?term=Prontosan&rank=4 - Acessed November 7, 2012

49. NCT01333670 - Efficacy of Prontosan Solution on Chronic Ulcers. http://www.clinicaltrials.gov/ct2/show?term=Prontosan&rank=5 - Acessed November 7, 2012

50. Valenzuela AR, Perucho NS. [The effectiveness of a 0.1% polihexanide gel]. Rev Enferm. 2008 Apr;31(4):7-12. [Article in Spanish]

51. González JA, Resúa MR. [Effective cleansing and decontamination of the base of an injury; reduction in time for cicatrization]. Rev Enferm. 2008 Feb;31(2):20-1. [Article in Spanish]

52. Romanelli M, Dini V, Barbanera S, Bertone MS. Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation. Skin Pharmacol Physiol. 2010;23 Suppl:41-4.

53. Eberlein T, Assadian O. Clinical use of polihexanide on acute and chronic wounds for antisepsis and decontamination. Skin Pharmacol Physiol. 2010;23 Suppl:45-51.

54. Hübner NO, Kramer A. Review on the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic. Skin Pharmacol Physiol. 2010;23 Suppl:17-27.

55. Kaehn K. polihexanide: a safe and highly effective biocide. Skin Pharmacol Physiol. 2010;23 Suppl:7-16.

56. Roth B, Brill FH. polihexanide for wound treatment--how it began. Skin Pharmacol Physiol. 2010;23 Suppl:4-6.

57. Protosan. http://www.prontosan.co.uk/evidence.html - Acessed October 17, 2012

58. Horrocks A. Prontosan wound irrigation and gel: management of chronic wounds. Br J Nurs. 2006 Dec 14-2007 Jan 10;15(22):1222, 1224-8.

59. Möller A, Kaehn K, Nolte A. [Experiences with the use of polihexanide-containing wound products in the management of chronic wounds – results of a methodical and retrospective analysis of 953 patients] Erfahrungen mit dem Einsatz polihexanidhaltiger Wundprodukte bei der Versorgung chronischer Wunden – Ergebnisse einer systematischen retrospektiven Untersuchung an 953 Patienten. Wund Management, 2004;. http://www.prontosan.co.uk/docs/Clinical%20Evidence/Moller%20A,Nolte%20A,%20Kaehn%20K.pdf - Acessed November 14, 2012

60. Eduardo José Ferreira dos Santos; Margarida Alexandra Nunes Carramanho Gomes Martins Moreira da Silva. Tratamento de Wounds colonizadas/infetadas com utilização de polihexanida *(Treating colonized / infected wounds with the use of polihexanide)* Rev. Enf. Ref. serIII n.4 Coimbra jul. 2011, pp.135-142. http://www.scielo.gpeari.mctes.pt/pdf/ref/vserIIIn4/serIIIn4a14.pdf - Acessed November 6, 2012

61. Forma O. Valutazione dell'utilizzo di una soluzione detergente "Prontosan" come coadiuvante nel trattamento delle ulcere. Acta Vulnologica 2006 Settembre;4(3):113-7. http://www.minervamedica.it/it/riviste/acta-vulnologica/articolo.php?cod=R45Y2006N03A0113 - Acessed November 6, 2012

62. Bradbury S, Fletcher J. Prontosan® made easy. Wounds International. Volume 2 | Issue 2 | May 2011. http://www.woundsinternational.com/pdf/content_9864.pdf - Acessed November 6, 2012

63. Kramer A, Hübner NO, Assadian O, Mulder G. polihexanide - perspectives on clinical wound antisepsis. Skin Pharmacol Physiol. 2010;23 Suppl:1-3.

64. Dissemond J, Gerber V, Kramer A, Riepe G, Strohal R, Vasel-Biergans A, Eberlein T. A practice-oriented recommendation for treatment of critically colonised and locally infected wounds using polihexanide. J Tissue Viability. 2010 Aug;19(3):106-15.

65. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011 Apr;64(4):407-15.

66. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

(for definitions of terms used see glossary at http://www.cebm.net/?o=1116) - http://www.cebm.net/index.aspx?o=1025 - Acessed November 26, 2012

67. Greenfield S, Platt R. Can observational studies approximate RCTs? Value Health. 2012 Mar-Apr;15(2):215-6.

68. de Araujo T, Valencia IC, Federman DG, Kirsner RS. Managing the patient with venous ulcers. Ann Intern Med. 2003;138(4):326-34.

69. Baptista CM, Castilho V. Cost survey of procedure with Unna boot in patients with venous ulcer. Rev Latinoam Enferm. 2006;14(6):944-9.

70. Collier M. Tissue viability. Leg ulceration: a review of causes and treatment. Nurs Stand. 1996;10(31):49-51.

71. Heit JA, Rooke TW, Silverstein MD, Mohr DN, Lohse CM, Petterson TM, et al. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. J Vasc Surg. 2001;33(5):1022-7.

72. Nelzén O. Leg ulcers: economic aspects. Phlebology. 2000;15:110-4.

73. Ruckley CV. Socioeconomic impact of chronic venous insuffciency and leg ulcers. Angiology. 1997;48(1):67-9.

74. Simon DA, Freak L, Kinsella A, Walsh J, Lane C, Groarke L, et al. Community leg ulcer clinics: a comprehensive study in two health authorities. BMJ. 1996;312(7047):1648-51.

75. National Prescribing Centre. Modern wound dressings: the absence of evidence. In: National Prescribing Centre. MeReC Extra Issue No. 31. NHS: Liverpool, 2008. p. 2. - http://www.npc.nhs.uk/merec/infect/commonresp/resources/merec_extra_no31.pdf - Acessed December 6, 2012

76. Sultan MJ, McCollum C. Don't waste money when dressing leg ulcers. Br J Surg. 2009;96(10):1099-100.

77. Ragnarson Tennvall G, Hjelmgren J. Annual costs of treatment for venous leg ulcers in Sweden and the United Kingdom. Wound Repair Regen. 2005 Jan-Feb;13(1):13-8.

78. Silva MdeC. Chronic venous insuffciency of the lower limbs and its socio-economic signifcance. Int Angiol. 1991;10(3):152-7.

79. Health Department - Hospital Information System of the Unified Health System (SIH / SUS). SUS hospital procedures - by place of detention - Brasil. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/qiuf.def - Acessed December 6, 2012

80. Bradshaw DJ, Marsh PD, Allison C, Schilling KM. Effect of oxygen, inoculum composition and flow rate on development of mixed culture oral biofilms. Microbiology 1996; 142: 623-629.

81. Gethin G. The significance of surface pH in chronic wounds. Wounds UK, 2007;(3):52-56. http://www.woundsinternational.com/pdf/content_124.pdf - Acessed October 18, 2012

82. Borges EL. Limpeza e Debridamento. In: Borges EL. Wounds; como tratar. Belo Horizonte: COOPMED, 2001. 130p.

83. Brasil. Methodological Guidelines: studies of economic evaluation of health technologies. Secretariat of Science, Technology and Strategic Inputs, Department of Science and Technology. Brasília: Health Department, 2009.

84. Treeage Software, Inc. Available at: http://www.treeage.com

85. Brazilian Institute of Geography and Statistics (IBGE). Complete mortality table of 2010 - Both genders. Available at: www.ibge.gov.br. Accessed on: June 2012.

86. Escandon J, Vivas AC, Tang J, Rowland KJ, Kirsner RS. High mortality in patients with chronic wounds. Wound Repair Regen. 2011 Jul-Aug;19(4):526-8. doi: 10.1111/j.1524-475X.2011.00699.x. Epub 2011 Jun 7.

87. Brazilian Medical Association (AMB). Hierarchical Brazilian Classification of medical procedures – CBHPM, 2010. Available at http://www.amb.org.br/teste/cbhpm_2010.htm. Acessed August 2012

88. National Agency for Sanitary Vigilance. Executive Secretary - CMED. List of prices of medications. Updated June 19, 2012. Accessed on: June 2012.

89. Hess, CT & Kirsner, RS. Orchestrating Wound Healing: Assessing and Preparing the Wound Bed, Adv Skin Wound Care 2003;16:246-59.

90. Care Protocol for Patients with Wound, Municipality of Belo Horizonte, Management and Assistance - Coordination of Health Care of Adults and the Elderly, 2006.

http://www.pbh.gov.br/smsa/biblioteca/atadulto/protocoloWounds.pdf - Acessed February 5, 2013

91. Wound Care Protocol, Florianópolis City Hall, the Municipality Health: IOESC, 2008. http://www.pmf.sc.gov.br/arquivos/arquivos/pdf/26_10_2009_10.46.46.f3edcb3b301c541c121c7786c676685d.pdf - Acessed February 5, 2013

92. BRASÍNDICE Magazine. Available at: http://www.brasindice.com.br/

93. SIMPRO Table. Available at: http://www.simpro.com.br

94. Brazilian Institute of Geography and Statistics (IBGE). Population Projection. Available at: www.ibge.gov.br. Acessed June 2012

Appendix I

Prices of saline solutions for hospital use

(closed system, leading manufacturers) *

			ICMS 19%	
Description CMED	**Manufacter**	**Units**	**Factory price: box**	**Factory price: unit**
SODIUM CHLORIDE - BAXTER - 9 MG/ML SOL INJ IV BOLS PVC INC SIST FECH X **100** ML	Baxter	01	4.19	4.19
SODIUM CHLORIDE - BAXTER - 9 MG/ML SOL INJ IV BOLS PVC INC SIST FECH X **250** ML	Baxter	01	3.61	3.61
1 SOLUÇÃO DE SODIUM CHLORIDE B.BRAUN - 9 MG/ML SOL INJ IV CX 50 FA PLAS INC SIST FECH x **100** ML	B.Braun	50	209.67	4.19
2 SOLUÇÃO DE SODIUM CHLORIDE B.BRAUN - 9 MG/ML SOL INJ IV CX 30 FA PLAS INC SIST FECH X **250** ML	B.Braun	30	108.44	3.61
SODIUM CHLORIDE 0.9% - 9 MG/ML SOL INJ IV CX BOLS PP TRANS SIST FECH X **100** ML	Eurofarma Segmenta	01	4.18	4.18
SODIUM CHLORIDE 0.9% - 9 MG/ML SOL INJ IV CX BOLS PP TRANS SIST FECH X **250** ML	Eurofarma Segmenta	01	3.58	3.58
SODIUM CHLORIDE - 9 MG/ML SOL INJ IV CX BOLS PLAS TRANS SIST FECH X 100 ML	Fresenius	01	4.17	4.17
SODIUM CHLORIDE - 9 MG/ML SOL INJ IV CX BOLS PLAS TRANS SIST FECH X **250** ML	Fresenius	01	3.59	3.59
SODIUM CHLORIDE - 9 MG/ML SOL INJ IV CX BOLS PLAS TRANS SIST FECH X **250** ML	Halex Istar	40	133.58	3.34
SODIUM CHLORIDE - 9 MG/ML SOL INJ IV CX 60 BOLS PP TRANS SIST FECH X **100** ML	Halex Istar	60	231.96	3.86
			Average Unit Cost	**R$ 3.83**

* Prices found on the list of compliance “LISTA DE PREÇOS DE MEDICAMENTOS - PREÇOS FÁBRICA E PREÇO MÁXIMO AO CONSUMIDOR” ("LIST OF PRICE OF MEDICATIONS - FACTORY PRICES AND MAXIMUM CONSUMER PRICE "), updated in January 21, 2013

Appendix II

Table 1. Coverage for non-infected wounds**

			ICMS 19%	
Description SIMPRO	**Manufacturer**	**Units**	**Factory price: box**	**Factory price: unit**
Dressing Hidrocellular Askina Transorbent 10x10cm Steril	B Braun	1	R$79.47	R$79.47
Dressing Hidrocellular Askina Transorbent 15x15cm Steril	B Braun	1	R$111.01	R$111.01
Dressing Hidrocellular Askina Transorbent Border 9x14cm Steril	B Braun	1	R$100.04	R$100.04
Dressing Hidrocellular Askina Transorbent Border 14x14cm Steril	B Braun	1	R$112.02	R$112.02
Dressing Hidrocellular Askina Transorbent Border 17x17cm Steril	B Braun	1	R$180.38	R$180.38
Dressing Hidrocellular Askina Transorbent Border 24x24cm Steril	B Braun	1	R$318.93	R$318.93
Dressing Hidrocellular Askina Transorbent Border 18x20cm Steril	B Braun	1	R$212.96	R$212.96
Dressing Foam Hhydropolymer Tielle 7x9cm 10 unit	Systagenix	10	R$308.25	R$30.83
Dressing Foam Hhydropolymer Tielle Plus 11x11cm 10 unit	Systagenix	10	R$546.44	R$54.64
Dressing Foam Hhydropolymer Tielle 15x15cm 10 unit	Systagenix	10	R$980.79	R$98.08
Dressing Foam Hhydropolymer Tielle Plus 15x20cm 5unit	Systagenix	5	R$672.54	R$134.51
Dressing Foam Hhydropolymer Tielle 18x18cm 5unit	Systagenix	5	R$672.54	R$134.51
Dressing Foam Hhydropolymer Tielle Sacral 18x18cm 5unit	Systagenix	5	R$574.47	R$114.89
Dressing Foam Hhydropolymer Tielle Plus 11x11cm 10 unit	Systagenix	10	R$546.44	R$54.64
Dressing Foam Hhydropolymer Tielle Plus 15x15cm 10 unit	Systagenix	10	R$1,022.83	R$102.28
Dressing Foam Hhydropolymer Tielle Plus 15x20cm 10 unit	Systagenix	5	R$672.54	R$134.51
Dressing Absorb. Steril Micro Selective Adherence Mepilex 10X10cm Molnlycke	Neve	1	R$45.44	R$45.44
Dressing Absorb. Steril Micro Selective Adherence Mepilex 15X15cm Molnlycke	Neve	1	R$91.14	R$91.14
Dressing Absorb. Steril Micro Selective Adherence Mepilex 10X20cm Molnlycke	Neve	1	R$82.62	R$82.62
Dressing Absorb. Steril Micro Selective Adherence Mepilex 20X20cm Molnlycke	Neve	1	R$153.18	R$153.18
Dressing Absorb. Steril Micro Selective Adherence Mepilex 7,5X7,5cm Molnlycke	Neve	1	R$43.92	R$43.92

Dressing Absorb. Steril Micro Selective Adherence Mepilex 10X10cm Molnlycke	Neve	1	R$65.50	R$65.50
Dressing Absorb. Steril Micro Selective Adherence Mepilex 15X15cm Molnlycke	Neve	1	R$129.45	R$129.45
Dressing Absorb. Steril Micro Selective Adherence Mepilex 15X20cm Molnlycke	Neve	1	R$167.06	R$167.06
Dressing Absorb. Steril Auto Adherence Mepilex Transfer 15X20cm Molnlycke	Neve	1	R$160.35	R$160.35
Dressing Absorb. Steril Auto Adherence Mepilex Transfer 20X50cm Molnlycke	Neve	1	R$500.38	R$500.38
Dressing Hydrocellular Plate Allevyn 5X5cm 10 unit	Politec	10	R$371.00	R$37.10
Dressing Hydrocellular Plate Allevyn 10X10cm 10 unit	Politec	10	R$603.00	R$60.30
Dressing Hydrocellular Plate Allevyn 10X20cm 10 unit	Politec	10	R$704.00	R$70.40
Dressing Hydrocellular Plate Allevyn 20X20cm 10 unit	Politec	10	R$2,276.00	R$227.60
Dressing w/ Film Adhes. 5X5cm 100unid Polymen	Recomed	100	R$680.00	R$6.80
Dressing w/ Film Adhes. 10X13cm 60unid Polymen	Recomed	60	R$2,722.00	R$45.37
Dressing w/ Film Adhes. 15X15cm 60unid Polymen	Recomed	60	R$4,588.00	R$76.47
Dressing w/ Film Adhes. 10X32cm 12unid Polymen	Recomed	12	R$830.00	R$69.17
Dressing w/ Adhesive Tela Hypoalerg 5X5cm 100 unit Polymen	Recomed	100	R$876.00	R$8.76
Dressing w/ Adhesive Tela Hypoalerg 10X13cm 60 unit Polymen	Recomed	60	R$2,913.00	R$48.55
Dressing w/o Adhesive 8X8cm 60 unit Polymen	Recomed	60	R$1,625.00	R$27.08
Dressing w/o Adhesive 10X10cm 60 unit Polymen	Recomed	60	R$2,333.00	R$38.88
Dressing w/o Adhesive 13X13cm 30 unit Polymen	Recomed	30	R$1,809.00	R$60.30
Dressing w/o Adhesive 17X19cm 30 unit Polymen	Recomed	30	R$3,434.00	R$114.47
Dressing w/o Adhesive 10X32cm 12 unit Polymen	Recomed	12	R$1,983.00	R$165.25
Dressing Hydrocolloid Askina Hydro 10X10cm w/ Psyllium Husk	B Braun	1	R$53.28	R$53.28
Dressing Hydrocolloid Askina Hydro 15X15cm w/ Psyllium Husk	B Braun	1	R$116.28	R$116.28
Dressing Hydrocolloid Askina Hydro 20X20cm w/ Psyllium Husk	B Braun	1	R$129.61	R$129.61
Dressing Hydrocolloid 4x6 Steril Comfeel Plus	Coloplast	1	R$35.00	R$35.00
Dressing Hydrocolloid 10x10 Steril Comfeel Plus	Coloplast	1	R$61.00	R$61.00
Dressing Hydrocolloid 15x15 Steril Comfeel Plus	Coloplast	1	R$120.00	R$120.00
Dressing Hydrocolloid 15x20 Steril Comfeel Plus	Coloplast	1	R$121.00	R$121.00
Dressing Hydrocolloid 20x20 Steril Comfeel Plus	Coloplast	1	R$156.00	R$156.00
Dressing Hydrocolloid Transparente 5X7 Comfeel Plus	Coloplast	1	R$26.00	R$26.00
Dressing Hydrocolloid Transparente 10X10 Comfeel Plus	Coloplast	1	R$39.00	R$39.00

Dressing Hydrocolloid Transparente 9X14 Comfeel Plus	Coloplast	1	R$48.00	R$48.00
Dressing Hydrocolloid Transparente 5X25 Comfeel Plus	Coloplast	1	R$48.00	R$48.00
Dressing Hydrocolloid Transparente 15X20 Comfeel Plus	Coloplast	1	R$121.00	R$121.00
Dressing Hydrocolloid CGF 10X10cm Duoderm	Convatec	1	R$36.00	R$36.00
Dressing Hydrocolloid CGF 15X20cm Duoderm	Convatec	1	R$112.00	R$112.00
Dressing Hydrocolloid CGF 20X20cm Duoderm	Convatec	1	R$116.00	R$116.00
Dressing Hydrocolloid Restore Plus 10X10cm	Hollister	1	R$39.51	R$39.51
Dressing Hydrocolloid Restore Plus 15X20cm	Hollister	1	R$126.70	R$126.70
Dressing Hydrocolloid Restore Plus 20X20cm	Hollister	1	R$136.11	R$136.11
Dressing Hydrocolloid Hydrocoll 10X10cm	Bace	1	R$65.74	R$65.74
Dressing Hydrocolloid Hydrocoll 15X15cm	Bace	1	R$112.20	R$112.20
Dressing Hydrocolloid Hydrocoll 20X20cm	Bace	1	R$158.40	R$158.40
Dressing Hydrocolloid Plate Suprasorb H 15X15cm Padrao	Amber	1	R$141.68	R$141.68
Dressing Hydrocolloid Plate Suprasorb H 20X20cm Padrao	Amber	1	R$206.36	R$206.36
Dressing Hydrocolloid 10X10cm Ultec	Covidien	1	R$68.15	R$68.15
Dressing Hydrocolloid 15X15cm Ultec	Covidien	1	R$151.48	R$151.48
Dressing Hydrocolloid 15X20cm Ultec	Covidien	1	R$145.34	R$145.34
Dressing Hydrocolloid 20X20cm Ultec	Covidien	1	R$184.84	R$184.84
Dressing Hydrocolloid 10X10cm Ultec	Covidien	1	R$70.76	R$70.76
Dressing Hydrocolloid 15X15cm Ultec	Covidien	1	R$109.79	R$109.79
Dressing Hydrocolloid 20X20cm Ultec	Covidien	1	R$165.07	R$165.07
Dressing Hydrocolloid Alginate 10X12,5cm Sacral Ultec	Covidien	1	R$89.63	R$89.63
Dressing Hydrocolloid Alginate 15X17,5cm Sacral Ultec	Covidien	1	R$141.18	R$141.18
Dressing Hydrocolloid Alginate w/ Borda 6X6cm Ultec Pro	Covidien	1	R$47.68	R$47.68
Dressing Hydrocolloid Alginate w/ Borda 10X10cm Ultec Pro	Covidien	1	R$89.42	R$89.42
Dressing Hydrocolloid Alginate w/ Borda 15X15cm Ultec Pro	Covidien	1	R$165.65	R$165.65
Dressing Alginate Calcium Tegagen 10X10cm 10 unit 90112	3M Brasil	10	R$799.12	R$79.91
Dressing Alginate Calcium Restore Calcicare 5X5cm 9938	Hollister	1	R$30.38	R$30.38
Dressing Alginate Calcium Restore Calcicare 10X10cm 9937	Hollister	1	R$48.35	R$48.35
Dressing Alginate Calcium Restore Calcicare 10X20cm 9939	Hollister	1	R$91.88	R$91.88
Dressing Alginate Calcium Restore CalcicareTira 30cm 9940	Hollister	1	R$68.92	R$68.92
Dressing Alginate Calcium Sodio Kaltostat 5X5cm 1115895	Convatec	1	R$21.50	R$21.50
Dressing Alginate Calcium Sodio Kaltostat 7,5X12cm 1115896	Convatec	1	R$43.00	R$43.00
Dressing Alginate Calcium Sodio Kaltostat 10X20cm 1197983	Convatec	1	R$81.00	R$81.00

Dressing Alginate Calcium Sodio Kaltostat 15X25cm 1197984	Convatec	1	R$135.00	R$135.00
Dressing Alginate Calcium Sodio Kaltostat Tape 2gr 1197985	Convatec	1	R$59.00	R$59.00
Dressing Alginate Calcium Suprasorb 5X5cm 20440	Amber	1	R$29.70	R$29.70
Dressing Alginate Calcium Suprasorb 10X10cm 20441	Amber	1	R$52.14	R$52.14
Dressing Alginate Calcium Suprasorb 10X20cm 20442	Amber	1	R$116.60	R$116.60
Dressing Alginate Calcium Suprasorb 30cm 2gr 20445	Amber	1	R$111.98	R$111.98
3 Dressing Alginate Calcium Corda 30cm Curasorb 9231	Covidien	1	R$64.84	R$64.84
Dressing Alginate Calcium 5X5cm Curasorb 9232	Covidien	1	R$19.29	R$19.29
Dressing Alginate Calcium 10X10cm Curasorb 9233	Covidien	1	R$46.58	R$46.58
Dressing Alginate Calcium 10X14cm Curasorb 9240	Covidien	1	R$41.21	R$41.21
Dressing Alginate Calcium 20X10cm Curasorb 9240	Covidien	1	R$64.82	R$64.82
Dressing Alginate Calcium 15X25cm Curasorb 9239	Covidien	1	R$137.08	R$137.08
Dressing Alginate Calcium 30X60cm Curasorb 9242	Covidien	1	R$914.33	R$914.33
4 Dressing Alginate Calcium Corda 60cm Curasorb 9243	Covidien	1	R$171.39	R$171.39
5 Dressing Alginate Calcium Corda 91cm Curasorb 9244	Covidien	1	R$134.28	R$134.28
Dressing Alginate Calcium Plate Sorbalgon 10X10cm 9995954	Bace	1	R$58.30	R$58.30
Dressing Alginate Calcium Plate Sorbalgon 10X20cm 9995891	Bace	1	R$119.20	R$119.20
Dressing Alginate Calcium Plate Sorbalgon 5X5cm 9995981	Bace	1	R$29.37	R$29.37
Dressing Alginate Calcium Tape 1gr/30cm Sorbalgon T Ribbons 99959	Bace	1	R$75.64	R$75.64
Dressing Alginate Calcium Tape 2gr/30cm Sorbalgon T Ribbons 99959	Bace	1	R$88.84	R$88.84
Dressing Hydrocolloid Transparente 5X7 Comfeel Plus 3530	Coloplast	1	R$26.00	R$26.00
Dressing Hydrocolloid Transparente 10X10 Comfeel Plus 3533	Coloplast	1	R$39.00	R$39.00
Dressing Hydrocolloid Transparente 9X14 Comfeel Plus 3536	Coloplast	1	R$48.00	R$48.00
Dressing Hydrocolloid Transparente 15X20 Comfeel Plus 3542	Coloplast	1	R$121.00	R$121.00
Dressing Hydrocolloid Extra Thin 10X10cm Duoderm1197973	Convatec	1	R$28.00	R$28.00

Dressing Hydrocolloid Extra Thin 7,5X7,5cm Duoderm1197975	Convatec	1	R$22.50	R$22.50
Dressing Hydrocolloid Extra Thin 10X5cm Duoderm1197976	Convatec	1	R$21.50	R$21.50
Dressing Hydrocolloid Extra Thin 20X5cm Duoderm1221679	Convatec	1	R$43.00	R$43.00
Dressing Hydrocolloid Plate Suprasorb H 5X10cm Thin 20410	Amber	1	R$36.74	R$36.74
Dressing Hydrocolloid Plate Suprasorb H 5X20cm Thin 20411	Amber	1	R$42.24	R$42.24
Dressing Hydrocolloid Plate Suprasorb H 10X10cm Thin 20412	Amber	1	R$47.30	R$47.30
Dressing Hydrocolloid Plate Suprasorb H 15X15cm Thin 20413	Amber	1	R$116.32	R$116.32
Dressing Hydrocolloid Plate Suprasorb H 20X20cm Thin 20414	Amber	1	R$154.00	R$154.00
Dressing Alginate Calcium Askina Sorb Carboximet 6X6cm Steril	B Braun	1	R$44.88	R$44.88
Dressing Alginate Calcium Askina Sorb Carboximet 10X10cm Steril	B Braun	1	R$110.86	R$110.86
Dressing Hydrocolloid Transparente Askina Biofilm 15X15cm	B Braun	1	R$90.47	R$90.47
Dressing Hydrocolloid Transparente Askina Biofilm 20X20cm	B Braun	1	R$141.87	R$141.87
Dressing Hydrocolloid Transparente Askina Biofilm Transparente 10X10cm Steril	B Braun	1	R$42.55	R$42.55
Dressing Hidrogel Amorfo Askina Gel 15gr Steril	B Braun	1	R$51.26	R$51.26
Duoderm Gel 15gr	Convatec	1	R$36.00	R$36.00
Duoderm Gel 30gr	Convatec	1	R$65.00	R$65.00
Dressing Aquaflo Hidrogel Disk 7,6cm	Covidien	1	R$111.02	R$111.02
Dressing Aquaflo Hidrogel Disk 12,1cm	Covidien	1	R$158.40	R$158.40
Dressing Hidrogel Plate Suprasorb G 5X7,5cm	Amber	1	R$101.86	R$101.86
Dressing Hidrogel Plate Suprasorb G 10X10cm	Amber	1	R$114.40	R$114.40
Dressing Hidrogel Plate Suprasorb G 20X20cm	Amber	1	R$305.80	R$305.80
Dressing Hidrogel Plate Suprasorb G 20gr	Amber	1	R$131.78	R$131.78
6 Gel Debrid. Wound 50gr Hypergel Molnlycke	Neve	1	R$38.78	R$38.78
7 Gel Debrid. Wound 15gr Hypergel Molnlycke	Neve	1	R$45.25	R$45.25
8 Moist. gel Wound 5gr Normlgel Molnlycke	Neve	10	R$452.50	R$45.25
9 Moist. gel Wound 15gr Normlgel Molnlycke	Neve	10	R$387.80	R$38.78
Gel Hidroativo Hydrocolloid Alginate 85gr gel	Convatec	1	R$72.00	R$72.00
Dressing Hidrogel w/ Alginate 15gr Nu-Gel	Systagenix	10	R$693.02	R$69.30
Dressing Hidrogel w/ Alginate 25gr Nu-Gel	Systagenix	6	R$693.02	R$115.50
Dressing Hidrogel 9,5X9,5cm Plate Nu-Gel	Systagenix	5	R$404.26	R$80.85
Dressing Hidrogel 15,2X20,3cm Plate Nu-Gel	Systagenix	5	R$1,010.66	R$202.13
Coverage for non-infected wounds			**Average unit cost**	**R$100.12**

Table 2. Coverage for infected wounds**

Description SIMPRO	Manufacturer	Units	ICMS 19%	
			Factory price: box	Factory price: unit
Dressing Alginate Silver Askina Calgitrol Ag 10X10cm Steril	B Braun	1	R$119.80	R$119.80
Dressing Alginate Silver Askina Calgitrol Ag 15X15cm Steril	B Braun	1	R$196.03	R$196.03
Dressing Alginate Silver Askina Calgitrol Ag 20X20cm Steril	B Braun	1	R$318.25	R$318.25
Antimicrobial Dressing 5X5cm Silvercel Alginate 10 unit	Systagenix	10	R$319.00	R$31.90
Antimicrobial Dressing 10X20cm Silvercel Alginate 5unit	Systagenix	5	R$507.50	R$101.50
Antimicrobial Dressing 11X11cm Silvercel Alginate 10 unit	Systagenix	10	R$507.50	R$50.75
Dressing alginate Silver Askina Calgitrol AG 10X10cm Steril	B Braun	1	R$119.80	R$119.80
Dressing alginate Silver Askina Calgitrol AG 15X15cm Steril	B Braun	1	R$196.03	R$196.03
Dressing alginate Silver Askina Calgitrol AG 20X20cm Steril	B Braun	1	R$318.25	R$318.25
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 10X10cm 12unit	Politec	12	R$2,512.00	R$209.33
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 10X20cm 12unit	Politec	12	R$3,882.00	R$323.50
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 20X40cm 6unit	Politec	6	R$6,825.00	R$1,137.50
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 10X12,5cm 5unit	Politec	5	R$2,545.00	R$509.00
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 2X30cm 5unit	Politec	5	R$2,459.00	R$491.80
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 5X5cm 5unit	Politec	5	R$746.00	R$149.20
Antimicrobial Dressing Poliuret. Impregnated c/Silver Acticoat 10X12,5cm 5unit	Politec	5	R$1,988.00	R$397.60
Antimicrobial Dressing Acticoat Flex 3 5X5cm 5unit	Politec	5	R$675.00	R$135.00
Antimicrobial Dressing Acticoat Flex 3 10X10cm 12unit	Politec	12	R$2,520.00	R$210.00
Antimicrobial Dressing Acticoat Flex 3 10X20cm 12unit	Politec	12	R$3,888.00	R$324.00
Antimicrobial Dressing Acticoat Flex 3 20X40cm 6unit	Politec	6	R$6,822.00	R$1,137.00
Antimicrobial Dressing Acticoat Flex 3 40X40cm 6unit	Politec	6	R$12,600.00	R$2,100.00
Antimicrobial Dressing Acticoat Flex 3 10X20cm 6unit	Politec	6	R$9,990.00	R$1,665.00
Antimicrobial Dressing Acticoat Flex 7 5X5cm 5unit	Politec	5	R$975.00	R$195.00
Antimicrobial Dressing Acticoat Flex 7 10X12,5cm 5unit	Politec	5	R$2,542.00	R$508.40

Antimicrobial Dressing Acticoat Flex 7 15X15cm 5unit	Politec	5	R$3,930.00	R$786.00
Antimicrobial Dressing Acticoat Flex 7 20X40cm 6unit	Politec	6	R$11,430.00	R$1,905.00
Antimicrobial Dressing Acticoat Flex 7 40X40cm 6unit	Politec	6	R$21,618.00	R$3,603.00
Dressing Foam Antibac. w/ Silver 10x10cmn/ Adhesive Biatain Ag	Coloplast	1	R$118.00	R$118.00
Dressing Foam Antibac. w/ Silver 5x8cmn/ Adhesive Biatain Ag	Coloplast	1	R$66.00	R$66.00
Dressing Foam Antibac. w/ Silver 15x15cmn/ Adhesive Biatain Ag	Coloplast	1	R$205.00	R$205.00
Dressing Foam Antibac. w/ Silver 12,5x12,5cmn/ Adhesive Biatain Ag	Coloplast	1	R$118.00	R$118.00
Dressing Foam Antibac. w/ Silver 18x18cmn/ Adhesive Biatain Ag	Coloplast	1	R$205.00	R$205.00
Dressing Foam Antibac. w/ Silver 23x23cmn/ Adhesive Biatain Ag	Coloplast	1	R$213.00	R$213.00
Dressing Foam Antibac. w/ Silver 19x20cmn/ Adhesive Biatain Ag	Coloplast	1	R$181.00	R$181.00
Dressing Activated Charcoal w/ Silver (Cutable) 10X10cm Curatec	Lm, Farma	1	R$48.00	R$48.00
Dressing Activated Charcoal w/ Silver (Cutable) 10X20cm Curatec	Lm, Farma	1	R$86.00	R$86.00
Hydrofiber Dressing Aquacel w/ Silver 5X5cm	Convatec	1	R$26.50	R$26.50
Hydrofiber Dressing Aquacel w/ Silver 10X10cm	Convatec	1	R$67.00	R$67.00
Hydrofiber Dressing Aquacel w/ Silver 15X15cm	Convatec	5	R$110.00	R$22.00
Antimicrobial Dressing 5X5cm Silvercel Alginate 10 unit	Systagenix	10	R$319.00	R$31.90
Antimicrobial Dressing 11X11cm Silvercel Alginate 10 unit	Systagenix	10	R$507.50	R$50.75
Antimicrobial Dressing 10X20cm Silvercel Alginate 10 unit	Systagenix	5	R$507.50	R$101.50
Activated Charcoal Dressing w/ Silver 6,5X9,5cm Actisorb Plus 25 10 unit	Systagenix	10	R$307.71	R$30.77
Activated Charcoal Dressing w/ Silver 10,5X10,5cm Actisorb Plus 25 10 unit	Systagenix	10	R$446.17	R$44.62
Activated Charcoal Dressing w/ Silver 19X10,5cm Actisorb Plus 25 10 unit	Systagenix	10	R$876.96	R$87.70
Coverage for infected wounds			**Average Unit Cost**	**R$420.92**

*** Prices searched in the electronic version of Simpr journal*