A cost-effectiveness analysis of Cutimed® Sorbion® Sachet S in the treatment of venous leg ulceration in the United Kingdom

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Abstract

Introduction: Venous leg ulceration causes significant pain and suffering for patients, additionally it places considerable financial and service burden on the National Health Service (NHS). A large proportion of venous leg ulceration do not heal within the standard time frames of 16 – 24 weeks, resulting in static wounds which commonly have issues with increasing exudate production. Static wounds can have significant negative impact on the patients quality of life, the wound bed and periwound skin, increased risk of infection all of which results in delayed wound healing and increased health service costs. As the NHS continues to face times of austerity, services need to find solutions to be able to reduce cost and release nursing time whilst maintaining standards of care. Cutimed® Sorbion® Sachet S is a treatment option for the management of patients with a venous leg ulceration. The objective of this study was to provide an update of the health economic analysis of Cutimed® Sorbion® Sachet S in comparison to relevant comparators in the UK with current cost data.

Methods: Cutimed® Sorbion® Sachet S was compared against Zetuvit Plus, DryMax extra, KerraMax Care and Eclypse from a cost effectiveness perspective. Clinical data were derived from literature and expert opinion. Cost input was utilized based on publicly available data and literature. The average patient in the model is assumed to be 65 years with a diagnosed venous leg ulcer. It is assumed that patients in the different treatment arms have the same background mortality, hence the endpoint mortality is not included in the model. The analysis is based on a deterministic Markov model derived from Harding et al. with weekly cycles. The following assumptions are made: First, all patients start in a static health state with a non-healed but non-progressing venous leg ulcer. It is assumed in the model that patients can transition to a deteriorating health state where a wound is improving or the wound could progress. Additionally, venous leg ulcers could be healed from a progressed wound (i.e. improved wound), they could develop into a severe wound with complications (infections) to be treated in hospitals. The time frame for the analysis was fixed for one year and no re-occurence after healing was assumed to happen.

Results: The cost-effectiveness analysis demonstrates health economic dominance of Cutimed® Sorbion® Sachet S being more effective and cost-saving against all analysed comparators. When using literature-based input values the incrementally higher healing rates for Cutimed® Sorbion® Sachet S are 11.04 months (versus Zetuvit Plus), 29.04 months (versus DryMax extra), 1.68 months (versus KerraMax Care) and 11.04 months (versus Eclypse). Cost savings per patient were 37.60£ (versus Zetuvit Plus), 171.68£ (versus DryMax extra), 3.13£ (versus KerraMax Care) and 43.63£ (versus Eclypse). Clinical benefits and cost savings are increasing when real life practice assumptions based on expert opinion are included.

Conclusions: Based on the underlying health economic model, Cutimed® Sorbion® Sachet S is more effective and less costly than other comparative products in venous leg ulcers in the UK.

Introduction

Patients with lower limb ulceration are common in clinical practice; within a 1 year period in the United Kingdom there were 730,000 leg ulcerations documented, equating to 1.5% of the adult population [1]. The most common cause of lower limb ulceration is attributed to venous hypertension with venous ulceration being reported to affect up to 1% of all adults increasing to 1.7% for those aged over 65 years [2,3]. Furthermore, the prevalence of leg ulceration is known to increase with age [4], with peak prevalence for the development of leg ulceration in patients aged between 60 – 80 years [5], therefore, due to an aging population the number of patients affected by venous ulceration is likely to rise. Venous ulceration often takes weeks or months to heal and frequently recur, during the time of ulceration high volumes of exudate may be produced, it is painful and even malodorous and all of these issues can negatively affect patient's quality of life [6,7]. The National Health Service (NHS) spends a substantial amount of money in the treatment of venous ulceration, mostly through community services, the annual spend on leg ulceration was estimated to be around £1.94 billion [8].

It is acknowledged that the most important treatment for venous ulceration is compression therapy which is designed to improve venous return, reduces venous hypertension and hence manages the underlying cause. However, it is also vital to ensure that venous leg ulcers are maintained in an ideal environment, which promotes wound healing, one of the most vital aspects is the adequate management of wound exudate. If exudate is not adequately controlled this can negatively affect the wound bed and periwound skin, increasing the risk of infection resulting in delayed wound healing [9]. The use of advanced wound treatments such as Cutimed® Sorbion® Sachet S could aid the management of venous ulceration by providing an ideal wound environment and ensuring effective exudate management, allowing for fewer dressing changes, resulting in less nursing visits and therefore providing overall cost savings.

Consideration of unit cost and comparing this with patient/service benefits is vital when trying to establish overall cost effectiveness. Disease and health economic models can be adopted to demonstrate costs and patient benefits. Health economic modelling is a globally recognized technique based on well-documented, international standards [10, 11]. Models are developed in order to demonstrate consequences of measurable effects which would only become clear in the future. By using health economic evaluation, the effects of cost reimbursement for new medical treatment methods may be quantified in relation to existing care modalities [12].

Cutimed® Sorbion® Sachet S has been evaluated as a treatment option to control exudate with the ability to progress patients from chronic or non-progressing wounds onto improving or healing wounds. In Panca et al. 2013 an initial assessment of various wound dressings in the UK was published. As the clinical basis as well as the cost basis might have changed since then. Hence, the objective of this study was to provide an update of the previously published health economic analysis of Cutimed® Sorbion® Sachet S [17] in comparison to relevant comparators in the UK with current cost data. Analysis of Cutimed® Sorbion® Sachet S was undertaken comparing to Zetuvit Plus, DryMax extra, KerraMax Care and Eclypse from a cost effectiveness perspective.

The question under investigation was: "Is Cutimed® Sorbion® Sachet S cost-effective when compared to alternative treatments used to manage venous leg ulcers in the UK?

Methods

To ensure a robust data base for the health economic model, a systematic literature search was conducted in the (standard) literature databases Medline through PubMed, INAHTA (International Network of Agencies for Healtth Technology Assessment), NHS Economic Evaluation Database and DIMDI (Deutsche Institut für Medizinische Dokumentation und Information; German institute for medical documentation and information) for Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and DAHTA database (German HTA database). The research question was defined on the basis of the PICO criteria [13] literature search parmaters were based on the PICO. PICO criteria were as follows:

- **Patient & Intervention:** chronic wounds, venous leg ulcer, wound care, therapy, diagnostics
- **Comparison:** Patients with or without medical therapy or therapy in support of medical devices including dressing and bandages
- **Outcomes:** Cost, cost-effectiveness, cost per QALY, cost minimization, cost comparison, cost of illness, health economics, health economic model, statistical model

The search was conducted over 12 years (2005 to 2017) in order to focus on the most relevant therapies (and models). Included languages were German and English. Inclusion criteria were health economic models and/or health economic analysis in the UK ideally with a special focus and clear guidance for a health economic model. Overall there were 831 hits across all included databases. After title selection and abstract review, full text evaluation was executed for 26 articles. Overall there were six articles identified in which a UK analysis was provided in venous leg ulcers [14-19]. Of these six articles, one was a multinational analysis [16] and four were analyses on specific products without a recommendation on health economic modelling approaches.

Harding et al. [19] was the only article where a general approach in terms of a new costing method was recommended which can be utilized as a health economic modelling frame in chronic wounds, and was deemed to be appropriate for the underlying research question on which a Markov model was developed. Based on this deterministic Markov model with weekly cycles, a cost-effectiveness analysis was performed from the UK NHS payer's perspective. The time frame for the analysis was fixed for one year. The average patient in the model is assumed to be 65 years with a diagnosed venous leg ulcer. It is assumed that patients in the different treatment arms have the same background mortality and hence it is not included in the model.

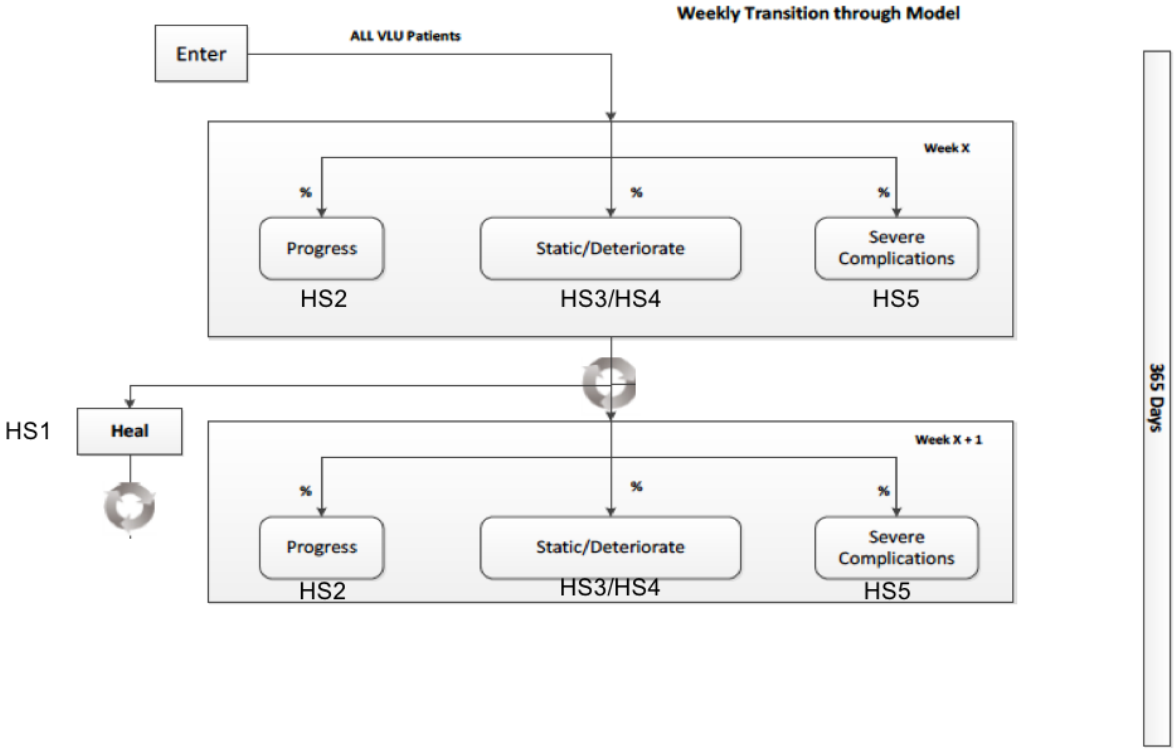
The health states in the model are defined as follows (see Figure 1):

- "Heal" – Skin is intact (HS 1)
- "Progress" – Ulcer is progressing towards healing (HS 2)
- "Static" – Ulcer is neither healing nor deteriorating (HS 3)
- "Deteriorating" – Ulcer is deteriorating (e.g. increasing in size, exudate or odour; surrounding skin is deteriorating) (HS 4)
- "Severe" – Ulcer is infected or with other complications which may require hospital admission and/or surgical intervention" (HS 5)

It is assumed that all patients start in the static health state (HS) with a non-healed and non-progressing venous leg ulcer (HS 3). Thereafter, patients can transition to a deteriorating health state (HS 2) where a wound is improving or the wound could progress (HS 4). From health state 2 venous leg ulcers could be healed (HS 1) from a progressed wound they could develop into a severe wound with complications (infections) to be treated in hospitals (HS 5).

In other words: All patients in the model start with a currently non healed wound which is not improved (HS 3). At this stage in the model, the treating clinician is choosing one of the dressings included in the model. Based on the probabilities for these dressings the patient's wound could improve (health state 2) or could worsen (health state 4). Such changes in the wound are being calculated on a weekly basis. Based on the improved wound (health state 2) the patient could be healed (health state 1). From a worsened wound (health state 4) the wound could improve (health state 3) or even develop complications which would need to be treated in hospitals (health state 5).

Figure 1: Health states within the model based on the patient's pathway based on Harding et al. [19]



Transition probabilities for the different health states and treatment options available in the model were derived from different sources (see Table 1). No re-occurence of wounds after healing happen in this model (HS 1 to HS 3), however there is the flexibility analysing such an option in sensitivity analyses. Transition probabilities for moving patients from unhealed grade 1 progression (HS 2) to healed were based on Panca et al. [17]. For Zetuvit Plus and Eclypse, neither are included in the Panca et al. 2013 analysis, the average transition probability was assumed between Drymax extra, KerraMax Care and that Cutimed® Sorbion® Sachet S as follows: Cutimed® Sorbion® Sachet S' efficacy in terms of healing was taken from Panca et al. 2013. Transition probabilities for unhealed grade 1 static to unhealed grade 1 progression (HS 3 to HS 2) and unhealed grade 1 deteriorating (HS 4) to unhealed grade 2 severe (HS 5) were both taken from Shannon et al. 2016 [20] and assumed to be independent to the underlying treatment. The transition

probability for unhealed grade 1 static to unhealed grade 1 deteriorating (HS 3 to HS 4) was based on Walzer et al. 2016 [21].

Furthermore, it was assumed that all patients received two wound dressing changes per week regardless of the underlying treatment.

Table 1: Transition probabilities for the different treatment in the various health states of the underlying model

	Model path	Transition probability (per week)					Reference
		Zetuvit Plus	DryMax extra	KerraMax Care	Eclypse	Cutimed® Sorbion® Sachet S	
Healed to unhealed grade 1 static	HS 1 to HS 3	0.0000	0.0000	0.0000	0.0000	0.0000	Assumption: No recurrence
Unhealed grade 1 progression to healed	HS 2 to HS 1	0.0180	0.0144	0.0200	0.0180	0.0204	Assumptions based on Panca et al. 2013 [17]
Unhealed grade 1 static to unhealed grade 1 progression	HS 3 to HS 2	0.0600	0.0600	0.0600	0.0600	0.0600	Shannon et al. 2016 [20]
Unhealed grade 1 static to unhealed grade 1 deteriorating	HS 3 to HS 4	0.0188	0.0188	0.0188	0.0188	0.0188	Walzer et al. 2016 [21]
Unhealed grade 1 deteriorating to unhealed grade 2 severe	HS 4 to HS 5	0.0040	0.0040	0.0040	0.0040	0.0040	Shannon et al. 2016 [20]
Unhealed grade 2 severe to unhealed grade 1 static	HS 5 to HS 3	0.8000	0.8000	0.8000	0.8000	0.8000	Walzer et al. 2016 [21]

The health state utilities were determined through investigation of EQ-5D data from a one-year pragmatic, randomized longitudinal venous leg ulcer study (VenUS III) completed in the United Kingdom [22]. An EQ-5D five-dimension score (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) recorded within 0 to 3 weeks of each documented health state was identified in the VenUS III dataset and then translated into a EQ-5D index score (utility value). Translation of five-dimension score to the index score was completed using an EQ-5D index calculator. The utilities for the health states “progressing“ and “deteriorating“ were assumed to be the same (see Table 2).

Table 2: Utilities of individual health states in the model based on Shannon et al. 2016 [22]

Health State	Utility
Healed (HS 1)	0.630
Progressing (HS 2)	0.534
Static (HS 3)	0.525
Deteriorating (HS 4)	0.534
Severe (HS 5)	0.130

The costs for the various health states were directly taken from Harding et al. [18] (see Table 3). Once a patient is healed quarterly outpatient visits are assumed (based on expert opinion), costs derived from experts at the University of Huddersfield.

Table 3: Cost input for the health economic model

Cost items	Cost per week	Reference
Healed (HS 1)	£ 6.04	Harding et al. 2013 [19]
Progressing (HS 2)	£ 87.59	Harding et al. 2013 [19]
Static (HS 3)	£ 100.27	Harding et al. 2013 [19]
Deteriorating (HS 4)	£ 159.45	Harding et al. 2013 [19]
Severe (HS 5)	£ 637.15	Harding et al. 2013 [19]
Cost per outpatient visit ("administration cost")	£ 2.48	Expert opinion

The individual costs of each therapy have been taken into account per dressing (see Table 4). It was assumed, that each time a wound dressing was changed, a new dressing was applied (from the same manufacturer). The costs of additional wound care products have not been included in the calculations, assuming that similar products and consequently similar cost would arise.

Table 4: Package price input per therapy and week (package assumption for pack size: 10x10)

Product	Cost per package (use per wound dressing)	Reference
Zetuvit Plus	£ 0.64	Public UK price (April 2017) [23]
DryMax extra	£ 0.87	Public UK price (April 2017) [23]
KerraMax Care	£ 1.29	Public UK price (April 2017) [23]
Eclypse	£ 0.73	Public UK price (April 2017) [23]
Cutimed® Sorbion® Sachet S	£ 1.49	Public UK price (April 2017) [23]

Healing of the wound is the primary efficacy endpoint and is also the basis for the cost per QALY analysis in the model. Both the total costs and the respective cost of care per health state were determined as cost endpoints. Finally, the efficacy and cost endpoints of the model are compared to calculate the incremental cost-effectiveness ratio (ICER). The calculation is performed as the difference of the total costs between a Cutimed® Sorbion® Sachet S therapy and the respective treatment options Zetuvit Plus, DryMax extra, KerraMax Care and Eclypse, respectively. Analogically, the incremental efficacy was calculated based on the respective efficacy values. Finally, the incremental cost-effectiveness has been calculated and both, the costs per additional year of healing and the costs per QALY (quality adjusted life year) gained, are determined [12].

The ICER was calculated as follows:

$$\text{ICER} = \frac{\textit{(Cutimed® Sorbion® Sachet S costs) – (comparative therapy costs)}}{\textit{(Cutimed® Sorbion® Sachet S efficacy) – (comparative therapy efficacy)}}$$

Sensitivity analyses were executed on key variables of the model. Expert opinion (VLU clinician in cooperation with a wound nurse) on the transition probabilities for each health state were utilized in order to implement a "real life" input into the model (see Table 5). Within that process experts were asked how many patients out of 100 patients would get one of the health states below. Health states were described for clinical personell in order to get adequate responses,

Table 5: Changed transition probabilities for the different treatments in the various health states of the underlying model in sensitivity analysis

	Model path	Transition probability (per week)					Reference
		Zetuvit Plus	DryMax extra	KerraMax Care	Eclypse	Cutimed® Sorbion® Sachet S	
Unhealed grade 1 static to unhealed grade 1 progression	HS 3 to HS 2	0.5000	0.5000	0.5000	0.5000	0.5000	Expert opinion
Unhealed grade 1 static to unhealed grade 1 deteriorating	HS 3 to HS 4	0.3000	0.3000	0.3000	0.3000	0.3000	Expert opinion
Unhealed grade 1 deteriorating to unhealed grade 2 severe	HS 4 to HS 5	0.1000	0.1000	0.1000	0.1000	0.1000	Expert opinion
Unhealed grade 2 severe to unhealed grade 1 static	HS 5 to HS 3	0.1000	0.1000	0.1000	0.1000	0.1000	Expert opinion

Results

The total costs per patient per year are reported in Table 6. According to the model, for a patient with Cutimed® Sorbion® Sachet S the costs amount to £ 61.99. The main cost drivers are the costs in the progression (HS 2) and deteriorating (HS 4) health states, which account for more than 71% of the total costs (£ 4,699.38). In contrast to this, the total annual costs with Zetuvit Plus, DryMax extra and Eclypse are £ 4,736.98, £ 4,871.07, £ 4,702.51 and £ 4,743.01 respectively.

Table 6: Cost comparison results in the treatment of venous leg ulcers in the UK

Health state	Zetuvit	DryMax extra	KerraMax Care	Eclypse	Cutimed® Sorbion® Sachet S
Healed (HS 1)	£ 56.49	£ 47.44	£ 61.22	£ 56.49	£62.07
Progression (HS 2)	£ 1,909.62	£ 2,040.90	£ 1,841.09	£ 1,909.62	£ 1,828.79
Static (HS 3)	£ 1,261.67	£ 1,267.36	£ 1,277.31	£ 1,264.04	£ 1,282.05
Deteriorating (HS 4)	£ 1,481.50	£ 1,487.66	£ 1,495.18	£ 1,485.15	£ 1,498.76
Severe (HS 5)	£ 27.71	£ 27.71	£ 27.71	£ 27.71	£ 27.71
Total cost	**£ 4,736.98**	**£ 4,871.07**	**£ 4,702.51**	**£ 4,743.01**	**£ 4,699.38**

The higher healing rates in the effect assumption (see Table 1 vs Table 5) for Cutimed® Sorbion® Sachet S can also be affirmed in the higher incremental effect in the total calculation (see Table 7). Given the higher utility values for the healed health state this advantage is also transferred into the incremental QALYs. The incremental cost-effectiveness, as reported in Table 7, is calculated from the modelled efficacy, calculated for an additionally healed patient, and the total costs accordingly. The difference in the incremental costs shows the difference in the total costs for the

treatments to be compared. Finally, the incremental cost-effectiveness puts the difference in the costs in relation to the difference in the healings. According to the model, a Cutimed® Sorbion® Sachet S therapy is more effective and cost-saving and can therefore be regarded as dominant in relation to the other four analysed therapies from a health economic's viewpoint.

Table 7: Cost-effectiveness results from a UK payer's perspective

Comparison	Incremental effect ("healed")	Incremental cost	Incremental utilities ("QALY")	Incremental cost-effectiveness	Incremental cost per QALY
Cutimed® Sorbion® Sachet S versus Zetuvit Plus	0.92 years (11.04 months)	£ 37.60	0.0017	- £ 40.75	- £ 22,073.30
Cutimed® Sorbion® Sachet S versus DryMax extra	2.42 years (29.04 months)	£ 171.68	0.0045	- £ 70.90	- £ 38,403.23
Cutimed® Sorbion® Sachet S versus KerraMax Care	0.14 years (1.68 months)	£ 3.13	0.0003	- £ 22.28	- £ 12,065.77
Cutimed® Sorbion® Sachet S versus Eclypse	0.92 years (11.04 months)	£ 43.63	0.0017	- £ 47.28	- £ 25,612.37

The results of the base case analysis are also confirmed in the sensitivity analysis (see Table 8). Sorbion® Sachet S remains to be dominant from a health economic perspective. It is more effective and less costly against the four different other wound care therapies.

Table 8: Sensitivity analysis results on the cost-effectiveness a UK payer's perspective

Comparison	Incremental effect ("healed")	Incremental cost	Incremental utilities ("QALY")	Incremental cost-effectiveness	Incremental cost per QALY
Cutimed® Sorbion® Sachet S versus Zetuvit	1.27 years (15.24 months)	£ 3792.71	0.0023	- £ 73.02	- £ 39,552.51
Cutimed® Sorbion® Sachet S versus DryMax extra	3.35 years (40.2 months)	£ 265.38	0.0062	- £ 79.26	- £ 42,932.70
Cutimed® Sorbion® Sachet S versus KerraMax Care	0.19 years (2.28 months)	£ 13.24	0.0004	- £ 68.71	- £ 37,219.82
Cutimed® Sorbion® Sachet S versus Eclypse	1.27 years (15.24)	£ 94.14	0.0023	- £ 74.15	- £ 40,163.92

Discussion

The present analysis is an updated cost-effectiveness analysis related to Cutimed® Sorbion® Sachet S in the UK [17]. The initial procurement costs of Cutimed® Sorbion® Sachet S are negated when compared to the improved wound healing rates leading to reduced dressing changes, time for nurse visits and improved outcomes. However, as there are no randomized controlled trials available comparing different wound therapies against each other based on patient relevant endpoints such as healing, assumptions had to be taken between the therapies. The transition

probabilities were assumed to be the same between the therapies for all health states except HS 2 transitioning to HS 1. These assumptions were taken from a published analysis by Panca et al. [17] and re-calculated into weekly probabilities. When changing the transition probabilities for the different health states from literature-based into real life expert opinions the results were quantitively different, however the direction of the results remains the same. Cutimed® Sorbion® Sachet S remains more effective and less costly.

Limitations

Markov models have been critised as they might simplify reality further in comparison to other modelling approaches [12]. A key issue may be the exclusion of the majority of items included in the analysis, such as patient characteristics. In Markov models, cohorts are modelled instead of individual patients with specific characteristics and its correlation and covariates to clinical outcome parameters. Nevertheless, the underlying model is a well defined clinical snapshot of the reality including detailed health states during the different steps of a patient's journey.

Additionally, the clinical input values for the five therapies included in the analysis are based on assumptions and clinical data without direct evidence between those; similar to already published health economic evidence [17]. Based on the limited data availability also a network meta-analysis to derive the adjusted indirect evidence was not feasible.

Cost data are based on Harding et al. [19]. However, their analysis mainly focused on testing a cost methodology even though the utilized data was derived directly from different treatment centers across the UK. In the analysis, it was shown that the key modelling parameter was the probability of healing, although healing was not proven in any of the underlying therapies. However, in Panca et al. [17] similar assumptions were utilized and also aligned with clinical experts in the UK who experienced similar numbers in real life settings.

Conclusion

The management of patients with venous leg ulceration is a daily challenge to many UK clinicians, the key to effective management is compression therapy, yet there are occasions when venous ulcerations fail to show signs of healing and issues with high volumes of exudate are common place. Cutimed® Sorbion® Sachet S provides an ideal wound environment to allow healing to occur with the added advantage of being able to handle high volumes of exudate ensuring that the wound is protected from the damaging effects of uncontrolled moisture. Based on this health economic modelling, Cutimed® Sorbion® Sachet S has been shown to be more effective in promoting healing and less costly when compared to other comparative dressings within the UK.

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