Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé

Québec

Agence d'évaluation des technologies et des modes d'intervention en santé

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des technologies
et des modes
d'intervention en santé

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(AÉTMIS 2000-5 RE)

THE TREATMENT OF VENOUS LEG ULCERS AND OPTIMAL USE OF APPLIGRAF™

SUMMARY
of the report submitted to the

Minister of Research, Science
and Technology of Québec

Information concerning this report or any other report published by the *Conseil d'évaluation des technologies de la santé* can be obtained by contacting *AÉTMIS*. On June 28, 2000 was created the *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*) which took over from the *Conseil d'évaluation des technologies de la santé*.

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Québec
Agence d'évaluation des technologies et des modes d'intervention en santé

MISSION

To support the *Ministre de la Recherche, de la Science et de la Technologie* and Québec's public health system decision-makers, namely the *Ministère de la Santé et des Services Sociaux,* through the assessment of technology and methods of intervention in health issues, notably the assessment of their effectiveness, safety, cost and cost-effectiveness, as well as ethical, social and economic implications.

To support the *Ministre de la Recherche, de la Science et de la Technologie* in the development and implementation of scientific policy.

THE TREATMENT OF VENOUS LEG ULCERS AND THE OPTIMAL USE OF APLIGRAF™

Leg ulcers affect approximately 1% of the population. Most are of venous origin, often chronic and recurrent. The highest proportion of leg ulcers occurs in the elderly. Their treatments are varied, and convincing data on their effectiveness are few. Evidence on the effectiveness of compression therapy is still recent. Studies on cost-effectiveness are practically non-existent.

Apligraf™, a product of tissue-engineering, is a bilayered human skin substitute classified as a medical device. Approved in Canada in 1997, it is indicated in the treatment of venous leg ulcers, and since August 2000, for the treatment of diabetic ulcers.

The Canadian distributor, Novartis, submitted a request to the Conseil consultatif de pharmacologie du Québec for Apligraf™ to appear on the list of exceptional medications. The request was not considered since the product is not a medication, and the current trend is to reduce the number of these inscriptions.

The Ministère de la Santé et des Services sociaux gave the *Conseil d'évaluation des technologies de la santé (CÉTS)* in 1998, which became the *Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS)* in June 2000, the mandate of studying the clinical and economic value of Apligraf™.

The objective of this report is to specify under what conditions the use of Apligraf™ would be optimal for the treatment of venous leg ulcers that are resistant to compression therapy. These conditions are defined as a temporary measure, while awaiting the results of a multicentre randomised controlled trial that will either confirm or invalidate current estimates, most likely in the summer of 2001.

In disseminating this report, *AÉTMIS* wishes to provide the best possible information to policy makers concerned with this issue at different levels in Québec's health services network.

Renaldo N. Battista

President and CEO

SUMMARY

Introduction

Apligraf™ is a human skin substitute composed of human dermal and epidermal cells. The terms "living skin equivalent" and "artificial skin" are also synonyms for "human skin substitute". At the present time, Apligraf™ is the only product consisting of two layers of cells that is indicated for the treatment of venous leg ulcers.

This bioengineered product is not a drug. Listed as a medical device by Health Canada, it could just as well be considered as a "biological dressing" from the practical standpoint and as a medical supply from the administrative standpoint.

Apligraf™ is manufactured in the United States by Organogenesis Inc. and distributed by Novartis Pharma Canada Inc. (Novartis). It was approved by Health Canada in April 1997 and its use is restricted to certified physicians. Shortly after this approval, Novartis submitted a request to the Ministère de la Santé et des Services sociaux du Québec for Apligraf™ to appear on the list of exceptional medications or to have patients treated with Apligraf™ recognised as exception patients.

In the fall of 1998, faced with the questions raised by the available information, the Ministère de la Santé et des Services sociaux du Québec, required that the *Conseil d'évaluation des technologies de la santé* (which became the *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*) in June 2000) document the clinical and economic value of the product. The resulting analysis is based on the epidemiology of venous leg ulcers, on current treatment options and their efficacy, as well as on estimated costs.

Compression therapy for leg ulcers has been known under various forms for a long time. It is only in recent years that modern treatment practices have been evaluated in various countries. Although some of the results of these evaluations are not yet available, the Cochrane Collaboration has paved the way with the publication of systematic reviews on compression therapy and skin grafting for the treatment of venous ulcers.

In this context, attention was focused on publications that would help document the conditions for the use of Apligraf™ and define these conditions in relation to currently recommended treatments. On the one hand, there is a progressive consolidation of the initial data on the safety and efficacy of Apligraf™ as new trial results are published. On the other hand, studies on the cost and effectiveness of Apligraf™ are still hypothetical, even in most recent models.

Moreover, there are still no evidence-based conditions for the use of Apligraf™ as recommended by the Canadian distributor, which suggests that the product be restricted to venous leg ulcers resistant to an initial compression therapy. In fact, this position reiterates the indication advocated in the American monograph, and thereby complements the less restrictive Canadian monograph.

Estimating the prevalence of venous leg ulcers in Québec

Since there are no Canadian or Québec data specific to this disease, venous leg ulcer prevalence is estimated mainly from European and Australian publications.

The range of prevalence of active leg ulcers (including those of the foot) in the general population is very broad, from 0.11 to 1.13%, with venous ulcers representing approximately 90% of all leg ulcers and the others being of arterial, mixed (venous and arterial) or other origin. Venous ulcers are chronic and recurrent. They often affect people over the age of 60, with their prevalence reaching a peak at age 70.

In Québec, different sources situate the number of prevalent cases of leg ulcers between 5,000 and 13,000, and incident cases at approximately 4,000 annually. Hospitalisation data show that between 1992 and 1997, the average hospital stay for cases with a principal diagnosis of leg ulcers was 21 days, although patients were treated for other conditions as well. The average hospital stay for patients treated only for leg ulcers was 6.5 days. In 1998 the Centre hospitalier universitaire de l'Université de Montréal evaluated the average hospital stay for venous ulcers at 17.3 days.

For modelling purposes, the number of cases of venous leg ulcers in Québec was approximated at 8,000, of which 4,000 would be known to home care services. The remaining cases would be divided between outpatient clinics and self-treatment, with the latter having no direct impact on the health care system.

Efficacy of treatments

Published data on the efficacy of vascular surgery, allografting or autografting are rather unconvincing. There are still no systematic reviews on pharmacological treatments of venous ulcers, and a report on the subject would go beyond the scope of this document. However, the results of a systematic review carried out by the Cochrane Collaboration, comparing compression therapy to its absence, lead to the following conclusions:

- Compression treatment increases the healing of ulcers as compared with no compression. Moreover, high compression appears superior to low compression.
- High compression is more effective than low compression but should only be used in the absence of significant arterial disease.
- No clear difference was found between different types of high compression systems (3-layer, 4-layer, short stretch bandages or Unna's boot).

Among human skin substitutes, Apligraf™ is the only product indicated for the treatment of venous leg ulcers. The pivot study on the efficacy and safety of Apligraf™, cited in the data submitted for its approval, is not supportive from an economic standpoint. In fact, healing occurred with an average application of 3.34 units of the product, which greatly exceeds the allegations of the distributor and the actual experience of Québec clinicians who have had the opportunity to use the product.

Costs

There are no published Canadian or Québec studies on the cost of leg ulcers. Some European and American studies on the cost of treating leg ulcers under different conditions have been published. Their results, however, cannot easily be transposed to the Québec context.

A consensus by Canadian experts from most provinces suggests estimates of $530/month for home care and $360/month for care obtained in clinics, without taking into account the eventual use of Apligraf™, the price of which is $950 per unit. Considering variations in the number and duration of different treatments, a global amount cannot, for the time being, be given. However, the modelling of various

treatment options allows for a few comparisons.

Modelling

Available models on the cost and the effectiveness of Apligraf™ are still based on mostly hypothetical parameters, namely the number of ulcers to treat, the efficacy of compression therapy as well as that of Apligraf™, and the number of units required for healing.

In order to illustrate the different conditions surrounding treatment with or without Apligraf™, two main approaches were investigated: the first, an analytical model developed at *AÉTMIS,* and the other, an economic analysis sponsored by Novartis. In the *AÉTMIS* model, the base case scenario takes into account three options: compression therapy without Apligraf™ for a duration of 12 weeks, followed by a second round of compression therapy without Apligraf™ for resistant cases; compression therapy and Apligraf™ simultaneously, followed by a second compression therapy with Apligraf™ for resistant cases; and compression therapy without Apligraf™, followed by compression therapy with Apligraf™ for resistant cases.

In the *AÉTMIS* base case scenario, 3.34 units of Apligraf™ are applied to each of the 8,000 ulcers, based on the average number of units used in the pivot study, which is the reference point for the product's efficacy. This scenario is a hypothetical upper limit, however. In fact, an optimistic scenario would be much more realistic, with 4,000 ulcers and the use of a single unit of Apligraf™ as well as a higher efficacy for compression therapy. This optimistic scenario, where Apligraf™ is restricted to cases that are resistant to an initial compression therapy, results in potential savings when compared to treatment without Apligraf™, and all the more so when compared with the simultaneous use of compression therapy and Apligraf™.

Planimetry, a technique used to measure reduction in ulcer area in order to identify cases that are resistant after 4 weeks of compression therapy, suggests significant potential savings. However, the conditions related to its implementation and integration into current practices still need to be determined.

Another model, this one sponsored by Novartis in the United States, also uses the clinical data from the reference pivot study. These data were combined with the results of a survey of twenty physicians on the costs of treating venous leg ulcers. Fourteen individual responses were compiled to estimate these costs in the US.

Within the perspective of a private health care regime that reimburses all costs, the model compares the estimated costs of treating hard-to-heal venous leg ulcers after a conventional compression therapy (Unna's boot) with the cost of a treatment using an average of 3.34 units of Apligraf™ over one year. The costs of additional treatments, which would be incurred in the event of adverse reactions or recurrences, are also included in the model.

The model estimates that the annual cost of treating hard-to-heal venous leg ulcers is US$20,041 for patients treated with Apligraf™ and US$27,493 for those treated with Unna's boot. Treatment with Apligraf™ would lead, for most patients, to nearly 3 additional months in the healed state than would treatment with Unna's boot (4.6 months with Apligraf™ and 1.75 months with Unna's boot). Of the patients treated with Apligraf™, 48.1% would still be healed after the 12-month follow-up, compared with 25.2% of those treated with Unna's boot.

By comparing the results of both models, one notes that they both lead to the same general conclusions: the use of Apligraf™ in patients whose ulcers seem hard to heal with compression therapy alone increases the probability or rate of healing and translates into

potential savings as compared to treatments without Apligraf™.

Example from an outpatient clinic

The outpatient dermatology clinic of the Hôtel-Dieu pavilion of the Centre hospitalier universitaire de Québec (CHUQ) was chosen to show current trends in the treatment of venous leg ulcers in Québec. This clinic is not participating in the pan-Canadian study currently underway that will be mentioned later. It is mentioned in order to highlight the currently limited use of Apligraf™. In fact, the introduction of Apligraf™ on the market, as well as its high price (when it stopped being offered free of charge after its introduction), has led to the re-evaluation of diagnostic and therapeutic approaches to venous leg ulcers, and especially of the criteria related to the application of compression therapy.

Since the implementation of a systematic approach for the diagnosis and treatment of venous leg ulcers, the use of Apligraf™ has not yet been considered necessary at the CHUQ outpatient dermatology clinic, even though its medical supply budgets allow for the purchase of the product when needed.

This situation would be similar in other Québec hospitals, such that a very limited number of Apligraf™ units would have been purchased in 1999. If the situation were generalised to venous leg ulcers resistant to compression therapy, a rough estimate of the costs of Apligraf™ used under these conditions would reach a maximum of a few hundred thousand dollars per year.

Furthermore, the results of a current clinical trial will soon complement the available information on Apligraf™.

Current clinical trial in Canada

The recruitment of a few hundred patients for a randomised controlled trial in various Canadian centres was intended to have ended on December 31, 1999, but it ended on April 30, 2000. The compared treatments are compression therapy alone and an identical compression therapy with Apligraf™ for cases resistant to treatment.

This trial includes the validation of initial ulcer healing rates measured by planimetry as a prognostic tool. If the validation is convincing, the use of the initial ulcer healing rate as a prognostic tool could become part of a nation-wide system of planimetry. This trial also allows for an important compilation of economic data, which will either validate or invalidate the results of current models. Results will most likely be known in the summer of 2001.

Criteria to complement the approval process

From a broader perspective, the example of Apligraf™ could be used to illustrate the difficulties inherent in the classification and reimbursement of tissue-engineered products. The number of these products will increase over the next few years and the problems faced by Apligraf™ today will be encountered again. This problem, generated both by the accessibility of a product and by the budgetary limitations to its acquisition, will soon create an impasse between the high costs of these products and the continuous increase in their numbers.

It would be advisable to define policies and to establish more precise procedures regarding their eventual reimbursement or inclusion in hospital supply budgets. Complementary information would be made available by adding cost data to the current processes for assessing new products. Actually, the only

criteria considered in the examination of products for approval by Health Canada is evidence of safety and efficacy, with no consideration of the cost of the products, as this is not part of the current mandate.

In a context where financial resources place increasing constraints on health care systems, the burden of proving cost-effectiveness still seems to be the responsibility of the paying organisations. These are often left without any relevant information or administrative (or even legal) leverage to counter constant pressure by manufacturers, distributors and potential users of the product. Considering economic data in the approval process would lighten this burden.

Conclusions and recommendations

Based on this assessment, the following preliminary conclusions can be drawn concerning the clinical and economic issues in the treatment of venous leg ulcers and the use of Apligraf™:

Clinical issues:

- the evaluation and diagnosis of patients should be properly performed;
- treatment of venous leg ulcers with compression therapy is more effective than treatment without compression;
- compression therapy in conjunction with Apligraf™ provides faster healing times than compression alone;
- compression therapy in conjunction with Apligraf™ averts more ulcer days than does compression alone.

Economic issues:

In the absence of validated data, the following statements remain provisional:

- compression therapy simultaneously with Apligraf™ generates very high costs in order to reduce the number of ulcer days;
- compression therapy plus Apligraf™ for cases that are unresponsive to initial compression therapy is less costly than compression and Apligraf™ simultaneously and offers potential savings for the health care system in an optimistic scenario;
- identifying hard-to-heal ulcers with planimetry at week 4 of initial compression therapy, and the subsequent addition of Apligraf™ to treatment can increase savings.

While these conclusions need to be validated with additional conclusive data, particularly from an economic standpoint, the *Agence d'évaluation des technologies et des modes d'intervention en santé* makes the following recommendations:

- to promote, on the one hand, continued efforts to generalise the management of leg ulcer patients according to the recommendations of advisory panels, and on the other hand, the use of compression therapy in the treatment of venous leg ulcers;
- to recognise, at the clinical and administrative levels, the potential role of Apligraf™ in the treatment of venous leg ulcers that are resistant to an initial compression, and the possible savings that could be generated;
- to maintain rigorous policies on the use of Apligraf™ by certified physicians in hospital outpatient clinics, which are or should start planning for specific budgets for this specialised supply;
- to promote the dissemination of clinical and administrative protocols on the use of

Apligraf™, which certain hospitals have developed and implemented, so that other institutions can consider and tailor them to their own internal policies, as needed;

- to ensure that current developments on the indications of Apligraf™ be followed up, and that this report be updated following the publication of results of the multicentre pan-Canadian randomised controlled

  trial in the summer of 2001;

- to initiate the research necessary to document the epidemiology of leg ulcers in Québec as well as the clinical effectiveness and the costs of various treatment strategies in clinical, CLSC and home care settings.

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LIST OF ABBREVIATIONS

ABPI ..... Ankle-brachial pressure index
AETMIS ..... *Agence d'évaluation des technologies et des modes d'intervention en santé*
ALU ..... Arterial leg ulcer
APR-DRG ..... All Patients Revised - Diagnosis Related Groups
ASPI ..... Ankle-systolic pressure index
CCOHTA ..... Canadian Coordinating Office for Health Technology Assessment
CÉTS ..... *Conseil d'évaluation des technologies de la santé*
CHSLD ..... *Centre d'hébergement et de soins de longue durée*
CHUM ..... *Centre hospitalier de l'Université de Montréal*
CHUQ ..... *Centre hospitalier universitaire de Québec*
CI ..... Confidence interval
CLSC ..... *Centre local de services communautaires*
CVU ..... Chronic venous ulcer
DFU ..... Diabetic foot ulcer
FDA ..... Food and Drug Administration
HBO ..... Hyperbaric oxygen therapy
HSS ..... Human skin substitute
HSE ..... Human skin equivalent
ICH ..... International Conference on Harmonization
ISTAHC ..... International Society for Technology Assessment in Health Care
LEPT ..... Low-energy photon therapy
LU ..... Leg ulcer
OR ..... Odds ratio
PDGF ..... Platelet derived growth factors
POEM ..... Patient-oriented evidence that matters
RAMQ ..... *Régie de l'assurance maladie du Québec*
SIGN ..... Scottish Intercollegiate Guidelines Network
RR ..... Relative risk
VLU ..... Venous leg ulcer
VEINES ..... Venous Insufficiency Epidemiologic and Economic Studies

1. INTRODUCTION

Apligraf ™ is a human skin substitute made of two layers of cells: human dermal fibroblasts and epidermal keratinocytes. This bioengineered living product, which can be preserved for up to 5 days, is used in the treatment of different types of ulcers. Venous leg ulcers represent approximately 90% of all leg ulcers, the others being of arterial, mixed (venous and arterial), or other origins. Its use in the treatment of burn victims has not yet been documented.

Apligraf ™ is manufactured in the United States by Organogenesis Inc. and distributed by Novartis Pharmaceuticals Canada Inc. (Novartis). It was listed as a medical device and approved for use in the treatment of venous leg ulcers by Health Canada in April 1997. Health Canada ordered a post-marketing study on the safety of Apligraf ™, as well as the implementation of a training program that would limit the product's availability and use to certified physicians.

Novartis complied with these demands, offering the product, which costs $950 per unit, free of charge to certified users. In May 1997, Novartis submitted a request to the Ministère de la Santé et des Services sociaux du Québec either for Apligraf ™ to appear on the list of exceptional medications or for patients treated with Apligraf ™ to be recognised as exception patients.

In 1998, the Conseil consultatif de pharmacologie of the Ministère de la Santé et des Services sociaux concluded that the assessment of the product did not fall within its jurisdiction. Indeed, bioengineered products, which include the definitions of medication, medical device, biological product or supply, generate an administrative ambiguity due in part to the fact that there are no established assessment guidelines for these products.

When Novartis did not receive an answer to its request, it ceased to offer Apligraf ™ free of charge. This prompted the certified users to submit a specific budget request to the Ministère de la Santé et des Services sociaux for the necessary funds to purchase 60 to 70 units (the quantity needed to treat patients for a year), while awaiting a decision by the Ministère and the Régie de l'assurance-maladie regarding the product's reimbursement.

The Ministère handed over the dossier to the *Conseil d'évaluation des technologies de la santé* (*CÉTS*) in July 1998, requesting its advice optimal use of Apligraf ™ in the treatment of venous leg ulcers, the total cost of its use throughout the province of Québec, as well as the cost-effectiveness of the product in relation to that of conventional treatment options. It also suggested that *CÉTS* draw up an outline of similar products that would appear on the market in the near future.

In an initial response in September 1998, *CÉTS* stated that the available information was sufficient to recognise the safety and efficacy of Apligraf ™, but that it was unable to express an opinion on its cost-effectiveness or on the total costs that would be incurred by its use.

In October 1998, the Ministère requested that *CÉTS* document the clinical and economic value of Apligraf ™. The following aspects of the use of Apligraf ™ were to be included in the assessment:

<u>Clinical Value</u>

- An assessment of the clinical benefits, limitations and drawbacks of the product in the treatment of hard-to-heal venous leg

ulcers resistant to high compression therapy.

- An estimate of the number of applications needed to treat the Québec population with venous leg ulcers.
- Insight into other possible applications of the product.
- A definition of prerequisites for the applicability and success of the treatment.

Economic Value

- A cost-effectiveness analysis with respect to conventional treatments.
- Identification of the cost aspects that are reduced or increased with the use of the product, in order to inform professionals and administrators of possible substitutions.

These aspects were to be documented in light of the results of an intra-hospital study by the Centres hospitaliers universitaires (CHU; university hospitals). Since 1991, according to the Act respecting Health Services and Social Services (S-4.2_A), CHUs have had the assessment of new technologies as one of their responsibilities. The Ministère offered to pay for 60 to 70 units of Apligraf ™, as well as part of the costs incurred in the collection of data.

The search for publications on the treatment of venous leg ulcers continued in the fall of 1998, in order to define the parameters to be considered in a clinical and economic study. Exploratory meetings were held at the end of 1998 with clinicians, Novartis representatives and other resource persons in epidemiology and methodology in order to design the projected study.

In May 1999, a group of physician-investigators, users of Apligraf ™, studied a proposal. The study's objective was to define conditions (as shown in Figure A.10, Appendix 10) for the use of Apligraf ™ in approximately 60 to 70 patients with hard-to-heal venous leg ulcers resistant to compression therapy (including the required human and material resources). The group concluded that it would be impossible to carry out such a study within the constraints of the budget allocated by the Ministère. They proposed the setting up of a Québec advisory panel similar to the Canadian panel (Dolynchuk et al., 1999) to develop practice guidelines for the optimal use of Apligraf ™.

CÉTS management reviewed this option. An advisory panel was considered difficult to set up in the current context, especially when results from an ongoing clinical trial should complement the available information. The recruitment of patients for this multicentre, pan-Canadian, randomised controlled clinical and economic trial was scheduled to end December 31, 1999 (later postponed to April 30, 2000), and results would most likely be known approximately one year later.

Meanwhile, this report will attempt to assess the number of venous leg ulcers in Québec from the most recent epidemiological data. Published evidence on the safety and efficacy of current treatment options and available cost estimates were also compiled. Preliminary models were used to assess the magnitude of the costs that would be incurred if certified physicians practising in clinical settings used Apligraf ™. Recommendations on the optimal use of Apligraf ™ lead to the broader recommendation of starting or pursuing representations for the inclusion of data on the foreseeable costs of using new therapeutic products in new product submissions to Health Canada.

2. DATA COLLECTION AND ANALYSIS

2.1 DATA COLLECTION

Data were collected from various sources. Literature searches were conducted online through the Medline and PubMed databases with the following MeSH terms: "leg ulcer", "varicose ulcer", "human skin substitute" or "human skin equivalent" or "apligraf" or "(varicose or leg) AND ulcer*". These are general terms rather than specific keywords and were used to promptly extract references that were not yet indexed. Additionally, the computer version of Current Contents was searched every two weeks. The search profile was generated with the following keywords: "leg or legs AND (ulcer or ulcerated or ulceration or ulcerations or ulcers)".

Information on new products, regulations governing these products, practice guidelines or recommendations was accessed on the World Wide Web through the websites of corporations or professional associations and governmental organisations, such as: Cochrane Collaboration (international organisation that performs systematic reviews of comparative trials on health interventions), International Society for Technology Assessment in Health Care (ISTAHC), Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Scottish Intercollegiate Guidelines Network (SIGN), Food and Drug Administration (FDA), Health Canada, etc.

Novartis promotional material on Apligraf ™ as well as Smith & Nephew's on Profore ™ (four layer compression bandage) were consulted.

Several unpublished reports were studied at Novartis' to complement the information submitted to the Ministère in 1997 and then to *CÉTS* in August 1998. These include a report of a survey in some Montréal CLSCs to identify the number of patients with venous leg ulcers as well as current clinical practices; extracts of the protocol for a current clinical trial on the efficacy of Apligraf ™ and estimates of the economic impact of its use in the treatment of venous leg ulcers resistant to compression therapy.

Various other institutional documents were reviewed, such as extracts relating to the management of leg ulcers from a manual published by the Association des CLSC et des CHSLD du Québec.

End references from the retrieved literature were also identified for assessment at a later date, when relevant.

MedEcho and APR-DRG databases were also consulted to complete the information on the burden of venous leg ulcers on the Québec health care system.

Aside from a few references added in October 2000, most of the cited references were from searches conducted up to September 2000.

2.2 DATA ANALYSIS

As in the literature search, methods for analysing the retrieved documentation were adjusted according to the nature of the information. More specifically, the compilation of epidemiological data was generally narrative rather than always critical, to show the wide range of incidence and prevalence rates found in the literature. This choice was made on the one hand because of the great diversity in epidemiological studies (selection of patients, demographics of studied populations, etc.), and on the other, because of the current practice of accepting the most often cited European or

Australian data and of directly transposing them to North American, Canadian or Québec populations.

Published critical reviews (those of the Cochrane Collaboration in particular) were exhaustively reported. Thus, the meta-analysis on the efficacy of compression therapy in relation to its absence was used as a starting point in the evaluation of various treatments. The Cochrane Collaboration published a meta-analysis on skin grafts or grafts of human skin substitutes in February 2000. Statements from evaluation protocols and relevant preliminary results were integrated into the appropriate sections of this document. Other protocols were also announced or published in 2000 by the Cochrane Collaboration (debridement, antibiotherapy) and were integrated where relevant.

The randomised controlled trial on the safety and efficacy of Apligraf ™ is described separately.

Finally, data on costs remain sparse at this time. Costs cannot often be transposed to the Québec health care system and the compilation of Québec data on the costs of leg ulcers is still incomplete.

3. ESTIMATING THE PREVALENCE OF VENOUS LEG ULCERS IN QUÉBEC

How many patients with venous leg ulcers in Québec would benefit from Apligraf ™? For want of Canadian or Québec data to answer this question, approximations derived mainly from European or Australian publications will be presented. It should be noted that North American studies on the incidence and prevalence of leg ulcers are scarce and that numbers given for the United States, Canada or Québec are simply estimates from studies conducted on other continents (Anick Bérard, Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital; Department of Epidemiology and Biostatistics, McGill University, personal communication, August 1998; Wienert, 1999).

Results of frequently cited studies on the importance of leg ulcers in various countries are listed in Appendix 1. The data is sorted according to various parameters: incidence and prevalence of active leg ulcers, including or excluding those of the foot; active ulcers only or including previous history; ulcers in the general population, in the adult population or according to age and sex; ulcers estimated in the entire population or ulcers known to health care systems; anatomical distribution of leg ulcers; male/female ratio; causes of leg ulcers; concomitant diseases; recurrence rates and risk factors. Healing rates for different treatments are shown in Appendix 4 and discussed in Section 5.

Wide variations exist in the publications cited in Appendix 1, regardless of the parameter considered. For example, the prevalence of active leg ulcers including those of the foot in the general population ranges from 0.11% in one region to 1.13% in another. Are these rates illustrative of an actual difference, of diagnostic inaccuracy, or of an inconsistency in methodology? The methodological aspect could be of secondary importance here because the populations on which data is reported may not necessarily correspond demographically to the Québec population. If the necessary data to determine this correspondence are lacking, another option is to transpose available data to the province of Québec and select a likely order of magnitude.

The expression "order of magnitude" is used because of the wide range of results obtained with various transpositions. In the United States, authors still cite estimates dating from 10 or 20 years ago and calculate that approximately 1% of the 5 million people who exhibit some evidence of chronic venous insufficiency have or will develop a venous leg ulcer (Alguire and Mathes, 1997). According to these estimates, it can be calculated for the Canadian population (which is approximately 10% that of the United States) that there are 50,000 cases of chronic venous insufficiency, and that 1% of these, or 5,000, represent potential cases of leg ulcers. If 25% of these can be found in Québec, this would translate into 1,250 potential cases of leg ulcers.

Other authors estimate that in Canada, chronic venous stasis ulcers affect over one percent of the general population (Jack, 1997, citing Kunimoto, 1994). According to this calculation, 300,000 people are affected by leg ulcers in Canada (although not necessarily simultaneously), and 75,000 of these people would be in Québec. One notes that a broad range is generated by such macroscopic transpositions.

In the general literature on venous leg ulcers, it is stated that more than half of these ulcers could be prevented with proper nutrition,

exercise and good leg and foot care (Jack, 1997; citing Margesson, 1996). The prevention of leg ulcers will not be elaborated upon in this document, which addresses more specifically the efficacy (proven or estimated) of Apligraf ™.

People affected by venous leg ulcers are most often over age 60, with prevalence peaking at 70 (Elder and Greer, 1995). The prevalence of a history of leg ulcers in the United Kingdom for people over the age of 65 is 3.6%. Only 20 to 25% of ulcers would be active at any time (Bandolier, 1998).

Venous ulcers represent approximately 90% of all leg ulcers, the others being of arterial, mixed (venous and arterial) or other origin. A venous ulcer most commonly appears above the malleoli and can become of considerable size and circumference (Grey and Harding, 1998). The surrounding skin may become pigmented and develop varicose eczema or lipodermatosclerosis. In severe cases the shape of the leg resembles that of an inverted champagne bottle.

Venous ulcers are chronic and can last for decades. According to data on patient follow-ups, 50% of ulcers last from seven to nine months, and between 8 and 34% may be present for over five years. Leg ulcers recur in 67 to 75% of patients (Alguire and Mathes, 1997, citing Callam et al., 1987; Baker et al., 1991).

Using the estimates mentioned previously, it can be hypothesised that if 1% of the estimated 1998 Québec population was affected by leg ulcers and 80% of those were of venous aetiology (according to Jack, 1997), 7.5 million x 1% x 80% = 60,000 people were affected with venous leg ulcers. If between 20 and 25% of these ulcers are active at any time (Bandolier, 1998), it can be calculated that active venous leg ulcers affect approximately 13,520 people at any time.

Authors from the Cochrane Collaboration (Cullum et al., 1999) use a prevalence of 0.15% (between 0.1 and 0.2%, according to Callam, 1992) for active leg ulcers, referring to often-cited studies (Callam et al., 1985; Lees and Lambert, 1992). This prevalence rate would translate, for Québec, into 7.5 million x 0.15% = 11,250 people. With the prevalence of 0.1-0.2% used by the original author (Callam, 1992), the number of affected Quebecers would range from 7,500 to 15,000.

With estimates from the United Kingdom (Bandolier, 1998), it can be calculated, for the Québec population over the age of 65, that 941,566 people x 3.6% with a history of leg ulcers x 22.5% active ulcers at any time = 7,627 people over age 65 have a leg ulcer. If 80% of these were of venous aetiology, and assuming only one ulcer per person, 6,100 people would be affected in this age group.

The simplification of this estimate would result in 11,000 Quebecers with active venous leg ulcers, of which about half would be over 65 years of age.

Experts set the number of cases of leg ulcers in Québec at 7,000 (Brassard, 1998).

In an article published in June 1999, the Venous Insufficiency Epidemiologic and Economic Studies – VEINES task force (Kurz et al., 1999) reported a great difference between prevalence rates found in different epidemiological studies, without, however, presenting the range in this variation. The task force cited the following rates: a prevalence of 0.3% for chronic leg ulcers in the adult population of Western countries, of two to four times higher for healed ulcers, and of 1% for both rates combined. A prevalence of 0.3% in the adult population (over 15 years of age) of

Québec in 1998 (6.1 million) would result in more than 18,000 chronic venous leg ulcers.

Estimates originating from internal data from Novartis would put the number of leg ulcers in Québec at 5,000 to 10,000. Estimates drawn from various sources and presented in Appendix 9 would put at close to 4,000 the number of annual new cases of ulcer among the 13,000 prevalent ulcers.

The variations between these different estimates is considerable (from 1,250 to 18,000). Overall, the approximations fluctuate between approximately 5,000 and 11,000 for Québec. For the models presented in Section 8.3, the number of cases of venous leg ulcers in Québec has been put at 8,000, of which approximately 4,000 would be known to home care workers, the rest being divided between external clinics and self-treatment, with the latter having no immediate impact on the health care system.

4. AETIOLOGICAL THEORIES AND DIAGNOSIS

Current definitions of leg ulcers are derived from various theories on their aetiology and physiopathology. The goal of this section is not to review these theories. Significant work already exists on the subject (i.e., Negus, 1995; Dormandy, 1997; Kurz et al., 1999). This section will only give two examples in order to illustrate the underlying concepts: "venous stasis" and "varicose ulcer".

Elder and Greer (1995) explain how the expression "venous stasis" implies a stagnation or sluggishness of the blood in the veins. According to a theory that has been accepted since its introduction by Homans in 1917 (cited by Dormandy, 1997), weak venous reflux should bring about tissue anoxia. Weakness in venous reflux, venous insufficiency, venous hypertension, venous stasis and tissue hypoxia are all related to venous leg ulcers. However, tissue oxygen supply would not be reduced in venous insufficiency (Stibe et al., 1990).

According to Elder and Greer (1995) the expression "varicose ulcer" would also be misleading. Superficial venous distension (varicosities) does not necessarily lead to skin breakdown and ulcers. These examples show a clear overlap of traditional but still current terms that directly or indirectly reflect other theories.

In a brief overview, Grey and Harding (1998) describe three main theories on the cause of venous ulcers. The first, the pericapillary fibrin cuff hypothesis, was proposed by Browse and Burnand in 1982, and suggests that a high ambulatory venous pressure can provoke the leakage of plasma proteins and red blood cells out of the capillaries. This would trigger the formation of an insoluble fibrin barrier around the capillary, secondary to inflammation. This barrier hinders the passage of oxygen, as measured experimentally by a reduction in cutaneous oxygen. At this point, a minor trauma could precipitate ulceration.

The second theory suggests the trapping of white blood cells (Coleridge-Smith et al., 1988). Venous hypertension leads to leukocyte activation, followed by the release of free radicals and proteolytic enzymes, which ultimately leads to tissue breakdown and precipitates ulceration (Grey and Harding, 1998).

The third theory is the "trap" hypothesis (Falanga and Eaglstein, 1993). The authors suggest that growth factors are trapped in the insoluble fibrin cuff surrounding the capillaries, thus starving the tissues, and eventually the wound, of vital trophic stimuli. As in the first theory, a minor trauma would be sufficient at this stage to cause ulceration.

From a more general standpoint (Aubin and Agache, 1998), the pathophysiology of venous leg ulcers is described as follows: a chronic venous insufficiency that is concomitant with lipodermatosclerosis ultimately leads to a venous leg ulcer.

From a practical standpoint, fundamental knowledge guides diagnosis, with the aim of confirming venous insufficiency, ascertaining its aetiology and localising the anatomic site and level of disease (Alguire and Mathes, 1997).

Assuming that the increase in publications on the subject reflects the trend, interest in the diagnosis of ulcers of the lower limbs has been growing. For 1992, only three or four articles could be found in Medline on this subject. This number doubled in 1997 and was five times greater in 1998. In addition, recent publications

focus more and more on the problem as a whole.

Since 1998, articles published by individual authors (i.e., Goldstein et al., 1998; Lautenschlager and Eichman, 1999; Zimmet, 1999) as well as reports by organisations (i.e., Scottish Intercollegiate Guidelines Network (SIGN), 1998) address the subject more specifically. The diagnosis of leg ulcers has actually been the focus of a thorough evaluation by SIGN and their recommendations were published in July 1998. The impact of these recommendations is being evaluated in a randomised controlled trial begun in July 1997, comparing the effect on leg ulcer healing rates of using SIGN guidelines alone with the effect of using SIGN guidelines expounded in an intensive formal training programme. The project involved a population of approximately 2.7 million in 16 communities randomised between the guidelines alone or the guidelines with the training of community nurses. The project included a six-month passive observation period, followed by 24 months of implementation of the guidelines with or without training. The compilation of data was to have ended in December 1999 (Finnie, 1999), and the results were to be published in June 2000, but were still not published at the end of July.

In order to document these steps towards the systematisation of leg ulcer diagnosis, the SIGN recommendations are presented below. Patient evaluation and diagnosis should include the following steps:

- "An initial assessment of the patient should be performed.
- Measurement of ankle brachial pressure ratio (index) (ABPI) by hand-held Doppler is essential.
- Patients with an ABPI < 0.8 should be assumed to have arterial disease. (*Refer to Appendix 2 for details on venous or arterial ulcers.*)
- The surface area of the ulcer should be measured serially over time.
- The ulcer edge often gives a good indication of progress and should be carefully documented (e.g. shallow, epithelialising, punched out, rolling.)
- The base of the ulcer should be described (e.g. granulating, sloughy, necrotic).
- The position of the ulcer(s) – medial, lateral, anterior, posterior or a combination – should clearly be described.
- The morphology is helpful in the diagnosis of less common causes, e.g. carcinoma and tuberculosis.
- A non-healing or atypical leg ulcer should be referred for biopsy.
- Bacteriological swabs should only be carried out where there is clinical evidence of infection such as cellulitis.
- Leg ulcer patients with associated dermatitis should be referred for patch-testing with a specific series for leg ulcers.
- Patients with the following features should be referred to the appropriate specialist at an early stage of management: diabetes mellitus; peripheral arterial disease (ABPI <0.8); rheumatoid arthritis/vasculitis; suspicion of malignancy; atypical distribution of ulcers; contact dermatitis or dermatitis resistant to topical steroids; patients who may benefit from venous surgery; failure to progress despite following this guideline."

Despite a few variations (i.e., on the use of epidermotests), these recommendations are similar to those of an advisory panel of dermatologists and nurses that was set up by Novartis to develop practice guidelines for the management of patients with leg ulcers and the appropriate use of Apligraf ™ (Dolynchuk et al., 1999).

It should be noted that these recommendations are presented here to show the growing interest in the management of patients with leg ulcers and not as guidelines proposed by *AÉTMIS*.

The responsibility for ratifying or modifying these recommendations (for example, points questioned by clinicians, such as the pertinence of biopsies and bacterial cultures) is that of the professional associations concerned.

5. TREATMENTS

Treatments are presented here in a somewhat arbitrary order. To reflect the relative importance of current practices and that of the number of publications found, compression therapy and surgery are presented first, followed by pharmacological treatments, and by other treatments. The order of presentation also reflects the focus of this report, namely Apligraf ™. Different aspects of the product will be discussed in depth in other sections.

The Cochrane Collaboration has reviewed several venous leg ulcer treatments and announced protocols for other reviews. These protocols or results from assessments will be mentioned when relevant.

5.1 BANDAGES WITH OR WITHOUT COMPRESSION

The Cochrane Collaboration published an exhaustive review of randomised controlled trials (published or not) in September 1997 (Fletcher et al., 1997). This review was updated on May 27, 1998 (Cullum et al., 1998) and revised again on May 26, 1999 (Cullum et al., 1999). The following summary introduces the main elements of this review.

The purpose of the review was to evaluate the effectiveness and cost-effectiveness of different compression bandaging and stockings in the treatment of leg ulcers. The evaluation of devices applying intermittent or pulsed compression will be assessed in an upcoming Cochrane review.

In their introduction, the authors set the global prevalence of active leg ulcers in Great Britain and Australia at 0.15%. They mentioned how leg ulcer aetiology remains mostly unexplained and how compression treatment can be applied to reverse hydrostatic pressure associated with venous insufficiency and ulceration.

Different countries favour different compression systems. Unna's boot (a non-compliant paste bandage) is the leading system in the United States. The United Kingdom opts mainly for a multi-layer elastic bandage, while in the rest of Europe, as well as in Australia, current practice makes use of short stretch bandages.

Specific topics were: 1) the effectiveness of compression in healing venous ulcers; 2) the optimum level of compression; 3) the type of compression that is most clinically effective; and 4) the system that is most cost-effective.

The strategy for the identification of studies consisted in searching 19 bibliographical databases, and hand searching of journals, conference proceedings and bibliographies. Compression bandage and stocking manufacturers and an advisory panel were contacted for unpublished data.

Criteria for selecting studies for this review were the types of studies, participants, intervention, and outcome measures. Studies considering patients of all ages with venous leg ulceration, in any type of care setting, were considered. Because of variations in diagnostic methods, a standardised definition cannot be given. However, compression had to be applied explicitly to venous ulcers (as opposed to arterial, mixed or vasculitic).

All types of bandages or compression stockings for patients with venous leg ulcers were included: elastic bandages, inelastic bandages, short stretch bandages, multi-layer systems, compression hosiery (i.e., stockings) and single-layer bandage systems. The authors

warn that these groupings are not mutually exclusive and that comparisons are complicated by the lack of standards in terminology and performance indicators.

Criteria for primary outcome were the objective measures of healing such as the rate of change in the ulcer area, the time to complete healing, and the proportion of ulcers healed within the trial period. Criteria for secondary outcome were costs, quality of life, pain, reliability and acceptability.

Studies eligible for inclusion included prospective, randomised controlled trials and controlled clinical trials that employed quasi-random methods of allocation. Trials that only reported surrogate outcome measures were rejected. There was no restriction regarding the language or publication status.

Results from 22 trials, reporting 24 comparisons (data shown in Appendix 11) are summarised below (Cullum et al., 1999):

- Compression was more effective than no compression (4/6 trials: 73% vs. 40% healing rate; for details, i.e., confidence intervals, etc., see Appendix 11).
- Multi-layered elastic compression was more effective than multi-layered non-elastic compression (5 trials: 57% vs. 37%).
- There was no difference in healing rates between 4-layer bandaging and other high compression multi-layer systems (3 trials: 70% vs. 69%).
- There was no difference between 4-layer bandages and inelastic short stretch bandages or Unna's boot (45% vs. 41%).
- Multi-layered high compression was more effective than single layer compression (4 trials: 57% vs. 42%).
- A high compression stocking plus a thrombo stocking was more effective than a short stretch bandage (1 trial: 84% vs. 52%).
- There was no difference between the compression stockings and Unna's boot (1 trial: 71% vs. 70%).
- There was insufficient data to draw a conclusion on the relative cost-effectiveness of different regimens.

From these results, the authors draw the following conclusions:

- Compression treatment increases the healing of ulcers compared with no compression. Moreover, high compression appears superior to low compression.
- High compression is more effective than low compression but should only be used in the absence of significant arterial disease.
- No clear difference was found between different types of high compression systems (3-layer, 4-layer, short stretch or Unna's boot).

The authors end by listing the impact of their work on research. They underline the poor quality of research on ulcer treatment, and list important points to consider in future studies:

- Sample sizes are often too small to reveal significant clinical effects.
- Appropriate comparators should be used to avoid bias.
- Better understanding of the healing process is needed to develop validated outcome measures and ensure that differences in reported healing rates are significant.
- Future studies should take the following into account:
  - The recruitment of patients should be based on an a priori sample size calculation: sample size is often too small to find a statistically significant difference between treatment groups. Multicentre trials should be considered in order to recruit a sufficient number of patients.

Large-scale trials have been conducted in other areas of health care, and despite the difficulties encountered in the field of wound care, there is no reason why large-scale trials should not be performed. The implementation of such trials requires a strong infrastructure to provide support and promote collaboration.

- Either truly objective outcome measures must be used or healing should be articulated as both a percentage and an absolute change in ulcer area.
- A single ulcer per patient must be used as reference in the study: multiple ulcers in a single patient should not be included in the analysis as they are not independent unless a specialised statistical analysis is performed to separate out the effects of the intervention (i.e., matched pairs analysis).
- Groups should be comparable at baseline: in small, randomised controlled trials, randomisation alone will not ensure comparability. Subjects should be paired by baseline characteristics. Then, the individuals in each pair should be randomised to treatment. This type of randomisation is particularly important when ulcers of a mixed aetiology are to be assessed in the same trial.
- Head-to-head comparisons are required for ulcers of a similar nature, e.g., sloughy, epithelialising.
- A thorough description of concurrent treatments (including primary and secondary dressings) should be reported.
- Assessment of outcomes should be blind to treatment.
- Survival rate analysis should be adopted for all studies that assess ulcer healing.
- Studies to determine the biological mechanism involved in ulcer healing are needed. A better understanding of the healing process will lead to the development of validated outcome measures.
- Prospective registration of research studies should be mandatory to prevent publication bias and ensure the inclusion of unpublished trials in systematic reviews. Primary research data should also be made available to those undertaking systematic reviews, particularly in trials where participants have given their written consent on the understanding that their involvement will add to medical knowledge.
- Economic evaluations, based on contemporaneous data, should be conducted in future trials.

The initial 1997 publication was the subject of a POEM (Patient-Oriented Evidence that Matters) by an American author who comments on the report and situates it in the context of the practice of general practitioners and family physicians (Adelman, 1997). The author's comments, which accurately depict the current reality, are quoted below:

> *"Recommendations for clinical practice:* This study confirms what we have been taught for years: An Unna's boot is an effective treatment for venous leg ulcers. Other types of compression are also effective, but which style of compression is more effective or less expensive has not been determined."

Paradoxically, while compression may be the leading treatment in terms of "new treatments", the novelty lies in the promotion of its proper application (Jack, 1997).

Recent data on the success rate of standardised high compression therapy are scarce. A Saskatchewan trial begun with 29 patients and then limited to 15 for treatment by compression, showed highly successful healing rates: 75 to 90 percent in 10 to 12 weeks (Jack, 1997).

Generally, healing rates for compression therapy vary between 30 and 90%. Many fall in a range of 30 to 50% after 12 weeks (see Appendix A.4.1). The unweighted average of the studies assessed by Cullum et al. (1999) of the Cochrane Collaboration gives a rate of 73% (Appendix 11: comparison 1).

5.2 SURGICAL TREATMENTS

Surgical treatments include vascular surgery and skin grafts. Results from the main publications on surgery for venous leg ulcers are presented in Appendix A.4.2.

Vascular surgery consists in correcting deep and superficial vein reflux, which is impaired by lesions or hypertension, and restoring appropriate venous pressure. In a study conducted by Scriven et al. (1998b), assessing 25 ulcers (9 combined reflux and 16 isolated reflux), success rates were 30 and 100% respectively, depending on the type of reflux and surgery. A review of various surgical interventions shows recurrence rates of 0 to 22% after one year (Padberg, 1999).

There are no comparative studies of vascular surgery with regard to other treatments. It should, however, be integrated sequentially into the global (pluridisciplinary) management of venous leg ulcers, especially when there is recurrence. The Cochrane Collaboration has recently published an assessment of surgical interventions in cases of deep venous incompetence (Abidia and Hardy, 2000), but no studies on patients with venous leg ulcers due to deep venous incompetence were found for this review.

Autografts are used more often than allografts in the treatment of leg ulcers. Their success rates were assessed in a few retrospective studies combined with telephone interviews and were determined to be between 82 and 90%, with a recurrence rate of 20% (Puonti and Asko-Seljavaara, 1998; Ruffieux et al., 1997). Studies comparing grafts with other leg ulcer treatments are uncommon. Recourse to skin grafting is often considered only after compression therapy.

The Cochrane Collaboration published a systematic review of skin grafting at the beginning of 2000 (Jones and Nelson, 2000). Seven randomised controlled trials of skin grafts for venous leg ulcers were identified. In six of the seven trials, patients also received compression therapy. Two trials (98 patients) assessed split thickness autografts, three trials (92 patients) assessed cultured keratinocyte allografts, one compared tissue engineered skin (artificial skin) to a dressing (309 patients), and another one compared artificial skin to a split thickness skin graft (7 patients, 13 ulcers). The trials comparing artificial skin to a dressing reported a significantly higher proportion of ulcers healing with artificial skin (40% vs. 60% after 6 months). There was insufficient evidence from the remaining trials to establish whether other types of skin grafts improved the healing of venous ulcers.

The authors conclude that there is limited evidence that artificial skin, used in conjunction with compression, increases venous ulcer healing when compared to compression therapy alone. Further research is needed to assess whether other types of skin grafts can enhance ulcer healing.

5.3 HUMAN SKIN SUBSTITUTES

In July 2000, Apligraf ™ was still the only product approved for the treatment of venous leg ulcers in Canada. The regulations concerning this product, as well as the approved indications, are presented in Section 6. However, there are other bioengineered skin substitutes or artificial skins that can be used in the treatment of leg ulcers. They are presented in Appendix 3: Dermagraft ™, Dermagraft-TC ™, Transcyte ™ and Integra ™.

Dermagraft ™ (manufactured by Advanced Tissue Sciences Inc. and distributed by Smith & Nephew) is made by growing newborn human dermal fibroblasts on a degradable three-dimensional scaffold and cryopreserved (Mansbridge et al., 1998).

Dermagraft-TC ™ or DG-TC ™ (manufactured by Advanced Tissue Sciences Inc.; distributed by Smith & Nephew) is a silastic membrane bonded to the surface of a nylon mesh and coated with porcine collagen. DG-TC ™ is a temporary skin replacement in which the silastic membrane functions as an epidermis to protect the underlying wound (Purdue et al., 1997).

Transcyte ™ (manufactured by Advanced Tissue Sciences Inc.; distributed by Smith & Nephew) contains human dermal tissue (basal layer of the epidermis), combined with a synthetic epidermal layer (upper layer of the epidermis). It is the first bioengineered temporary skin substitute indicated in the treatment of burns to have received FDA approval in the United States.

Integra ™ (manufactured by Chiron / J&J; distributed by Ortho-McNeil) is a matrix of chondroitin-collagen covered with a silastic membrane. It is grafted onto the wound bed so that new blood vessels and cells can spread through the matrix. The silastic membrane is removed after two to three weeks, after which a split-thickness skin graft (or keratinocyte graft) is applied (Martin, 1999).

No attempts to obtain data (published or unpublished) on the effectiveness of these treatments for venous leg ulcers were made for this report.

5.4 PHARMACOLOGICAL TREATMENTS

There are many medications for leg ulcers and a detailed account would go beyond the scope of this report. The same applies to medicated

dressings. Appendix A.4.4 shows results from a several randomised controlled trials, compiled in the course of this assessment, on the effectiveness of some pharmacological treatments. In 1999, the Cochrane Collaboration announced a protocol for the assessment of antibiotics (The Leg Ulcer Team: South Manchester University, 1999), oral zinc (Wilkinson and Hawke, 1999) and local interventions for pain in venous leg ulcers (Briggs and Nelson, 1999). The results of the latter two assessments were recently published.

From a review of the six randomised controlled trials corresponding to the strict inclusion criteria of the Cochrane Collaboration, Wilkinson and Hawke (2000) concluded that generally, there is no evidence that oral zinc sulphate improves the healing of venous or arterial leg ulcers but that it could benefit patients with venous leg ulcers who have a low serum zinc level at the start of the treatment. More research should be conducted to further document this.

While there are no studies on interventions for the management of persistent pain in patients with venous leg ulcers, three studies have compared a eutectic mixture of local anaesthetic (EMLA) with a placebo for the relieving of pain during debridement. The authors (Briggs and Nelson, 2000) conclude that while EMLA may provide effective pain relief for venous leg ulcer debridement, its impact on healing and on the incidence of adverse events such as burning and itching is not clear. Further research is needed to answer these questions, as well as those pertaining to the benefit or harm caused by ulcer debridement, and to the treatment of the persistent pain associated with leg ulcers.

Regranex ™ (becaplermin, a topical gel consisting of a platelet-derived growth factor, PDGF) has been proven effective in the treatment of diabetic ulcers. It was approved in early 1998 by the FDA (FDA News and Product Notes, 1998) and more recently, by Health Canada. The product costs approximately $500 per tube, and since it takes about three tubes to heal one ulcer, the total cost is approximately $1,500.

While Regranex ™ may be peripheral to the treatment of leg ulcers, it is interesting to note that the product (distributed by Janssen-Ortho Inc.) was rejected for inclusion on the list of medications reimbursed by RAMQ. Regranex ™ was later placed on the list of exceptional medications with very strict reimbursement requirements.

Oxpentifylline is a vasodilator with fibrinolytic effects on the behaviour of leukocytes. It can be used in the treatment of venous leg ulcers. A double-blind, randomised, prospective, placebo-controlled, parallel group study was performed on the treatment of venous leg ulcers with oxpentifylline (Colgan et al., 1990). The analysis showed significant results of 64% of ulcers healed at six months in the treatment group (400 mg of oxpentifylline, three times daily) and 34% in the group treated with a placebo (OR = 1.81, 95% CI 1.20 – 2.71). The authors concluded that oxpentifylline, when used in conjunction with compression therapy, improves the healing of venous leg ulcers. It would be interesting to further explore the active properties of this medication and determine its impact on recurrence rates, when administered in small doses after the ulcer has healed (Dormandy, 1995).

Two other studies have been published on the topic. One has confirmed the results obtained by Colgan et al. (1990) while the other has not shown any significant difference.

In the first (Falanga et al., 1999), patients were randomised in three groups. Two groups were treated with oxpentifylline, administered three times daily in doses of 400 mg or 800 mg, and

the third received a placebo. Complete wound closure occurred at least four weeks earlier in the majority of patients treated with oxpentifylline than in the patients who received a placebo (p = 0.043, Wilcoxon test). The higher dose of oxpentifylline (800 mg, three times daily) was more effective than the lower dose. The authors conclude that oxpentifylline improves ulcer healing.

In the second study (Dale et al., 1999), patients were administered a dose of 400 mg of oxpentifylline three times daily or a placebo. Complete wound closure occurred in 64% of patients in the treatment group, compared with 53% in the group receiving a placebo (p > 0.05).

5.5 HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen therapy (HBO) consists of exposing the patient to between 1.5 and 3 atmospheres of pure oxygen in a compression chamber. It can be used as an adjuvant therapy for leg ulcers. A few studies have shown the effectiveness of HBO in reducing the size of venous leg ulcers.

The main study is summarised in Appendix A.4.5 (Hammarlund and Sundberg, 1994), in a table taken from an assessment report on HBO (*CÉTS*, 2000). This double-blind, randomised trial of HBO in patients with chronic leg ulcers showed a 36% reduction in the size of ulcers after six weeks in patients receiving HBO in conjunction with their usual treatment. In comparison, the size of ulcers in patients treated only with the prescribed treatment (compression stockings, etc.) was reduced by only 3%.

Generally, comparative studies do not include compression therapy, which makes HBO data difficult to compare with data on the currently most common treatment, which is high compression therapy.

5.6 ULTRASOUND AND LASER THERAPY

Still rarely used, these treatments are mainly experimental, as shown in studies summarised in Appendices A.4.6, A.4.7 and A.4.8. There is no indication that their use will become more widespread in the medium term.

The Cochrane Collaboration has announced a protocol for reviews on therapeutic ultrasound (Flemming et al., 1999) and laser therapy (Flemming and Cullum, 1999a) for venous leg ulcers.

The use of therapeutic ultrasound goes back almost 50 years (Peschen et al., 1997, citing Hill, 1982). Several experiments with ultrasound have shown that its application in the treatment of skin lesions is more effective in small rather than large doses (Peschen et al., 1997, citing Ernst, 1995). Low-frequency ultrasound (30 kHz) can be used as an adjuvant therapy to conventional leg ulcer treatments. In appropriate settings, ultrasound is safe and easy to use (Peschen et al., 1997, citing Dyson, 1990).

Different types of lasers are used in medicine: crystalline lasers, semiconductor lasers, liquid lasers and gas lasers. Gas lasers, such as helium neon (HeNe) and gallium arsenide (GaAs), are the main types of lasers on the market and are used for the biostimulation of cutaneous wounds.

The HeNe laser was the first on the market and its beneficial effect has been demonstrated for cutaneous wounds as well as in dentistry (Flemming and Cullum, 1999a, citing the Swedish Laser-Medical Society, 1998). The advantage of the HeNe laser is that it emits visible red light that triggers the eye's blink reflex, protecting it from harm.

The GaAS laser has been used mostly in the treatment of pain and inflammation. Of all conventional therapeutic lasers, it is the GaAS that penetrates deepest into tissue, suggesting that it is less suited to the treatment of cutaneous wounds. GaAS doses are lower than HeNe doses, but GaAS has the disadvantage of emitting invisible light, and protective gear is therefore required (Flemming and Cullum, 1999a, citing Swedish Laser-Medical Society, 1998).

The irradiation intensity of low energy laser therapy is so low that it is suggested that any biological effect is caused by the radiation rather than by the heat generated. Low energy therapy delivers treatment energies of less than $10J/cm^2$ using lasers operating at 50mW or less. There is a running hypothesis that by exposing cells in a wound to the photon energy produced by low-level laser therapy, repair can be improved via cellular proliferation or migration (Flemming and Cullum, 1999a, citing Basford, 1989).

The results of the review on low energy laser therapy were recently published (Flemming and Cullum, 2000). Of the four studies evaluated, only one suggests that a combination of laser and infrared light may enhance venous leg ulcer healing. More research is needed.

The Cochrane Collaboration has announced protocols for the review of other treatments, and the results should be published in the foreseeable future: dressings (Palfreyman et al., 1999) and electrical stimulation (Flemming and Cullum, 1999b).

6. APLIGRAF ™

6.1 REGULATORY STATUS

Apligraf ™ is a human skin substitute made of dermal cells (composed of human fibroblasts in a bovine collagen lattice) and of epidermal cells (human keratinocyte with a well-differentiated stratum corneum). In Canada, Apligraf ™ is indicated for use in the treatment of partial and/or full-thickness skin loss in ulcers of venous aetiology.

It is manufactured by Organogenesis Inc. in the United States and distributed by Novartis Pharma Canada Inc. Apligraf ™ was approved by Health Canada in 1997 and filed under section 36 of the Medical Device Regulations of the Food and Drugs Act.

Health Canada studied the case of Apligraf ™ according to both the assessment criteria for Class IV medical devices (high risk for the patient) and the criteria applicable to biological products relating to manufacture, transport, expiry date, etc. (information received from Dr. Fred Lapner, who examined the Apligraf ™ submission to Health Canada's Therapeutic Products Programme, personal communication, July 1999).

The procedure for the processing of requests for the approval of similar products has not yet been established. In fact, such requests seem to be dealt with on a case-by-case basis. Since "biological products" are sometimes listed as "devices", the applicable regulations must be adapted to each new product.

Health Canada ordered a post-marketing study on the safety of Apligraf ™. Results for 308 patients have confirmed previous data on the product's safety (documents received from Novartis by *CÉTS* in August 1998; an update to this study was not available for this report in June 2000).

6.2 CERTIFICATION OF USERS

Like the Food and Drug Administration (FDA), which requires the training and supervision of users of products such as Integra ™ (a dermal analogue – Phillips, 1998), Health Canada and Novartis have agreed to implement a training program for users of Apligraf ™.

The program allows for a limited number of users. To place an order for Apligraf ™, a physician must have participated in a 3-hour information session including a demonstration. Most of the 47 certified Québec physicians are dermatologists associated with wound care centres or units.

For the treatment of venous leg ulcers, the increase in the number of certified users of Apligraf ™ should not exceed 10% on the whole in the next few years. No new users were certified in 1999.

Requests for approval of the product for other indications (e.g., burn victims) are not likely to be submitted in the next three to five years in Canada (according to Novartis, February 1999). The indication of diabetic ulcers was approved in the US in June 2000, and in Canada in August 2000.

The advisory committee of the FDA did, however, recommend the approval of Apligraf ™ for the treatment of diabetic ulcers in early May 2000 (Business Wire, 2000). This recommendation led to approval for this indication in the United States on June 21, 2000.

6.3 AMERICAN AND CANADIAN MONOGRAPHS

In its promotional material, Novartis advocates that Apligraf ™ be restricted to the treatment of venous leg ulcers resistant to compression therapy. This recommendation is based on the American monograph, as the indication found in the Canadian monograph mentions only that the ulcer treated must be of venous aetiology. The texts below highlight these differences.

Canadian monograph, approved in April 1997:

"INDICATIONS AND CLINICAL USE

APLIGRAF is indicated for the treatment of partial thickness and full thickness skin loss in ulcers of venous aetiology.

CONTRAINDICATIONS

APLIGRAF is not indicated for use on patients with severe dermatitis. APLIGRAF should not be used over exposed bone, tendon or capsule or applied over frankly infected wounds until the underlying condition has been resolved.

ADVERSE EVENTS

In the controlled clinical study conducted in patients with ulcers of venous aetiology, infection (regardless of attribution) was reported more frequently in the 161 APLIGRAF-treated patients than in the 136 control patients treated with standard care (multi-layered compression). There was however no significant difference between the two groups in the frequency of infection reported as related or possibly related to treatment. Infection was diagnosed by clinical judgement without confirmatory cultures.

There was no difference in the incidence or severity of any other adverse event in APLIGRAF-treated patients when compared to control patients."

It can be presumed, theoretically, that the immediate and generalised use of Apligraf ™ would generate very high costs. The use of Apligraf ™ as prescribed by Novartis corresponds more closely to the American monograph, approved by the FDA in May 1998.

American monograph, approved in May 1998

"INTENDED USE / INDICATIONS

Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy.

CONTRAINDICATIONS

- Apligraf is contraindicated for use on clinically infected wounds.
- Apligraf is contraindicated in patients with known allergies to bovine collagen.
- Apligraf is contraindicated in patients with a known hyper-sensitivity to the components of the Apligraf agarose shipping medium.

ADVERSE EVENTS

There were 1 life-threatening and 3 severe infections reported in the Apligraf group and none in the control arm. Of the four events, two severe infections were considered related to treatment, however, one occurred one month after the last application of Apligraf and the other occurred following application on a pre-existing *Pseudomonas* infection."

In the American monograph, the use of Apligraf ™ in the treatment of venous leg ulcers is clearly restricted to ulcers with two specific characteristics: greater than 1 month's duration and that have not adequately responded to compression therapy.

There is also a difference in the contraindications: the Canadian monograph is

more explicit on the correction of underlying conditions before the application of Apligraf ™.

The regulations pertaining to the use of Apligraf ™ have evolved since its approval for use in the treatment of diabetic ulcers in the United States (June 2000) and in Canada (August 2000).

6.4 STUDIES ON APLIGRAF ™

Studies summarised below include the pivot study (Falanga et al., 1998), which is the basis for the main evidence of the safety and efficacy of Apligraf ™. Other studies explore different conditions for the optimal use of Apligraf ™, particularly the use of planimetry as a prognostic tool for the assessment of a venous ulcer's response to proper compression therapy.

The pivot study is a randomised controlled trial (Falanga et al., 1998) on the safety, efficacy and immunological impact of an allogeneic cultured human skin equivalent in the treatment of venous leg ulcers.

The demographic and clinical characteristics (particularly ulcer duration between <6 months and >2 years) of patients recruited for this study were similar in both groups (129 controls and 149 patients treated with Apligraf ™). Inclusion criteria for the study are shown in Table 1, while Table 2 summarises the results.

Table 1: Inclusion criteria for the pivot study
(From Falanga et al., 1998)

INCLUSION	EXCLUSION
Venous insufficiency, determined by the following criteria: 1. presence of clinical signs and symptoms of venous ulceration, such as hyperpigmentation of the surrounding skin, varicosities, and lipodermatosclerosis; 2. absence of significant arterial insufficiency (as determined by an ankle brachial index >0.65); 3. evidence of venous insufficiency by air plethysmography or photoplethysmography, with venous refilling time being less than 20 seconds. Other criteria: the ulcer had to be free of cellulitis and exudation indicative of heavy bacterial contamination and could not contain an eschar or obvious necrotic material that would interfere with graft take and healing.	Clinical signs of cellulitis, vasculitis or collagen vascular diseases, pregnancy or lactation, uncontrolled diabetes mellitus, and other clinically significant medical conditions that would impair wound healing, inclusive of renal, hepatic, hematologic, neurologic, or immunological diseases. Patients receiving corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy within 1 month prior to entry into the study were also excluded.

Table 2: Time to wound closure
(From Falanga et al., 1998)

	HSE* (1)	Controls (2)	Δ (2) - (1)
Time to wound closure, according to ulcer (days):			
Ulcers of greater than 6 months' duration	92	190	98
Ulcers of less than 6 months' duration	46	89	43
Stage III ulcers (down to muscle)	83	183	100
Stage II ulcers (superficial ulcer)	57	98	41
Large ulcers (> 1000 mm^2)	181	231	50
Small ulcers (< 1000 mm^2)	56	98	42
Median days to 50% wound closure (range)	23 (3-185)	29 (3-232)	6
Median days to 75% wound closure (range)	30 (3-189)	50 (4-232)	20
Median days to 100% wound closure (range)	**61 (9-233)**	**181 (10-232)**	**121**
No. (%) of patients with 100% wound closure by 6 months	92/146 (63.0)	63/129 (48.8)	(14.2)
Average number of HSE applications for each patient	3.34		
Ulcer recurrence	11/92 (12%)	10/63 (15.9%)	(3.9%)

* Human skin equivalent: the terminology evolved to human skin "substitute" in publications and in Novartis' material during 1998.

Wound closure occurs more rapidly with Apligraf ™: 61 vs. 181 days. The average number of units of Apligraf ™ needed per patient in this study was 3.34. Recent clinical observations would yield similar results with only one application (Michael Sabolinski, Organogenesis Inc., Canton, Mass.; personal observations communicated to Novartis, 1999). These observations will have a significant impact on the cost models presented in Sections 7 and 8.

In another study (Sabolinski et al., 1999a), ulcers of more than 1 year's duration were treated with compression therapy alone (48 subjects) or with compression therapy and Apligraf ™ (74 subjects). Demographic and clinical characteristics of patients were similar. Inclusion and exclusion criteria were those of the previous study (Falanga et al., 1998). The percentage of healed ulcers after six months was higher in patients treated with Apligraf ™ than in controls (47% vs. 19%; p= 0.002) and the median time to complete wound closure was shorter (181 days vs. not attained; p= 0.0038).

It should be noted that in the American monograph (Section 6.3), and in the Canadian distributor's (Novartis) recommendations to certified physicians, Apligraf ™ is restricted to hard-to-heal venous leg ulcers (ulcers that remain unhealed after conventional treatment).

The ability to recognise hard-to-heal ulcers early in the treatment would be an asset. A few studies have addressed the issue. Sabolinski and Falanga (1999b) have determined that after four weeks of treatment, the initial healing rate would be predictive of complete wound closure at 24 weeks. This conclusion was made after a prospective study that was carried out with 136 venous ulcer patients treated in 15 centres. The ulcer healing rate was calculated by computerised planimetry: it was measured at baseline, then weekly for 8 weeks, and again at weeks 12 and 24. The average initial heal rates in all ulcers, whether healed or not, expressed in cm/wk (standard error), was 0.1206 (0.0196)

and 0.0542 (0.0133). In the 71 patients who did not achieve complete healing by six months, the healing rates at four weeks were significantly different from those observed in the 65 patients who achieved complete healing.

In another multicentre trial with 104 patients (Kantor and Margolis, 2000), the percent reduction in venous ulcer area from baseline, rather than the healing rate, predicted ($p < 0.05$) in the first four weeks of treatment, which ulcers would be completely healed at 24 weeks (68.2%) and which ulcers would remain unhealed (74.7%).

Planimetry is a subject of interest: rapid identification of ulcers most likely to resist compression after only four weeks could trigger the alteration of treatment. Vascular surgery to correct the underlying venous insufficiency, autografts or allografts, and Apligraf ™ are among the alternatives or complements to compression therapy.

The prognostic validity of planimetry will be supported by the results of a clinical trial with several objectives and whose patient recruitment ended on April 30, 2000 (Novartis: APL-CDN-02 study).

The purpose of this multicentre, pan-Canadian, randomised controlled trial is to reproduce the most realistic conditions for the use of Apligraf ™, based on effectiveness data compiled since the publication of the pivot study (Falanga et al., 1998). This new study addresses both the clinical and economic aspects of Apligraf ™. The comparison of healing rates and costs, after compression therapy alone or compression with Apligraf ™ in ulcers recognised as resistant by planimetry after four weeks of treatment, should provide convincing results, which will either validate or invalidate current models that recommend the use of Apligraf ™. The primary and secondary objectives of this study were obtained from Novartis and are reproduced in Appendix 6. Results should be known in the summer of 2001.

Regarding planimetry (see Appendix 7 for summaries of current computerised or manual techniques), a planimetry service for the prognosis of hard-to-heal venous leg ulcers could be offered at a rather low cost (Mr. Pierre Gauthier, biomedical engineer, Sacré-Cœur Hospital, personal communication, June 1999).

The following sections will summarise the literature and present data on the cost of leg ulcers.

7. ESTIMATING THE COST OF TREATING LEG ULCERS

Inasmuch as the epidemiological data on leg ulcers for North America, Canada and Québec are approximations transposed from European or Australian data (see Section 3), the estimates of the costs of treating leg ulcers are also partial transpositions. A few European studies provide global costs of leg ulcers (see Appendix A.5.1). To date, no North American publications are comprehensive enough to figure on this list.

Estimates of the global cost of venous diseases of the leg were compared in five European countries and are presented in Table 3 (Laing, 1992). These compilations take into account hospital inpatient and outpatient costs, costs of community-based nursing services, of consultations with general practitioners, of prescription medicines and compression hosiery.

The following data show the cost of venous diseases of the leg, followed by the percentage of costs for all conditions, in each country.

Table 3: Costs of venous diseases of the legs (Europe)

COUNTRY*	COSTS FOR VENOUS DISEASES OF THE LEG	PERCENTAGE (%) OF COSTS FOR ALL CONDITIONS
United Kingdom	294 £	2.0
France	7834 FF	1.9
West Germany	1426 DM	1.5
Italy	1638 LIT	1.0
Spain	1724 PTA	1.0

*(1989 geography and 1992 currency)

In these five European countries, there is a two-fold difference in the percentage of costs for all conditions. The order of magnitude of these costs (aside from those of the United Kingdom, where compilations would be more specific and thorough) is similar to that of many other estimates of venous leg ulcer costs, with some being twice as high as the figures presented here for all venous diseases of the leg.

Global estimates for the United States are both rare and poorly documented. Existing estimates are derived from clinical trials distinguishing healing ulcers from those that are hard to heal.

The direct medical cost of leg ulcers was estimated to be between US$600 and US$2,000 per ulcer (Bonadeo et al., 1992). However, an ulcer that remains unhealed at 12 weeks may generate direct medical costs of up to US$10,000 in 1987 currency (Blair et al., 1988).

The correspondence between the European and Québec systems in terms of leg-ulcer data handling has not been established. Published European cost data therefore cannot be transposed to the Québec context without validation. Some compilations in Appendix 5 show various aspects of these costs and their extent. The distribution of costs according to various interventions (home care, specialised

centres, clinics, hospital stays, etc.) could be used as an outline for data collection for determining the costs to the Québec health care system.

In order to identify the cost parameters that have been studied since the renewed interest in this subject in recent years, three publications will be presented. The current trend is not only to provide a better breakdown of costs, but also to implement quality-assurance programs for the management of leg ulcers.

In Sweden, 345 patients from the public sector were incorporated in a cost analysis, as part of an epidemiological survey. Table 4 shows the breakdown of these patients according to level of care as well as the percentage of weekly costs per patient and annual costs in the region studied, namely Linköping and surrounding areas (Faresjö et al., 1997).

Table 4: Breakdown (%) of the direct costs of treating leg ulcers

(From Faresjö et al., 1997)

	Venous leg ulcer patients %	Weekly cost per patient %	Estimate of annual cost for the region %
Primary health care			
At home	51	2.2	10.9
Primary health care centre	24	3.4	8.1
Nursing home	1	26.0	2.2
Hospital care			
Hospital managed care at home	2	7.8	1.5
Hospital outpatient unit	8	6.9	5.2
Hospital inpatient clinic	14	53.7	72.1

According to this data, half of the patients are treated at home, and account for 11% of the costs for the region. In contrast, 14% of patients are hospitalised, accounting for 72% of the costs. The authors stress that the weekly cost for hospitalised patients is 24 times higher than the cost for home care patients.

It would be tempting to extrapolate these data to the Québec population and health care system. The two following examples, however, show that the available information is very diverse, and without any established correspondence between these clinical practices and the Québec health care system, the reliability of the estimated values would be questionable.

In a Cleveland (USA) clinic, 78 patients with venous leg ulcers were followed until healing or for a maximum of one year, whichever occurred first (Olin et al., 1999). Several parameters were considered: demographic characteristics of patients, clinical characteristics of ulcers, as well as patient utilisation of health services.

The average cost per patient for the observation period was US$9,685 (1997). Table 5 shows the percentage of costs according to the health services used. In this group of patients, home care costs are dominant.

Table 5: Health services used by patients with leg ulcers
(After Olin et al., 1999)

Health service	Cost breakdown %
Total outpatient	5.4
General fees	2.6
Physician	2.8
Hospitalization	25
Home dressings	21
Prescriptions	0.3
Home care	48

In the UK, the objective of a randomised controlled trial was to establish the cost-effectiveness of two interventions (Morrell, 1998; Morrell et al., 1998). Compression therapy performed in community clinics (120 patients) was compared with usual care (mostly without compression), provided in home care settings (113 patients). Demographic and clinical characteristics of patients were equivalent in both groups.

The initial healing rate was measured with the Cox model and was 1.45 (1.04 - 2.03) times higher in the clinic than at home. After adjustment of healing times for prognostic variables, it was 1.65 (1.15 – 2.35) times higher in the clinic. The median healing rate was 20 weeks in the clinic and 40 at home. Recurrence was 35% in the clinic and 23% at home. The mean time that each patient was free from ulcers during follow-up was 20.1 weeks in the clinic and 14.2 weeks at home. The annual treatment costs were similar: £878 in the clinic and £859 for the control group (p = 0,89).

Morrell et al. (1998) conclude that treatment in a clinic is more effective. The cost of treatment in a clinic could be significantly reduced by a simple reorganisation of services. The authors also stress that the healing rate they obtained (34%) was lower than those of 74% and 69% published by Blair et al. (1998) and Moffat et al. (1992), which could be explained by the duration and size of ulcers at baseline.

The three examples shown above were meant to illustrate the extent to which the available information differs from one health care system to another. They were also meant to stress the need for a compilation of validated data, based on current practices in venous leg ulcer treatment in Québec, in order to develop verifiable comparators.

The Québec data compiled to date is fragmentary. While no primary data collection has been done for this report, some data on hospitalisations are presented in Appendix 8. Between 1992 and 1997, the mean length of

stay for cases of main diagnosis was 21 days, and for single cases, 6.5 days. A 1998 survey by the Centre hospitalier de l'Université de Montréal (CHUM) sets the number of mean lengths of stay for venous leg ulcers at 17.3 days (see Section 8.2 for more information on this survey).

The APR-DRG (All Patients Revised - Diagnosis Related Groups) group together all types of skin ulceration, which prevents the compilation of specific data on venous leg ulcers.

Rough estimates calculated after consulting home care workers suggest that there are 1,100 leg ulcer patients in 29 CLSCs in Central Montréal (according to field data compiled by Novartis in 1998). These numbers were confirmed by telephone communications with the persons responsible for home care co-ordination in various Central Montreal CLSCs during the summer of 1999.

8. MODELLING THE COST OF USING APLIGRAF ™

The following estimates are based on models with different premises. First, an analysis by Innovus Research is presented (Section 8.1), followed by a study performed at the Centre hospitalier de l'Université de Montréal (CHUM) in 1998 (Section 8.2) and an analytical prediction model developed at *AÉTMIS* by assembling the information found in previous models, the success rates and the available costs for various treatment options (Section 8.3). Lastly, an economic analysis model recently published is reported (Section 8.4).

8.1 INNOVUS

This cost-effectiveness analysis is derived from models based on estimates of clinical practices from a survey of seven Canadian clinicians, experts in the treatment of wounds (and more specifically, leg ulcers), using a modified Delphi technique (Attard and Walker, 1997). The following experts were consulted: Dr. Alain Brassard, Montréal, Québec; Dr. Lyn Guenther, London, Ontario; Dr. Wayne Gulliver, St. John's, Newfoundland; Dr. Vincent Ho, Vancouver, British Columbia; Dr. Shane Inlow, Calgary, Alberta; Dr. David Keast, London, Ontario; and Dr. Gary Sibbald, Toronto, Ontario. These physicians provided their input on Canadian practice patterns in the treatment of venous leg ulcers. Prices were calculated using Ontario rates for 1996 and 1997 and assigned to the estimated resources to determine the costs. Except for Dr. Gary Sibbald, these physicians were not involved in the study design, data analysis or the writing of the final report for this study.

The economic estimates for this analysis came from the internal data of the Organogenesis prospective clinical trial (Novartis, data on file, cited by Attard and Walker, 1997) "which compared Apligraf ™ and a single pressure bandage of Coban ™ (mild compression) to no Apligraf ™ and Duke's boot (moderate compression). The study reported that Apligraf ™ combined with Unna's boot provided a reduction in time to 100% wound closure and an increase in frequency of 100% wound closure compared to not using Apligraf ™. The comparator, Duke's boot, is Unna's boot plus an additional layer of compression. Therefore the group receiving Apligraf ™ received less compression than the comparator group. Since there was less compression in the Apligraf ™ group the results may have underestimated the effectiveness in the Apligraf ™ arm" (Attard et Walker, 1997).

Models for three months and six months of treatment were used for the analysis of "typical outpatients". They were treated with a single unit of Apligraf ™ at a cost of $950. In the 3-month model, "the primary measure of effectiveness employed in the economic analysis was the number of ulcer days during the model time horizon. There were 22 ulcer days averted in the Apligraf ™ +4-Layer bandage system alone. The incremental cost-effectiveness ratio provided the cost per ulcer day averted by the addition of Apligraf ™ to the 4-Layer bandage system compared to the 4-Layer bandage system alone. The cost per patient was higher by $304 (societal perspective) and $316 (health care perspective) in the Apligraf ™ +4-Layer bandage group. This led to virtually identical cost-effectiveness ratios of $14 per ulcer day averted from both the societal and health care perspectives" (Attard and Walker, 1997).

In the 6-month model, three scenarios were designed, varying the number of ulcer days per patient during months 4-6, based on the results

obtained in terms of reduction in ulcer days with Apligraf ™ during the first three months.

Innovus scenarios:

1. The reduction in ulcer days due to Apligraf ™ that occurred in months 1-3 would also occur in months 4-6, even though no new Apligraf ™ was applied in months 4-6.
2. The assumption is that the effect of Apligraf ™ ends after the first three months.
3. The assumption is that only half the number of patients would heal in the second three months because they had not healed in months 1-3 and have harder to heal ulcers (Attard and Walker, 1997).

All three scenarios yielded cost-effectiveness ratios below $5 per ulcer day averted. The authors conclude that the differential cost-effectiveness analysis "indicated that Apligraf ™ +4-Layer bandage was more costly and more effective than 4-Layer bandage. The question is whether $14 per ulcer day averted is good value for money or not. Another way to look at it is whether, over 12 weeks, it is worth $304 per patient to avert 22 ulcer days, from 67 to 45 ulcer days, given that an ulcer day involves pain, impaired mobility, exudate and odour from the ulcers" (Attard and Walker, 1997).

The authors conclude by underlining the importance of improving their model with validated clinical data. "Although these results are the best estimate we have at this time, given that all 3-month model parameters were based on expert opinion, a more thorough collection of resources via retrospective chart review or prospective data collection would provide more confidence in the findings" (Attard and Walker, 1997).

8.2 CENTRE HOSPITALIER DE L'UNIVERSITÉ DE MONTRÉAL

Data were collected at the Centre hospitalier de l'Université de Montréal (CHUM) for the period of April 1, 1996 to March 31, 1997, in order to measure the impact of Apligraf ™ on hospital costs when used in patients suffering from ulcers resistant to compression therapy. For the period studied, 106 patients hospitalised for venous leg ulcers were identified.

Taking into account the total length of stay for these patients (1,835 days) and a daily cost of $547, and adding monthly costs of visits to clinics ($122) for 11 months, the annual cost per patient would be $10,811.

Assuming that a treatment with Apligraf ™ ($950) leads to healing within 12 weeks in an outpatient clinic, the cost per patient would be:

$$(3 \times \$122 = \$366) + \$950 = \$1,316.$$

However, a failed treatment with Apligraf ™ would incur annual costs of $11,761 per patient according to this model. These total costs include the mean annual cost for an inpatient whose ulcer is resistant to compression therapy + the cost of Apligraf ™ + the cost of visits to outpatient clinics for 11 months:

$$\$9,469 + \$950 + (11 \times \$122) = \$11,761.$$

With a success rate of 80% (obtained by four Montréal physicians who are users of Apligraf ™), it is calculated that CHUM could save $740,623 dollars annually for 100 patients, or approximately $7,400 annually per patient.

Both the conclusions of the Innovus model, which lead to an additional cost, and those of CHUM, which anticipate potential savings, set benchmarks that will be discussed later.

8.3 ANALYTICAL PREDICTION MODEL

8.3.1 Scenarios

An analytical prediction model was developed by *AÉTMIS* to assess the effectiveness of Apligraf ™ in various treatment regimens. As advocated by the Washington panel (Russell et al., 1996), a reference case was used for the analysis.

Three cohorts of venous leg ulcer patients were assigned to the following treatments:

- compression alone,
- compression and Apligraf ™ simultaneously,
- compression alone, followed by Apligraf ™ plus compression for ulcers that proved resistant in the first round.

The decision tree that was generated with the DATA™ 3.5 software (TreeAge) is shown in Appendix 12. The option of compression alone represents the currently recommended treatment for venous leg ulcers. The model considers outpatients only and excludes patients treated in CLSCs or at home, as these locations are not suitable for the use of Apligraf ™ under current conditions.

For each option, the model considered 2 rounds of treatment: an initial 12-week treatment, followed by a second round of treatment for ulcers that remain unhealed. The second round of treatment for groups treated with compression alone or with compression and Apligraf ™ simultaneously corresponds to a continuation of the initial treatment. The third group (patients receiving compression therapy with Apligraf ™ for resistant cases) receives compression alone in the initial treatment round, followed by Apligraf ™ in the second round for ulcers resistant to the initial treatment.

The first step was to simulate a base case scenario to determine the impact of Apligraf ™ on costs, as well as its health effects. Two additional scenarios were simulated (optimistic and pessimistic). These scenarios are detailed in Section 8.3.2.

The second step was to compare the costs and effects of the Apligraf ™ options with those of compression alone. Results are expressed in absolute cost and effects and in incremental ratios of cost-effectiveness, where the effectiveness of Apligraf ™ is represented by the number of ulcer days averted.

Cost perspectives are those of society and of the health care system. Sensitivity analyses were performed on three variables whose values were considered uncertain.

8.3.2 Data used

Efficacy:
Apligraf ™ and compression therapy

According to the results of the pivot study described in Section 6.4 (Falanga et al., 1998), the percentage of healed ulcers at 12 weeks is 82% with Apligraf ™ compared with approximately 47% in the control group. At CHUM, the rate of healing achieved by four physicians with Apligraf ™ was 80%. For this model, an efficacy rate of 80% was used for compression plus Apligraf ™.

For the efficacy of compression alone, an average rate of 73% was calculated from the results of the Cochrane review (Cullum et al., 1999: see Section 5.1 and Appendix 11). This average was used even though the authors of

the review had not done these calculations because of the great diversity in study methods. The average rate is approximately halfway between rates generally found in the literature, which range from 50 to 90%. Based on these data, the effectiveness rate for compression therapy was set at 73% in the base case scenario, at 90% in the optimistic scenario, and at 50% in the pessimistic scenario.

To calculate the number of ulcer days averted, data from the pivot study by Falanga was used: 61 ulcer days for Apligraf ™ and 181 days for compression alone.

Epidemiological variables

Based on estimates from transpositions of epidemiological data from other countries to Québec (see Section 3 and Appendix 9), on experts' opinions, and on estimates from the Novartis Marketing Department, the base case scenario sets the number of patients at 8,000 ± 4,000 (12,000 for the pessimistic scenario and 4,000 for the optimistic scenario).

Economic variables

Intangible costs are not considered in these scenarios. Costs for treatment in a clinic were taken from the Innovus report (Attard and Walker, 1997). These costs have been validated by a panel of Canadian physicians from all provinces, who are experts in the treatment of wounds. Average monthly costs per patient were $385.31 in the societal perspective (including patient time loss from work) and $358.50 in the health care perspective, which include the costs of human resources (nurses and dermatologists) as well as the costs of supplies and services (dressings, Profore™ compression bandages, medications, laboratory tests).

The number of units of Apligraf ™ per patient was set at 3.34, as per the pivot study (Falanga et al., 1998). The current price of an Apligraf ™ unit was used ($950). In the optimistic scenario, the number of units of Apligraf ™ was set at 1, and in the pessimistic scenario, at 5.

8.3.3 Assumptions

The costs and effects of the three options were assessed according to the following assumptions:

- The effectiveness of compression and of Apligraf ™ remains constant in both rounds of treatment.
- The effectiveness of compression and of Apligraf ™ in the option of Apligraf ™ for hard-to-heal ulcers are equivalent to those of the other options.
- No additional unit of Apligraf ™ was used in the second round of treatment.
- Ulcers that heal in the first or second round of treatment do not recur during the period considered in each scenario.
- The duration and size of ulcers at baseline are not taken into consideration.
- Potential infections are not taken into consideration specifically, as costs include an average amount for antibiotics.
- The numbers of ulcer days for compression and Apligraf ™ simultaneously and for compression alone, 61 and 181 days respectively (Falanga et al., 1998), are used in the option of compression therapy followed by Apligraf ™ for hard-to-heal ulcers.
- Costs related to the management of patients in the second round of treatment are the same as in the first round.
- Planimetry can identify hard-to-heal ulcers in the fourth week of compression therapy.
- Potential hospitalisations and related costs after treatment failure are not taken into consideration.

8.3.4 Sensitivity analysis

Because of the uncertainty generated by some of the variables, a sensitivity analysis was performed on the following variables: the number of units of Apligraf™ used, the number of cases treated, and the effectiveness of compression therapy. A threshold analysis was also conducted on the most important variables in the base case scenario.

8.3.5 Results

The cost of a program for the management of venous leg ulcers in the 8,000 patients considered in the compression alone scenario would be 13 million dollars. The option of compression and Apligraf™ simultaneously would generate costs of 37 million dollars, and if Apligraf™ were used only for hard-to-heal ulcers, the cost would be 17 million dollars (Table 6). In other words, society would have to pay 24 million more to implement the option of compression and Apligraf™ simultaneously, compared to 4 million more for the option of Apligraf™ for hard-to-heal ulcers only, assuming complete substitution between the options.

As for the number of ulcer days averted, the option of compression plus Apligraf™ simultaneously and that of Apligraf™ for hard-to-heal ulcers would avert 930,437 and 191,851 ulcer days, respectively, as compared to compression alone.

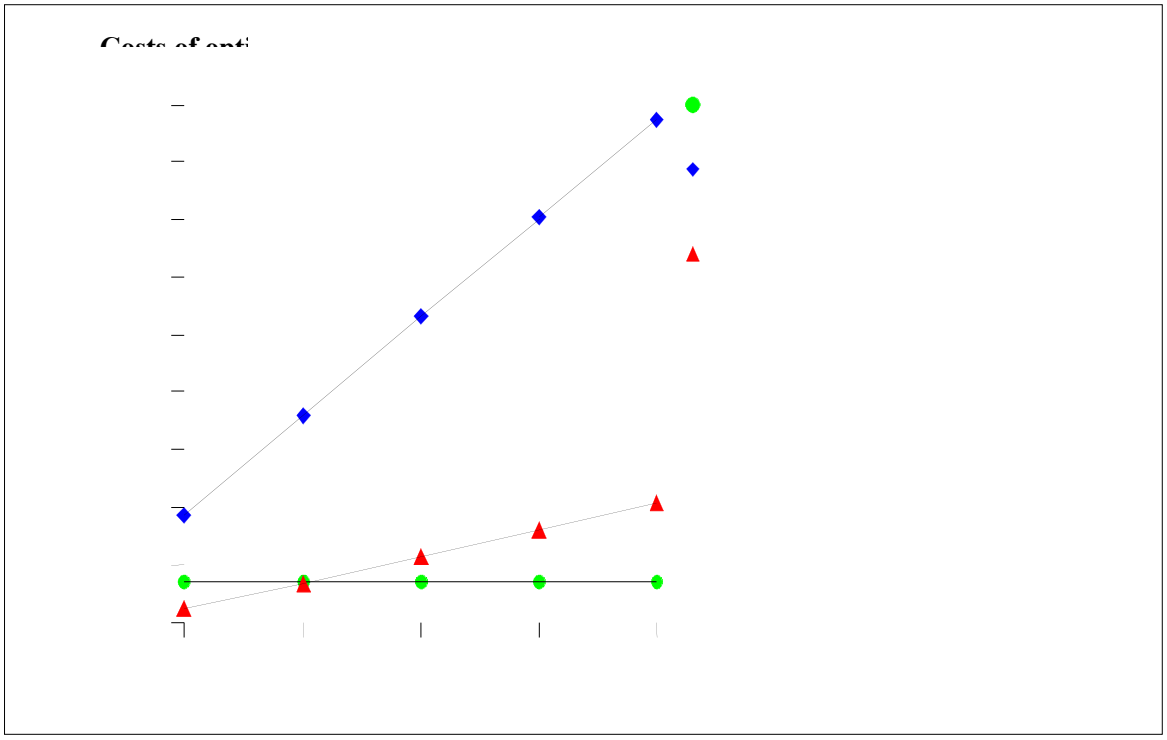
The cost for each ulcer day averted is $26 when compression and Apligraf™ are used simultaneously, and $22 when Apligraf™ is restricted to hard-to-heal ulcers.

The value attributed to the benefit of reduced healing times was not considered, because of a lack of data. A few studies have been published on pain, sleep, mobility and quality of life with or without ulcers (e.g., Franks et al., 1999a; Krasner, 1998; Noonan and Burge, 1998), however, the measuring tools are still being validated (Walters et al., 1999). The benefits achieved by healing have not yet been translated into monetary terms.

To validate the prediction model, sensitivity analyses were conducted on potentially sensitive variables: the effectiveness of compression therapy, the effectiveness of Apligraf™, and the cost of Apligraf™.

As shown in figure 1, only the total cost of Apligraf™ can have an impact on the results of the base case scenario.

Figure 1: Sensitivity analysis on the cost of Apligraf ™



Thus, if the cost of Apligraf ™ were approximately three times less for treatments considered in the base case scenario, the option of Apligraf ™ for hard-to-heal ulcers would generate savings as compared to compression therapy alone. In other words, if the number of Apligraf ™ units were 1.2 rather than 3.34, as in the base case scenario, the option of Apligraf ™ for hard-to-heal ulcers would be the most favourable.

An analysis of the effectiveness of compression, the number of cases, and the number of units of Apligraf ™ was done according to both the optimistic and pessimistic scenarios by varying three parameters at a time, while keeping the others constant. The optimistic scenario shows that Apligraf ™ for hard-to-heal ulcers would generate savings of $82,000 compared to compression therapy alone (Table 6).

In the pessimistic scenario, costs almost double for all three options, as compared to the effects, which increase only marginally (except for compression + Apligraf ™ simultaneously). In this scenario, the cost-effectiveness ratio would favour the option of compression plus Apligraf ™ simultaneously.

Table 7 shows the results from the health care system perspective. These results are very similar to those of the societal perspective (Table 6).

By using planimetry to identify hard-to-heal ulcers after only 4 weeks in the base case scenario, eight weeks of compression therapy alone can be avoided. This intervention would save 5.3 million dollars (11.3 million instead of the 16 million in Table 6 for compression plus Apligraf ™), a reduction of 32%.

Both the scenarios considered in the analytical prediction model and the sensitivity analysis on parameters of the base case scenario suggest that the addition of about one Apligraf ™ unit, on average, to compression therapy in hard-to-heal ulcers offers potential savings compared to compression therapy alone or compression therapy and Apligraf ™ simultaneously.

The three scenarios of the analytical model also suggest that identifying hard-to-heal ulcers at week 4 of compression therapy offers substantial potential savings as well.

The model clearly reconciles various aspects of the current situation. On the one hand, the theoretical data on effectiveness are those of the pivot study (Falanga et al., 1998), in which 3.34 units of Apligraf ™ were used on average. This figure generates very high costs from the start.

On the other hand, the sensitivity analysis shows that only a threshold value of the cost of Apligraf ™, set close to the price of one unit, would have an impact on the results of this model. Therefore, the use of a single unit of Apligraf ™, with the same effectiveness as in the pivot study (Falanga et al., 1998), would corroborate the general opinion of current users as well as the assumptions of current models such as the Innovus model (Attard and Walker, 1997).

Furthermore, the number of patients (8,000) of the base case scenario remains hypothetical. A realistic number could correspond more closely to that of the optimistic scenario (4,000), which would reduce the amounts needed for treatment. An optimised effectiveness of Apligraf ™ in the optimistic scenario (90%) compared to that of the base case scenario (73%) is also plausible.

In addition, the model corroborates the recommendations of the Canadian distributor, Novartis, which are based on the American monograph: the use of Apligraf ™ in hard-to-heal ulcers is the most favourable option.

Finally, the model reveals an extremely important issue: the potential savings that would be generated by the identification of hard-to-heal ulcers at week 4 of compression alone. The benefit of this aspect of treatment will be validated or invalidated by the results of the clinical trial currently underway (see Section 6.4 and Appendix 6), which should be available in the summer of 2001.

In the meantime, it can be stated that the results favour the use of Apligraf ™ in ulcers that are resistant to an initial compression therapy, despite the limits inherent in the assumptions on which the scenarios of the model were based.

Table 6: Typology of scenarios, societal perspective

Variables	Base Case	Optimistic	Pessimistic
Cohort	8,000	4,000	12,000
Efficacy of Apligraf	1	1	1
Efficacy of compression therapy	1	1	1
Clinical costs of compression therapy	1,156	1,156	1,156
Cost of a unit of Apligraf	950	950	950
Number of units of Apligraf	3	1	5
Number of ulcer days with compression and Apligraf	61	61	61
Number of ulcer days with compression alone	181	181	181
Results			
Cost: compression alone	$12,496,939	$5,086,224	$20,807,280
Cost: compression + Apligraf simultaneously	$37,008,280	$9,359,421	$73,678,263
Cost: compression + Apligraf for a hard-to-heal ulcers	$16,637,937	$5,003,840	$42,371,520
Efficacy: compression alone	1,428,441	716,760	1,629,000
Efficacy: compression + Apligraf simultaneously	498,003	234,010	702,031
Efficacy: compression + Apligraf for hard-to-heal ulcers	1,236,589	671,063	1,377,944
Incremental cost			
Compression + Apligraf simultaneously	$24,511,341	$4,273,197	$52,870,983
Compression + Apligraf for hard-to-heal ulcers	$4,140,998	$-82,384	$21,564,240
Incremental efficacy			
Compression + Apligraf simultaneously	-930,437	-482,750	-926,969
Compression + Apligraf for hard-to-heal ulcers	-191,851	-45,697	-251,056
Incremental C/E ratio			
Compression + Apligraf simultaneously	$26.34	$8.85	$57.04
Compression + Apligraf for hard-to-heal ulcers	$21.58	Savings	$85.89

Table 7: Typology of scenarios, health care perspective

Variables	Base Case	Optimistic	Pessimistic
Cohort	8,000	4,000	12,000
Efficacy of Apligraf	1	1	1
Efficacy of compression therapy	1	1	1
Clinical costs of compression therapy	1,156	1,156	1,156
Cost of a unit of Apligraf	950	950	950
Number of units of Apligraf	3	1	5
Number of ulcer days with compression and Apligraf	61	61	61
Number of ulcer days with compression alone	181	181	181
Results			
Cost: compression alone	$11,630,664	$4,733,652	$19,364,940
Cost: compression + Apligraf simultaneously	$36,188,157	$8,974,047	$72,522,142
Cost: compression + Apligraf for a hard-to-heal ulcers	$15,955,830	$4,683,320	$41,409,960
Efficacy: compression alone	1,428,441	716,760	1,629,000
Efficacy: compression + Apligraf simultaneously	498,003	234,010	702,031
Efficacy: compression + Apligraf for hard-to-heal ulcers	1,236,589	671,063	1,377,944
Incremental cost			
Compression + Apligraf simultaneously	$24,577,493	$4,240,395	$53,157,202
Compression + Apligraf for hard-to-heal ulcers	$4,325,166	$-50,332	$22,045,020
Incremental efficacy			
Compression + Apligraf simultaneously	-930,437	-482,750	-926,969
Compression + Apligraf for hard-to-heal ulcers	-191,851	-45,697	-251,056
Incremental C/E ratio			
Compression + Apligraf simultaneously	$26.39	$8.78	$57.35
Compression + Apligraf for hard-to-heal ulcers	$22.54	Savings	$87.81

8.4 ECONOMIC ANALYSIS MODEL

The purpose of this study, sponsored by the Novartis Pharmaceuticals Corporation (United States), was to assess the economic impact of Apligraf ™ in the treatment of venous leg ulcers resistant to compression therapy (Schonfeld et al., 2000). With this objective, the authors designed a model comparing the medical cost and the cost-effectiveness of treating venous leg ulcers with Apligraf ™ compared to compression with Unna's boot (a non-compliant paste bandage).

8.4.1 Patients and treatments

The model used clinical data obtained in the pivot study described in Section 6.4 (Falanga et al., 1998). As a reminder, patients (whose ages ranged from 18 to 80 years) were suffering from venous insufficiency associated with noninfected partial and/or full thickness skin loss ulcers (Stage 2 or 3, according to the International Association of Enterostomal Therapy). Ulcer duration was longer than 1 month, and less than two years, with no favourable response to conventional therapy.

Treatments, as well as healing and recurrence rates observed for 12 months, were incorporated into a semi-Markov analysis developed using SML Tree decision analysis software (version 2.9).

Patients were randomly assigned to 1 of 2 treatment regimens and healing rates were obtained according to cumulative probabilities derived from unpublished data, observed during the pivot study (Falanga et al., 1998). These probabilities are shown in Table 8.

Table 8: Cumulative probabilities of ulcer healing for patients treated with Apligraf ™ or Unna's boot
(From Schonfeld et al., 2000)

	Cumulative probability of healing by end of month	
Time (months)	**Apligraf ™**	**Unna's boot**
1	0.0972	0.0625
2	0.3194	0.1042
3	0.4028	0.1250
4	0.4256	0.1458
5	0.4490	0.1667
6	0.4721	0.1875
7	0.5000	0.1944
8	0.5278	0.2013
9	0.5556	0.2083
10	0.5602	0.2430
11	0.5648	0.2778
12	0.5694	0.3125

In this model, patients with leg ulcers unresponsive to conventional treatment can either move to a healed state, stay in the unhealed state, or move to a recurrent ulcer state after healing. Recurrent ulcers remain in the recurrent state or move again to the healed state. Costs of treating patients depend on their state of health (unhealed, healed or recurrent) and how long they remain in that state. Since the patient follow-up period is only 12 months, no costs associated with patient death were taken into account. The method that was used to assess these costs will be described later.

The probabilities of adverse events or of recurrences were calculated from primary data from the pivot study (Falanga et al., 1998). These probabilities are shown in Table 9.

Table 9: Probabilities of adverse events and recurrence
(From Schonfeld et al., 2000)

	Apligraf™	Unna's boot
Adverse events*	0.087	0.052
Discontinuation of therapy as a result of adverse events*	0.008	0.030
Recurrence ✿	0.30	0.037

* Among all patients with unhealed ulcers at the beginning of the model. (Probabilities of adverse events and discontinuation of treatment are applied only in the first month of the model.)
✿Among patients with healed ulcers at the beginning of each month. (Probability of recurrence is assumed to be constant from month to month.)

8.4.2 Costs

The model is placed in the perspective of a commercial health plan with first-dollar coverage. Costs were estimated from a survey of American dermatologists, vascular surgeons and podiatrists. They were asked to estimate monthly resource utilisation for patients in each state (unhealed, healed and recurrent). Separate estimates were obtained for patients treated with Apligraf ™ and for those treated with Unna's boot. Resource use was evaluated according to physician office visits, home care visits, use of Apligraf ™, use of Unna's boot, additional compression dressings, laboratory tests and procedures, treatment for the management of adverse events, and hospitalisations.

The questionnaire was distributed in 2 rounds. A first version obtained responses from eight physicians, and the second version (reviewed and clarified) obtained responses from 11 physicians, some of whom had also responded to the first version. In total, 14 individual responses were compiled. The average of these responses on resource use for each treatment regimen and each health state was incorporated into the model.

Apligraf ™ had never been used in the United States when this model was developed (except in clinical trials), and the average number of applications was set at 3.34 (data from the pivot study) rather than using responses from the survey.

Costs for Apligraf ™ include the price of acquisition of the product (approximately US$975) as well as professional fees (US$450 per application). Thus, the global cost of a single application of Apligraf ™ was set at US$1,425. The cost of a single application of Unna's boot was US$12.05.

Overall, according to the survey and to the average number of units of Apligraf ™ used in the pivot study, the average monthly costs are distributed according to health states and treatments, as seen in Table 10.

Table 10: Average monthly costs (US$)

Treatment	Unhealed ulcers*	Healed ulcers
Apligraf ™		
No adverse events	2,342	219
Extra costs for adverse events	68	0
Unna's boot		
No adverse events	2,637	264
Extra costs for adverse events	107	0

*These costs are for initial ulcers or recurrent ulcers

The authors of this model evaluated the average monthly cost of hospitalisations at US$1,502 for cases that remain unhealed with Apligraf ™ and at US$2,637 for cases that remain unhealed with Unna's boot. The probability of hospitalisation for each treatment was not mentioned, making it impossible to assess the contribution of this difference between treatments to total average monthly costs.

8.4.3 Results

The model estimated that the annual cost of treating hard-to-heal venous leg ulcers would be US$20,041 for patients treated with Apligraf ™ and US$27,493 for those treated with Unna's boot. Over one year, Apligraf ™ lead to 4.6 months in the healed state, and Unna's boot, to 1.75 months, almost 3 months' difference. Of the patients treated with Apligraf ™, 48.1% remained in the healed state after the 12-month follow-up, compared to 25.2% of those treated with Unna's boot.

8.4.4 Sensitivity of the model

To test the robustness of the model, the authors made certain probabilities vary.

When monthly healing rates for Apligraf ™ were set equal to those for Unna's boot, the effectiveness was similar in both groups, even though Apligraf ™ was associated with a slightly higher number of months in the healed state.

When the cost of Apligraf ™ was increased by $4,700, treatment with Apligraf ™ remained the dominant strategy (in other words, the least costly, and most effective).

When recurrence rates for patients treated with Apligraf ™ were set equal to those for patients treated with Unna's boot, results barely changed and Apligraf ™ remained dominant over Unna's boot. When using the healing rates of the base case, and even when probability of recurrence with Apligraf ™ was doubled from 0.3 to 0.6, the annual cost of treating patients with Apligraf ™ was increased by only $1,100: $6,400 less than the annual cost of treating patients with Unna's boot.

When the probabilities of adverse events and of the consequent discontinuation of treatment with Apligraf ™ were doubled, the model remained insensitive to change, resulting in an

impact that is even less significant than that produced by doubling the recurrence rates.

The authors conclude by stressing that their results were obtained from an analytical decision model, and not based on clinical observations. Indeed, studies submitted for publication (Schonfeld et al., 2000) suggest that the number of Apligraf ™ units needed to heal an ulcer would be closer to 1.5 than to the 3.34 units used in the model, which would improve even further the performance of the product. Actually, compression therapy (Unna's boot), as applied in the pivot study, would probably have been more effective if current practice guidelines (e.g., Scottish Intercollegiate Guidelines Network, 1998) had been followed.

The two models described in Sections 8.3 and 8.4 were built independently, from different perspectives and premises. The first compares the healing rates and estimated costs of treating leg ulcers according to three scenarios, over a period of 12 weeks for compression alone and for compression plus Apligraf ™ simultaneously, and 24 weeks for compression alone followed by another compression therapy plus Apligraf ™ for hard-to-heal cases. Both the societal perspective and the health care perspective are considered. Costs were estimated from a reconstitution of "typical treatments" in Canada.

The perspective of the second model is that of an American health care system. It compares the medical costs and the cost-effectiveness of treating hard-to-heal ulcers with either compression therapy alone, or compression therapy plus Apligraf ™. Unlike the first model, the second considers the probabilities of infection and recurrence. The time frame of the model is one year.

Both models, however, lead towards the same general conclusions: the use of Apligraf ™ in patients whose ulcer is unresponsive to compression therapy alone increases the rate or the probability of healing and generates potential savings over treatment without Apligraf ™.

9. DISCUSSION

Judging from the increase in recent publications on the treatment of venous leg ulcers, interest in the subject has been growing in the last few years. These publications show that there is an important need for the standardisation of diagnostic and therapeutic practices. As the efficacy of a treatment is indeed subject to the pathological entity for which it has been proven effective, it is necessary to determine whether the ulcer is from venous, arterial or mixed aetiology. The evaluation of the general health condition of a patient should not be neglected in diagnostic practices, as insisted upon by expert panels who have studied the question (Scottish Intercollegiate Guidelines Network, 1998; Dolynchuk et al., 1999).

The conditions for treatment efficacy, particularly that of compression therapy and Apligraf ™, are also of prime importance and are discussed below.

9.1 CONDITIONS FOR THE EFFECTIVENESS OF COMPRESSION THERAPY

Compression therapy has been used to treat ulcers since ancient times. In recent decades, however, it has benefited from many technological improvements (Moffatt and Harper, 1997). It is only in the last few years that the most effective conditions for its use have been supported by convincing data from randomised clinical trials comparing it to treatment without compression, despite the passable, if not mediocre methodological quality of these trials (Cullum et al., 1999).

It should also be noted that expert consensuses on the diagnosis and treatment of venous leg ulcers are just as recent (Scottish Intercollegiate Guidelines Network, 1998; Dolynchuk et al., 1999). The proper application of compression therapy requires an operational setting that is more closely in line with the conditions found in hospital clinics or specialised wound care centres than in home care (facilities, diagnostic tools, medical resources and specialised nurses, etc.). The CLSC setting for the treatment of venous leg ulcers would be at midpoint between hospital clinics and home care.

Home care for venous leg ulcers probably represents the major part of the costs (Section 7: Olin et al., 1999). Moreover, the effectiveness of home care, which is often performed without compression, is not well documented: according to one randomised controlled trial, home care would be less effective than treatment with compression in a specialised clinic (Section 7: Morrell et al., 1998).

To date, a few publications from other health care systems have reported attempts at improving compression practices in home care settings. While available information on compression therapy in Québec is not sufficient to fully illustrate the situation, it should be mentioned that distributors of compression dressings have attempted to disseminate information on the basic principles of this treatment. These efforts are carried out in a collaboration between universities, within a continuing education program intended for the nursing staff (Janine Lepage, technical director, Smith & Nephew Inc., personal communication, 1999).

By and large, in the opinion of the Québec experts consulted, the standardisation of compression therapy protocols in wound care centres has only recently been undertaken. This position calls for the use of Apligraf ™ to be

restricted to certified physicians in specialised centres.

It is in this context that the contribution of Apligraf ™ could be beneficial for hard-to-heal ulcers, but only when the initial compression therapy was correctly applied. In practice, the effect of this reservation is usually the repetition of diagnosis and compression therapy in patients newly treated by specialists, to ensure that current recommendations on diagnostic testing and treatment practices have been followed (see Sections 4 and 5). When current recommendations have been followed, the use of Apligraf ™ will be limited to venous leg ulcers that are unresponsive to compression therapy.

9.2 CONDITIONS FOR THE USE OF APLIGRAF ™

The makeup of Apligraf ™ involves strict made-to-order manufacturing requirements and its short shelf-life limits transport times. The use of Apligraf ™ must also be subjected to a specialised care protocol (patient selection, restriction to certified physicians, etc.). Product handling (ordering, receiving, storage, etc.) should also be subject to a strict protocol. Therefore, its use in the current context must fall within the framework of hospital outpatient clinics and does not easily lend itself to treatment in a home care setting, in CLSCs, or in private clinics.

In this respect, Apligraf ™ is similar to other specialised supplies for specific treatments, such as those that exist in other specialities (for example, disposable cardiology products).

The costs of Apligraf ™ must therefore be considered in terms of integrated care settings, within the framework of care protocols designed by the institutions concerned.

9.3 FORESEEABLE COSTS OF COMPRESSION THERAPY AND APLIGRAF ™ FOR HARD-TO-HEAL ULCERS

The results of the models suggest that the use of Apligraf ™ in the treatment of ulcers unresponsive to compression therapy would maintain costs at acceptable levels (Section 8.3). When compression therapy effectiveness is high (optimistic scenario, Tables 6 and 7) and treatment with Apligraf ™ is restricted to ulcers that are unresponsive to an initial compression treatment, this scenario does indeed generate savings.

The optimistic scenario uses only one unit of Apligraf ™, an amount that corresponds more closely to current practice than the 3.34 units used in the pivot study and transposed to the base case scenario. Furthermore, the use of a single unit is consistent with the results of a sensitivity analysis that set at 1.2 the threshold for savings (Figure 1, Section 8.3.5).

Planimetry, used to measure changes in the size of ulcers in order to identify hard-to-heal ulcers in the fourth week of compression therapy, offers sizeable potential savings. Conditions for implementing this prognostic approach and integrating it into current practice, however, still have to be clarified. Biomedical engineers have performed preliminary investigations on the operational aspects of planimetry and judged it promising (Appendix 7).

Again, the multicentre, pan-Canadian randomised controlled trial (for which the recruitment of patients ended on April 30, 2000) will clarify in the summer of 2001 the clinical and eco-

nomic aspects of the use of Apligraf ™ in hard-to-heal cases. Pending the publication of these results, which should support currently available information, purchasing procedures should be implemented within hospital supply budgets to allow certified physicians to obtain Apligraf ™ units when needed.

The example of the outpatient dermatology clinic of the Centre hospitalier universitaire de Québec (CHUQ) shows how limited the use of Apligraf ™ in the treatment of leg ulcers could actually be (Dr. Richard Cloutier, personal communication, June 2000). This clinic is mentioned as an example because it is not involved in the multicentre randomised controlled trial that is underway (Appendix 6), and its patient population is not reduced by the cases eligible for the trial, and therefore, current operations are not restricted. The introduction of Apligraf ™ on the market, as well as its high price, has brought into question diagnostic and therapeutic practices related to venous leg ulcers, particularly those related to compression therapy.

Of the 27 patients with leg ulcers treated at the CHUQ outpatient dermatology clinic in 1999, two did not receive compression therapy (because of a mixed or arterial aetiology). For the other 25, compression was progressive at first (3 layers instead of 4), with a few exceptions: three received high compression from the start, and two were treated with intermittent pump compression.

These treatments were successful in 19 patients (19/25 = 76%). The six patients for whom treatment was a failure suffered from a single (3) or multiple (1) recurrence, a lack of change (1) or other conditions (2). Ever since the implementation of a systematic approach for diagnosing and treating venous leg ulcers, the use of Apligraf ™ has not been considered necessary, even though this clinic's supply budget allows for its purchase when needed.

A similar situation may prevail in some of the other Québec hospitals, meaning that very few units of Apligraf ™ were bought in 1999. If the situation were generalised to ulcers that are hard to heal with compression therapy, the total cost of Apligraf ™ would be limited to a few hundred thousand dollars per year.

The inclusion of compression therapy kits in supply budgets should be considered. The number used in Québec in 1999 may be approximately 15,000 (estimates from internal data obtained from distributors). This figure translates into less than half a million dollars, a large portion of which already figures in the supply budgets of various institutions (hospitals, CLSCs, etc.), while the rest is being paid by the patients themselves.

Without a standardisation of the use of these compression kits outside outpatient clinics, it would be premature to generalise this budgetary practice and certainly wiser to let each CLSC make its own decision, as is currently the case.

9.4 ADDITIONAL APPROVAL CRITERIA TO BE CONSIDERED

From a broader perspective, the example of Apligraf ™ calls attention to difficulties inherent in the classification and reimbursement of bioengineered tissue products. Many more of these products will be introduced in the near future and will, more or less, face the same problems.

An impasse could occur between the availability of these new products and budgetary constraints on their acquisition. Guidelines could be set more easily if economic analyses were incorporated into the approval process. Actually, the only criteria for approval by Health Canada are the product's safety and efficacy, with no regard to the price

of these products, since this aspect is not part of the current mandate.

From a few brief surveys of market analysis web sites, the market for biological products and medical devices, particularly that of tissue engineering and biotechnology, can be set at billions of dollars (US).

The inclusion of economic considerations in the current criteria for approval of new products such as drugs, biological products and medical devices, is still not a subject for deliberation in current work by the International Conference on Harmonization (ICH). Created by important governmental regulatory organisations in the United States, Japan and Europe (Canada, like many other countries, participates as an interactive observer in meetings), the ICH has helped in standardising and accelerating the approval process for pharmaceutical products world-wide. The total lack of economic considerations in current and future concerns of world legislators in this field is something to think about, considering the impact of costs.

In a context where financial resources impose increasing constraints on health care systems, the burden of proving cost-effectiveness for new products seems to remain the responsibility of the health care systems that are paying for these products. These are often lacking pertinent information or administrative (or even legal) leverage to counter the constant pressure from manufacturers, distributors and potential users. Representations to Health Canada should be initiated or pursued, as needed.

10. CONCLUSIONS

The objective of this assessment was to determine optimal conditions for the use of Apligraf ™ in the treatment of venous leg ulcers. This tissue-engineered 2-layer human skin substitute has been approved by Health Canada and filed as a medical device. The assessment primarily shows that the use of this device falls within an overall approach and calls for well-defined procedures for the management of leg ulcers. These questions are currently being considered at the international level, as well as in Canada and Québec.

10.1 COMPRESSION THERAPY AND THE TREATMENT OF VENOUS LEG ULCERS

At the international level, recent publications have reported attempts at standardising diagnostic and therapeutic procedures for venous leg ulcers. Of interest are the recommendations of the Scottish Intercollegiate Guidelines Network on complete patient evaluation and rigorous diagnostic procedure as well as the systematic reviews published by the Cochrane Collaboration. These analyses, while pointing out the methodological flaws in the studies reviewed, conclude that treatment with compression is more effective than no compression for venous leg ulcers. As for all the other treatments, current data are not sufficiently conclusive to either recommend or discontinue their use, with a few exceptions (i.e., oxpentifylline, whose effectiveness has been established.)

In Canada, an advisory panel of experts from various provinces, including Québec, share the same views, with slight variations regarding certain diagnostic procedures. These experts support the use of compression therapy and specify conditions for the use of Apligraf ™.

In Québec, the situation is rapidly evolving. First, a growing number of specialised clinics are reconsidering their approach to the management of leg ulcers in favour of a more appropriate use of compression therapy. Second, the nursing staff has, in the last few years, been able to benefit from university-level continuing education programs set up in collaboration with distributors of compression kits. Instructional information can also be found in home care manuals prepared by CLSCs. The global approach in Québec remains unclear, however, as there are no hard data on the prevalence and treatment of leg ulcers, nor on the cost of treatments.

For the purpose of this analysis, prevalence had to be based on approximations derived mostly from European or Australian estimates and from Québec experts' and professionals' opinions. Thus, the number of venous leg ulcers was estimated to be between approximately 5,000 and 11,000 in Québec.

10.2 CONTRIBUTION OF APLIGRAF ™

What is the potential use of Apligraf ™ in Québec? The assessment reveals that the introduction of this new product on the market has raised many issues as to its potential economic impact, in the event that each ulcer is treated with 3.34 units of Apligraf ™ on average (as per the pivot study), at a cost of $950 per unit. Other potential uses for this "biological dressing" have been considered, but their impact has not yet been determined.

The issues raised are all the more significant because the conditions for the use of Apligraf ™ were not clearly defined in the Canadian monograph, approved by Health Canada in April 1997: the indication is generalised to the treatment of all venous leg

ulcers. In contrast, the American monograph, approved in May 1998, included an important piece of information: Apligraf ™ should be used with a recognised compression treatment to treat venous leg ulcers that are unresponsive to an initial compression treatment. This major distinction is reflected in the recommendations of the Canadian distributor, which had already promoted this practice in the information material on the product.

However, clinical and economic data remain insufficient to substantiate these recommendations. Results from an important clinical study expected to be published in the summer of 2001 will validate or invalidate the assumptions of current models, on which arguments supporting the use of Apligraf ™ are based.

Efforts towards the optimisation of compression therapy in the management of patients with leg ulcers in specialised wound care centres indicate success rates such that the need for Apligraf ™ would be far less than originally anticipated. The case of the outpatient dermatology clinic of the Centre hospitalier universitaire de Québec should be mentioned again, not having required any units of Apligraf ™ in 18 months, even though provisions for its purchase were made in supply budgets. In this centre, the use of this specialised supply is managed within a clinical and administrative framework.

This example shows that the potential need for Apligraf ™ could be limited to a few units per year in the clinic mentioned. The situation would most likely be similar in other clinics with certified physicians. According to the scenario in which Apligraf ™ is restricted to venous leg ulcers that are unresponsive to initial compression therapy, the general impact on costs would not exceed a few hundred thousand dollars per year.

10.3 BASIS FOR THE OPTIMAL USE OF APLIGRAF ™

Based on this assessment, the following preliminary conclusions can be drawn concerning the clinical and economic issues in the treatment of venous leg ulcers and the use of Apligraf ™:

Clinical issues:

- the evaluation and diagnosis of patients should be properly performed;
- treatment of venous leg ulcers with compression therapy is more effective than treatment without compression;
- compression therapy in conjunction with Apligraf ™ provides faster healing times than compression alone;
- compression therapy in conjunction with Apligraf ™ averts more ulcer days than compression alone.

Economic issues:

In the absence of validated data, the following statements remain provisional:

- compression therapy in conjunction with Apligraf ™ generates very high costs in order to reduce the number of ulcer days;
- compression therapy plus Apligraf ™ for cases that are unresponsive to initial compression therapy is less costly than compression and Apligraf ™ simultaneously and offers potential savings for the health care system in an optimistic scenario;
- identifying hard-to-heal ulcers with planimetry at week 4 of initial compression therapy, and the subsequent addition of Apligraf ™ to treatment can increase savings.

10.4 RECOMMENDATIONS

While these conclusions need to be validated by additional conclusive data, particularly from an economic standpoint, the Agence d'évaluation des technologies et des modes d'intervention en santé makes the following recommendations:

- to promote, on the one hand, continued efforts to generalise the management of leg ulcer patients according to the recommendations of the expert panels, and on the other hand, the use of compression therapy in the treatment of venous leg ulcers;
- to recognise, at the clinical and administrative levels, the potential role of Apligraf ™ in the treatment of venous leg ulcers resistant to an initial compression, and the possible savings that could be generated;
- to maintain rigorous policies on the use of Apligraf ™ by certified physicians in hospital outpatient clinics, which are or should start planning for specific budgets for this specialised supply;
- to promote the dissemination of clinical and administrative protocols on the use of Apligraf ™, which certain hospitals have developed and implemented, so that other institutions can consider and tailor them to their own internal policies, as needed;
- to ensure that ongoing developments on the indications of Apligraf ™ be followed up, and that this report be updated following the publication of results of the multicentre pan-Canadian randomised controlled trial in the summer of 2001;
- to initiate the research necessary to document the epidemiology of leg ulcers in Québec as well as the clinical effectiveness and the costs of various treatment strategies in clinical, CLSC and home care settings.

APPENDIX 1:
EPIDEMIOLOGY OF LEG ULCERS

APPENDIX 1: EPIDEMIOLOGY OF LEG ULCERS

Table A.1.1: Prevalence of active leg ulcers (including those of the foot)

POPULATION	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
General Population	0.148	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1985
	0.11	Australia	238,000/259	Baker and Stacey, 1994
	0.1-0.3	Worldwide	(not specified)	Gillies and Ruckley, 1996
	0.18	United Kingdom	(n.s.)	Cornwall et al., 1986
	0.5-1	Europe and Occident	(n.s.)	Labropoulos et al., 1995, citing Callam et al., 1985 and Cornwall, 1983
	0.12	Stockholm, Sweden	241,804/294	Ebbeskog et al., 1996
	0.1-0.3	United Kingdom	(gen. pop.)	Callam, 1992; citing Baker et al., 1991; Callam, 1987; Cornwall et al., 1986; Henry, 1986; Nelzen et al., 1991 and Widmer, 1978
	0.3	Skaraborg County	270,800/827	Nelzen et al., 1991
	0.46-0.77	Malmö and Skaraborg	507,453/12,000	Nelzen et al., 1996
	0.06-0.2	Australia	238,000/259	Baker et al., 1991
Adult Population (> age 15)	0.015	United Kingdom	(gen. pop.)	Thomas, 1998
	0.3	Skaraborg	270,800/827	Nelzen et al., 1991
> age 45	0.19	Newcastle Region	107,400/206	Lees and Lambert, 1992
Age 51-60	0.8	Northwick Park	198,900/ 357	Callam, 1992, citing Cornwall, 1990
Age 50-59	0.38(m)*-0.46(f)	Perth, Australia	238,000/259	Baker et al., 1991
	0.9	Malmö and Skaraborg, Sweden	53,089	Nelzen et al., 1996
Age 61-70	3.0	Northwick Park	198,900/ 357	Callam, 1992, citing Cornwall, 1990
Age 60-69	1.5(m)-1.3(f)	Perth, Australia	238,000/259	Baker et al., 1991
	1.5	Malmö and Skaraborg, Sweden	57,127	Nelzen et al., 1996
Age 71-80	7.0	Northwick Park	198,900/ 357	Callam, 1992, citing Cornwall, 1990
Age 70-79	3.3(m)-4.0(f)	Perth, Australia	238,000/259	Baker et al., 1991
	1.5	Malmö and Skaraborg, Sweden	46,310	Nelzen et al., 1996
Age 80-89	3.2	Malmö and Skaraborg, Sweden	21,867	"
> age 80	21	Northwick Park	198,900/ 357	Callam, 1992, citing Cornwall, 1990
	8.3(m)-9.1(f)	Perth, Australia	238,000/259	Baker et al., 1991
In diabetic patients	3.5		104 (diab.) + 278 (non-diab.)	Nelzen et al., 1993

* (m) = male (f) = female

Table A.1.2: Prevalence of active leg ulcers (above the foot)

POPULATION	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
General Population	0.18	Harrow Region	200,000/357	Cornwall et al., 1986
	0.148	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1987
	0.11	Perth, West Australia	238,000/259	Baker et al., 1991
Adult Population	1.52 (vlu♦ only)	Dublin	2,012 households/89	Henry, 1986
Age 25-44	0.36 (vlu only)	Dublin	2,012 households/89	"
> age 40	0.38	Harrow Region	200,000/357	Cornwall et al., 1986
Age 45-64	2.81 (vlu only)	Dublin	2,012 households/89	Henry, 1986
> age 60	0.33	Perth, West Australia	238,000/259	Baker et al., 1991
Age 65-74	3.5(m)-6.3(f)	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1987
	4.9(m)-8.1(f)	Skaraborg	270,800/827	"
> age 65	4.71 (vlu only)	Dublin	2,012 households/89	Henry, 1986
Age 74-85	5.1(m)-11.6(f)	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1987
	15.6(m)-23.8(f)	Skaraborg	270,800/827	"
>age 85	7.2-18.9	Lothian and Forth Valley	1,000,000/1,477	"
	33.3-34.5	Skaraborg	270,800/827	"

♦ vlu = venous leg ulcers

Table A.1.3: Prevalence of active leg ulcers (all leg ulcers / venous leg ulcers)

POPULATION	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
	All lu / vlu			
	0.105 / 0.062	Perth	238,000/259	Baker et al., 1991
	0.148 / 0.112	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1985
	0.180 / 0.146	Northwick Park	198,900/357	Cornwall, 1990
	- / 1.52	Dublin	2,012 households/89	Henry, 1986
	0.305 / 0.220	Skaraborg County	270,800/827	Nelzen et al., 1991

Table A.1.4: Prevalence of active or healed leg ulcers

POPULATION	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
General population	0.8	Edinburgh	549 patients	Dale et al., 1983
	0.06	Perth, Australia	238,000/259	Baker et al., 1991
	1-1.3	UK data, extrapolated to the US		Alexander House Group, 1992; Callam et al., 1985 and Widmer, 1978
	1.8	Malmö and Skaraborg, Sweden	507,453/12,000	Nelzen et al., 1996
Adult population (> age 15)	1.0	Edinburgh	549 patients	Dale et al., 1983
	1.0	Sweden	(not specified)	Fowkes, 1996; Nelzen et al., 1996 and 1994
	1.0 (0.8-1.2)	Klatov, Czechoslovakia	15,060/153	Bobek et al., 1966
	1.17	Sweden	(gen. pop.)	Nelzen et al., 1996
	1.0	Basle, Switzerland	4,529/45	Widmer, 1978
	2.1	Malmö and Skaraborg, Sweden	507,453/12,000	Nelzen et al., 1996
	2.7	Tübingen	(not specified)	Nelzen et al., 1996, citing Fischer, 1981
Age 41 to 50	0.03	Harrow, UK	200,000/ 100 patients (193 ulcers)	Cornwall et al., 1990
Age 50 to 89	2.0	Malmö and Skaraborg, Sweden	507,453/12,000	Nelzen et al., 1996
> age 65	3.6	Lothian and Forth Valley	1,000,000/1,477	Dale et al., 1983
	4.8 (f)	Basle, Switzerland	4,529/45	Widmer, 1978
	3.6	Edinburgh	549 patients	Dale et al., 1983
> age 80	2.07	Harrow, UK	200,000/ 100 patients (193 ulcers)	Cornwall et al., 1990
Patients with peripheral venous disease	4%	Munich	1,000 outpatients/37	Callam, 1992, citing Eberth-Willershausen et al., 1984

Table A.1.5: Prevalence of skin changes

SKIN CHANGE	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
General population				
- Hyperpigmentation (with varicose veins)	5.7	Brazil	Pop. w. varicosities	Maffei et al., 1986
- Eczema	1.4	Brazil	Pop. w. varicosities	"
- Dilatation of sub-cutaneous veins and hyper/hypopigmentation	8.7-9.6	Basle, Switzerland	4,529/45	Widmer 1978; Widmer, 1992
- Hyperpigmentation, eczema and oedema	3.0-3.7	Tecumseh study	6,389 (> age 10)	*
Age 30-39				
- Hyperpigmentation, eczema and oedema	1.8	Tecumseh study	6,389 (> age 10)	*
> age 70				
- Hyperpigmentation, eczema and oedema	20.7	Tecumseh study	6,389 (> age 10)	*

* Anick Bérard, Clinical Epidemiology and Community Studies Centre, Jewish General Hospital Department of Epidemiology and Biostatistics, McGill University, personal communication, August 1998

Table A.1.6: Anatomical sites of leg ulcers

SITE	PROPORTION (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Calf	30.8	Mid Essex	331 patients	Purvis, 1998
Gaiter	44.3	"	"	"
Foot	24.1	"	"	"
Other or not specified	0.6	"	"	"

Table A.1.7: Prevalence of peripheral venous disorders

DISORDERS	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Unimportant	25%	Munich	1,000 outpatients/37	Callam, 1992, citing Eberth-Willershausen et al., 1984
'Relevant'	10%	"	"	"
Pathological	15%	"	"	"

Table A.1.8: Leg ulcer incidence

CONCOMITANT DISEASES	INCIDENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Venous leg ulcers				
In the general population	0.02	Switzerland	4,529/45	Widmer, 1992
In the population aged 45 +	0.35	Newcastle, UK	107,400/206	Lees and Lambert, 1992
Dilatation of sub-cutaneous veins, hyper- and hypo-pigmentation	1.4	Basle, Switzerland	4,529/45	Widmer, 1978; Widmer, 1992
Ulcers associated with other diseases (follow-up)				
Patients with varicosities	0.002	Basle, Switzerland	4,529/45	Widmer, 1992
Patients with severe varicosities	0.02	Basle, Switzerland	4,529/45	"
Patients with deep venous thrombosis and pulmonary embolia	0.005	Perth, West Australia and Copenhagen, Denmark		*

* Anick Bérard, Clinical Epidemiology and Community Studies Centre, Jewish General Hospital Department of Epidemiology and Biostatistics, McGill University, personal communication, August 1998

Table A.1.9: Leg ulcers – female: male ratio

	COUNTRY OR REGION	RATIO F : M	POPULATION STUDIED / PATIENTS (ULCERS)	REFERENCES
All ulcers	Lothian and Forth	2.8 : 1	1,000,000/1,477	Callam et al., 1985
	Skaraborg	1.75 : 1	270,800/827	Nelzen et al., 1991
	Perth, Australia	1.8 : 1	238,000/259	Baker et al., 1991
	Northwick Park	2.2 : 1	198,900/357	Panders, 1998, citing Cornwall, 1990
	Perth, Australia	1.9 : 1	238,000/ 259 (304)	Baker and Stacey, 1994
Ulcers above the foot	Harrow Region	2.1 : 1	200,000/357	Cornwall et al., 1986
	Lothian and Forth	2.46 : 1	1,000,000/1,477	Callam et al., 1987
Chronic venous ulcers above the foot	Basle	1 : 1	4,529/45	Widmer, 1978
	Dublin	2.1 : 1	2,012 households/89	Henry, 1986
Chronic venous ulcers (all)	Perth, Australia	1.8 : 1	238,000/ 259 (304)	Baker and Stacey, 1994
	Klatov	1.5 : 1	15,060/153	Bobek et al., 1966
	Gothenberg	1.5 : 1	< 500,000/970	Andersson et al., 1984
	Munich	1 : 1	1,000/37	Callam, 1992, citing Eberth-Willershausen et al., 1984
	Sweden	1.6 : 1	270,800/827	Nelzen et al., 1994
	Boston	1 : 1.4	93 patients	Scott et al., 1995

Table A.1.10: Prevalence of different causes of leg ulcers

CAUSE		PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Venous disease		73	Skaraborg, Sweden	270,800 / 827	Nelzen et al., 1991
		75	Not applicable (literature review)	(not applicable)	Peters, 1998
		54	Sweden	270,800 / 827	Nelzen et al., 1994
		42	Stockholm, Sweden	241,804 / 294	Ebbeskog et al., 1996
		62	Northampton, UK	134 ulcers	Musgrove et al., 1998
		48.9	Mid Essex, UK	331 patients	Purvis, 1998
		37	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
	Elderly	70-90	(not specified)	(not specified)	Goodfield, 1997, citing Ryan et al., 1992
Arterial disease		8	Skaraborg, Sweden	270,800 / 827	Nelzen et al., 1991
		3	Northampton, UK	134 ulcers	Musgrove et al., 1998
		20	Bridgend, UK	(not specified)	Thomas, 1998
		12.8	Mid Essex, UK	331 patients	Purvis, 1998
		0	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
(Arterial and diabetes)		9	Malmö and Skaraborg, Sweden	82 patients	"
	Elderly	5-20	(not specified)	(not specified)	Goodfield, 1997, citing Ryan et al., 1992
Diabetes mellitus		3	Skaraborg, Sweden	270,800 / 827	Nelzen et al., 1991
		6.9	Mid Essex, UK	331 patients	Purvis, 1998
		13	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
	Elderly	2-5	(not specified)	(not specified)	Goodfield, 1997, citing Ryan et al., 1992
Minor trauma		2	Skaraborg, Sweden	270,800 / 827	Nelzen et al., 1991
		3	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
Vasculitis	Elderly	2-5	(not specified)	(not specified)	Goodfield, 1997, citing Ryan et al., 1992
Metabolic	Elderly	1	"	"	"
Neoplasis	Elderly	1	"	"	"
Pressure sores		9	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
Mixed (venous and arterial)		15	Northampton, UK	134 ulcers	Musgrove et al., 1998
		13	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
		15.8	Mid Essex, UK	331 patients	Purvis, 1998
Lymphoedema		5.6	Mid Essex, UK	331 patients	"
Others		20	Northampton, UK	134 ulcers	Musgrove et al., 1998
		5.8	Mid Essex, UK	331 patients	Purvis, 1998
		14	Skaraborg, Sweden	270,800 / 827	Nelzen et al., 1991
Multifactorial single cause		7	Malmö and Skaraborg, Sweden	82 patients	Nelzen et al., 1996
		5	Malmö and Skaraborg, Sweden	82 patients	"

Table A.1.11: Prevalence of various diseases concomitant with leg ulcers

CONCOMITANT DISEASE		PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Diabetes					
- venous ulcers (vlu)		18(9)	Sweden	382 patients (206 vlu)	Nelzen et al., 1997
		27(33)	Malmö and Skaraborg, Sweden	82 patients, (44 vlu)	Nelzen et al., 1996
- arterial ulcers (alu)		47(56)	Sweden	382 patients (84 alu)	Nelzen et al., 1997
Peripheral vascular disorder in diabetic patients		(67)	"	104 (diab.) +278 (non-diab.)	Nelzen et al., 1993
Peripheral vascular disorder in non-diabetic patients		(42)	"	"	"
Arterial impairment in diabetic patients		(72)	"	"	"
Arterial impairment in non-diabetic patients		(45)	"	"	"
Hypertension	(vlu)	61(30)	"	382 patients (206 vlu)	Nelzen et al., 1997
	(alu)	25(30)	"	382 patients (84 alu)	"
Thoracic angina	(vlu)	30(15)	"	382 patients (206 vlu)	"
	(alu)	16(19)	"	382 patients (84 alu)	"
Myocardial infarction	(vlu)	18(9)	"	382 patients (206 vlu)	"
	(alu)	13(16)	"	382 patients (84 alu)	"
Intermittent claudication	(vlu)	22(11)	"	382 patients (206 vlu)	"
	(alu)	20(24)	"	382 patients (84 alu)	"
Arthritis	(vlu)	89(43)	"	382 patients (206 vlu)	"
	(alu)	28(33)	"	382 patients (84 alu)	"
Deep vein thrombosis	(vlu)	76(37)	"	382 patients (206 vlu)	"
	(alu)	8(10)	"	382 patients (84 alu)	"
Varicosities	(vlu)	117(57)	"	382 patients (206 vlu)	"
		18	Malmö and Skaraborg, Sweden	82 patients, 44 ulc.	Nelzen et al., 1996
	(alu)	23(27)	"	382 patients (84 alu)	Nelzen et al., 1997
Leg oedema	(vlu)	136(66)	"	382 patients (206 vlu)	"
	(alu)	43(51)	"	382 patients (84 alu)	"
History of smoking	(vlu)	49(24)	"	382 patients (206 vlu)	"
	(alu)	24(29)	"	382 patients (84 alu)	"

Table A.1.12: Healing times for most leg ulcers

HEALING TIMES	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
1 year	most	Lothian and Forth Valley	1,000,000/1,477	Callam et al., 1985
5 years	12	"	"	"
10 years	10	"	"	"

Table A.1.13: Prevalence of recurrences

RECURRENCES	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Non-venous leg ulcer	45	Sweden	270,800/827	Nelzen et al., 1994
	33	(non specified)	600 (827 limbs)	Mayberry et al., 1991
	26	Dublin 8, Ireland	126	Dinn and Henry, 1992
Venous ulcers	72	Sweden	270,800/827	Nelzen et al., 1994
1 time	33	Scottish study	(not specified)	*
	24	Australian study	(not specified)	*
2-3 times	32	Scottish study	(not specified)	*
	31	Australian study	(not specified)	*
4 times or more	35	Scottish study	(not specified)	*
	44	Australian study	(not specified)	*
In 3 months	49	Hampstead, London	39 patients (89 ulcers)	Monk and Sarkany, 1982
In 1 year	69	Hampstead, London	39 patients (89 ulcers)	"
	26	Riverside	166	Moffatt and Franks , 1995
	69	(not specified)	(not specified)	Moffatt et al., 1992; Wright et al., 1991; Monk and Sarkany, 1982
In 18 months	31	Riverside	166	Moffatt and Franks, 1995
In 7 years (same limb)	53	Harrow	200,000 / 357	Peters, 1998, citing Cornwall, 1990
In 7 years (other limb)	18	"	"	"
In 1 year, after surgery	3	France, Belgium,	1,531/24	*
In 1 year, after skin grafting	28	Italy and Canada		
			"	*
In 1 year, after compression	6	"	"	*

* Anick Bérard, Clinical Epidemiology and Community Studies Centre, Jewish General Hospital Department of Epidemiology and Biostatistics, McGill University, personal communication, August 1998

Table A.1.14: Prevalence of permanent side effects of venous diseases
(such as oedema and trophic changes)

	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
	3.4.% (f) and 1.9% (m)	Klatov, Czechoslovakia	15,060/153	Bobek et al., 1966

Table A.1.15: Leg ulcer risk factors

RISK FACTORS	PREVALENCE (%)	COUNTRY OR REGION	POPULATION STUDIED / PATIENTS	REFERENCES
Sex		France, Belgium, Italy and Canada	1,531/24	*
Age		"	"	*
History of varicosities	55.5	Basle, Switzerland	4,529/45	Widmer, 1978
History of deep venous thrombosis		France, Belgium, Italy and Canada	1,531/24	*
Arterial disease		"	"	*
Minor trauma and arthritis		"	"	*
Chronic venous insufficiency	15	Basle, Switzerland	4,529/45	Widmer, 1978

* Anick Bérard, Clinical Epidemiology and Community Studies Centre, Jewish General Hospital Department of Epidemiology and Biostatistics, McGill University, personal communication, August 1998.

APPENDIX 2:
ANKLE-BRACHIAL PRESSURE INDEX WITH DOPPLER ULTRASOUND

APPENDIX 2: ANKLE-BRACHIAL PRESSURE INDEX WITH DOPPLER ULTRASOUND

Table A.2.1: Indication

Compression is indicated for venous leg ulcers with ankle-brachial pressure index (ABPI) of:	REFERENCES
>0.8	Moffat, 1992
>0.85	Ghauri et al., 1998
>0.8	Morrell, 1998
>0.9	Nelzen et al., 1997 (see definitions)
>0.7	Lopez et al., 1998
>0.8	Guillaume, 1995 (Consensus OSLO)
>0.6	Sieggreen et al., 1998
>0.8	Franks et al., 1999b
>1.0	Thomas, 1998

Table A.2.2: Contraindication

Compression is contraindicated in venous leg ulcers with an ankle-systolic pressure index (ASPI) of:	REFERENCES
< 0.6-0.8	Goodfield, 1997
≤ 0.7-1.01	Lopez, 1998

Table A.2.3: Interpretation of the ABPI

ABPI:	Significance of the ankle-brachial pressure index (ABPI):	REFERENCES
≥ 1.2	Calcification of arteries	Hislop, 1997
> 1	Normal arterial circulation	
	Arterial disease	
< 0.9	Mild	
0.8 – 0.6	Important	
≤ 0.5	Severe	
≥ 0.8	*Application of compression therapy*	

Factors that can create false Doppler recordings

- Diabetes
- Calcification of arteries
- Oedema

APPENDIX 3:
HUMAN SKIN SUBSTITUTES

APPENDIX 3: HUMAN SKIN SUBSTITUTES

Table A.3: Human skin substitutes

	APLIGRAF ™	DERMAGRAFT ™	DERMAGRAFT-TC ™	INTEGRA ™ ARTIFICIAL SKIN
Company (manufacturer: marketer)	Organogenesis: Novartis	Advanced Tissue Sciences: Smith & Nephew	Advanced Tissue Sciences: Smith & Nephew	Chiron / J&J: Ortho-McNeil
Description	Tissue-engineered living human skin Bilayered: Dermis/Epidermis	Dermal layer on synthetic mesh Fibroblasts only No epidermis (keratinocytes)	Temporary protective cover Synthetic (nylon loops) interspersed with fibroblasts Must be removed within 1-2 weeks (foreign body, non-absorbable)	Made from bovine collagen / synthetic materials Removed after 10 days and replaced with autograft
First indication (approved or pending)	Venous leg ulcers (VLU)	Diabetic foot ulcer (DFU)	Severe burns	Severe burns
Status	FDA approval for VLU and DFU Health Canada approval for VLU	Pending at FDA for DFU	FDA approval 3/97	FDA approval 3/96

From: American Venous Forum, 1997; updated in July 2000

APPENDIX 4:
LEG ULCER TREATMENTS

APPENDIX 4: LEG ULCER TREATMENTS

Table A.4.1: Compression therapy

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Below-knee stockings and above-knee stockings 106 patients: 30-40 mm Hg below the knee; 8 patients: 30-40 mm Hg above the knee; 3 patients: 40-50 mm Hg below the knee and 2 patients : 20 mm Hg. Stockings were replaced every 6 months or sooner, if fitting loosened.	Retrospective cohort of 119 patients with stasis leg ulcers	100% complete healing: 105/119 (93%)	5.3 months	29% (in 5 years)	Mayberry et al., 1991
Scholl soft grip (graduated compression) Ankle pressure,19.2 mm Hg; calf, 12.8 mm Hg, and thigh, 10.9 mm Hg. Stocking changed when necessary, at follow-up (3 months)	Prospective study 126 patients successfully healed by injection compression sclerotherapy After 5 years, only 105 patients remained in the study	(not specified)	(not specified)	33/105 (26%)	Dinn and Henry, 1992
Scholl or Medi Class II, below knee 23 mm Hg at the ankle Stocking replaced at each follow-up (3 months)	Randomised controlled trial 166 patients recently healed	(not specified)	(not specified)	26% in 1 year and 51% in 18 months (% of the incidence of recurrrence)	Moffatt and Franks, 1995
Multilayer compression Non-adherent dressing with gauze bolster, Unna's boot and self-adherent elastic wrap	Multicentre, prospective randomised controlled trial 136 patients with venous leg ulcers	71 unhealed vs 65 healed 0.0859 cm/week 0.0730 cm/week 0.0691 cm/week	 4 weeks 12 weeks 24 weeks	(not specified)	Sabolinski and Falanga, 1999b
Unna's boot					
a) Synthederm (hydrophilic occlusive polyurethane foam dressing) vs b) Unna's boot	Prospective randomised controlled trial (12 months) 36 patients	100% healing: a) 7/17 (41.2%) ⇒ b) 18/19 (94.7%)	12 months	(not specified)	Rubin et al., 1990
a) DuoDerm vs b) Unna's boot	Randomised trial (6 months) 66 patients, 69 ulcers	a) 15/39 (38%) b) 21/30 (70%)		(not specified)	Kikta et al., 1988
a) Unna's boot vs b) DuoDerm CGF (ConvaTec) with Coban wrap (3M)	Randomised comparison 30 patients	a) 6/14 (43%) ⇒ b) 8/16 (50%)	14 months	(not specified)	

Table A.4.1: Compression therapy (cont.)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
UlcerCare system (Jobst, Toledo, OH) 1) polyurethane dressing, applied directly over the ulcer bed and changed daily; 2) inner liner white stocking (10-15 mm Hg), worn over the dressing and 3) outer zippered compression stocking (30 mm Hg) worn during walking hours	Prospective study 53 patients with deep venous insufficiency or venous ulcers	(not specified)	Median: 6 weeks; Average: 10 weeks	23/73 (1 recurrence) 3/73 (2 recurrences); 2/73 (3 recurrences); and 1/73 (4 recurrences) In total, 32 ulcers recurred	Samson and Showalter, 1996
Scholl vs DuoMed stockings 23 mm Hg at the ankle	Randomised trial 166 recently healed patients (venous or arterial) 92 patients assigned to DuoMed (a) and 74 to Scholl (b)	(not specified)	8 months	a) 24% b) 32%	Franks et al., 1995
4-layer high compression	Assessment clinic 438 patients (514 venous ulcers) treated, 28 of which were diabetic	62%	2 years Median: 55 weeks	(of 318 healed) 81%: no recurrence 13%: 1 recurrence + healing 2%: 2 recurrrences + healing 5%: 2 recurrrences (without healing)	Thomson et al., 1996
4-layer high compression vs short-stretch	Prospective randomised trial 53 patients (64 ulcers) 32 ulcers assigned to (a) 4-layer bandage and 32 ulcers to (b) short-stretch	a) 55% b) 57%	1 year	(not specififed)	Scriven et al., 1998a

Table A.4.1: Compression therapy (cont.)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
	Literature review				(cited by Nelson, 1997)
a) 4-layer vs b) 2-layer high compression	Retrospective study 70 patients (venous leg ulcers -vlu)	a) 47% vs b) 32%	12 weeks	(not specified)	Cameron et al., 1996
a) 4-layer vs b) short stretch vs c) elastocrepe and tubular elastic	Randomised study 67 patients (vlu)	a) 44% vs b) 40% vs c) 23%	12 weeks	(not specified)	Duby et al., 1993
a) elastic 3-layer vs b) inelastic 3-layer	Type of study not specified 132 patients (vlu)	a) 54% vs b) 28%	12 weeks	(not specified)	Callam, 1992
a) elastic 3-layer vs b) cotton-crepe 3-layer	Type of study not specified 106 patients (vlu)	a) 64% vs b) 51%	12 weeks	(not specified)	Unpublished data (Northeast et al., 1990)
a) class 3 compression vs b) short-stretch	Type of study not specified 50 patients (vlu)	a) 84% vs b) 52%	12 weeks	(not specified)	Horakova and Partsch, 1994
Non-adherent dressing a) long-stretch vs b) short-stretch The long-stretch bandage was changed every 1 to 7 days, when necessary and the short-stretch bandage was changed daily or every two days	Prospective randomised trial 34 patients (1st month) 32 patients (6 months) 27 patients (12 months)	 4/15 (27%) 1/19 (5%) 9/18 (50%) 5/14 (36%) 12/17 (71%) 3/10 (30%) 81% vs 31%	 1 month 6 months 12 months 12 months	(not specified)	Danielsen et al., 1998

Table A.4.2: Surgery

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Felder procedure (32) Linton procedure (10) Local ligation of perforating veins (5) Follow-up for an average of 8.5 years per ulcer	Literature review (Padberg, 1999) - 37 patients, 47 ulcers	(not specified)	(not specified)	No recurrence after 1 year: 78%; 2 years: 64%; 3 years: 59%; 4 years: 55%; 5 years: 49%	Johnson et al., 1985
Endoscopic approach	Literature review (Padberg, 1999) - 40 patients	(not specified)	(not specified)	No recurrence after 1 year: 100%; 2 years: 97%; 3 years: 97%	Pierik et al., 1995
Combined: superficial and perforator ablation					
With clinical diagnosis	Literature review (Padberg, 1999) - 43 patients	(not specified)	(not specified)	No recurrence after 3 years: 74%	Bradbury et al., 1993
With deep reflux	Literature review (Padberg, 1999) - 11 patients	(not specified)	(not specified)	No recurrence after 1 year: 100%; after 2 years: 100%	Padberg et al, 1996
Deep venous reconstruction					
Kistner procedure	Literature review (Padberg, 1999) - 29 patients	(not specified)	(not specified)	No recurrence after 1 year: 86%; 2 years: 80%; 3 years:66 %; 4 years: 62% ; and 5 years: 58%	Kistner et al., 1996
Raju procedure	Literature review (Padberg, 1999) - 198 patients	(not specified)	(not specified)	No recurrence after 1 year: 83%; 2 years: 75%; 3 years: 70%; 4 years: 66% and 5 years: 62%	Raju et al., 1996
Saphenous vein surgery					
After surgery, the ulcers were dressed with a simple non-adherent dressing, gauze and a graduated below-knee tubigrip. (a) Healing began after 1 month (b) Ulcers deteriorated and dressing replaced with 4-layer compression	Comparative study 24 patients (25 venous ulcers): a) 16 with isolated saphenous vein reflux; b) 9 with combined superficial and deep reflux	(not specified)	a) 81 days b) 3 ulcers healed (after compression therapy) at 136, 168 and 196 days. 6 unhealed		Scriven et al., 1998b

Table A.4.2: Sugery (cont.)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Shave therapy For persistent ulcers Shave therapy in flat layers with a Schink dermatone and covered with a meshed split-skin graft	Prospective study Total of 80 patients (105 ulcers): 59 patients (76 ulcers) were assessed for short-term results; the first 18 patients (26 ulcers) were assessed for long-term results	Successful grafts: 80% 60/76 (79%) 59 patients 11/13 12/13 (88%) 18 patients	1 week 3 months (short-term) 2 years-8 months 1 year-8 months (long-term)	 3 recurrrences 2 of which caused by the stopping of compression therapy after healing had started	Schmeller et al., 1998
Excision and skin grafts					
Autologous graft The wound was dressed with paraffin and wet saline compresses. Miniheparin prophlaxis against thrombosis was given for 3-5 days following surgery	Retrospective review of patient files and telephone interviews 48 patients with leg ulcers due to trauma, varicosities, pressure wound, infection, diabetes or venous or arterial insufficiency	90%	Approx. 4.5 months Range (0-18)	17%	Puonti and Asko-Seljavaara, 1998
Autologous skin graft	Retrospective long-term assessment + interview 188 patients (144 having had one or more autologous skin grafts for a vlu)	Wound closure: 82.5% - graft 97% - without graft	2.2 months 4.7 months	24.5% 23%	Ruffieux, et al., 1997
Free tissue transfer	Retrospective analysis 11 patients (14 ulcers) with chronic venous insufficiency	8/14 stable	30 days post-surg. (average time: 17 months)	12/14 after 30 days 100% long-term	Steffe and Caffee, 1998
Davies' pinch graft	Prospective study 25 patients with venous leg ulcers (31 ulcers)	5/31 (16%) 9/31 (29%) 1/31 (3%) 3/31 (10%) 13 unhealed (42%)	< 6 weeks 7 to 12 weeks 13 to 24 weeks ≥ 25 weeks	(not specified)	Öien et al., 1998

Table A.4.3: Human skin substitutes (HSS)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Dermagraft The control group received a conventional treatment (debridement, infection control, saline-moistened gauze dressing and standardised off-weighting). The Dermagraft group received a conventional treatment + an application of Dermagraft on day 0, then once a week, for up to 8 applications .	Multicentre study 235/281 (109/139 Dermagraft and 126/142 controls) diabetic patients with a plantar ulcer	38.5% / 31.7%	Dermagraft: 13 weeks Controls: 28 weeks	(not specified)	Naughton et al., 1997
Apligraf (human skin substitute - HSS) The control group was treated bycompression (non-adherent dressing, gauze bolster, Unna's boot and self-adherent elastic wrap) applied weekly, for the first 8 weeks. In the Apligraf group, the HSS was applied directly onto the wound bed and covered with a cotton gauze dressing folded in a bolster and the same elastic wrap. None of the patients received more than 5 applications of HSS	Prospective randomised trial 275 patients: (129 controls/ 146 HSS)	100% healing HSS: 92/146 (63%) Controls: 63/129 (48.8%)	6 months (Mean time to 100% healing 61 days (9-233) HSS; 181 days (10-232) controls	12% HSS (12 months) 15.9% controls (12 months)	Falanga et al., 1998
a) HSS vs b) conventional treatment (compression + Unna's boot). The HSS was covered with a non-adherent primary dressing and a cotton gauze layer folded in a bolster, and stabilised with a self-adherent elastic wrap	Multicentre randomised clinical trial 233 patients with venous insufficiency a) 127 HSS vs b) 106 compression	a) 61.4% b) 44.3%	57 days 181 days	(not specified)	Sabolinski et al., 1996

Table A.4.3: Human skin substitutes (cont.)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Apligraf (2-layer living skin - - HSS) HSS group: skin graft + 3-layer compression. Control group: multi-layer conventional compression-	Multicentre prospective, randomised controlled trial 120 (72 HSS vs 48 controls) patients with venous leg ulcer of long duration	Complete wound closure: HSS: 24% Controls: 8% HSS: 47% Controls: 19%	 6 weeks 24 weeks	(not specified)	Sabolinski and Falanga, 1999a
Cryopreserved cultured allogeneic keratinocytes Keratinocytes + compression (donor skin obtained from healthy women having undergone breast reduction - see Lindgren et al for details) vs compression alone for 8 weeks	Randomised controlled trial 27 outpatients (15 treated vs 12 controls) with venous leg ulcers	Average ulcer area reduction: 35% treated and 14% controls In patients treated: 8 improvements, 2 healings, 5 deteriorations or no improvement. In controls: 6 improvements, 2 healings, 4 deteriorations or no improvement			Lindgren et al., 1998

Table A.4.4: Pharmacological treatments

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Oxerutins and rutosides To prevent venous ulcer recurrence	Double-blind randomised trial 298 patients	(not specified)	(not specified)	58/154 patients treated vs 56/144 controls	Neuman et al., 1990
Prostanoids a) Intravenous prostaglandin E_1, 3 hrs/day for 6 weeks vs b) placebo	Double-blind controlled trial with placebo 42 patients with venous leg ulcers resistent to conventional treatment	100% complete healing: a) 8/20 vs b) 2/22	(not specified)	(not specified)	Rudofsky, 1990
Oxpentifylline 400 mg Oxpentifylline for 6 to 8 weeks	Double-blind controlled trial 59 patients with venous leg ulcers resistant to conventional treatment (30 patients treated vs 29 controls)	Reduction in ulcer area 86% treated and 44% controls	(not specified)	(not specified)	Dormandy, 1995, citing Weitgasser, 1983
Oxpentifylline or placebo for 6 months	Double-blind trial 22 patients (12 patients treated vs 10 controls)	Major improvement: 74.9% patients treated and 30% controls 100% complete healing: 3 patients treated and 1 control	(not specified)	(not specified)	Dormandy, 1995, citing Arenas and Atoche, 1988
a) Oxpentifylline + conventional compression vs b) Placebo + conventional compression	Double-blind prospective controlled trial with placebo carried out in 4 centres 80 patients	100% complete healing: a) 64% patients treated b) 34% controls	6 months	(not specified)	Colgan et al., 1990

Table A.4.4: Pharmacological treatments (cont.)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Aloe Vera Aloe vera gel drink (98% stabilised): 30 ml fluid, twice daily. Daily, the ulcer is irrigated with tap water and filled with a topical aloe vera jelly (with 86% stabilising gel). The ulcer - is covered with a waterproof short-. stretch bandage .	Limited pilot study 7 patients with venous leg ulcers resistant to conventional treatment (including skin grafting) for a duration of 4 to 15 years (1 patient left the study).	100% complete healing: 3/6 Partial healing: 1/6 No improve-ment: 1/6 Side effect: improvement in hair, nail and skin condition	(not specified)	(not specified)	Atherton, 1998
Oral zinc sulfate a) zinc sulfate (220 mg) twice daily vs b) Placebo until healing or the end of the study (10 months)	Double-blind randomised controlled trial 42 ambulatory patients with venous leg ulcers	a) 10/19 (53%) b) 12/23 (52%)	10 months	(not specified)	Phillips et al., 1977
a) zinc sulfate (200 mg) 3 times a day for 18 weeks vs b) placebo	Double-blind randomised trial 27 patients with venous leg ulcers (100 to 1,000 mm^2)	a) 9/13 (69%) b) 8/14 (57%)	18 weeks	(not specified)	Hallbrook et Lanner, 1972

Table A.4.5: Hyperbaric oxygen (HBO)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Hyperbaric oxygen a) HBO 90 min at 2.5 ATA 5days/7 b) Air 90 min at 2.5 ATA 5days/7 For 6 weeks (30 treatments) Ulcer area was measured at weeks 0, 2, 4, 6 and 18	Double-blind randomised controlled trial 16 patients with chronic leg ulcers (non diabetic)	Reduction in ulcer area: a) 22.0% b) 3.7% a) 35.7% b) 2.7%	 4th week 6th week		Hammarlund and Sundberg, 1994

Table A.4.6: Laser treatment

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Helium neon laser (HeNe) a) 4 J/cm^2 vs b) HeNe 4 J/cm^2 + infrared light vs c) nonpolarised noncoherent light at 4 J/cm^2	Randomised trial 45 patients with leg ulcers resistant to conventional treatment	a) 10/15 (67%) b) 12/15 (80%) c) 5/15 (33%)	(not specified)	(not specified)	Bihari and Mester, 1989
a) 4 J/cm^2 b) Placebo + conventional treatment with cleansing with saline, application of a paste bandage plus advice on exercising twice weekly on an instruction sheet for 12 weeks	Randomised trial 46 patients with venous leg ulcers	a) 4/23 (17%) b) 3/23 (13%)	(not specified)	(not specified)	Lundeberg and Malm, 1991
Gallium arsenide laser (GaAs) a) 1.96 J/cm^2 vs b) fictive laser (placebo) bi-weekly for 12 weeks + conventional treatment with saline cleansing, paste saline, paste bandage and elastic support bandage, at 15-25 mm Hg pressure as well as exercise guidelines	Randomised trial 42 patients with venous leg ulcers	a) 13/21 (62%) b) 11/21 (52%)	(not specified)	(not specified)	Malm and Lundeberg, 1991
Unspecified laser a) Laser vs b) Ultraviolet light 10 min treatments, 3 times weekly, for 4 weeks	Double-blind randomised trial 6 patients with chronic venous leg ulcers	Reduction in ulcer area a) 49.6% b) 33.6%	(not specified)	(not specified)	Crous and Malherbe, 1988

Table A.4.7: Ultrasound treatment

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Low-frequency ultrasound a) conventional treatment (compression) + placebo vs b) conventional treatment + ultrasound (flexible 30 kHz sound head transducer) - 10 min., 3 times weekly for 12 weeks	Blind randomised controlled trial with placebo 24 outpatients with chronic venous ulcers 2 patients of the control group quit after 2 weeks	Reduction in ulcer area: a) 16.5% b) 55.4% 100% complete healing: a) 0/12 b) 2/12	12 weeks	Reduction in ulcer area (follow-up at 3 months after last visit): a) 70.2% b) 30.6%	Peschen et al., 1997

Table A.4.8: Low-energy photon therapy (LEPT)

TREATMENT	TYPE OF STUDY AND NO. OF PATIENTS STUDIED	HEALING RATE	HEALING TIME	RECURRENCE RATE	REFERENCES
Ulcers are treated 3 times weekly for 10 weeks, for a total of 30 treatments (LEPT vs Controls)	Double-blind controlled trial with placebo 9 outpatients with 12 venous leg ulcers in total	(mm^2/week) 19.3/7.5 LEPT 1.46/3.6 Controls *(% of ulcer area still unhealed after 10 weeks*) 13.8% LEPT 26.5% Controls		(not specified)	Gupta et al., 1998

APPENDIX 5:
COSTS OF LEG ULCERS

APPENDIX 5: COST OF LEG ULCERS

Table A.5.1: Global cost of venous leg ulcers in different health care systems

COSTS / YEAR	COUNTRY OR REGION / HEALTH CARE SYSTEM	REFERENCES
230 to 400 million pounds sterling (1990-1991)	United Kingdom	Bosanquet, 1992
300 to 600 million pounds sterling	United Kingdom	Moffat et al., 1992; Hampton, 1997, citing Cherry, 1990
3 million pounds sterling	Leeds, United Kingdom (pop. 750,000)	Goodfield, 1997
200 million pounds sterling	United Kingdom / NHS	Freak et al., 1995
2.3 billion Deutsche marks	Germany	Fischer et al., 1982; Munnich et al., 1987
2% of the total costs to the health care system of the European community are attributed to the care of leg ulcers	Europe	Puonti et al., 1998, citing Laing, 1992; Harris et al., 1993 and Bosanquet, 1992

Table A.5.2: Breakdown of the cost of treating leg ulcers

COUNTRY	MEAN COST PER OUTPATIENT / YEAR (including physicians + general fees)	COST OF HOSPITALISA-TIONS	TOTAL COST OF DRESSINGS	TOTAL COST OF PHYSICIAN CONSULTATIONS AND PRESCRIPTIONS	(% OF NURSING TIME) TOTAL COST OF NURSING TIME IN THE CARE OF VLUs ULCERS	TOTAL COST (OR PROPORTION %) OF HOME CARE	TOTAL ESTIMATED COST OF TREATING LEG ULCERS	REFERENCES
U.S. (in US$)	524	2,445 / patient / year	2,035 / patient / year (home care)	29 (prescr. only) 3 (topical med. only) / patient / year	(not specified)	4,652 / patient / year	9,685 / patient / year	Olin et al., 1999
U.K. (in £)	(not specified)	(not specified)	(not specified)	(not specified)	(not specified)	(not specified)	2,000 / patient / year	Bandolier, 1998
U.K. (in £, 1990-91value)	670-1,067 / year	50 million	50 million	20 million	(15%): 108 million; (33%): 240 million; (40%): 288 million.	(not specified)	(*120 million + nursing time)* (15%): 228 million; (33%): 360 million; (40%): 408 million.	Bosanquet, 1992
U.S.	5%	(not specified)	21%	< 1% (prescriptions); < 1% (topical med.)	(not specified)	48%	(not specified)	Olin et al., 1999

Table A.5.3: Cost of treating leg ulcers with compression therapy

TYPE OF DRESSING	COUNTRY	TOTAL COST OF SUPPLIES / PATIENT/ WEEK	COST OF A DIAGNOSIS / PATIENT	GENERAL FEES (equipment, facilities, etc.) / PATIENT / WEEK	COST OF STAFF / PATIENT / WEEK	TOTAL COST / PATIENT / WEEK	COST / REDUCTION (CM) IN ULCER AREA / PATIENT	REFERENCE
Dressing with Vaseline	Germany (in DM)	68.14	10.46	4.80	151.29	234.69	482	Augustin et al., 1999
Hydrocolloid dressing	Germany (in DM)	78.98	14.12	2.82	80.43	176.35	300	Augustin et al., 1999

		COST OF DRESSINGS OR PRODUCTS	COST OF A VISIT IN A CLINIC	COST OF A VISIT AT HOME	COST OF CARE IN A CLINIC (OR HOSPITAL)	COST OF HOME CARE / PATIENT	COST / DAY OF A HOSPITAL ROOM	
(not specified)	U.K. (cost in £)	For 6 clinics per year 35-40,000	(not specified)	(not specified)	(not specified)	(not specified)	(not specified)	Moffat et al., 1992
(not specified)	U.K. (cost in £)	(not specified)	19.35	(not specified)	(not specified)	(not specified)	(not specified)	Franks and Moffatt, 1998
(not specified)	U.K. (cost in £)	(not specified)	29.90	10.60	/ patient / year 877.60	/ year 913.89	(not specified)	Morrell et al., 1998
(not specified)	U.K. (cost in £)	(not specified)	(not specified)	(not specified)	/ patient / year 878.06	/ year 859.34	(not specified)	Morrell et al., 1998
(not specified)	U.S. (cost in US$)	"Home Health Care": 75-150	30 (reimbursement by "Medicare": 14)	159 (reimbursement by "Medicare": 105)	/ patient / day 900	/ day 200	280-600	O'Brien et al., 1999
(not specified)	U.K. (cost in £)	(not specified)	(not specified)	(not specified)	/ clinic / year 25,000	(not specified)	(not specified)	Bosanquet, 1992

Table A.5.4: Cost of treating leg ulcers with hyperbaric oxygen (HBO)

COUNTRY	COST FOR A FACILITY WITH ONE PIECE OF EQUIPMENT	MEAN COST / CASE	TREATMENT EFFECTIVENESS (*amputation and re-habilitation increase costs substantially*)	COST OF AMPUTATION AND RE-HABILITATION / PATIENT	% OF PATIENTS TREATED WITH HBO AND WHO REQUIRE SUBSEQUENT AMPUTATION	REFERENCE
Alberta, Canada (cost in CAN$)	270,000-630,000	9,702	67%	120,000	8%	Mitton and Hailey, 1998
U.S. (cost in US$)	(not specified)	9,000	(not specified)	(not specified)	(not specified)	Tibbles and Edelsberg, 1996

Table A.5.5: Nursing time dedicated to treating venous leg ulcers (VLU)

% OF NURSING TIME DEDICATED TO VLUS	COUNTRY, REGION	REFERENCES
30-50%	Walsall and Rochester, UK	Bosanquet, 1992
10-20%	Norwich, UK	"
25%	Riverside, UK	
10%	United Kingdom	"
33%	United Kingdom	"
40%	United Kingdom	"
50%	United Kingdom	Moffat et al., 1992; Podmore, 1994

APPENDIX 6:
SYNOPSIS OF THE APL-CDN-02 STUDY (NOVARTIS)

APPENDIX 6: SYNOPSIS OF THE APL-CDN-02 STUDY (NOVARTIS)[1]

OPEN, RANDOMIZED, POSITIVE-CONTROL, MULTICENTER STUDY ON THE EFFICACY AND COST-EFFECTIVENESS OF APLIGRAF ™ IN VENOUS STASIS ULCER SUBJECTS WITH SUBOPTIMAL HEALING AFTER 4 WEEKS OF HIGH COMPRESSION THERAPY.

In APL-CDN-02, difficult to heal ulcers will be identified with the healing rate developed by Margolis, Gross et al. (1993). It is anticipated that this study will demonstrate that Apligraf™ is a clinically efficacious and cost effective addition to optimal compression therapy when the later has failed to demonstrate significant clinical benefits at 4 weeks.

Study Objectives:

Primary:
To compare the time to complete wound closure of Apligraf™ plus high compression therapy versus high compression therapy alone in subjects with venous stasis ulcers of less than one year[2] duration with sub optimal healing after four weeks of high compression therapy.

Secondary:
To compare the health care resource utilization including direct and indirect costs of Apligraf™ plus high compression therapy versus high compression therapy alone.

To compare the impact of Apligraf™ plus high compression therapy versus high compression therapy alone on the Quality of Life of subjects with venous stasis ulcers.

To compare the relapse rate at End of study of Apligraf™ plus high compression therapy versus high compression therapy alone in subjects who obtained wound closure before week 24.

To prospectively validate the predictive value of the healing rate as calculated by the method described by Margolis, Gross et al. (1993).

[1] Synopsis received from Novartis on April 13, 1999
[2] This restriction was removed in April 1999

APPENDIX 7:
PLANIMETRY

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A.7.1 COMPUTERIZED PLANIMETRY

Ulcer area and perimeter are currently being measured in the clinical trial implemented by Novartis (CDN-02 - synopsis shown in appendix 6). At the start of the treatment, and then at different intervals, a double-layer transparent film is applied to the wound. After the contour of the wound is traced on the film, the bottom layer is disposed of and the top layer is sent to the United States for analysis.

Novartis could make this service available at a cost of approximately US$35 per contour. While this may be useful in terms of research, the exportation procedure seems ill-suited to widespread use under current conditions (logistics, costs).

While the measure of ulcer area may be a valuable prognostic tool, other more accessible methods could be considered:

- contour tracing, as above;
- scanning the contour and converting it into parameters that would enable the measurement of ulcer perimeter and area with easily available software, such as AutoCAD or even QuickCAD;
- keying in, calculating and compiling data in a spreadsheet (e.g., Excel).

This procedure could be generalized to wound care clinics as costs would be low: approximately $25 according to promising preliminary results obtained in June 1999 by biomedical engineers of the Montréal's Sacré-Coeur Hospital (Pierre Gauthier and Guy Mailloux).

A.7.2 "MANUAL" PLANIMETRY

The area of circular ulcers can be measured from the diameter (D):

$$\text{as } D = 2r(\text{radius}),$$
$$\text{area } A = \pi r^2 \text{ or } \pi (D/2)^2$$
$$\text{and } \pi = P(\text{perimeter})/D = 3.1416$$

For elliptical ulcers, if D = length and d = width, the formula becomes:

$$\text{Area} = (D/2 \cdot d/2)\cdot\pi = D\cdot d\cdot\pi/4 = \text{length}\cdot\text{width}\cdot 0.785$$

The accuracy and precision of these measurements should be documented in the light of existing publications on the question (e.g., Plassmann, 1995) and of results obtained in studies.

APPENDIX 8:
HOSPITALISATIONS FOR LEG ULCERS IN QUÉBEC (1992-1997)

APPENDIX 8: HOSPITALISATIONS FOR LEG ULCERS IN QUÉBEC (1992-1997)

Table A.8: Hospitalisations for leg ulcers in Québec (1992-1997)

	No. of cases			Average length of stay	No. of single	Average length of stay
REGION	**Princ.***	**Sec.****	**Total**	**Princ. Diagn.**	**cases**	
Bas St-Laurent	75	149	224	20.2	7	10.7
Saguenay-Lac-St-Jean	87	149	236	21.5	16	19.6
Québec	195	434	629	20.3	18	10.6
Mauricie-Bois-Francs	150	286	436	19.4	39	8.3
Estrie	49	147	196	14.8	8	6.9
Montréal-Centre	748	2395	3143	24.0	109	7.9
Outaouais	82	106	188	19.9	16	5.1
Abitibi-Témiscamingue	47	86	133	17.1	2	3.5
Côte-Nord	43	52	95	17.0	1	1.0
Nord-du-Québec	1	4	5	56.0	0	
Gaspésie-Iles-de-la-Madeleine	63	91	154	17.2	14	4.5
Chaudière-Appalaches	68	211	279	29.9	10	6.4
Laval	98	253	351	26.1	9	8.7
Lanaudière	92	170	262	15.2	8	5.4
Laurentides	74	192	266	20.1	3	7.0
Montérégie	333	904	1237	17.8	56	3.2
Nunavik	3	4	7	13.0	1	2.0
Terres-Cries-de-la-Baie-James	2	7	9	6.5	1	
Origin not specified	9	22	31	23.4	1	1.0
TOTAL	2219	5662	7881	21.0	319	6.6
Annual average over 5 years	444	1132	1576		64	
* *Princ.: principal diagnosis*						
** *Sec. secondary diagnosis*						

Source: Fichier des hospitalisations Med-Echo, Ministère de la Santé et des Services sociaux du Québec

APPENDIX 9:
ESTIMATE OF CASES OF VENOUS LEG ULCERS IN QUÉBEC

APPENDIX 9: ESTIMATE OF CASES OF VENOUS LEG ULCERS IN QUÉBEC

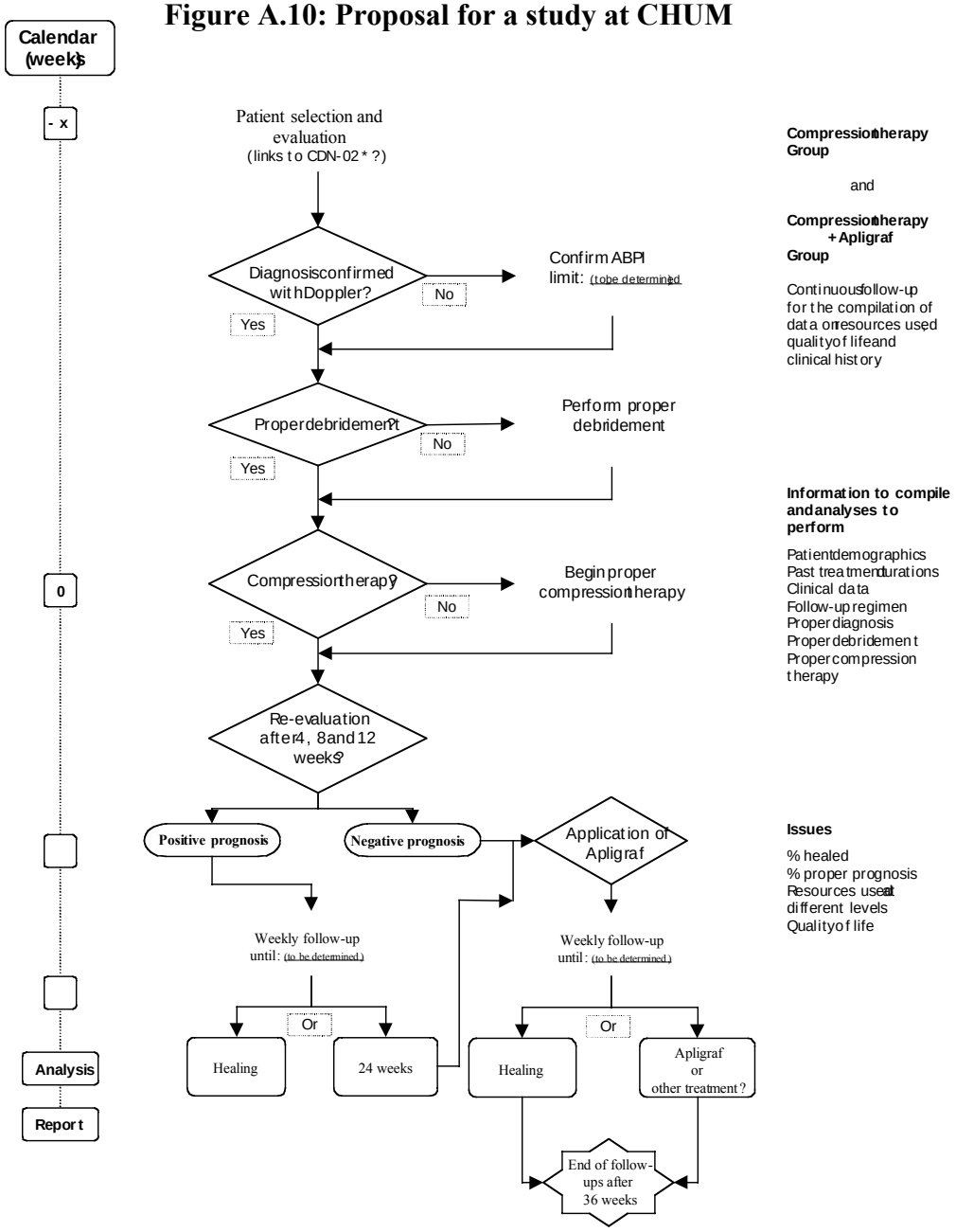
Table A.9: Estimate of cases of venous leg ulcers in Québec

			Total	> age 50	≥ age 60	age 65-74
			a	b	c	d
I	Estimated population in 1998 (MSSS, 1997):	Male:	3,706,207	973,114	534,141	247,587
		Female:	3 804 941	1,168,122	720,554	303,589
		Total:	7,511,148	2,141,336	1,254,695	551,176
II	Active or healed leg ulcers:		(1% of total "Ia")	(Bandolier, 1998)	(0.33% of "Ic")	(Morrel, 1996)
			75,111		4,14	
		Male:	37,062		1,763	
		Female:	38,049		2,378	
III	Active or healed venous leg ulcers					
	(76% of "II"): (Jack, 1997)		57,085			
IV	History of leg ulcers (3.6% of > age 60 "Ic"): (Bandolier, 1998)		...	...	45,169	...
V	Number of ulcers prevalent at same time (20 to 25% - here 22.5% -					
	of "III" would be active at the same time): (Bandolier, 1998)		12,844			
VI	Recurrent ulcers (67 to 75% - here 71% - of "V")		9,119			
VII	New ulcers ? ("V" - "VI"):		3,725			
VIII	Active ulcers:	As per Novartis, between 5,000 and 10,000; according to the above estimates, a minimum				
		of approximately 4,000 and a "maximum" of approximately 12,000, namely for calculation purpos				
		approximately 8,000 (see Sections 3 and 8.3)				
	Ratio of chronic venous ulcers					
	female vs male: (Morrel, 1996)	1.8:1				

APPENDIX 10:
TREATMENT WITH APLIGRAF ™ OF CASES RESISTANT TO COMPRESSION THERAPY

APPENDIX 10: TREATMENT WITH APLIGRAF ™ OF CASES THAT ARE RESISTANT TO COMPRESSION THERAPY

Figure A.10: Proposal for a study at CHUM



*CDN-02: Number of a clinical trial sponsored by Novartis *(Synopsis shown in Appendix 6)*

APPENDIX 11:
THE COCHRANE COLLABORATION ON COMPRESSION THERAPY: DATA PRESENTED

APPENDIX 11: THE COCHRANE COLLABORATION ON COMPRESSION THERAPY: DATA PRESENTED

Table A11.1: Comparison 1 - with compression vs no compression (RR and confidence intervals at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Charles, 1991	19 / 27	6 / 23		5.67 (1.89 – 17.07)
Eriksson et al., 1984 and 1986	9 / 17	7 / 17		1.58 (0.42 – 5.96)
Kikta et al., 1988	21 / 30	15 / 39		3.48 (1.35 – 8.95)
Rubin et al., 1990	18 / 19	7 / 17		11.64 (2.87 – 47.21)
Sikes, 1985	17 / 21	15 / 21		1.67 (0.41 – 6.79)
Taylor et al., 1995 and 1998	12 / 18	4 / 18		5.75 (1.57 – 21.04)
Total❖	*96 / 132*❖	*54 / 135*❖		
Average (%)	*73*	*40*		

* Odds ratio

❖ The Cochrane Collaboration did not group these data for comparison 1. The unweighted average of 73% was added above to show the healing rates obtained in 12 weeks in 4 studies, 8 and 52 in the other two.

Table A11.2: Comparison 2- elastic high compression vs inelastic compression (multilayer)
(RR and confidence interval at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Callam, 1992	35 / 65	19 / 67	47.7	2.85 (1.43 – 5.68)
Gould et al., 1992, 1993 and 1998	11 / 20	7 / 20	15.1	2.20 (0.64 – 7.52)
Northeast et al., 1990	31 / 49	26 / 52	37.2	1.71 (0.78 – 3.73)
Total (CI 95%) Chi-square 0.93 (dl=2) Z=3.35	77 / 134	52 / 139	100.0	2.26 (1.40 – 3.65)
Total (%)	*57*	*37*		

Table A11.3: Comparison 3 - multilayer high compression vs single-layer comression (RR and confidence interval at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Colgan et al., 1996	6 / 10	2 / 10	8.1	4.87 (0.85 – 27.86)
Krajl et al., 1996	7 / 16	8 / 18	13.8	0.97 (0.26 – 3.70)
Nelson et al., 1995	69 / 100	49 / 100	78.1	2.28 (1.30 – 3. 99)
Travers et al., 1992	0 / 13	0 / 13	0.0	Not estimable
Total (CI 95%)	82 / 139	59 / 141	100.0	2.15 (1.31 – 3.54)
Chi-square 2.24 (dl=2) Z=3.03				
Total (%)	*59*	*42*		

Table A11.4: Comparison 4 - multilayer high compression vs inelastic compression (RR and confidence interval at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Danielsen et al., 1998	9 / 21	5 / 19	24.6	2.03 (0.56 – 7.34)
Duby et al., 1993	11 / 25	10 / 25	32.8	1.17 (0.39 – 3.57)
Knight et al., 1996	0 / 5	0 / 5	0.0	Not estimable
Scriven et al., 1998a	17 / 32	18 / 32	42.6	0.88 (0.33 – 2.35)
Total (CI 95%)	37 / 83	33 / 81	100.0	1.19 (0.63 – 2.25)
Chi-square 1.02 (dl=2) Z=0.54				
Total (%)	*45*	*41*		

Table A11.5: Comparison 5 - 4-layer compression vs multilayer high compression (RR and confidence interval at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Colgan et al., 1996	7 / 10	6 / 10	8.0	1.52 (0.25 – 9.10)
McCollum et al., 1997	82 / 115	85 / 115	76.9	0.88 (0.49 – 1.56)
Wilkinson et al., 1997	10 / 17	7 / 18	15.1	2.17 (0.59 – 8.02)
Total (CI 95%)	99 / 142	98 / 143	100.0	1.05 (0.63 – 1.75)
Chi-square 1.72 (dl=2) Z=0.19				
Total (%)	*70*	*69*		

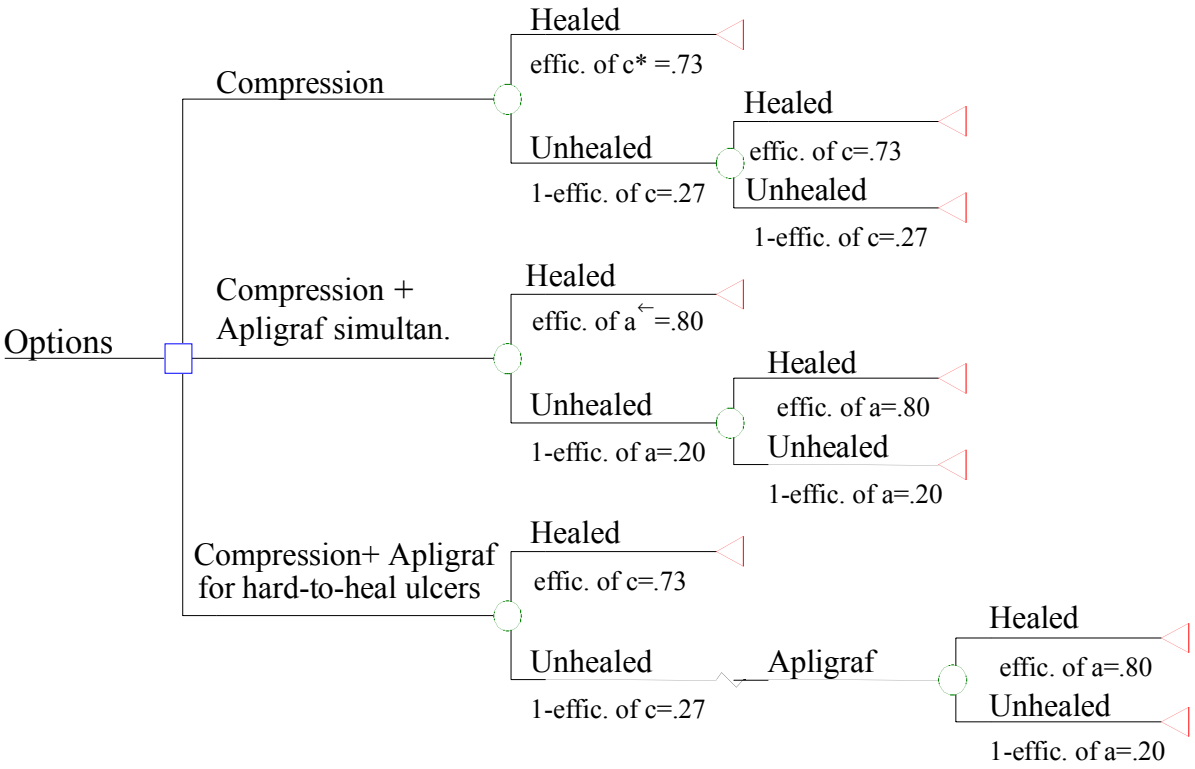
Table A11.6: Comparison 6 - compression stocking vs compression bandage (RR and confidence interval at 95%)

Study	Experimental group n/N	Control group n/N	Weight %	OR* Peto (95% CI – fixed effects)
Hendricks et al., 1985	10 / 14	7 / 10	31.2	1.07 (0.19 – 6.14)
Horakova et al., 1994	21 / 25	13 / 25	68.8	4.23 (1.30 – 13.70)
Total (IC 95 %)	31 / 39	20 / 35	100.0	2.75 (1.04 – 7.30)
Chi-square 1.64 (dl=1) Z=2.03				
Total (%)	*80*	*57*		

APPENDIX 12:
TREATMENT OPTIONS

APPENDIX 12: TREATMENT OPTIONS

Figure A.12: Treatment options



* c = compression
♦ a = Apligraf MC

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