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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

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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.

MEMBERS

SCIENTIFIC DIRECTOR

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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