Volume 3 • Suppl. 1 • 2000
VALUE IN HEALTH

The Cost-effectiveness of Treating Diabetic Lower Extremity Ulcers with Becaplermin (Regranex): A Core Model with an Application Using Swedish Cost Data

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ABSTRACT

Objectives: The objective of this study was to develop a model capable of assessing the cost-effectiveness in Sweden of treating diabetic neuropathic lower extremity ulcers with becaplermin gel (Regranex) plus good wound care (GWC) relative to treating them with GWC alone.
Methods: A Markov simulation model was developed that includes six health states: Uninfected Ulcer, Infected Ulcer, Gangrene, Healed Ulcer, Healed Ulcer-History of Amputation, and Deceased. To predict clinical outcomes, information was taken from a specially designed prospective 9-month follow-up study of 183 neuropathic patients in the US treated with GWC. Cost of treatment data were taken primarily from a study of a cohort of 314 patients in Sweden. The efficacy of becaplermin was assumed equal to that achieved in a pooled analysis of four randomized clinical trials. A model application provides expected clinical outcomes for a cohort of patients. Annual treatment costs per patient were estimated using treatment practice and unit prices from Sweden.
Results: Due to a higher rate of healing and a shorter average healing time, treatment with becaplermin gel was predicted to increase the average number of months spent in the healed state over the first year following development of an ulcer by 24% relative to GWC alone. In addition, the corresponding number of amputations was 9% lower for the becaplermin-treated cohort. The average expected cost of $12,078 US for an individual treated with GWC alone declines to $11,708 US for one treated with becaplermin, in spite of $1262 becaplermin costs. Expenses related to topical treatment and inpatient care account for 83% of the resources conserved.
Conclusions: Our results suggest that in Sweden treatment with becaplermin in conjunction with GWC consumes fewer resources and generates better outcomes than treatment with GWC alone for diabetic neuropathic ulcers. In light of the high and increasing incidence of such ulcers, the potential savings in costs and suffering may be important. Results are difficult to extrapolate internationally because they are strongly related to country-specific treatment practices and price levels.
Keywords: cost-effectiveness, diabetic foot ulcer, model.

Introduction

Lower extremity ulceration is a common but serious complication of diabetes Mellitus (DM), often resulting in chronic nonhealing wounds that leave sufferers vulnerable to infection, gangrene and ultimately to amputation. In fact, it has been singled out as one of the most common and costly of the diabetic complications [1,2]. Every year, between 2.2 and 5.9% of DM patients in industrialized nations develop a lower extremity ulcer [3].

Recent studies illustrate the economic burden of lower extremity ulcers. In the US, for example, it was estimated that $150 million was spent treating NIDDM patients for chronic skin ulcers, a subset of all lower extremity ulcers, and this did not even include costs for amputations [4]. At a disaggregate level, Medicare reimbursement for inpatient treatment of skin ulcers (DRG 271) was $4862 in 1995, reflecting an 8.8-day length of hospital stay [5]. Private insurance reimbursed almost twice as much, some $8,988, in part the consequence of almost three additional inpatient days [5]. In Sweden, it has been estimated that the average direct cost for patients who heal primarily are $8500 [6]. The corresponding costs for patients requiring minor amputation and major amputation are $43,000 and $65,000, respectively [6]. Current treatment of neuropathic ulcers is multidisciplinary [6,7]. In centers of excellence, treatment is successful and heals 80

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 1098-3015/00/$15.00/S-39 S-39–S-46

and 90% of the ulcers [3]. In other settings, the healing rate is often lower.

Becaplermin gel (Regranex), a novel biotechnology product containing recombinant human platelet derived growth factor (rhPDGF-BB), has been shown to stimulate the healing process in ischemia-free, neuropathic ulcers when combined with good wound care (GWC) practices.

The objective of this study was to develop a model capable of assessing the cost-effectiveness in Sweden of treating diabetic neuropathic lower extremity ulcers with becaplermin gel plus GWC relative to treating them with GWC alone.

Methods

Computer simulation techniques can be used to combine data from different sources into a cohesive epidemiological model [8]. The Markov approach is well suited to modeling decision problems that involve probabilities of transition among discrete states for which timing is important [9]. For diabetic lower extremity ulcers, a sequence of well-defined health states exists and transition between them is easily measurable.

As part of a recent cost of illness study, Abt Associates, Inc. (Abt Inc., Cambridge, MA) developed a Markov model of diabetic neuropathic lower extremity ulcers [10]. At any point in time, model subjects are considered to be in one of five health states: Uninfected, Infected, Healed, Amputated, or Deceased. Based on a US sample of 194 IDDM and NIDDM patients, rates of transition between the various health states were estimated. Several important features of the pathology of lower extremity ulcers are overlooked in this model, however. For instance, gangrene, which can be a costly outcome of chronic ulcers and usually results in amputation, is not included. Moreover, the model treats amputation as an endpoint, even though amputees incur long-term costs related to reduced mobility and are at risk for re-amputation.

Starting with the Abt model, a more complete model of lower extremity ulcers for cost-effectiveness analysis was developed. It includes Gangrene as a separate health state and it models postamputation pathology explicitly. An important conceptual difference is that Amputated is no longer considered a health state, but is modeled instead as a treatment that may promote healing.

The Core Simulation Model

Our model of lower extremity ulcers includes six health states: Uninfected (Deep) Ulcer, Infected (Deep) Ulcer, Gangrene, Healed Ulcer, Healed Ulcer-History of Amputation, and Deceased (Fig. 1). The first three health states correspond to Wagner grades 2, 3, and 4, respectively [11]. Superficial ulcers (Wagner grade 1) are not included. Initially, each member of a cohort of DM patients has an uninfected ulcer. Over the course of the first month, uninfected ulcers can either heal, remain the same, or become infected, or the patient can die. The transitions are governed by transition probabilities. Those that remain in the Uninfected Ulcer health state face similar risks the next time period. The cohort is followed on a monthly basis for one year.

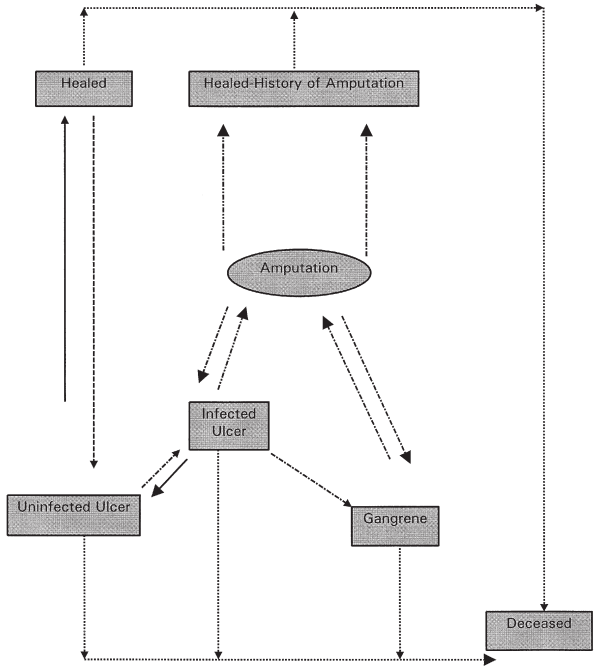

Figure 1 Diabetic foot ulcer transition diagram.

Patients with infected ulcers may remain the same, experience successful healing of the underlying infection (return to Uninfected Ulcer), undergo a successful or an unsuccessful amputation, develop gangrene or die. It should be noted that successful primary healing of an infected ulcer requires two steps. First, successful healing of the infection must be achieved. In subsequent months, successful healing of the uninfected ulcer can be achieved.

Patients with gangrene may undergo amputation, they may die, or they may remain in Gangrene. Amputation can lead either to successful healing or to continued gangrene with a subsequent exposure to re-amputation.

Patients who heal primarily, that is, who transit to Healed Ulcer from Uninfected Ulcer, face a risk of dying and a risk of ulcer recurrence. The latter is modeled as a transition back to Uninfected Ulcer. To simplify the model and increase its transparency, patients who achieve healing with amputation face no risk of ulcer recurrence. That is, the only transition out of Healed Ulcer-History of Amputation is to Deceased. A comparison of results suggests that this assumption is minor. Finally, Deceased is an absorbing state.

Epidemiological Data

Monthly probabilities for the transition between the various health states are presented in Table 1. The transition probabilities that were estimated by Abt formed the starting point because the patients in that study were recruited to assess the cost of deep, ischemia-free, diabetic neuropathic lower extremity ulcers, exactly the type of wounds for which becaplermin is indicated.

The Abt model and the one presented here do not coincide exactly; several assumptions and additional estimates were necessary.

The proportion of amputations that are successful is used to subdivide the Abt probability that an Infected Ulcer is amputated into the probabilities of successful healing and failure (i.e., remaining in Infected Ulcer).

The direct transition from Uninfected Ulcer to Gangrene was disallowed.

Table 1 Monthly probabilities for lower extremity ulcer transitions (%)

Transition	Probability (%)
Uninfected Ulcer→Healed Ulcer	7.87*
Uninfected Ulcer→Infected Ulcer	4.73*
Infected Ulcer→Uninfected Ulcer	13.97*
Infected Ulcer→Gangrene	0.75†
Infected Ulcer→Amputation Healed Ulcer, History of Amputation	4.45‡
Infected Ulcer→Amputation→Infected Ulcer	0.37‡
Gangrene→Amputation→Healed, History of Amputation	30.82§
Gangrene→Amputation→Gangrene	18.18§
Healed Ulcer→Uninfected Ulcer	3.93*
Healed Ulcer→Deceased	0.40*
Uninfected Ulcer→Deceased	0.40*
Infected Ulcer→Deceased	0.98*
Gangrene→Deceased	0.98*
Healed Ulcer, History of Amputation →Deceased	0.40*

*Abt data [10]. †Calibrated to match observed amputation patterns (see text). ‡The probability of amputation is drawn from Abt data [10]. The proportion of successful and unsuccessful procedures is drawn from Apelqvist et al data [12,13]. §The probability of amputation was estimated using Apelqvist et al data [12,13], as was the proportion of successful and unsuccessful procedures.

The monthly probability that Gangrene is amputated was estimated to be 49% (calculations based on data described in [6]) and, as with Infected Ulcer, it is subdivided between successful healing (31%) and failure (i.e., remaining in Gangrene) (18%).

The probability of transition between Infected Ulcer and Gangrene was calibrated using an assumption that infected ulcers are the cause of about 80–85% of ulcer-related amputations and gangrene is the cause of the remaining 15–20%. A monthly transition probability of 0.75% achieves this balance.

Mortality risks, also based on Abt data, are 0.40% per month (4.7% per year) for Healed Ulcer and Uninfected Ulcer and 0.98% per month (11.1% per year) for Infected Ulcer and Gangrene. Conservatively, it was assumed that gangrene has the same mortality risk as Infected Ulcer. That is, no incremental mortality risk for amputation is modeled. Based on the outcomes of 274 Swedish patients, it was assumed that 92% of amputations are successful for patients with infected ulcers and 63% are successful for patients with gangrene (calculations based on data described in [6]).

Cost Estimates

Long-term follow-up data on resource utilization in Sweden were taken from a series of studies in Sweden [6,7,12,13]. Only direct costs are included and presented in 1999 US dollars. Monthly cost estimates for each of the various health states and amputation are shown in Table 2.

The cost of topical treatments (not including becaplermin) was taken from [12] where the categories Deep Ulcer, Abscess, and Gangrene match our categories Uninfected Ulcer, Infected Ulcer, and Gangrene. Specifically, resource intensity weights were combined with weekly costs for each of the categories, and then the costs were converted from 1990 Swedish kronor (SEK) to 1999 dollars per month. The cost of antibiotics was taken directly from Appendix 1 in [6], though it was allocated only to Infected Ulcer. The cost of outpatient care for Uninfected Ulcer was assumed to include one physician visit and one test battery per month [6]. Two physician visits were assigned for Infected Ulcer and Gangrene.

The average costs for episodes of superficial, uninfected, infected, and gangrenous ulcers were taken from [6]. We arrived at average monthly costs by dividing these episodic costs by average healing times of three months for superficial ulcers, six months for uninfected and infected ulcers,

Table 2 Treatment costs for lower extremity ulcers in Sweden (1999 $US)

Treatment (monthly unless otherwise indicated)	Healed Ulcer	Uninfected Ulcer	Infected Ulcer	Gangrene	Healed Ulcer-History of Amputation	Amputation
Topical Treatment [12]	0	677	718	689	0	0
Antibiotics [7]	0	0	80	0	0	0
Other Outpatient Care [7]	0	117	188	188	0	0
Inpatient Care [7]	0	540	540	1,440	0	0
Orthopedic Appliances [7]	0	33	45	32	0	0
Social Services/Home Care [7]	0	0	0	0	779	0
Amputation (per procedure) [13,14]	0	0	0	0	0	6,789
Prosthesis (per amputation procedure) [13,14]		0	0	0	0	1,821
Total	0	1,367	1,572	2,349	779	8,610

and seven months for gangrenous ulcers [7]. Inpatient care costs that were attributable to the foot ulcer were estimated by calculating the difference between the cost of each ulcer type and that of superficial ulcers. The cost of orthopedic appliances was estimated using a price list for custom-made treatment shoes, individually fitted insoles, handmade orthopedic shoes, and walking casts [6], and ulcer-specific data on average yearly consumption.

We estimate the average cost of an amputation procedure in Sweden (not including follow-up costs) as a weighted average of the costs of DRG 114 (minor amputation) and DRG 285 (major amputation) plus a weighted average of the costs of prostheses [13]. According to official Swedish sources [14], DRG 114 is reimbursed at $2928 (SEK 25,485) and DRG 285 is reimbursed at $8719 (SEK 75,900). Average prosthesis costs have been estimated at $1211 and $2126 for minor and major amputations, respectively [6].

Lower extremity ulcers are associated with an increased dependence on social services and home care, particularly following amputation [6]. A monthly cost for the postamputation health state was calculated as a weighted average of the costs for minor and major amputation. The monthly costs for primarily healed patients are assumed to be zero.

Intervention

We model becaplermin treatment as administered for an initially Uninfected Ulcer according to European guidelines. Treatment is continued until the first of the following markers is reached: healing occurs, the ulcer progresses, the patient dies, or a five-month time limit expires. Only one episode of treatment is approved for use in Europe, so ulcer recurrences are treated only with GWC.

A series of randomized clinical trials (RCTs) compared becaplermin gel plus GWC vs. GWC alone. In the analysis that pooled the results of all the RCTs covering more than 500 patients, the 20-week healing rate was 35% for GWC alone and 47% for GWC in combination with becaplermin gel. The detailed bi-weekly data available from the largest of the RCTs, Regranex Study 2 (the K-Trial), enables estimation of the monthly healing probabilities [15]. An exponential survivor curve was seen to provide a good fit, giving rise to time-invariant monthly healing probabilities of 13.5% for becaplermin and 9.0% for GWC alone. Therefore, becaplermin improved the estimated monthly healing probability of GWC alone by 50%. Because the K-trial and the pooled trials had virtually the same healing rates, we model becaplermin treatment as a 50% improvement in the Abt 7.87% monthly probability of healing.

In Sweden, one tube of becaplermin gel is expected to cost the pharmacy about $418. After adding the appropriate mark-ups, the price will rise to about $445. It has been assumed that a tube lasts 5 weeks. The effective monthly price is thus $356.

The recommended becaplermin protocol in Sweden consists of dry saline gauze dressings changed once daily by a nurse. Savings in nursing resources are not modeled here. Savings in materials are easier to document and hence are modeled here. The monthly cost of once daily dry saline gauze is $132 less than the average dressing cost estimated for Uninfected Ulcer by Apelqvist et al. [12]. This reduces the effective cost of becaplermin by the same amount.

Outcomes

Becaplermin can benefit patients both by increasing the fraction of ulcers that heal primarily and, in those that do heal, by shortening the average healing time. As a consequence, reductions in episodes of infection, gangrene, and amputation, will translate into long-run resource savings and improved quality of life. Our primary outcome measure is the cost per ulcer-day averted.

Discounting

Costs are discounted at 0.42% per month (5% per year), which is consistent with widely followed guidelines in Europe [16]. Drummond et al. [16] provide arguments both in favor of and against discounting the benefits, and it is often good practice to present both sets of results. In our case, however, the short one-year time frame ensures that both sets of results are nearly identical and our finding of cost savings makes a direct comparison of costs and benefits unnecessary. We present only undiscounted benefit measures because they provide a better representation of the actual benefits of therapy, for example, the number of ulcer-months and amputations that can be avoided.

Sensitivity to Model Assumptions

In order to test the sensitivity of the results to some of our key assumptions, the following parameters were varied:

(i) The relative improvement in monthly healing rates (efficacy) attributable to becaplermin (minimum 24%, maximum 76%);
(ii) Baseline monthly healing rate for GWC alone (9%);
(iii) Longer time frame (18 and 24 months);
(iv) No short-run conservation of topical treatment resources; and
(v) Number of weeks that a tube of becaplermin lasts (minimum 4 weeks, maximum 6 weeks).

The minimum and maximum values of the relative improvement in monthly healing rates (efficacy) in sensitivity test (i) were chosen to correspond with the individual RCTs that had the lowest and highest 20-week healing rates, respectively. More specifically, when compared to the baseline 35% 20-week healing rate for GWC alone, the 42% healing rate for becaplermin observed in the least successful RCT translates into a 24% relative improvement in the monthly healing rate. Similarly, the healing rate with becaplermin in the most successful RCT, 52% over 20 weeks, translates into a 76% improvement in the monthly healing rate. The 9% monthly healing rate for GWC alone in sensitivity test (ii) is based on the results of the placebo arm of the RCTs [15]. The duration of a tube will vary in actual practice, so the model is also simulated in sensitivity test (v) using durations of 4 weeks and 6 weeks.

Results

In the cohort simulated with only GWC, 30.4% of the patients healed from the initial ulcer within the first five months. In the becaplermin-treated cohort, 42.1% healed from the initial ulcer during the five-month treatment phase. Though only minor gains in life expectancy were seen over the course of the year, the increase in the healing rate translates directly into more months free of ulcers and fewer months spent suffering from them (Table 3). The average number of months spent in the healed state rose from 3.41 to 4.22, an increase of 24%. The number of amputations declined by 9%.

These sizable health gains translate into cost-savings over 12 months (Table 3). The expected cost of $12,078 for an individual treated with

Table 3 The benefits and costs of becaplermin over a 12-month time horizon

	Good wound care alone	Becaplermin	Difference
Benefits:			
Months in Healed State	3.41	4.22	+0.81
Months with Ulcers	8.30	7.49	−0.81
Amputations (per 100 individuals)	6.50	5.91	−0.59
Costs (1999 $US):			
Recurring Costs:			
• Topical Treatment	5,560	4,550	−1,009
• Antibiotics	90	82	−8
• Other Outpatient	1,032	932	−100
• Inpatient	4,414	3,985	−429
• Orthopedic Appliances	285	257	−28
• Social Service/Home Care	189	176	−13
Sub-Total	11,570	9,983	−1,587
One-time Costs:			
• Amputation	401	365	−36
• Prostheses	108	98	−10
Sub-Total	508	463	−46
Becaplermin	0	1,262	+1,262
Grand Total	12,078	11,708	−370

GWC alone declines to $11,708 for an individual treated with becaplermin, in spite of $1262 becaplermin costs. Topical treatment (not including becaplermin) and inpatient care account for 83% of the resources conserved. Fully $1009 can be saved in topical treatment expenses and $429 in inpatient care can be avoided. The savings in antibiotics, physician visits, orthopedic appliances, social services/home care, amputations, and prostheses are modest.

Sensitivity Analysis

The sensitivity analysis suggests our estimates are relatively insensitive to changes in most key parameters. Table 4 shows the following results of varying five key assumptions, one at a time. In Panel A, it can be seen that becaplermin is not cost saving at only a 24% improvement in monthly healing rates (42% 20-week RCT healing rate). The break-even point occurs at about 34% improvement in healing (43% 20-week RCT healing rate). The cost savings are $942 when the improvement in efficacy is 76%.

Discussion

This is the first comprehensive model developed that is suitable for cost-effectiveness analyses of diabetic foot ulcer treatments. Clinical and economic outcomes are predicted using data from a specially designed follow-up study of 183 neuropathic ulcer patients treated with usual GWC in the US. The model is applied to Sweden using published cost of treatment data from a study of the treatment patterns and unit costs of 314 patients in the south of Sweden, the only such study available.

Using efficacy data from a pooled analysis of four RCTs of becaplermin gel to model the improvement over GWC, an economic evaluation of GWC plus becaplermin vs. GWC alone in Sweden was conducted. The results suggest that treating neuropathic lower extremity foot ulcers with becaplermin treatment plus GWC is less expensive than treating them with GWC alone in Sweden, and this holds true even when various model parameters are altered. The principal explanation is that a greater fraction of ulcers healed, and those that did so healed faster on average, thus reducing the number of patient-months that require costly treatment.

The model relies heavily on data compiled by Abt so several features of the data may influence the results. First, only 194 patients were recruited, so the transition probability estimates may be imprecise. Second, the transition probabilities may not be applicable to cohorts of all ages. Rather, our results may apply best to cohorts similar in age to the Abt sample, where the median patient age was 60 years and 60% of the sample was between the ages of 51 and 70. Care must be used in extrapolating results to a group of either very young or very old patients. Third, the sample members were drawn from the US and not the Swedish population.

Nevertheless, two important strengths of the Abt data act to offset these shortcomings. The sample inclusion criteria correspond exactly to pa-

Table 4 Sensitivity of the results to alternative assumptions (1999 US$)

	Good wound care alone	Becaplermin	Difference
Improvement in Efficacy:			
24% (i.e., 42% 20-Weeks Healing Rate)	12,078	12,324	246
50% (i.e., 47% 20-Weeks Healing Rate)	12,078	11,708	−370
76% (i.e., 52% 20-Weeks Healing Rate)	12,078	11,136	−942
Good Wound Care Healing Rate:			
7.87% per Month	12,078	11,708	−370
9.00% per Month	11,597	11,120	−477
Time Horizon:			
12 Months	12,078	11,708	−370
18 Months	16,034	15,348	−686
24 Months	19,370	18,521	−849
Becaplermin Treatment Protocol:			
Savings in Topical Treatment Costs	12,078	11,708	−370
Equivalent Topical Treatment Costs	12,078	12,176	98
Duration of 1 Becaplermin Tube			
4 Weeks per Tube	12,078	12,023	−55
5 Weeks per Tube	12,078	11,708	−371
6 Weeks per Tube	12,078	11,498	−580

tients that are eligible for treatment with becaplermin and the transition probabilities were estimated using an epidemiological model very similar to ours. It should also be noted that the Abt healing rate of 7.87% per month, used in this application, is lower than the implied monthly healing rate of 9% found in the becaplermin RCTs. In a RCT for another product in the UK, the implied monthly healing rate for GWC alone was of the same magnitude; 13% when calculated over only the first 12 weeks and 7% when calculated over 32 weeks [17]. RCTs typically have higher healing rates than seen in normal treatment settings, however, so this application is based on conservative assumptions about the baseline efficacy.

The reduction in the incidence of gangrene and amputation suggests there may be important life quality differences between patients treated with becaplermin plus GWC and patients treated with GWC alone. Because no satisfactory life quality weights were available, however, the model results do not include this human dimension and hence are likely to be conservative.

Our model was also run for 18 and 24 months (see Table 4). As becaplermin treatment is not indicated for ulcer recurrences in Europe, it has no direct effect during these additional months. However, the costs of treating complications and post-amputation follow-up continue to accumulate so the healthier distribution of patients in the becaplermin-treated cohort continues to generate cost savings. Moreover, with a longer time frame, the model is more sensitive to changes in the incidences of gangrene and amputations, though extrapolation of results over this longer time frame also increases modeling uncertainty.

Though the epidemiological data in the model were taken primarily from US Abt study data, the economic analysis has been customized to conditions seen in Sweden. In particular, monthly treatment costs are based on treatment patterns, resource usage and unit costs as practiced in south Sweden. It may be that the economic data reflect above-average resource consumption, thus, and that the actual cost-effectiveness may be lower in less resource-intensive settings. Moreover, reimbursement systems, relative prices, and treatment patterns may have important impacts on resource usage and costs, so even if becaplermin was associated with cost savings in Sweden under a variety of assumptions, it is tenuous to extrapolate these results to countries with different health care systems.

Becaplermin is not approved for superficial ulcers and ischemia and the cost-effectiveness of treating patients with such ulcers is not established. The model can be modified to analyze other types of diabetic foot ulcer, however. Economic evaluations can also be undertaken in a way that facilitates analyzing more than one country with the same, or nearly the same, model.

Conclusion

Model results presented here suggest that, for diabetic neuropathic ulcers in Sweden, becaplermin treatment in conjunction with GWC consumes fewer resources and generates better outcomes than does GWC alone. In light of the high and increasing incidence of such ulcers, the potential savings in costs and suffering may be important. Results are difficult to extrapolate internationally because they are strongly related to treatment practices and price levels in different countries.

This work was supported by R.W. Johnson Pharmaceutical Research Institute, USA. The insightful comments of two anonymous referees are gratefully appreciated.

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