Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of becaplermin gel (a biotechnology product containing recombinant human platelet-derived grown factor), in combination with good wound care (GWC), for the treatment of diabetic foot ulcers. GWC consisted of sharp debridement to remove callus, fibrin and necrotic tissue, and a moist saline dressing.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with diabetic ischaemia-free foot ulcers. Superficial ulcers were excluded.

Setting
The setting was secondary care. The economic study was carried out in France, the UK, Sweden and Switzerland.

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 1999. Some resource and cost data were obtained from studies published between 1994 and 2000. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was used to assess the clinical and economic outcomes associated with the two strategies under evaluation in a hypothetical cohort of patients with diabetic foot ulcers. The time horizon of the model was one year and the cycle length was one month. Patients entered the model with uninfected ulcers and, each month, moved across health states. The health states considered were uninfected ulcer, infected ulcer, gangrene, healed ulcer, amputation and death. The structure of the model was reported in the paper.

Outcomes assessed in the review
The outcomes estimated from the literature were efficacy of becaplermin plus GWC over GWC alone, and all transition probabilities across the model health states.
Study designs and other criteria for inclusion in the review
It appears that a systematic review of the literature was not undertaken to identify the primary studies. The evidence on becaplermin efficacy came from a clinical trial of 449 patients. The transition probabilities were mainly derived from a US study involving 183 patients. Other data were derived from Swedish studies.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Five primary studies provided the data.

Methods of combining primary studies
A narrative method appears to have been used to combine the primary estimates in the decision model.

Investigation of differences between primary studies
Not reported.

Results of the review
The 20-week healing rate was 35% for GWC alone and 47% with becaplermin plus GWC, (p=0.009).

The time to healing at the 25th and 75th quartiles fell from 84 and 131 days to 71 and 92 days, respectively, (p=0.008).

The following transition rates were used in the model:

- 7.87% from uninfected ulcer to healed ulcer;
- 4.73% from uninfected ulcer to infected ulcer;
- 13.97% from infected ulcer to uninfected ulcer;
- 0.75% from infected ulcer to gangrene;
- 4.45% from infected ulcer to amputation to healed ulcer, history of amputation;
- 0.37% from infected ulcer to amputation to infected ulcer;
- 30.82% from gangrene to amputation to healed ulcer, history of amputation;
- 18.18% from gangrene to amputation to gangrene;
- 3.93% from healed ulcer to uninfected ulcer;
0.40% from healed ulcer to death;
0.40% from uninfected ulcer to death;
0.98% from infected ulcer to death;
0.98% from gangrene to death; and
0.40 from healed ulcer, history of amputation, to death.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the number of months free of ulcer. This was derived using a modelling approach. The number of amputations and the number-needed-to-treat to avoid one amputation were also reported.

**Direct costs**
Discounting was not relevant as the costs were incurred within a 1-year time frame. The resource use data were reported whereas unit costs, with the exception of becaplermin, were not. In fact, the costs were presented as macro-categories. The health services included in the economic evaluation were becaplermin, inpatient care, topical treatment (labour and treatment), outpatient care (consultations and tests), antibacterials and orthopaedic appliances. The cost/resource boundary of the national health system was used. Both the resource use and costs were estimated from country-specific data, which were generally based on experts' opinions. For example, in the UK some data were collected from a limited Delphi-style interview of three physicians, while other data were not available and came from modified Swedish sources. The costs were expressed using 1998/1999 prices whenever possible. Otherwise, all figures were inflated to 1999 values using local price indices.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
The costs were gathered in local currencies and then converted into US dollars ($) based on 1999 exchange rates.

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to examine the robustness of the cost-effectiveness estimates to variations in efficacy rate, transition probabilities, and nursing services for more or less persistent ulcers. Two alternative scenarios for resource use (i.e. high- and low-intensity treatment patterns) were also considered. The ranges of values used were based on published values or authors’ assumptions.

**Estimated benefits used in the economic analysis**
Patients in the GWC alone group spent an average of 3.41 months in the healed state and 8.30 months in one of the ulcer states.

Patients in the becaplermin plus GWC group spent an average of 4.32 months in the healed state and 7.49 months in one of the ulcer states. Thus, becaplermin led to an increase of 24% in the time spent in the healed state.

The expected number of amputations per 100 patients was 5.91 in the becaplermin group and 6.50 in the GWC alone group. This implied that one amputation could be prevented for every 169 individuals receiving treatment.
Cost results
In France, the total costs were $11,977 with GWC alone and $11,993 with becaplermin (difference $15).

In Sweden, the total costs were $12,168 with GWC alone and $11,783 with becaplermin (difference -$384).

In Switzerland, the total costs were $14,112 with GWC alone and $13,832 with becaplermin (difference -$279).

In the UK, the total costs were $17,601 with GWC alone and $17,133 with becaplermin (difference -$468).

The cost analysis revealed that there was substantial variation in the composition of costs among countries (i.e. mix between inpatient and outpatient services).

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER; the incremental cost per ulcer-free month gained) was calculated to combine the costs and benefits.

In France, the ICER with becaplermin over GWC alone was $19. In Sweden, Switzerland and the UK, becaplermin dominated GWC alone, which was both less effective and more expensive.

The source of savings was different across countries. The most important categories of savings were topical treatment resources in Sweden, inpatient care in France and Switzerland, and both topical treatment and in- or outpatient care in the UK.

The sensitivity analysis showed that the breakeven efficacy rate (above which the becaplermin led to cost-savings over GWC alone) was 50.6% in France, 33.8% in Sweden, 39.8% in Switzerland and 36.4% in the UK. Clearly, higher values of vaccine efficacy led to greater cost-savings, and vice versa.

Becaplermin was more cost-effective for less persistent ulcers and less cost-effective for more persistent ulcers.

Using a high-intensity resource use scenario (as adopted in Sweden), the ICER was $437 in France and becaplermin was dominant in Switzerland and the UK (as well as in Sweden).

Using a low-intensity resource use scenario (as adopted in Switzerland), the ICER was $603 in France, $21 in Sweden and $186 in the UK (becaplermin was cost-effective in Switzerland).

Authors' conclusions
Becaplermin was a cost-effective treatment for diabetic foot ulcers in several European countries, being cost-saving in Sweden, Switzerland and the UK. The analysis revealed substantial differences in treatment patterns and in the nature of cost-savings among countries.

CRD COMMENTARY - Selection of comparators
The comparator (GWC) was selected on the basis of the comparator used in the clinical trial of becaplermin. GWC was the type of care that most patients received. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from several published studies. The authors did not state explicitly whether a systematic review of the literature had been undertaken and the primary studies appear to have been identified selectively. Some evidence came from a trial and some prospective studies, which were partially described. The methods used to extract and then combine the primary data were not described. Some key model inputs were varied in the sensitivity analysis. The authors noted that the application of US data to European countries could have been controversial. Similarly, the use of the same probabilities as different European countries could be questioned.
Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study and is not comparable with the benefits of other health care interventions. The impact of the treatments on quality of life was not investigated.

Validity of estimate of costs
The perspective of the national health system was adopted. However, the authors noted that such a perspective could have been more relevant for some countries than for others, owing to the differences in the health care systems across Europe. Limited information on the unit costs was provided, although resource use was generally reported for most items. The source of the data was reported and most economic inputs were derived from a panel of experts. However, only some items were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises. The authors stressed their concern on how representative the resource use data was, as it could have been biased in favour of becaplermin.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was extensively addressed by considering four different European countries. Thus, the results of the analysis could be extrapolated to settings with similar characteristics. Further, sensitivity analyses were carried out, which further enhanced the external validity of the study. The authors noted that conservative assumptions were made in the decision model.

Implications of the study
The study results supported the use of becaplermin for the treatment of diabetic foot ulcer.

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Other publications of related interest


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