CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: Dermatologic and Ophthalmic Drugs Advisory Committee

DATE OF MEETING: 07/14/97

QUESTIONS

QUESTIONS FOR THE DERMATOLOGIC AND OPHTHALMIC DRUG ADVISORY COMMITTEE

JULY 14, 1997

1. Consistency of efficacy results

Variability of about 10% in absolute difference was observed in the incidence of complete healing in similar treatment arms across the four efficacy trials. Explanations for this lack of consistency likely reflect aspects of trial design and/or conduct. It is important in planning the trial to carefully consider: 1) use of controls (e.g. standard care or placebo); 2) blinding techniques (e.g. double-blinding or third-party blinding); 3) enrollment criteria that determine the heterogeneity of study subjects with respect to covariates and co-morbidities (e.g. ulcer location, stage, duration, area at baseline; peri-ulcer $TcpO_2$; nutritional status; organ dysfunction etc.) that affect ulcer healing. With regard to trial conduct, variations of standard of care including infection control, debridement (type and frequency), non-weight bearing compliance and methods, and patient glycemic control also influence ulcer healing.

Please discuss which of the covariates mentioned above are most critical in healing diabetic neuropathic ulcers. Please discuss what mechanisms might be used to address these important covariates (e.g. by stratification, covariate analyses). To what extent might more consistent trial design/conduct be used to control variability?

Despite measures to minimize variability, a similar degree of inconsistency might be seen in trials of relatively small size. To overcome "noise" due to chance the individual trials should be of sufficient size to detect a statistically significant difference between becaplermin and control arms.

Does the committee agree that this degree of variability is to be expected for studies of the size presented in the application? Does the committee agree that fewer larger trials are preferable to smaller trials that have a more homogeneous diabetic population at entry?

2. Extent of benefit from becaplermin treatment.

Despite the variable clinical results, there is some consistency of treatment effect. In all studies, for example, the percentage of complete ulcer closure in the becaplermin groups is higher than in the placebo control or standard care group. In the combined analyses the absolute percentage of subjects who benefited by the use of becaplermin was observed to be 10% compared to placebo and 15% compared to standard care (43% incidence in the 100 µg/g becaplermin, 33% in the placebo, 28% in standard care). However, given that in all arms about 30% of healed ulcers recurred within three months, treatment with becaplermin resulted in only about seven to ten percent of subjects experiencing a durable benefit over placebo or standard care, respectively.

Is an approximately 10% absolute difference in durable complete closure (30% relative) of clinical interest?

Has becaplermin been demonstrated to be effective in the treatment of neuropathic diabetic ulcers?

3. Patients most likely to benefit from becaplermin

a. Standard Care

It is necessary to optimize standard care and concomitant therapy in wound healing to compare the benefit derived by becaplermin treatment. Among factors in standard care, there is consensus that non-weight bearing is essential. Contact casts were not allowed because this modality is incompatible with daily application of becaplermin. However, for diabetic ulcers that are located over the heel or metatarsal head, total contact casting is considered by many to be the treatment of choice for pressure relief for this class of ulcers.

Please discuss whether the standard of care in these trials was appropriate to allow determination that becaplermin contributed significantly to the healing of neuropathic ulcers. Please discuss your experience with the use of contact casting. If approved, is becaplermin appropriate for treatment of all neuropathic ulcers irrespective of location?

b. Ulcer Staging

Clinical trials of becaplermin were performed in diabetic patients with Stage III (defined as full thickness tissue loss extending through dermis to involve subcutaneous tissue) or Stage IV neuropathic ulcers. The sponsor has not examined becaplermin in trials of more superficial Stage II ulcers. The phrase, full thickness through epidermis and dermis, has been proposed by the Sponsor to describe ulcers appropriate for treatment with becaplermin. Likewise, becaplermin has not been examined in diabetic patients with ulcers due to vascular impairment: all becaplermin-treated patients had a $TcpO_2 > 30$ mm of Hg.

If approved, should the Sponsor's definition be used or should labeling specifically state that becaplermin is intended for treatment of neuropathic ulcers that extend at least through subcutaneous tissue (Stage III), and in which there is an adequate blood supply?

4. Appropriate formulation (drug concentration) and administration (drug amount) of becaplermin

a. Selection of Drug Concentration

The 30 and 100 µg/g formulations were effective in some of the trials, but in the "K" trial, where both formulations were compared, only the 100 µg/g formulation was effective.

Does the committee agree that the 100 µg/g formulation should be the approved formulation?

b. Amount of Drug Administered

In studies "F", "K", and "001" measured doses were used based on ulcer area. In study "002" the dose was not measured, and the proportion of becaplermin-treated subjects that had complete healing was the lowest of all the major trials. A comparison of drug usage and clinical outcome in the "002" trial showed even greater excessive usage (about 8-fold more, µg/cm^2, on average) than the expected amount. In actual usage, the potential exists for dose application even in greater excess than that which occurred in study "002".

Topical agents are not delivered in measured doses. The Sponsor believes that the data demonstrate that concentration (µg/g), and not amount of gel applied, is associated with the efficacy outcome of becaplermin gel. Consequently, the Sponsor has proposed the gel be applied as a thin continuous layer (thickness of a dime) and does not wish to include instructions for

measured dosing in the label.

If becaplermin is approved, should instructions for measuring dosage based on ulcer area, as was used in three of the efficacy trials, be recommended in the label? Please discuss the possibility that excessive administration of drug might diminish efficacy.

If becaplermin is approved, please discuss whether there should be further post-marketing exploration of drug concentration, amount applied to the ulcer, or other dose-related issues such as schedule.

5. Safety of Drug Product

Becaplermin is manufactured as a preserved, multi-use, low bioburden product with the absence of specified objectionable microbes. Several types of data support the microbial safety of this product. 1) No differential incidence in infection-related adverse events was observed in clinical trials between product, placebo, or standard care arms. 2) No bacteria, fungi or yeast have yet been detected in tubes of the finished product using the Microbial Limits Test (limit of detection is 10 CFU/g of gel product). 3) The preservative system is bacteriocidal and fungicidal in the Preservative Effectiveness Test, which challenges the product with individual microbes of 10^5 each per gram of product. 4) Lower extremity diabetic ulcers are inherently microbially contaminated, and are considered to be in "bacterial balance" even if they contain up to 10^5 CFU per gram of wound tissue.

Becaplermin is not systemically bioavailable. The drug is well tolerated. Theoretical concerns raised by the biology of PDGF (i.e. increased vascular events or neoplasms) have not been observed. Product discontinuations, infectious adverse events, tumorigenicity, cardiovascular problems, and deaths were similar between standard care, vehicle and product treatment arms. The vehicle alone did not adversely affect healing, but in fact outperformed standard care. No serious or clinically significant adverse effects have been observed thus far in subjects treated with becaplermin.

Considering the information above, does the committee concur that becaplermin has been adequately demonstrated to be safe for its intended use?