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Assessment report for REGRANEX

International non-proprietary name: becaplermin

Procedure No. EMA/H/C/000212/A20/0033

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. EXECUTIVE SUMMARY

Regranex (becaplermin) is indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2.

Regranex contains the active ingredient becaplermin, a recombinant human Platelet Derived Growth Factor-BB (rhPDGF-BB). The formulation of Regranex is a colourless to straw-coloured preserved gel for topical use that contains 100µg of becaplermin per gram of gel.

The product was authorised for marketing in the European Union via the Centralised procedure on 29 March 1999. In January 2009, the CHMP assessed the application for the second renewal of the marketing authorisation for Regranex. The Committee concluded that although the benefits of Regranex continued to outweigh its risks, its safety should be closely monitored because of reports of cancer in a small number of patients using it, and therefore recommended the need for an additional five-year renewal.

In view of the above concerns of the CHMP on the potential risk of cancer, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 17 March 2009 to assess the above concerns and its impact on the benefit/risk for Regranex and to give its opinion on measures necessary to ensure the safe and effective use of Regranex, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. SCIENTIFIC DISCUSSION

Regranex (becaplermin) is indicated, in association with other good wound care measures, to promote granulation and thereby the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2.

Regranex contains the active ingredient becaplermin, a recombinant human Platelet Derived Growth Factor-BB (rhPDGF-BB). Becaplermin has biological activity similar to that of naturally occurring PDGF, which includes promoting the chemotactic recruitment and proliferation of cells involved in wound repair. The formulation of Regranex is a colourless to straw-coloured preserved gel for topical use that contains 100µg of becaplermin per gram of gel.

From launch on 1 February 1998 to 30 November 2008, the MAH estimate the exposure to be approximately 103,132,046 person-days. This corresponds to a worldwide cumulative total exposure of 282,554 person-years.

The European exposure is approximately 4% the worldwide exposure, the majority of which is in North America. The cumulative number of 20-week courses can be estimated to 26,422 in the EU. The treatment, as indicated, should not exceed 20 weeks and may be less than this for some patients. During the pivotal clinical trial the average time to complete healing was approximately 12 weeks in patients treated with becaplermin (43% of patients achieved complete healing). Consequently the number of treatment courses may exceed the estimated 26,422 in the EU and variations in daily dose would also influence this estimate.

2.1. Clinical Aspects

2.1.1. Clinical Efficacy

The MAH reports of clinical trials for becaplermin are listed in Table 2.

Table 2: MAH clinical trial programme for becaplermin in diabetic foot ulcers

Study number	Description
Trials supporting marketing authorisation:	
Pivotal study 92-22120-K	Vehicle alone versus becaplermin (30µg/g and 100 µg/g) for 20 weeks; n=395.
Supporting studies 90-22120-F	Vehicle alone versus becaplermin 30µg/g for 20 weeks; n=118 Vehicle alone versus standard therapy versus becaplermin 100µg/g for 20 weeks; n=172.
PDGF-DBFT-001 PDGF-DBFT-002	Standard therapy versus becaplermin 100µg/g for 20 weeks; n=252
Additional efficacy trials	
92-22120-M	Vehicle alone versus becaplermin 20µg/g, 100µg/g and 300µg/g for 4 weeks; n=78
PDGF-DBFT-006	Becaplermin 100µg/g either: once daily for 20 weeks; once daily for 8 weeks plus 12 weeks of placebo; every other day, alternating with placebo for 20 weeks. n=94
PDGF-DBFT-027	Open-label becaplermin 100µg/g followed by up to 52 weeks double-blind becaplermin or placebo. n=136
CAPSS-083	Becaplermin with good wound care versus good wound care alone with and without educational reinforcement post-healing; 20 weeks; n=146
PDGF-DBFT-009	Open-label becaplermin 100µg/g for 20 weeks; n=134
Trials for the sterile formulation	
PDGF-DBFT-003	Placebo versus sterile becaplermin 100µg/g for 20 weeks; n=326
PDGF-DBFT-005	Placebo versus sterile becaplermin 100µg/g for 20 weeks; n=325

2.1.1.1. Trials supporting marketing authorisation

At the time of granting Marketing Authorisation for Regranex, the CHMP concluded that the product had modest efficacy in healing full thickness diabetic ulcers of less than 5cm^2. Long term safety had not been demonstrated and the duration of use was restricted to 20 weeks in total.

The conclusions on efficacy were based on a meta-analysis of 4 clinical trials (92-22120K, 90-22120-F, PDGF-DBFT-001, PDGF-DBFT-002), comprising one pivotal study (92-22120-K) in which 123 patients received becaplermin gel 100µg/g and three supporting studies in which 162 patients received becaplermin gel 100µg/g (in 2 studies) and 61 patients received becaplermin gel 30µg/g (in one study). In the pivotal study, 49.6% of patients treated with becaplermin gel 100µg/g achieved healing compared with 34.6% with vehicle alone. Time to healing was 79 days for vehicle alone and 71 days for becaplermin 100µg/g. The relative ulcer area and weekly healing rate were not significantly different between groups.

In the 2 supporting studies using becaplermin 100µg/g, efficacy was not demonstrated (PDGF-DBFT 001 and 002). In the supporting study using 30µg/g becaplermin, there was a significant difference in healing of ulcers with the active treatment (90-22120-F).

All patients received a programme of ulcer care that included sharp debridement, systemic control of infection as required, moist saline dressings changed daily and a non-weight bearing regimen.

2.1.1.2. Additional controlled trials for becaplermin 100µg/g

PDGF-DBFT-006

This double-blind randomised parallel group study compared three treatment regimens of becaplermin 100 µg/g in combination with good wound care for the treatment of full-thickness diabetic ulcers of the forefoot. The three treatment groups were:
becaplermin 100 µg/g once daily for 20 weeks (n=30);
once daily for 8 weeks plus 12 weeks of placebo (n=33);
every other day, alternating with placebo for 20 weeks (n=31).

This study did not include a placebo arm therefore the results do not contribute to the evidence of efficacy for Regranex. All three regimens demonstrated healing of ulcers, although fewer patients in the group receiving becaplermin once daily for 20 weeks achieved complete healing compared with the other two groups. Time to complete healing was also longer for the 20-week treatment group.

PDGF-DBFT-027

The aim of this study was to evaluate safety and efficacy of becaplermin 100µg/g when applied to recurring or non-healing neuropathic diabetic lower extremity ulcers for up to 52 weeks. The randomised, multi-centre trial design included an initial 20 week open-label period followed by a double-blind phase for treatable ulcers remaining after the initial open label phase. A total of 136 patients were recruited. Complete healing of all new and recurrent ulcers was achieved for 28/51 (55%) of becaplermin-treated subjects compared with 10/25 (40%) in the placebo group during the double-blind phase. However, the study was terminated early due to lack of recruitment and did not have sufficient power to demonstrate efficacy.

CAPSS-083

The study aimed to evaluate efficacy of becaplermin 100µg/g for treatment of full thickness diabetic neuropathic foot ulcers which had a duration of 4 to 52 weeks. Treatment was for 20 weeks. The study planned to recruit 340 subjects. However, the study was terminated due to slow accrual with 146 subjects enrolled. The MAH reports 31 (41.9%) of becaplermin-treated patients achieved complete healing compared with 24 (34.8%) treated with standardised good wound care alone. No statistically significant efficacy results for complete healing were achieved (p=0.316).

Sterile formulation

Two studies (PDGF-DBFT-003 and PDGF-DBFT-005) examined efficacy of a sterile formulation of the product in diabetic foot ulcers. No statistically significant difference in complete healing was observed between groups, neither for all subjects nor in a subgroup with ulcers below 5cm2. There was also a lack of superiority over placebo in terms of secondary endpoints (time to complete healing, relative and absolute changes in target ulcer area). The sterile formulation is not the marketed formulation. In view of the lack of efficacy, the request by the CHMP to develop a sterile formulation was not further pursued.

2.1.1.3. Published efficacy studies

Publications of relevance to the efficacy of becaplermin and containing data not already discussed are summarised below:

Niezgoda JA *et al,* 2005. This is a small randomized controlled trial comparing a product derived from pig small intestine submucosa and consisting primarily of collagen-based extracellular matrix (OASIS wound matrix) with Regranex gel (becaplermin) for healing of full-thickness diabetic foot ulcers over a period of up to 12 weeks. Efficacy data were obtained for 73 patients receiving either OASIS wound matrix (n=37) or becaplermin (n=36) and a secondary dressing. Of 98 patients enrolled, 13 OASIS-treated patients and 12 Regranex-treated patients were lost to follow-up during the 12 week study period. Patients in the Regranex group were instructed to apply the gel daily, cover with saline-moistened gauze for 12 hours, before cleaning the ulcer and replacing the gauze. No statistically significant difference in healing was observed between the treatment groups. In the OASIS group, 18/37 (49%) patients had complete wound closure compared with 10/36 (28%) of the becaplermin-treated patients. The mean time to healing was 67 days for the OASIS group and 73 days for the Regranex group (p=0.245).

Embil JM *et al*, 2000. This is an open-label uncontrolled multi-centre trial to evaluate the efficacy of becaplermin gel 100µg/g for the healing of chronic lower-extremity diabetic ulcers. A total of 135 patients were enrolled in the study and received treatment but efficacy data were not available for one patient. Data were analysed on the basis of a study population of n=134. The population comprised adult patients with either type 1 or type 2 diabetes and at least one and no more than two full thickness neuropathic ulcers of the lower extremity. The target ulcer must have been present for at least 8 weeks and have an area of 1 – 10 cm^2. Embil and colleagues comment that the findings emphasize the importance of using becaplermin gel within a comprehensive wound care regimen that includes infection control measures as well as off-loading of pressure from the area of ulceration. However the proportion of patients achieving complete healing with becaplermin (57.5%) is higher than that observed in the trials supporting marketing authorisation. This study does not contain a placebo arm and therefore does not provide supporting evidence on the efficacy of becaplermin.

Margolis DJ *et al*, 2005. Effectiveness of becaplermin therapy in clinical practice was examined in a cohort study of patients with diabetic neuropathic foot ulcers (DNFU) identified in a database of speciality wound care clinics (Curative Health Services database) between 1998 and 2004. Rates of ulcer healing within 20 weeks and amputation at any time were compared for becaplermin exposed and unexposed patients. Subjects with DNFU were eligible if the ulcer was known to have not healed during an 8 week period. Subjects were follow-up for 20 weeks or until the ulcer healed. The two exposure groups were matched using propensity scores which took into account the variables of age; sex; number of wounds; wound duration, size and grade at first visit; CHS centre; the likelihood that a centre used becaplermin and calendar year. A total of 2,934 eligible patients received becaplermin out of a total of 24,898 subjects included in the study. The authors observed a greater percentage of healed ulcers in the becaplermin-exposed group (33.5%) compared with the unexposed group (25.8%; RR=1.32, 95% CI: 1.22 – 1.38). With regard to amputation, the relative risk for undergoing amputation after becaplermin-exposure was observed to be 0.65 (95% CI: 0.54-0.78).

For this study a number of potential confounders including microbiologic status of the wound and compliance with standard wound-care therapy were not available in the dataset. These are likely to be important factors in wound healing and an imbalance between the two groups would bias the result. It is interesting to note that the propensity score groups with smaller ulcers and exposed to becaplermin achieved similar rates of complete healing compared to those with larger ulcers.
Margolis and colleagues found a lower risk for becaplermin-treated patients of amputation occurring at any time while under the care of the centre compared with matched controls. However it is not stated whether exposed and unexposed groups were balanced with regard to follow-up time therefore the relevance of this observation is doubtful. Concerns over the design limit the usefulness of this study in evaluating the effectiveness of becaplermin.

Robson MC *et al*, 2005. The authors describe a postmarketing clinical trial comparing becaplermin gel 100µg/g (n= 74) with standardized therapy alone (n=72) for up to 20 weeks. No statistically

significant difference between groups was observed in the proportion of subjects achieving complete healing (42% of becaplermin-treated patients versus 35% receiving standard care alone (p=0.316)). This postmarketing study, which found no statistically significant difference in healing for becaplermin 100µg/g versus standard care alone, is assumed to be the same as study CAPSS-083 described above.

Davis MD *et al,* 2004. In a letter to the editor, the authors describe a retrospective review of becaplermin treatment in refractory lower extremity ulcers present for longer than 3 months. Twenty-one patients received becaplermin for ulcers attributable to various causes including five diabetic neuropathic ulcers. A total of 14 ulcers healed completely. The mean time to complete healing was 111.1 +/- 81.5 days. Six of the ulcers were neuropathic (of which 5 were ascribed to diabetes) and three of these ulcers healed completely. Less than a quarter of the patients examined in this small retrospective review had a neuropathic diabetic ulcer. Half (n=3) of the patients with neuropathic ulcers had complete ulcer healing. Davis and colleagues note that becaplermin treatment was accompanied by intensive instruction and standard ulcer care which alone may increase the rate of healing.

2.1.1.4. Conclusions on Efficacy

At the time of granting the Marketing Authorisation for Regranex, the CHMP concluded that the product had modest efficacy in healing full thickness diabetic ulcers of less than 5cm^2. Long term safety had not been demonstrated and the duration of use was restricted to 20 weeks in total.

The conclusions on efficacy were based on a meta-analysis of 4 clinical trials, comprising one pivotal study in which 123 patients received becaplermin gel 100µg/g and three supporting studies in which 162 patients received becaplermin gel 100µg/g (in 2 studies) and 61 patients received becaplermin gel 30µg/g (in one study). In the pivotal study, 49.6% of patients treated with becaplermin gel 100µg/g achieved healing compared with 34.6% with vehicle alone.

Additional, company-sponsored, placebo-controlled studies conducted since marketing authorisation was granted, have not had sufficient power to demonstrate efficacy and have not obtained statistically significant results. No statistically significant results were obtained for company-sponsored studies which examined efficacy of a non-marketed, sterile formulation.

From the review of the published literature, no studies have been identified which provide additional evidence to demonstrate efficacy beyond that already discussed at the time of the Marketing Authorisation. One small, comparative study comparing becaplermin to a collagen-based wound matrix found no statistically significant difference in complete healing or time to healing but the lower healing rate versus the comparator is notable alongside the other data suggesting only marginal benefit for Regranex.

In view of all the above it is still considered that the efficacy of Regranex is overall limited.

2.1.2. Clinical Safety

Long term safety had not been demonstrated at the time of the Marketing Authorisation of Regranex and the treatment, as indicated, should not exceed 20 weeks and may be less than this for some patients. During the pivotal clinical trial the average time to complete healing was approximately 12 weeks in patients treated with becaplermin (43% of patients achieved complete healing). During the second renewal application of the product the CHMP has expressed some concerns on the risk of cancer in patients. This is further investigated during this Article 20 review of the Benefit-Risk of the product.

2.1.2.1. Adverse events in clinical trials

The safety of becaplermin was evaluated in 1,883 adult patients who had at least one topical administration of Regranex during clinical trials. Adverse events reported by ≥1% of becaplermin-treated patients are summarised in Table 3 below.

Table 3: Adverse Events reported by ≥1% of becaplermin-treated patients in 17 clinical trials

System/Organ Class Adverse Event	REGRANEX® (n=1,883) %	Placebo (n=1,069) %	Standard therapy (n=190) %
Infections and Infestations			
Infected skin ulcer	12.3	11.9	18.9
Cellulitis	10.3	7.5	18.9
Osteomyelitis	7.2	5.4	14.2

The incidence of infected skin ulcer, cellulitis and osteomyelitis is slightly higher in the becaplermin group compared with the placebo group but lower than in the standard therapy group.

2.1.2.2. Potential systemic effects

The MAH noted that potential for systemic absorption of becaplermin from sites of topical application of becaplermin is low in animals and humans. Nevertheless, the product should be used with caution in patients with known malignant neoplasms.

In the preclinical setting, absorption was studied in Fisher rats, beagle dogs and cynomolgus monkeys. Negligible absorption was observed after single and multiple topical administrations to full thickness wounds in rats. Three of 21 rats tested showed plasma levels above the lower limit of quantification following a single topical application of 127µg/kg. Rapid elimination occurred following intravenous administration in dogs and monkeys.

The MAH described studies PDGF-PHIO-005 and PDGF-PHI-007, which examined systemic absorption in patients with diabetic ulcers. In study PDGF-PHIO-005, 10 subject received becaplermin 100µg/g topically once daily for 14 days. The estimated quantity administered was 7µg/cm^2. No statistically significant differences were observed between the mean platelet-rich plasma PDGF-BB area under the curve values for the pre-dose period and after single and 14 daily applications.

Study PDGF-PHI-007 involved 10 subjects. PDGF-BB plasma concentrations following becaplermin administration were slightly elevated relative to baseline in one subject. In the remainder of subjects, either there was no consistent increase across sampling periods compared with baseline or the measured plasma levels were below the lower limit of quantification.

In the clinical studies discussed above, there was a lack of account for fluctuations in endogenous PDGF-BB. More sensitive measurements such as those using radio-labelled rhPDGF-BB were not made. On the basis of the evidence presented at the time of the initial marketing authorisation, when applied topically to diabetic ulcers, becaplermin does not appear to be significantly systemically absorbed at a dose concentration up to 100µg/g.

The MAH has been requested to discuss further the feasibility of contacting a further pharmacokinetics study to evaluate the systemic absorption of the product. This issue has been discussed extensively in the Risk Management Plan (see below in this report).

2.1.2.3. Cancer risk

a) Case reports of neoplasms

As part of a Follow-up measure (FU2 22.5), the MAH has provided a cumulative summary (17 December 1997 – 16th December 2008) of reports of neoplasms received via spontaneous reporting, published literature, regulatory authorities and clinical trials.

The MAH identified 40 unique serious cases from the Neoplasms SOC in patients receiving becaplermin (33 clinical, 7 spontaneous). The majority of cases were received from the USA and twelve cases (all from clinical trials) were from the EU. The majority of patients (33/40) received becaplermin for diabetic foot ulcers. The average age was 66.9 years (range 38 to 87 years). The proportion of male and female cases was approximately equal.

Clinical trial cases
Of the 33 serious clinical trial cases, 28 were assessed by the investigator as unlikely or not related to becaplermin. In the remaining five cases, the MAH considered a causal association as unlikely. Table 4 summarises the number of neoplasm cases reported as serious adverse events during clinical trials.

Table 4: Number of neoplasm cases reported as serious adverse events during clinical trials

Adverse Event MedDRA Preferred Term	Count
Adenocarcinoma	1
Basal cell carcinoma	6
Benign breast neoplasm	1
Breast cancer recurrent	1
Breast cancer female	2
Cervix carcinoma	1
Colon cancer	2
Colon cancer metastatic	1
Lymphoproliferative disorder	1
Malignant melanoma	1
Multiple myeloma	1
Neoplasm	3
Neoplasm malignant	5
Non-Hodgkin's lymphoma recurrent	1
Prostate cancer	1
Recurrent cancer	1
Skin cancer	2
Squamous cell carcinoma	1
Testis cancer	1
Total	**33**

The most frequently reported malignancy was basal cell carcinoma (6/33, 18%). In 32 of the cases, the neoplasm was distal to the site of becaplermin application.

There is no clear pattern in the types of malignancies reported in association with becaplermin during clinical trials. Basal cell carcinoma was the most frequently reported neoplasm during clinical trials but this may be a reflection of the incidence of this malignancy in the general population.

Spontaneous cases
Seven spontaneous cases of neoplasms were reported cumulatively up to 16th December 2008. These involved patients who developed benign neoplasm (2), malignant melanoma (1), squamous cell carcinoma (1), lung cancer (1), renal cell carcinoma (1) and pancreatic cancer (1).

Two of the cases involved patients who developed benign neoplasms. Melanocytic naevus below the big toe were reported for an 81-year-old female. Pyrogenic granuloma at the wound was reported within 6 weeks of becaplermin administration in a 55-year-old female. The MAH commented that the term may be an interpretation of granulation, which is part of wound healing.

Five of the cases involved malignant neoplasms. The only case occurring at the site of application concerned a male in his late 50s diagnosed on biopsy with malignant melanoma. However, the malignancy was considered to be pre-existing and not related to becaplermin treatment according to the reporting physician.

On the basis of the information available, a relationship to becaplermin is considered to be unlikely; however under-reporting of possible cancer reactions is to be expected and no firm conclusions can be drawn.

b) Epidemiological study

A Cohort Study of the Risk of Cancer in Users of Regranex (becaplermin) and Matched Comparators was undertaken and assessed through a Follow up Measure (FUM 020) The final report for the initial study was submitted to competent authorities in June 2006. A follow-up report for an extension to the cohort study, which contained three additional years of mortality data, was submitted in October 2008.

The initial study used a health insurance claims database to examine cancer incidence and cancer mortality in 1,622 becaplermin-exposed subjects and 2,809 matched comparators between 1 January 1998 and 30 June 2003. Propensity scoring was used for matching. A statistically significant difference in cancer incidence was not observed during the initial phase (see Table 5). However, the study was only powered to detect a relative risk of 1.8 or greater. With regard to mortality secondary to malignancy, the data in the initial phase did suggest an increased risk for patients treated with 3 or more tubes of Regranex; though the numbers were small (see Table 6).

Table 5 – Unadjusted and adjusted rate ratios for all malignant neoplasms in initial study (Initiators: n=1,622; Comparators: n=2,809)

	Initial Study (RR (95% CI))		
No. dispensings	**No. cancers**	**Unadjusted RR**	**Adjusted RR**
None	43		
All	28	1.1 (0.7 – 1.8)	1.2 (0.7 – 1.9)
1	19	1.3 (0.7 – 2.2)	1.3 (0.7 – 2.2)
2	4	0.8 (0.3 – 2.3)	0.8 (0.3 – 2.4)
3	5	1.0 (0.4 – 2.4)	1.1 (0.4 – 2.8)

The extension phase included three additional years of data for deaths due to cancer. Rate ratios for cancer mortality in both the initial and extension studies are summarised in Table 6. The data provided from the extension study give narrower 95% confidence intervals, which also include the null value for the association between high cumulative use (3 or more dispensings) and cancer mortality. However, no exposure data was gathered during the extension phase.

Table 6 – Unadjusted and adjusted rate ratios for cancer deaths in initial and extension studies (Initiators: n=1,622; Comparators: n=2,809)

	Initial Study (RR (95% CI))			Extension Study (RR (95% CI))		
No. dispensings	**No. deaths**	**Unadjusted RR**	**Adjusted RR**	**No. deaths**	**Unadjusted RR**	**Adjusted RR**
None	8			16		
All	8	1.7 (0.6-4.6)	1.8 (0.7-4.9)	9	1.0 (0.4-2.2)	1.0 (0.5-2.3)
1	4	1.4 (0.4-4.8)	1.5 (0.4-4.9)	4	0.7 (0.2-2.2)	0.7 (0.3-2.2)
2	0	0	0	1	0.5 (0.1-4.0)	0.6 (0.1-4.2)
3	4	4.2 (1.3-13.9)	5.2 (1.6-17.6)	4	2.1 (0.7-6.2)	2.4 (0.8-7.4)

The initial study report concluded that *'In general, the results of this study are consistent with no increased risk from cancer among becaplermin initiators relative to comparators who did not receive becaplermin therapy. (RR = 1.2, 95% CI = 0.7-1.9 for all cancers combined).'* However these results were also consistent with an almost doubling of the risk of cancer, and the number of events was quite small. The initial study was only powered to detect a relative risk of 1.8 or greater - as a smaller relative risk was observed, it is possible that the study was not adequately powered to detect whether this difference in cancer risk was significant.

An absence of exposure data during the extension phase and part of the initial phase is an important limitation which increases the potential to observe conservative estimates of effect size. The study therefore did not reassure that there is not a risk of cancer with becaplermin use.

For that reason the CHMP requested to the MAH to conduct a new pharmacoepidemiological study. This new study and study protocol is discussed as part of the Risk Management Plan of this report.

2.1.2.4. Serious Infections

As part of a Follow-Up measure (FU2 22.5), the MAH has provided a cumulative summary (17 December 1997 – 16 December 2008) of reports of serious infections received via spontaneous reporting, published literature, regulatory authorities and clinical trials.

The MAH identified 48 serious cases from the Infections and infestations SOC in patients receiving becaplermin. Thirty cases were from clinical trials and there were 16 spontaneous and two solicited (compassionate use) reports.

Clinical trial cases

Half of the 30 clinical trial cases were from the USA and 14 were from the EU. One third concerned female patients and two-thirds were male. Ages ranged from 43 to 91 years and the mean age was 62.8 years.

A total of 47 events of serious infections were reported in the 30 cases and the majority were wound related. Cellulitis (n=17) and osteomyelitis (n=15) were the most frequently reported events (summarised in table 7). The time to onset of the infection was known for all of the cases and ranged from 24 hours to 313 days, with a mean latency of 98.2 days.

The outcome of the 47 events was reported as recovered or recovering for 19 events, 5 events were not recovered and the outcome was unknown for 23 events. In four cases, the infectious organism

was identified: three cases of *staphylococcus aureus* and one case of recurring methicillin-resistant *staphylococcus aureus* (MRSA) and *acinetobacter spp*.

Risk factors for wound-related infections were known in one third of the cases and included co-morbidities such as peripheral neuropathy and peripheral vascular disease and previous history of osteomyelitis, cellulitis or wound infection. Of the remaining cases, diabetes was the only relevant co-morbidity reported in 17 cases.

Spontaneous cases
The majority of the 18 spontaneous and solicited cases were from the USA and one was from the EU. There were equal numbers of reports for male and female patients. Ages ranged from 40 to 88 years, with a mean age of 61.7 years.

A total of 28 reactions were reported in the 18 cases. The most frequently related terms were infection (n=6), cellulitis (n=4) and osteomyelitis (n=3) and the majority of infections were wound-related.

The outcome of the events was known for 9 out of the 28 events. Eight events were recovered or resolving and one event did not recover. The event of urosepsis was fatal and occurred in a patient who was hospitalised with general exanthema, increased creatinine, urea and watery diarrhoea. The reporter was stated to consider the events as doubtfully related to becaplermin.

Risk factors were reported in 7 of the 18 spontaneous and solicited cases and included peripheral neuropathy, peripheral vascular disease, inadequate blood supply and previous medical history of amputation, grafts or surgical treatment. Diabetes was a known co-morbidity in 13 of the cases.

The MAH stated that amputation and osteomyelitis were reported for 15 and 19 cases overall amongst the 48 cases identified in the cumulative analysis. On the basis of an estimated exposure of 282,554 person-years (PY) from launch to 30th November 2008, the MAH calculates a reporting rate of 0.53 cases per 10,000 PY for amputation and 0.67 cases per 10,000 PY for osteomyelitis. The MAH cited a rate of lower extremity amputation in patients with diabetes of 4.1 per 1,000 PY which is greater than the reporting rate observed in association with becaplermin.

Osteomyelitis and cellulitis are known complications in patients with diabetic ulcers. The cumulative review does not raise a signal for serious infections beyond what is already captured in the product information. The SPC for Regranex includes a contraindication in patients with clinically infected ulcers. Section 4.4 of the SPC states that infection should be treated prior to the use of Regranex and that the product should be discontinued if the wound becomes infected during therapy. Conditions such as osteomyelitis should be excluded prior to use of Regranex. Infections and cellulitis are listed as very common side effects and osteomyelitis as a common side effect in section 4.8 of the SPC.

2.1.2.5. Conclusion on Safety

Malignant neoplasms occurring distant from the site of application have been reported in Regranex users in both clinical trials and in post-marketing use. The available evidence for becaplermin is not supportive of a direct carcinogenicity in terms of *de novo* tumour formation. Taking into account the current evidence which suggests that systemic absorption after topical application is negligible, the MAH concludes that the promoting effect of becaplermin on tumours distant from the application site appears to be unlikely.

Based on pooled safety data from clinical trials in 1,883 patients who received at least one dose of becaplermin, the most commonly reported adverse events were infected skin ulcer , cellulitis and osteomyelitis . Taking into consideration the underlying risk and co-morbidities in diabetic patients with foot ulcers, the MAH does not consider the clinical features, severity and frequency of these events to be suggestive of a signal. These events were reported with a slightly greater frequency in becaplermin-treated compared with placebo-treated patients.

Osteomyelitis, cellulitis and ulcer infection are not unexpected in diabetic patients with neuropathic foot ulcers. In the pooled safety data from clinical trials, these events were reported with a slightly greater frequency in becaplermin-treated compared with placebo-treated patients. The data presented do not suggest that additional risk minimisation measures are necessary beyond the current warnings in the SPC with regard to the risk of these infections.

The MAH has not compared the incidence of cancers in becaplermin- and placebo-treated patients in the pooled safety data from clinical trials. Review of the individual cases does not suggest a clear pattern in the types of malignancies reported during clinical trials or through spontaneous reporting.

A epidemiological study was conducted following the observation of an excess of cases of neoplasms in the becaplermin arm compared with placebo in PDGF-DBFT-10. A statistically significant difference in the incidence of cancers was not observed in the cohort study (RR =1.2, 95% CI: 0.7 – 1.9). The initial study was only powered to detect a relative risk of 1.8 or greater and therefore may not have been adequately powered to detect whether the difference in cancer risk was significant. In the initial study there was an indication that mortality secondary to malignancy was increased in patients with high cumulative exposure to becaplermin (3 or more tubes), though statistically significant results were not found in the extension phase. However, an absence of exposure data during the extension phase and part of the initial phase is an important limitation and increases the potential to observe conservative estimates of effect size. This study therefore is not conclusive that there is not a risk of cancer with becaplermin use. For that reason the CHMP propose the performance of a new pharmacoepidemiological study which the MAH has accepted. This study is discussed further below.

2.2. Risk minimisation activities

Risk Management Plan

The first Risk Management Plan for Regranex was submitted by the MAH following List of Questions from the May 2009 CHMP as requested with specific attention to

i) a further pharmacoepidemiology study on the risk of cancer;
ii) the feasibility of further systemic absorption studies

These points are discussed further below.

i) Pharmacoepidemiology study on the risk of cancer – VA study

The CHMP requested a further pharmacoepidemiological investigation on the risk of cancer which would overcome the limitations identified in the previous cohort study. The MAH was requested to pay particular attention to the power of the study and obtaining sufficient exposure data.

The MAH has provided a study proposal to investigate the risk of cancer and cancer mortality in association with becaplermin use based on a cohort of subjects from the national Department of Veterans Affairs Health Care System (VA) in the USA. The proposed study is larger, with more follow-up than the previous epidemiological study conducted. Information from a heath status and health behaviour questionnaire is available for approximately one fifth of the cohort. This sub-sample is expected to provide sufficient power to detect a cancer incidence rate ratio of 1.2 and cancer mortality rate ratio of 1.4 and should contain information on potential confounders not available for the full study population.

A number of questions were raised following the assessment of the proposed protocol of this new study during the October 2009 CHMP. The study protocol has been revised for the proposed pharmacoepidemiology study using the US Veterans Affairs (VA) database. The study will evaluate the risks of incident cancer and cancer mortality by retrospectively following-up VA patients with diabetic foot ulcers and no history of cancer. Those treated with becaplermin will be compared to those in the cohort who did not receive such treatment. The study is expected to include over 7,000 becaplermin users and an equal number in the comparison group with up to eight years of follow-up for cancer outcomes. An analysis will be conducted in a sub-sample of patients who completed health surveys in 1999 and provided additional information on potential confounding factors. Outcomes will include cancer deaths, incident cancers (other than skin cancer), skin cancer, and "local" cancers occurring near the site of the foot ulcer where becaplermin may have been applied. The power of the study is estimated such that the smallest detectable relative risk for incident cancer would be 1.25 (upper 95% CI: 1.47).

In this patient population the female patients will be a minority; however it is not expected that the observations would be different in a male or female population.

The CHMP concluded that all of the points which related to this new pharmacoepidemiology study have been adequately addressed. Once the results of this study become available the MAH will submit them to the CHMP for assessment. At that point in time a new benefit/risk assessment of the product may be needed.

ii) Feasibility of further systemic absorption studies

The CHMP observed that it cannot be assumed that becaplermin is not systemically absorbed. The MAH was requested to investigate the feasibility of further systemic absorption studies. Specific consideration was requested with regard to the sensitivity of methods available for pharmacokinetic studies of biological agents. Consideration to the possible effects of becaplermin uptake on the feedback mechanisms that regulate endogenous PDGF levels was also requested.

In the discussion of non-clinical safety data, the MAH states that systemic absorption and dose-related increases in PDGF plasma concentrations were observed following subcutaneous administration in dogs and monkeys. In contrast, rapid plasma clearance of PDGF was observed following intravenous administration in rats and monkeys. Topical administration to full-thickness wounds in rats lead to a level of systemic absorption too low to be quantified. The possibility of uptake by the lymphatic system has not been thoroughly investigated but is considered by the MAH to be a more likely means of absorption than via a vascular route. Of note, in the discussion of immunogenicity in the RMP, the MAH refers to a publication (Castronuovo et al 1998) which examined wound fluid collected from 12 subjects with diabetic or pressure ulcers and found that biologically active becaplermin remains in wound fluid for 12 hours after topical application of becaplermin gel.

Overall, the MAH concluded that although the potential for systemic absorption is low, becaplermin should be used with caution in patients with known malignant neoplasms. This was further presented following the List of Questions of the October 2009 CHMP meeting. In its response on systemic absorption, the MAH argues that it is not possible to investigate the systemic absorption of becaplermin because exogenous PDGF that may enter into systemic circulation would be rapidly cleared and rendered undetectable. The MAH's two studies (one in rats, one in monkeys) of intravenous administration are consistent with a rapid elimination from plasma and its studies of topical application to wounds did not find significant differences in PDGF post-dose. However, the limits of assay sensitivity have to be considered. A lack of differentiation between exogenous and endogenous PDGF-BB, other than by comparison to controls is also a limitation of the assay. These arguments that it is not possible to investigate systemic absorption were not accepted by the CHMP.

The MAH considers the ELISA assay used in pharmacokinetic studies to be highly sensitive but does not provide any evidence to justify this view. The lower limit of detection was 31.3-62.5pg/mL in the non-clinical studies and 200pg/mL or 500pg/mL in the clinical studies in patients with diabetic ulcers. Further evidence is required from the MAH in order to justify its view that systemic absorption is negligible. As described by the MAH PDGF/PDGFR signalling may typically occur within a localised environment but this does not preclude the possibility that exogenous PDGF could promote malignancy. The CHMP has requested to the MAH to commit to providing further evidence to justify the its view that systemic absorption is negligible. A pharmacokinetic study which employs a more sensitive and specific assay, such as radio-labelling may be appropriate.

In addition the contraindication in section 4.3 of the SPC in patients with pre-existing malignancy is therefore required, as agreed by the MAH.

The proposed additional label warnings with regard to neoplasms will further improve the risk benefit profile by ensuring becaplermin is used in the appropriate individual. Residual concerns over the risk of cancer remain and this potential risk requires risk minimisation measures. The current warnings in section 4.4 of the SPC, which recommend caution in patients with known malignancies, is not adequate and the only clear measure available is to contraindicate the use in patients with pre-existing malignancies.

iii) Changes of the Product Information

The proposed changes of the Product Information which are also part of the Risk Minimisation measures are described immediately below.

2.3. Product Information

The CHMP recommended the amendments to be introduced in the Summary of Product Characteristics (SPC) and Package Leaflet (PL).

In section 4.3 of the SPC "Contraindications" the contraindication of the use of the product in patients with any known malignancies has been added.

In section 4.4 of the SPC "Special warnings and precautions for use" the paragraph has been amended to warn the prescribers on the contraindication of the use in patients with pre-existing malignancies.

In section 5.3 of the SPC "Preclinical safety data" a deletion was made of the reference that no malignancies have been reported in clinical trials.

The Annex II of the Product Information was updated to include the version of the RMP.

The PL has been amended accordingly in order to inform the patients who have already been diagnosed with cancer not to use the product.

3. Discussion AND Benefit/risk assessment

During the initial MA, a meta-analysis of the four initial efficacy studies showed modest efficacy for becaplermin over vehicle, for treatment of diabetic ulcers $\leq 5cm^2$ in combination with standard wound-care. Long-term efficacy and safety of treatment duration in excess of 20 weeks has not been demonstrated.

Additional, company-sponsored, placebo-controlled studies conducted since marketing authorisation did not obtain statistically significant results. Published studies, including an epidemiological study examining incidence of healing and amputation in becaplermin-treated subjects provide some new data. Although the studies were not adequately designed or powered to make firm conclusions, collectively they do not seem to give much reassurance in relation to efficacy, which overall seems marginal.

Infected skin ulcers, cellulitis and osteomyelitis are identified risks with becaplermin use. A pooled analysis of safety data from clinical trials found a greater incidence of these events in becaplermin-treated patients than in the placebo group. Risk minimisation measures are in place in the current SPC with regard to the risk of these infections.

The absolute number of cases of cancers reported in association with becaplermin is not vast but is of importance given its biological plausibility in tumour initiation or promotion, and the potential for under reporting. The MAH reports 33 serious adverse events of neoplasms from clinical trials. There have been seven spontaneous reports during the post-marketing experience since launch in February 1998. Systemic absorption of becaplermin maybe negligible at normal doses but the evidence did not allow us to conclude that becaplermin is able to promote malignancies that are distant from the site of application. The MAH has agreed to provide further evidence to justify the the view that systemic absorption is negligible or propose a pharmacokinetic study which employs a more sensitive and specific assay, such as radio-labelling. Furthermore, the MAH committed to discuss the consequences of an increase in PDGF levels in the light of the product's pharmacodynamics and the inherent risk of this growth factor.

A total of 28 cancers were reported for becaplermin-exposed patients during the initial phase of the epidemiological study for cancer risk (follow-up time approximately 20 months). Nine deaths secondary to malignancies were identified during the initial and extension phases (follow-up time

approximately 36 months). A statistically significant difference in the incidence of malignant neoplasia between becaplermin-exposed and non-exposed patients was not observed. However, the study was only powered to detect a relative risk of 1.8 or greater. The performed epidemiological study has not delivered firm evidence on the risk of cancer but did not exclude the association between the use of becaplermin and the occurrence of cancers, especially with prolonged dosing.

For that reason, the CHMP recommended that a new pharmacoepidemiological study (VA study) should be perfomed and the results be submitted to the CHMP for assessment. At that point in time a new evaluation of the benefit-risk of Regranex may be needed.

Cancer remains a potential risk and collection of further data on this issue is warranted provided that the limitations identified in previous investigations can be overcome.

The risk/benefit balance of the product remains positive. Marginal efficacy has to be balanced against a weak signal of a potentially important adverse effect. Whilst the strength of evidence is insufficient, the CHMP concluded that risk minimisation measures are appropriate. The recommendation to contraindicate use in patients with pre-existing cancer has been accepted by the MAH.

Benefit/Risk Balance

Taken this into account, the benefit/risk balance for Regranex is considered favourable.

4. Overall Conclusion

Having considered the overall submitted data provided by the MAHs in writing the CHMP concluded that benefit still outweighs the risks for the patients treated with Regranex.

The CHMP also concluded that the Product Information for Regranex should include safety information aiming at contraindicating the product in patients with pre-existing malignancies and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflet. Furthermore, Risk Minimisation Measures aiming at further investigating the effect of Regranex in malignancies local and through systemic absorption have been included in the first Risk Management Plan of the product.

Therefore, the CHMP recommended the maintenance of the Marketing Authorisation for which the Summary of Product Characteristics and Package Leaflet are set out respectively in annexes I and III of the Opinion.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below:

Area[1]	Description	Due date
Clinical	Provide an updated Risk Management Plan in accordance with the CHMP agreed pharmacovigilance and risk minimisation measures.	18 Apr 2010
Clinical	Provide further evidence to justify the MAH's view that systemic absorption is negligible or propose a pharmacokinetic study which employs a more sensitive and specific assay, such as radio-labelling. Furthermore, the MAH should discuss the consequences of an increase in PDGF levels in the light of the product's pharmacodynamics and the inherent risk of this growth factor.	1 Jun 2010
Clinical	Provide the final study report of the pharmacoepidemiology study using the US Veterans Affairs (VA) database.	Feb 2012

1. Quality, Pre-clinical, Clinical, Pharmacovigilance

5. ACTION PLAN

As part of this procedure, the MAH and the CHMP agreed the wording of a Dear Healthcare Professional Communication designed to inform prescribers of the Regranex.

6. Conclusion and GROUNDS FOR THE Recommendation

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for Regranex initiated by the European Commission.

- The Committee considered all the available data submitted by the MAH on the efficacy and safety in relation to the risk of malignancies of Regranex.

- The Committee concluded that benefit still outweighs the risks in the currently authorised therapeutic indication for Regranex.

- The CHMP concluded that the Product Information for Regranex should include safety information aiming at contraindicating the product in patients with pre-existing malignancies and therefore recommended the amendments to the relevant sections of the Summaries of Product Characteristics and Package Leaflet. Furthermore, Risk Minimisation Measures aiming at further investigating the effect of Regranex in malignancies local and through systemic absorption should be included in the first Risk Management Plan of the product. As part of the Risk Management Plan, the MAH shall design and conduct a PK study which overcomes the limitations of the existing absorption studies. If such a study is not deemed feasible, the MAH is to provide full justification for this position. The final study report of the pharmacoepidemiology study shall also be submitted as part of the Risk Management Plan.