HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 February 2006

Kepivance 6.25 mg powder for solution for injection
6 glass vials of 6.25 mg: 370 226-3

Applicant: Amgen Europe BV

Palifermin

List I
Medicine for hospital prescription only – prescription reserved for oncologists, haematologists or physicians competent in oncology.

Date of Marketing Authorisation (MA) : 25/10/2005

Reason for request: Inclusion on the list of drugs approved for hospital use

Health Technology Assessment Division

CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Palifermin

1.2. Background

Kepivance is a human keratinocyte growth factor/ growth factor (KGF) obtained by genetic engineering (rHuKGF) which stimulates the proliferation and differentiation of epithelial cells.

1.3. Indications

Kepivance is indicated to decrease the incidence, duration and severity of oral mucositis in patients with haematological malignancies receiving myeloablative therapy associated with a high incidence of severe mucositis and requiring autologous haematopoietic stem-cell support.

1.4. Dosage

Kepivance treatment should be supervised by a physician experienced in anti-cancer therapy.

- Adults

The recommended dose of Kepivance is 60 µ/kg/day, administered as an intravenous bolus injection for 3 consecutive days before and after myeloablative treatment, i.e. a total of 6 doses of palifermin (see below). Kepivance should not be administered subcutaneously because of poor local tolerability.

Reconstituted Kepivance solution should not be left more than an hour at room temperature and should be protected from light. Before administration, visually inspect the solution for discolouration or particulate matter (see SPC section 6.6).

Pre myeloablative treatment: the first 3 doses should be administered before myeloablative treatment, with the third dose given 24 to 48 hours before myeloablative treatment

Post myeloablative treatment: the last 3 doses should be administered after myeloablative treatment; the first of these 3 doses should be administered after, but on the same day as infusion of haematopoietic stem cells and at least 4 days after the final administration of pre - myeloablative Kepivance (See SPC section 4.4).

- Children and adolescents

The safety and efficacy of Kepivance have not been established in children and adolescents. Kepivance should not be used in children and adolescents until further data becomes available.

- Renal impairment

No dosage adjustment is necessary in patients with renal impairment (see SPC section 5.2).

- Hepatic Impairment

Safety and efficacy have not been established in patients with hepatic impairment (See SPC section 5.2).

- Elderly patients

Safety and efficacy have not been established in elderly patients (See SPC section 5.2).

2 SIMILAR MEDICINAL PRODUCTS

2.1. 2005 ATC Classification

V : Various
V03 : All other therapeutic products
V03A : All other therapeutic products
V03AF : Detoxifying agents for antineoplastic treatment
V03AF08 : Palifermin

2.2. Medicinal products in the same therapeutic category

Comparator drugs

None

2.3. Medicinal products with the same therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

The company's dossier includes:

- Phase I clinical trial (960189) in healthy volunteers and cancer patients,
- Phase II clinical trial (980231),
- Pivotal Phase III clinical trial (20000162).

As the Phase I clinical trial was a dose-ranging trial (dose steps: 5, 20, 40, 60 and 80 µg/kg/day) which arrived at a dosage of 60 µg/kg/day for 3 consecutive days before and after myeloablative treatment approved by the Marketing Authorisation (MA); only the Phase II and III clinical trials are analysed below.

3.1. Efficacy

Phase II trial (980231)

Phase II randomised, double-blind, placebo-controlled trial evaluating the efficacy of Kepivance in reducing the severity of oral mucositis in patients with haematological malignancies treated by total-body irradiation (TBI) and high-dose chemotherapy followed by autologous haematopoietic progenitor stem-cell support

Kepivance was administered in a pre- and post-therapy regimen (i.e. for 3 consecutive days before conditioning therapy and for 3 consecutive days from the end of reinjection of stem cells), or in a pre-therapy regimen (3 consecutive days before conditioning therapy).

Primary endpoint: duration (number of days) of WHO grade 3 or 4 oral mucositis.

Secondary endpoints: incidence of severe mucositis, duration of severe mucositis (all WHO grades), requirement for opioid analgesics, degree of patient-reported mouth and throat soreness, incidence and duration of diarrhoea, febrile neutropenia, need for antibiotic and antifungal therapy, safety.

Results

Analysis of efficacy and safety concerned 163 patients divided into 2 groups:

- group 1 (initial protocol) received 7 doses of the trial drug and consisted of 34 patients (11 placebo, 12 palifermin administered pre myeloablative therapy, and 11 palifermin administered pre and post myeloablative therapy

- group 2 (after the protocol amendment) received 6 doses of the trial drug and consisted of 129 patients :
  - 40 patients in the placebo group,
  - 43 patients given Kepivance pre conditioning therapy for 3 consecutive days at a dose of 60µg/kg/day,
  - 46 patients given Kepivance pre and post conditioning therapy for 3 consecutive days as one 60 µg/kg/day.

Only the results for group 2 will be reported as this is the dosage regimen of the Marketing Authorisation (6 doses).

The number of patients recruited was based on the hypothesis of a 50% reduction in duration of severe mucositis (grade 3 or 4). It was expected that, without treatment, this duration would be 10 days (±7.5). Thirty-seven (37) patients were needed in each group for such a difference to be detected with a 5% risk. 129 patients received 6 injections

For these patients, duration of WHO grade 3 or 4 mucositis was 8.6 ± 8.2 days in the placebo group, 5.2 ± 6.1 days in the pre-therapy group (p=0.003), and 4.7 ± 5.7 days in the pre- and post-therapy group (p=0.004). Differences between placebo and Kepivance were significant. Differences between the two treatment modalities (pre-therapy or pre- and post-therapy) were similar.

The percentage of patients with WHO grade 3 or 4 mucositis was not significantly different between the three groups (80% in the placebo group, 72% in the pre-therapy group, and 67% in the pre- and post-therapy group).

Frequency of occurrence of WHO grade 4 mucositis was reduced by Kepivance: 50% in the placebo group, 33% in the pre-therapy group (p=0.029), 26% in the pre- and post-therapy group (p=0.029). However, frequency was similar for both treatment modalities (pre-therapy and pre- and post-therapy)

Antibiotic therapy was administered in a similar proportion of patients in all three groups. Antifungal treatment was administered to fewer patients and for a shorter time in the pre-therapy and pre- and post-therapy groups. Opioids were administered to 95% of patients in the control group compared with 80-81% of patients receiving Kepivance.

Trial (20000162)

A published[1] randomized, double-blind Phase III clinical trial, which evaluated the efficacy of Kepivance in patients with haematological malignancies receiving conditioning therapy with high-dose chemotherapy (etoposide and cyclophosphamide) and fractionated total-body irradiation (TBI)[2] followed by autologous stem cell transplantation.

The patients received either 6 injections of Kepivance (3 days before the conditioning therapy, then 3 days starting with the day of re-injection of stem cells) at a 60 µg/kg dose, or placebo. Filgrastim was also administered until the neutrophil count recovered.

Primary endpoint: duration of WHO grade 3 or 4 oral mucositis.

Secondary endpoints: incidence, duration and severity of oral mucositis, requirement for morphine analgesics, clinical consequences associated with patient-reported mucositis such as soreness of the mouth and throat, and safety.

[1] Spielberger R, Stiff P, Bensinger W et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med 2004;351:2590-2598.

[2] Total dose: 12 Gy

Results

The treated haematological malignancies were non Hodgkin's lymphoma (about 66% of cases), Hodgkin's disease (about 20%), cases of malignant myeloma, and cases of leukaemia in remission.

The trial had to include 105 patients in each group to observe a difference of 3.0 days (±6.6) with a 5% risk. 214 patients were randomised (107/group). Of these, 212 (106/group) received at least one dose of Kepivance. A similar number of patients (102 in the placebo group, 103 in the Kepivance group) received all of the planned treatment; 92% received an antiviral drug.

Incidence of WHO grade 3 or 4 oral mucositis (63% vs 98%, $p<0.001$) and duration (5.9 days vs 10.6 days; $p<0.001$) were both reduced in the treatment group.

WHO Grade 4 oral mucositis affected 20% of patients receiving Kepivance against 62% of patients in the control group ($p<0.001$). In patients with WHO grade 4 mucositis, mean duration of mucositis was 6.2 days under placebo and 3.3 days under Kepivance ($p<0.004$).

Incidence of swallowing problems was lower for Kepivance than for controls but this difference was not statistically significant. The score assessing mouth soreness was significantly lower in the treatment group (difference: -38%). Use of opioid analgesics was lower with Kepivance (mean cumulative dose of morphine equivalents 212 mg against 535) and shorter (7 days against 12 days).

3.2. Safety

In the Phase III clinical trial, the incidence of febrile neutropenia was lower in the treatment than control group (75% against 92%).

The side effects observed in 409 patients treated with Kepivance and 241 patients treated with placebo were reported in an EPAR[3] report.

There were more undesirable effects with Kepivance (56% vs 29%). The most common effects were rash (23% vs 10%), erythema (18% vs 4%) and changes in tongue thickness or discolouration (13% vs 3%). These effects appeared 5 days after the last injection and lasted a mean of 5 days. There were no problems of immunogenicity although this was only monitored for 3 months.

The observation period was extended to nearly 2 years for patients with haematological malignancies. No side effects could be attributed to Kepivance. The 650 patients (in total) treated to date should be followed up until 2015.

3.3. Conclusion

In a randomised double-blind placebo–controlled clinical trial in 212 patients with haematological malignancies receiving myeloablative therapy with high-dose chemotherapy (etoposide et cyclophosphamide) and total-body irradiation and after autologous haematopoietic stem-cell transplantation, Kepivance decreased both incidence (63% vs 98%, $p<0.001$) and duration (6 days vs 9 days, $p<0.001$) of WHO grade 3 or 4 oral mucositis.

WHO grade 4 mucositis affected 20% of patients on Kepivance versus 60% of patients on placebo.

The myeloablative therapy used in the pivotal trial (chemotherapy with etoposide and cyclophosphamide, TBI) is different from that used in France where TBI is used less than in other countries. Combined chemotherapy BEAM involving carmustine (BCNU), etoposide,

[3] European Product Assessment Report for products given a Marketing Authorization via the Centralised Procedure.

aracytine and melphalan is the most common conditioning therapy, except in the case of multiple myeloma, when melphalan is preferred. The frequency of occurrence of WHO grades 3 and 4 oral mucositis is about 95% when conditioning therapy includes TBI, 50% when high-dose melphalan is used, and 20% with BEAM (EPAR p52).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

Actual benefit

Oral mucositis is a common and potentially severe complication of anticancer treatment with radiotherapy and chemotherapy. It is one of the most difficult-to-bear side effects for patients receiving intensive treatment after a bone marrow transplant.

The efficacy/safety ratio of this medicinal product is substantial.

Public Health Benefit

Severe oral mucositis in patients with haematological malignancies receiving myeloablative treatment are serious clinical conditions. Their frequent occurrence is closely linked to the type of conditioning therapy. In public health terms, the burden caused by these clinical conditions, rare in the general population, is low.

There is a public health need which Kepivance meets to some extent.

In view of the Phase III clinical trial results, the expected theoretical impact of Kepivance on morbidity and mortality is moderate. However, because of the problems of generalising these trial results to clinical practice in France (type of conditioning therapy used and frequency of oral mucositis episodes caused), the expected population impact of Kepivance on morbidity and mortality under real-life conditions can but be low.

Consequently, a public health benefit is expected from Kepivance. This benefit is minor.

This is a prevention treatment.
This medicinal product is a first-line drug.
There is no known alternative drug.

The actual benefit of Kepivance is substantial.

Improvement in actual benefit

Kepivance provides a moderate improvement in actual benefit (level III) in the management of patients with haematological malignancies and receiving myeloablative treatment known to cause increased incidence of severe oral mucositis.

Therapeutic use

There is no generally accepted strategy for preventing and treating these cases of mucositis. Analysis of 52 randomised trials where the data could be examined by the authors of the 2003 Cochrane meta-analysis showed (unusually for scientific publications) a great many negative trials. Guidelines have nevertheless been developed by the ”mucositis” group of the International Society of Oral Oncology and The Multinational Association for Supportive Care in Cancer (Rubenstein 2004[4]).

[4] Rubenstein EB, Peterson DE, Schubert M et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(9 suppl): 2026-2046.

A strict programme of oral hygiene should precede and accompany anti-cancer chemotherapy (treatment of dental caries, dental plaque, etc.). The patient should be educated in correct tooth-brushing technique. This requires a soft brush and should be stopped if thrombocytopenia occurs. Mouth washing with an antiseptic and antifungal treatment (nystatin and fungizone) is usually prescribed.

Non-drug methods include two which seem to be particularly effective: sucking ice cubes and the use of low intensity lasers. Such lasers are available in only very few treatment centres

Agreement has not been reached on the usefulness of drug methods such as amifostine and GM-CSF, for which presumption of efficacy is based on few trials with small patient numbers.

The only unanimously-approved drug therapy is the use of morphine to relieve pain. The type of morphine, the administration route, and the dose should be adjusted for each patient.

Kepivance is the first drug which has shown significant efficacy against placebo in reducing the incidence, duration, and severity of oral mucositis in patients with haematological malignancies receiving myeloablative therapy known to increase the incidence of severe mucositis. The benefit of Kepivance lies mainly in the context of myeloablative therapy with melphalan for myeloma.

Target population

According to the annual report of the *Établissement Français des Greffes*, 2814 patients received autologous haematopoietic stem-cell transplantation after myeloablative therapy in 2004,

Overall, 86.4% of patients received autologous transplantation as part of treatment for blood haemopathies.

Taking into account the lack of predictive factors for onset of severe mucositis in a given patient, the target population will include all patients with haematological malignancies treated with myeloablative chemotherapy, requiring autologous haematopoietic stem-cell support and likely to have ulcerative mucositis. This target population is estimated to be about 2 400 people a year.

Transparency Committee recommendations

The Committee recommended inclusion on the list of medicinal products approved for use by hospitals and various public services.

As trial results cannot be generalised to French clinical practice (type of conditioning therapy used and frequency of mucositis caused), the Transparency Committee asked for a study to be conducted in France on Kepivance under real-life conditions. Its aim would be to evaluate the public health benefit of Kepivance. The following details would be needed:

- patient characteristics (in particular, the disease treated);
- patient management, especially the myeloablative therapy used and Kepivance treatment modalities (dose, duration, and schedule of administration);
- incidence, duration, and severity of oral mucositis, together with associated morbidity (including infections).

The duration of the study should be determined by a scientific committee. Reasons should be given for the duration. The duration should be long enough to provide a response to the Transparency Committee’s request.