



# CIGNA HEALTHCARE COVERAGE POSITION

Subject **Palifermin (Kepivance®)**

Effective Date ..... 10/15/2005  
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## Related Coverage Positions

### INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. ©2005 CIGNA Health Corporation

## Coverage Position

**CIGNA HealthCare covers palifermin (Kepivance®) as medically necessary when the following indication is met:**

- prevention and treatment of severe oral mucositis in patients who have hematologic cancers and are undergoing high-dose chemotherapy, with or without radiation, followed by bone marrow or stem cell transplantation

**CIGNA HealthCare does not cover palifermin (Kepivance®) for the following indication because it is considered experimental, investigational or unproven:**

- treatment of oral mucositis in patients with non-hematologic malignancies

## General Background

Palifermin is a recombinant human keratinocyte growth factor (KGF) produced by recombinant DNA technology in Escherichia coli. It works at the cellular level by binding to epithelial cell-surface receptors and stimulating epithelial cell proliferation, differentiation, and upregulation of cytoprotective mechanisms to help protect patients with hematologic malignancies undergoing high-dose chemotherapy and/or radiation followed by bone marrow transplant from severe oral mucositis. Palifermin reduces the incidence and duration of severe oral mucositis in these patients by protecting the epithelial cells that line the mouth and throat from the damage caused by chemotherapy and radiation and by stimulating the growth and development of new epithelial cells to build up the mucosal barrier.

After single intravenous (IV) doses of 20-250 mcg/kg (healthy subjects) and 60 ug/kg (cancer patients), palifermin concentrations declined rapidly (over 95% decrease) in the first 30 minutes post-dose. Levels then plateau or increase slightly at approximately 1-4 hours, followed by the terminal decline phase. The mean elimination half-life is 4.5 hours.

The assessment of oral mucositis in clinical studies was based on the World Health Organization (WHO) scale which ranges from 0 (no oral mucositis) to 4 (most severe) (Table 1).

<b>Table 1. WHO Scale for Grading the Severity of Oral Mucositis</b>	
<b>Grade 0</b>	No oral mucositis
<b>Grade 1</b>	Presence of mucosa redness (erythema) together with mouth soreness but without overt ulceration (mouth sores); the patient is able to eat a normal diet
<b>Grade 2</b>	Presence of sores, though patient is still able to swallow solid foods
<b>Grade 3</b>	Patient experiences extreme difficulty swallowing solid food and requires a liquid diet
<b>Grade 4</b>	Patient is unable to swallow and must receive nutrition IV or via surgically implanted feeding tube

Limited data are available regarding palifermin use. Only two studies are published in the medical literature, one of which is a phase I study using palifermin in patients who have colorectal cancer, a population for which it is currently not approved. There are four studies available in abstract form only; three for hematologic cancer patients and one for colorectal cancer patients.

Palifermin is the first drug of its kind, indicated for prevention and treatment of oral mucositis. Prior to palifermin, treatment of oral mucositis consisted of supportive care. Because of this, all studies used palifermin and placebo as treatment groups with both groups receiving supportive care. All studies have found palifermin effective for preventing and treating oral mucositis associated with high-dose chemotherapy regimens. Studies also report a decreased use of total parenteral nutrition (TPN) and analgesics in the palifermin treatment groups. Patients receiving palifermin report less mouth and throat soreness and an increase in physical and functional well-being.

The single published trial for palifermin's approved indication demonstrated significant decreases in the incidence and duration of grade 2-4 oral mucositis, and incidence of febrile neutropenia, ( $p=0.001$ ). The use of TPN and total dose of narcotic analgesics administered decreased significantly, ( $p=0.001$ ). Patients reported significant decreases in mouth and throat soreness and swallowing limitation ( $p=0.001$ ); with significant increases in physical ( $p=0.003$ ) and functional ( $p=0.036$ ) well-being.

The following information represents the available data on palifermin use and will provide a summary of the safety and effectiveness of palifermin for treatment and prevention of oral mucositis.

### **Hematologic Cancers**

Durrant et al. (1999) conducted a phase I study, available in abstract form only, with the purpose of determining the maximum tolerated dose of palifermin. The study included patients ( $n=234$ ) diagnosed with lymphoma undergoing high-dose chemotherapy in preparation for autologous peripheral blood progenitor cell transplantation (auto-PBPCT). Patients received either palifermin or placebo for three days

before chemotherapy or three days before and three days after chemotherapy. Patients randomly received 5, 20, 40, 60, or 80 mcg/kg/day of palifermin. Adverse events included mild to moderate erythema of the skin or mouth. The palifermin group had transient, asymptomatic increases in amylase and lipase levels. The treatment group reported decreases in the incidence, severity, and mean duration of oral mucositis; however, no p-values are reported. Also reported were decreases in analgesic use and mouth and throat soreness. Based on the outcomes of this study, palifermin dosed at 60 mcg/kg was recommended for further investigation.

Spielberger et al. (2001) conducted a phase II study, available in abstract form only, with the purpose of determining the efficacy of palifermin use in patients with hematologic cancers (n=129). Secondary outcomes included TPN and IV analgesic use and mouth and throat soreness. Patients underwent high-dose chemotherapy regimens and received total body radiation. Patients received either palifermin or placebo for three days before chemotherapy and radiation, three days after autologous stem cell transplantation, or both. Raw data for those patients who received palifermin or placebo for only the three days after transplant were not included in the abstract. When compared with placebo, palifermin use before and after chemotherapy and radiation resulted in a significant decrease in the duration of severe mucositis (p=0.001). Palifermin also decreased duration of severe mucositis in patients who received the drug for only the three days before chemotherapy and radiation therapy (p=0.04). A decrease in TPN and IV opioid analgesic use was reported only in the palifermin group which received treatment before and after chemotherapy. Patients experienced side effects similar to previous studies, including skin and oral erythema along with increases in amylase and lipase levels. No dropouts were reported.

Spielberger et al. (2004) published a phase III study, with the purpose of studying palifermin's effect on oral mucositis in patients with various types of hematologic cancers (n=212). The primary outcome focused on the duration of grade 3 or 4 oral mucositis. Secondary outcomes accounted for incidence and duration of grade 2-4 oral mucositis and duration of lesions. Investigators also measured use and duration of narcotic analgesics and use of TPN therapy as well as incidence of neutropenia and infections. Patients reported self-assessment of physical and functional well-being using the Functional Assessment of Cancer Therapy (FACT) questionnaire. Safety data measures included the incidence, frequency, and severity of adverse effects graded on a five point scale, with grade 1 indicative of mild adverse effects and grade 5 representing fatal adverse effects. Alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase and creatinine accounted for clinical laboratory data measured. Investigators used immunoassay to determine the presence of palifermin antibodies and the Kaplan-Meier method to measure rates of secondary cancers and progression-free survival.

Randomized patients received either palifermin or placebo. Both treatment groups received the drug for three days before and three days after radiation and chemotherapy. Patients in the palifermin group received a 60 mcg/kg/day bolus infusion. All other patients received infusions of similar volumes of placebo. The placebo contained the same ingredients as Kevance without the palifermin, including histidine, sucrose, mannitol, and polysorbate. Evaluation of oral mucositis occurred daily until 28 days after transplant.

Results from the Spielberger trial demonstrate significant decreases in the incidence (63% vs. 92%, p=0.001) and duration (3 vs. 9 days, p=0.001) of grade 2-4 oral mucositis. Palifermin-treated subjects experienced a reduced incidence of febrile neutropenia (75% vs. 92%, p=0.001). Use of TPN was 31% for palifermin-treated and 55% for placebo-treated patients (p=0.001). The total dose of parenteral and transdermal narcotic analgesics administered decreased significantly from 535 mg morphine equivalents in the placebo group to 212 mg in the palifermin group (p=0.001). Patients reported significant decreases in mouth and throat soreness and swallowing limitation (p=0.001), on the FACT questionnaire. Patients also reported significant increases in physical (p=0.003) and functional (p=0.036) well-being. Adverse reactions to palifermin occurred at a rate similar to placebo. Both the palifermin and placebo treatment groups reported asymptomatic, transient elevations in both serum amylase and lipase levels. No patients developed detectable antibodies. The treatment groups had no difference in clinical laboratory values. Reported survival rates are similar between treatment groups.

Elting et al. (2004) conducted a cost analysis study, available in abstract form only, of palifermin use in patients with hematologic cancers using the outcomes from a phase III study by Spielberger et al. (2004). Investigators analyzed costs associated with bacteremia, febrile neutropenia, TPN, intubation, and number of days spent in the hospital. Hospital costs were estimated from a national sample of hematologic cancer patients undergoing total body radiation and autologous stem cell transplantation. The average cost of therapy for patients receiving palifermin was \$61,160 versus \$76,104 for patients receiving placebo, resulting in a mean savings of \$14,943 per patient when using palifermin, (\$12,043-\$17,845). The cost of palifermin was not included in the analysis and could offset the outcome depending on the acquisition cost of palifermin. Investigators concluded that use of palifermin will lead to significant cost savings; however, the degree of savings depends on the cost of palifermin.

### **Off-label Indications**

In order to provide maximum benefit from palifermin use, a specific dosing regimen must be followed. The dosing regimen is specific for patients with hematologic cancers undergoing a combination of high-dose chemotherapy, total body radiation, and stem cell transplantation. Palifermin use in alternative indications has been studied, but the optimal dose and schedule have not been determined. Caution is warranted should palifermin be used for reasons other than U.S. Food and Drug Administration (FDA)-approved indications.

Meropol et al. (2003) published a randomized phase I study with the purpose of evaluating the safety, toxicity, and maximum tolerated dose of palifermin. Study participants, diagnosed with metastatic colorectal cancer, underwent therapy with fluorouracil and leucovorin (n=81). Patients received placebo or palifermin dosed at 1, 10, 20, 40, 60, or 80 mcg/kg/day for three days before beginning chemotherapy. Investigators used WHO guidelines to evaluate the incidence, duration, and severity of oral mucositis. Investigators combined all six dosage groups when performing statistical analysis of outcomes. Results are not statistically significant; however, there is a trend toward a decrease in incidence and duration of oral mucositis and mouth soreness. Three patients taking palifermin (one patient taking 60 mcg/kg and two patients taking 80 mcg/kg) discontinued therapy due to side events involving the skin.

Clarke et al. (2001) performed a phase II study, available in abstract form only, with the purpose of evaluating the efficacy of palifermin in patients with advanced colorectal cancer. Investigators evaluated oral mucositis in patients randomized to receive palifermin or placebo (n=64). Patients in the treatment group received palifermin 40 mcg/kg/day based upon the Meropol study in which a similar patient population was used. Results indicate a significant decrease in the incidence and duration of WHO grade 2-4 oral mucositis (p=0.001). Palifermin had no effect on survival. Patients experienced mild to moderate rash, flushing and edema. Asymptomatic increases in amylase and lipase are reported with levels returning to baseline after therapy. No dropouts were reported.

The most common serious adverse reaction in clinical trials reported was skin rash, occurring in less than 1% of patients. The most frequently reported serious adverse events in palifermin-treated patients were fever, gastrointestinal events, and respiratory events. The most commonly reported adverse reactions were rash, erythema, edema, pruritus, dysesthesia, mouth/tongue thickness/discoloration, and taste alteration. Patients should be closely monitored for the occurrence of edema.

Palifermin should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. In clinical trials, administration of palifermin within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

The recommended dosage is 60 µg/kg/day given as an intravenous (IV) bolus injection for three days before chemotherapy/radiation therapy and three days after chemotherapy, for a total of six doses. Palifermin should not be given on the same day as chemotherapy or radiation therapy.

Palifermin should be used only in patients with hematologic cancers undergoing chemotherapy or total body radiation. The use of palifermin decreases the need for supportive care due to oral mucositis. Palifermin should not be used in disease states in which it is not indicated until more data are available for dosing and efficacy.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT <sup>®*</sup> Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

**Experimental/Investigational/Unproven/Not Covered:**

CPT* Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

**\*Current Procedural Terminology (CPT<sup>®</sup>) © 2004 American Medical Association: Chicago, IL.**

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