Effective Date **9/1/2022**
Next Review Date… **9/1/2023**
Coverage Policy Number **IP0436**

Difelikefalin

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, 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 Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. 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 benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for difelikefalin for intravenous use (**Korsuva**®).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Difelikefalin (Korsuva) is considered medically necessary when the following are met:

1. **Chronic Kidney Disease Associated Pruritus.** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Individual is 18 years of age or older
    B. Individual is currently receiving hemodialysis
    C. Individual has moderate-to-severe pruritus

D. Documented inadequate response, contraindication or intolerance to **ONE** of the following (i, ii, or iii):
    i. Gabapentin
    ii. Oral antihistamine (for example, diphenhydramine, hydroxyzine, loratidine)
    iii. Pregabalin
E. The medication is prescribed by, or in consultation with, a dermatologist or nephrologist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Difelikefalin (Korsuva) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Chronic Kidney Disease-Associated Pruritus in Peritoneal Dialysis**
   Korsuva has not been studied in patients on peritoneal dialysis and is not recommended for use in this population.[1]

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3490	Unclassified drugs

Background

OVERVIEW
Korsuva is a kappa opioid receptor agonist indicated for the treatment of **moderate-to-severe pruritus associated with chronic kidney disease** (CKD-aP) in adults undergoing hemodialysis (HD).[1]
Limitation of use: Korsuva has not been studied in patients on peritoneal dialysis and is not recommended for use in this population.

Disease Overview
CKD-aP is a common problem for patients with CKD and end-stage renal disease (ESRD). The estimated prevalence is 20% in CKD and 40% in ESRD.[4] Most commonly, CKD-aP is attributed to toxin build-up, peripheral neuropathy, immune system dysregulation, or opioid dysregulation.

Clinical Efficacy

The efficacy of Korsuva was evaluated in two randomized, multicenter, double-blind, placebo-controlled trials that enrolled a total of 851 subjects 18 years of age and older undergoing HD who had moderate-to-severe pruritus (KALM-1 [published] and KALM-2 [unpublished].[1-3] In both trials, patients received intravenous (IV) bolus injections of Korsuva 0.5 mcg/kg of dry body weight into the venous line of the hemodialysis circuit at the end of each hemodialysis session or placebo three times per week for 12 weeks. In both trials, a 7-day run-in period prior to randomization was used to confirm that each patient had moderate-to-severe pruritus and to establish a baseline itch intensity, as measured by the patient-reported daily 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores (0 "no itch" to 10 "worst itch imaginable"). The mean (SD) baseline WI-NRS score was 7.1 (1.5) in KALM-1 and 7.2 (1.4) in KALM-2. At baseline in KALM-1, 40% of patients were using prior anti-pruritic medications, most commonly diphenhydramine (32% to 37%), hydroxyzine (11%), hydrocortisone (3% to 4%), triamcinolone (2% to 3%), ammonium lactate (1% to 2%), and loratidine (0.5% to 2%); use continued throughout the trial.[2] In KALM-2, at baseline 36% of patients were using prior anti-pruritic medications (including sedating antihistamines) and continued the use throughout the trial (information regarding specific anti-pruritic medications is not available).[1] In each trial, efficacy was assessed based on the proportion of patients achieving a 4-point or greater improvement (reduction) from baseline in the weekly mean of the daily 24-hour WI-NRS score at Week 12.

Table 1. KALM-1 and -2: Efficacy Results in Patients with Moderate to Severe CKD-aP Undergoing HD at Week 12.[1]

	KALM-1		KALM-2	
	Korsuva 0.5 mcg/kg TIW (n = 189)	**Placebo (n = 189)**	**Korsuva 0.5 mcg/kg TIW (n = 237)**	**Placebo (n = 236)**
Patients with ≥ 4 point improvement from baseline in WI-NRS score.	40%	21%	37%	26%
Difference from Placebo (95% CI)	19% (9, 28)		12% (3, 20)	

CKD-aP – Chronic kidney disease associated pruritus; HD – Hemodialysis; TIW – Three times weekly; WI-NRS – Worst Itching Intensity Numerical Rating Scale; CI – Confidence interval.

Guidelines

There are no guidelines specific to CKD-aP. However, most experts recommend taking a stepwise approach to treatment.[4,5] First, optimization of dialysis adequacy, calcium and phosphorous levels, skin hydration, and nutrition, and patient education on the importance of avoiding or minimizing scratching is recommended.[5] If symptoms persist, pharmacologic and/or nonpharmacologic therapy may be offered. Aggressive skin moisturization is recommended; if pruritus is localized to a limited area of skin, a trial of topical capsaicin may be considered. Gabapentin is an option for pharmacologic treatment, for those intolerant to gabapentin, pregabalin is an option. Other measures offered are an opioid receptor modulator (note: Korsuva is an opioid receptor modulator), acupuncture, or UVB phototherapy.

References

1. Korsuva™ Injection [prescribing information]. Stamford, CT: Cara Therapeutics; August 2021.
2. Fishbane S, Jamal A, Munera C, et al; for the KALM-1 Trial Investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med.* 2020; 382(3):222-232.
3. Cara Therapeutics. CR845-CLIN3103: A Global Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus (KALM-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2022 May 23]. Available at: https://clinicaltrials.gov/ct2/show/study/NCT03636269?term=NCT03636269&draw=2&rank=1. NLM Identifier: NCT03636269.
4. Verduzco HA and Shirazian. CKD-associated pruritus: new insights into diagnosis, pathogenesis, and management. *Kidney Int Rep.* 2020; 5:1387-1402.
5. Combs SA, Teixeira JP, and Germain MJ. Pruritus in kidney disease. *Semin Nephrol.* 2015; 35(4):383-391.