NEW DRUG APPROVAL

Brand Name	Korsuva™
Generic Name	difelikefalin acetate
Drug Manufacturer	Cara Therapeutics Inc

New Drug Approval

FDA Approval Date: August 23, 2021

Review Designation: Priority

Review Type: Type 1 – New Molecular Entity; New Drug Application (NDA): 214916

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

The reported prevalence of uremic pruritus varies depending on the source or study, but it is thought to affect between 40% and 50% of CKD patients on hemodialysis. There is very limited data in CKD patients with uremic pruritus who are not dialysis dependent. Patients with more severe CKD are more likely to suffer from itching; severe itching has been reported in about 10%-20% of the non-dialysis CKD population. Moderate to severe uremic pruritus is associated with decreased quality of life, higher probability of depression, and poor sleep quality.

Although the cause of uremic pruritus is unknown, it is thought to be either immunologically mediated and/or opioidergic. It is either caused by systemic inflammation or has to do with mu-receptor activation and kappa-receptor blockade (opioid hypothesis). Mast cell release of histamine is also thought to contribute it uremic pruritus. Risk factors for uremic pruritus include inadequate dialysis, hyperparathyroidism, elevated calcium x phosphorus product, xerosis and elevated serum magnesium and aluminium, which all should be evaluated and managed before continuing to other therapies.

There are currently no FDA-approved therapies for uremic pruritus.

Current therapies used generally consist of topical and systemic treatments including emollients, topical analgesic agents, UVB phototherapy, thalidomide, cromolyn sodium, oral antihistamines such as hydroxyzine, diphenhydramine, and loratadine.

Other therapies studied for uremic pruritus have included: gabapentin, pregabalin, sertraline, montelukast, naltrexone, nalbuphine and butorphanol

Efficacy

The efficacy of Korsuva™ was evaluated in two randomized, multicenter, double-blind, placebo-controlled trials (KALM-1 [NCT03422653] and KALM-2 [NCT03636269], Tables 3 and 4) that enrolled a total of 851 subjects 18 years of age and older undergoing HD who had moderate-to-severe pruritus. In both trials, subjects received intravenous bolus injections of Korsuva™ 0.5 mcg per kilogram 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 subject 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 Trial 1 (KALM-1) and 7.2 (1.4) in Trial 2 (KALM-2). At baseline in Trial 1, 61% of subjects were male, 49% were White, 42% were Black or African American, the mean age was 57 years (range 22 to 88 years), and 40% of subjects were using prior anti-pruritic medications (including sedating antihistamines) and continued the use throughout the trial. At baseline in Trial 2, 58% of subjects were male, 70% were White, 19% were Black or African American, the mean age was 60 years (range 23 to 90 years), and 36% of subjects were using prior anti-pruritic medications (including sedating antihistamines) and continued the use throughout the trial.

In each trial, efficacy was assessed based on the proportion of subjects 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.

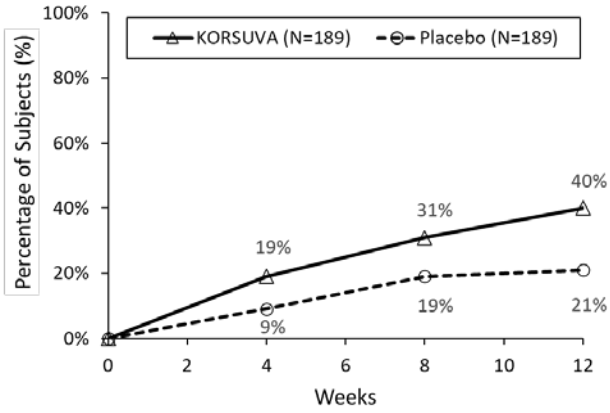
The results of the Korsuva™ Trial 1 (KALM-1) and Trial 2 (KALM-2) are presented in Table 1 and Figure 1.

Table 1. Efficacy Results of Subjects with Moderate-to-Severe CKD-aP Undergoing HD at Week 12 (Trials 1 & 2)

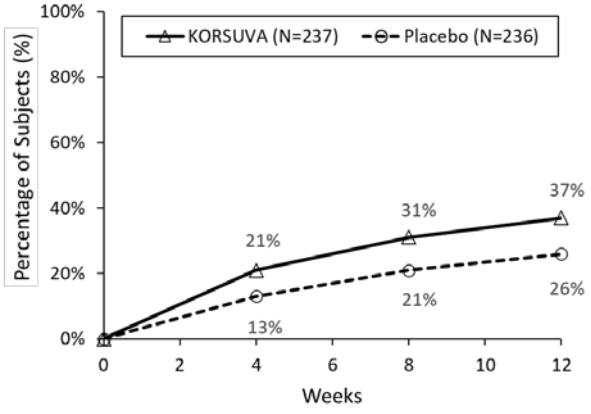
	Trial 1 (KALM-1)		**Trial 2 (KALM-2)**	
	Korsuva™ 0.5 mcg/kg 3 times weekly N=189	**Placebo N=189**	**Korsuva™ 0.5 mcg/kg 3 times weekly N=237**	**Placebo N=236**
Percentage of subjects with ≥4-point improvement from baselinein WI-NRS score	**40%**	**21%**	**37%**	**26%**
Difference from Placebo (95% CI)	19% (9%, 28%)		12% (3%, 20%)	

Figure 1: Percentage of Subjects with Moderate-to-Severe CKD-aP Undergoing HD with a ≥4-pointImprovement from Baseline on the WI-NRS in Trial 1 and Trial 2

Trial 1 (KALM-1)



Trial 2 (KALM-2)



Itch reduction was seen by Week 4 and sustained through Week 12.

Safety

ADVERSE EVENTS

The most common adverse reactions (incidence ≥2% and ≥1% higher than placebo) were diarrhea, dizziness, nausea, gait disturbances, including falls, hyperkalemia, headache, somnolence, and mental status change

WARNINGS & PRECAUTIONS

- Dizziness, Somnolence, Mental Status Changes, and Gait Disturbances: Dizziness, somnolence, m ental status changes, and gait disturbances, including falls, have occurred.Centrally-acting depressant medications, sedating antihistamines, and opioid analgesics should be used with caution during treatment with Korsuva™.
- Risk of Driving and Operating Machinery: May impair mental or physical abilities. Advise patients not to drive or operate dangerous machinery until the effect of Korsuva™ on a patient's ability to drive or operate machinery is known.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Korsuva™ is a kappa opioid receptor (KOR) agonist. The relevance of KOR activation to therapeutic effectiveness is not known.

Dose & Administration

ADULTS

The recommended dosage of Korsuva™ is 0.5 mcg/kg administered by intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD treatment.
If a regularly scheduled HD treatment is missed, resume Korsuva™ at the end of the next HD treatment.

PEDIATRICS

N/A

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

Mild to moderate impairment: No dosing adjustments required.
Severe impairment: Use not recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 65 mcg/1.3 mL (50 mcg/mL) of difelikefalin as a clear, colorless solution in a single-dose glass vial.