CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214916
PDUFA Goal Date	August 23, 2021
OSE RCM #	2020-2731
Reviewer Name	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	August 12, 2021
Subject	Evaluation of Need for a REMS
Established Name	Difelikefalin
Trade Name	Korsuva (proposed)
Name of Applicant	Cara Therapeutics, Inc.
Therapeutic Class	Selective kappa opioid receptor agonist
Formulation(s)	(b) (4) intravenous (IV) injection
Dosing Regimen	IV bolus three times per week following each hemodialysis session

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1 Introduction

This review by the Division of Risk Management evaluates whether a REMS for the new molecular entity (NME) Korsuva (difelikefalin) is necessary to ensure the benefits outweigh its risks. Cara Therapeutics, Inc. (Cara) submitted a New Drug Application, NDA 214916, for difelikefalin with the proposed indication for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis. This application is under review in the Division of Dermatology and Dental Products. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

a. Product Information

Difelikefalin, a new molecular entity[a], is a kappa opioid receptor agonist proposed for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis. It is thought to relieve pruritus by activation of kappa opioid receptors on peripheral sensory neurons and immune cells. Difelikefalin is proposed as a ready-to-use (b) (4) intravenous injection to be administered as an intravenous bolus (0.5 mcg/kg per dose) three times per week following each hemodialysis session.[b] Breakthrough therapy designation was granted in June of 2017. Difelikefalin is not currently approved in any jurisdiction.

b. Regulatory History

The following is a summary of the regulatory history for NDA 214916 relevant to this review:

- **06/21/2017:** Breakthrough therapy designation granted for difelikefalin (IND 123140).
- **12/23/2020:** NDA 214916 submission for treatment of moderate-to-severe pruritis associated with chronic kidney disease in adult patients undergoing hemodialysis received.
- **03/08/2021:** Priority review granted for difelikefalin, NDA 214916.
- **04/06/2021:** A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for difelikefalin[1].

3 Therapeutic Context and Treatment Options

a. Description of the Medical Condition

Chronic kidney disease-associated pruritus ([CKD-aP); also known as uremic pruritus] is characterized by a generalized, persistent and intractable itch affecting up to 60% of patients undergoing hemodialysis

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

(HD).[2] It is estimated that 37 million people in the US have chronic kidney disease, and approximately 500,000 of them require hemodialysis.[3,c] Patients with CKD-aP experience an insistent itch sensation that can lead to considerable skin damage due to scratching. CKD-aP commonly affects the patient's back but may also involve the arms, head and abdomen and may be intermittent or continuous. Moderate-to-severe disease can impair physical and mental health due to skin infections, sleep disturbance, chronic fatigue, shame, social isolation and depression.[d] CKD-aP is an independent predictor of mortality among HD patients, mainly related to the increased risk of inflammation and infections.[4] The specific cause of the disease has not been identified, although it is hypothesized to result from systemic inflammation, mast cell release of histamine and/or imbalances in the expression of mu and kappa opioid receptors.[5]

b. DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no FDA-approved products for the treatment of moderate-to-severe CKD-aP.
Several medications have been used as off-label treatments, e.g., antihistamines, corticosteroids, analgesics, gabapentin, and pregabalin. However, these off-label therapies are not always well tolerated by patients, and the evidence for their antipruritic efficacy is limited and lacking support from randomized, well-controlled studies.[6] Emollients, such as those containing glycerol and paraffin, are the preferred topical treatment, especially if dry skin is present on examination.[7] Other topical treatments have included the use of the analgesic agents capsaicin and pramoxine, though capsaicin use is not frequently recommended due to the erythema and burning associated with wide-spread use on the body. Both topical and oral antihistamines have frequently been used to manage CKD-aP, with patients often requiring both sedating and non-sedating products. If antihistamines do not provide adequate relief, gabapentin or pregabalin may be prescribed, though these patients should be monitored closely for neurologic side effects such as dizziness and somnolence. Antidepressants, such as sertraline, have also been used in conjunction with other agents to treat severe cases of CKD-aP where symptoms of depression are present.

Non-pharmacological approaches to treat CKD-aP are limited. Phototherapy (ultraviolet-B irradiation) has been shown to improve pruritis associated with CKD[8], however it is associated with an increased risk of carcinogenesis. Kidney transplantation also improves CKD-aP; one retrospective study reported resolution of pruritis following successful transplantation.[9] Despite the off-label use of various drug therapies and non-pharmacological treatments, there is a significant unmet medical need among CKD patients with chronic uremic pruritis. On June 21, 2017, difelikefalin was granted Breakthrough Therapy designation.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

4 Benefit Assessment

The efficacy of difelikefalin for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis was evaluated in two randomized, multicenter, double-blind, placebo-controlled trials (CLIN3102 [NCT03422653]; CLIN3103 [NCT03636269]) that enrolled a total of 851 subjects who received intravenous bolus injections of difelikefalin (0.5 mcg per kilogram) into the venous line of the hemodialysis circuit at the end of each hemodialysis session or placebo three times per week for 12 weeks. Both of the studies had the same primary efficacy endpoint: reduction of itching intensity defined as the proportion of subjects achieving ≥3-point improvement (reduction) from baseline with respect to the weekly mean of the daily 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) at Week 12 of the double-blind treatment period. The secondary efficacy endpoint was similar to the first but used ≥4-point improvement as the efficacy threshold.

The Division of Dermatology and Dental Products determined that a 3-point improvement from baseline on the WI-NRS is not clinically meaningful.[10] 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 efficacy results are summarized below in Table 1.

Table 1. Efficacy Results of Subjects with Moderate-to-Severe CKD-aP Undergoing HD at Week 12

	CLIN3102		CLIN3103	
	Difelikefalin 0.5 mcg/kg 3 times weekly N=189	Placebo N=189	Difelikefalin 0.5 mcg/kg 3 times weekly N=237	Placebo N=236
Percentage of subjects 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%)	

The clinical reviewer concluded that the two phase 3 studies met their primary efficacy endpoints and demonstrated the superiority of difelikefalin compared with placebo, with a statistically significant

greater proportion of subjects on difelikefalin than subjects on placebo achieving a ≥ 4 point improvement in WI-NRS at Week 12.[11,e]

5 Risk Assessment & Safe-Use Conditions

Throughout the clinical development program that consisted of eighteen studies, a total of 1879 patients received at least one dose of difelikefalin. The primary safety population is based on the pooled analysis of the pivotal phase 3 trials (CLIN3102, CLIN3103) and includes data from 848 subjects (424 difelikefalin, 424 placebo).

a. Serious Adverse Reactions

Eight deaths were reported in the primary safety pool (3 difelikefalin – infection, cardiac arrest/failure, anaemia, 5 placebo – 3 infections, cardiac arrest, unknown). The applicant stated that the incidence rate of deaths was consistent with the rates reported in the literature for patients undergoing hemodialysis and concluded that none of the deaths were related to difelikefalin treatment.

At least one non-fatal serious treatment emergent adverse event (TEAE) was reported in 58 difelikefalin subjects (13.7%) compared to 54 (12.7%) in the placebo group. The most common serious TEAEs were hyperkalemia (1.7% for difelikefalin and 0.5% for placebo), diarrhea (0.9% and 0.7%, respectively), constipation (0.7% and 0.2%), chest pain (0.7% and 0.5%), sepsis (0.7% and 0.9%), mental status changes (0.7% and 0.2%), and hypotension (0.7% and 0.7%).

Treatment emergent adverse events that lead to study discontinuation occurred in less than 10% of subjects in the pooled primary safety group (6.8% difelikefalin, 4.0% placebo). The most common (≥0.5% of subjects) events were somnolence (1.1%), dizziness (0.9%), nausea (0.7%), headache (0.6%), vomiting (0.5%), and paresthesia (0.5%).

b. Adverse Events of Special Interest

Dizziness, somnolence, mental status changes and gait disturbances, including falls, were observed in patients taking difelikefalin. In both phase 3 trials (CLIN3102, CLIN3103) 17.0% of patients taking difelikefalin reported at least one of these adverse reactions, compared to 12.0% of patients who received placebo. The incidence and/or severity of these reactions may subside over time with continued treatment. Draft labeling advises that patients should not drive or operate dangerous machinery until the effects of difelikefalin on the ability to drive or operate machinery is known. It also states that concomitant use of centrally acting depressant medications, antihistamines and opioids should be approached with caution.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

6 Expected Postmarket Use

Difelikefalin is to be administered as an intravenous bolus injection into the venous line of the dialysis circuit at the end of each HD session, therefore it is likely to be given in a healthcare facility that provides dialysis services. Hospitals, clinics and dialysis centers are likely settings for administration. In most cases difelikefalin will be prescribed by a nephrologist managing a patient's CKD, and a dialysis nurse would be responsible for administration. Healthcare providers can counsel patients at the point of care regarding the increased risk of dizziness, somnolence and gait disturbances with concomitant use of centrally acting depressants, antihistamines and opioids. The CKD-aP patient population will likely be able to recognize these side effects and take necessary actions to manage them.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for difelikefalin beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of difelikefalin on the basis of the efficacy and safety information currently available.[12]

Chronic kidney disease-associated pruritus is a frequent and compromising symptom in patients with advanced or end-stage renal disease.[13] Moderate-to-severe disease can impair physical and mental health due to skin infections, sleep disturbance, chronic fatigue, shame, social isolation and depression[f]. CKD-aP is an independent predictor of mortality among HD patients, mainly related to the increased risk of inflammation and infections.[14] Cara Therapeutics, Inc. submitted two pivotal phase 3 trials to support the efficacy and safety of difelikefalin in the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis. Results from the trials demonstrated that treatment with difelikefalin significantly reduced pruritus compared to placebo, as indicated by the proportion of subjects achieving ≥4-point improvement (reduction) from baseline with respect to the weekly mean of the daily 24-hour WI-NRS at Week 12 of the double-blind treatment period.

The most important risks associated with difelikefalin include dizziness, somnolence, mental status changes and gait disturbances, including falls. The proposed labeling includes a warning and precaution for these risks, as well as for driving or operating dangerous machinery until the effects of difelikefalin on the ability to drive or operate machinery is known. The label also advises to use caution with

[f] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug*

concomitant use of centrally acting depressant medications, antihistamines and opioids, as they could increase the risk of these side effects in difelikefalin patients.

Based on the observed benefit of difelikefalin, the likelihood that difelikefalin will be prescribed by physicians with expertise in the management of patients with CKD-aP and the ability of the CKD-aP patient population to likely recognize the side effects and take necessary actions to manage them, DRM is not recommending a REMS for difelikefalin.

9 Conclusion & Recommendations

Based on the draft clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for difelikefalin to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

a. REFERENCES

[1] Marcus, K. Mid-cycle Communication for difelikefalin, NDA 214916, May 4, 2021.

[2] Kobrin, SM. Uremic Pruritis. In: UpToDate, Berns, JS, Motwani, S (Ed), UpToDate, Waltham, MS (Accessed on June 1, 2021).

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[4] Cara Therapeutics, Inc. (2017 June 23). Cara Receives Breakthrough Therapy Designation from FDA for I.V. CR845 for the Treatment of Chronic Kidney Disease-Associated Pruritus in Hemodialysis Patients [Press release]. https://ir.caratherapeutics.com/news-releases/news-release-details/cara-receives-breakthrough-therapy-designation-fda-iv-cr845.

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[6] Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2021*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html.

[7] Kobrin, SM. Uremic Pruritis. In: UpToDate, Berns, JS, Motwani, S (Ed), UpToDate, Waltham, MS (Accessed on June 2, 2021).

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[9] PubMed. Normalization of uremic skin changes following kieney transplantation. Altmeyer P, Kachel HG, Schäfer G, Fassbinder W.- Hautarzt. 1986;37(4):217.

[10] Buonaccorsi, L. Office of Prescription Drug Promotion. Consult Review for Korsuva (difelikefalin) NDA 214916, May 28, 2021.

[11] Division of Dermatology and Dental Products. Draft Unireview for Korsuva (difelikefalin), NDA 214916, August 6, 2021.

[12] Division of Dermatology and Dental Products. Draft Unireview for Korsuva (difelikefalin), NDA 214916, August 6, 2021.

[13] Pisoni RL, Wikstro¨m B, Elder SJ et al. Pruritus in Hemodialysis Patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2006; 21: 3495–3505.

[14] Cara Therapeutics, Inc. (2017 June 23). Cara Receives Breakthrough Therapy Designation from FDA for I.V. CR845 for the Treatment of Chronic Kidney Disease-Associated Pruritus in Hemodialysis Patients [Press release]. https://ir.caratherapeutics.com/news-releases/news-release-details/cara-receives-breakthrough-therapy-designation-fda-iv-cr845.

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