Difelikefalin (KORSUVA) National Drug Monograph September 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Difelikefalin is a kappa opioid receptor (KOR) agonist. Per the product information, the relevance of KOR activation to therapeutic effectiveness is unknown.

Indication(s) Under Review in This Document

- Difelikefalin is indicated for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis.

Dosage Form(s) Under Review

- Difelikefalin is available as a 65 mcg/1.3 mL (50 mcg/mL) solution for injection. The recommended dose is 0.5 mcg/kg by intravenous (IV) bolus injection into the venous line of the dialysis circuit at the end of each hemodialysis treatment. Refer to product information for instructions on preparation and administration.

Clinical Evidence Summary[1-3]

Efficacy Considerations[1-3]

- Approval of difelikefalin is based primarily on data from KALM-1 (U.S. population; published data) and KALM-2 (global population), two phase 3 randomized, double-blind, placebo-controlled trials in patients on hemodialysis with moderate-to-severe pruritus that evaluated treatment with difelikefalin (at a dose of 0.5 mcg/kg three times per week) for 12 weeks.
- The trials included patients with end-stage kidney disease (ESKD) receiving hemodialysis at least three times per week for at least 3 months, with moderate-to-severe pruritus defined as a weekly mean score of more than 4 points on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS), a validated scale with scores ranging from 0 to 10 with higher scores depicting greater itch intensity.
- The primary outcome of the two trials was the percent of patients with a decrease of at least 3 points from baseline in weekly mean score on the WI-NRS. Results of this primary outcome from the publication of KALM-1 are included in Table 1 below. The percent of patients with a decrease of at least 4 points in the weekly mean WI-NRS score was recommended as the primary outcome per FDA review, with results also included in the manufacturer's product information.

Table 1: Primary Outcome Results (KALM-1)[2]

Primary Outcome	Difelikefalin N=189	Placebo N=188
Percent with >=3 point decrease WI-NRS	82/158 (51.9%)	51/165 (30.9%)
Least-squares mean (95% Confidence Interval)	49.1% (36.8 to 61.5)	27.9% (20.5 to 36.8)
Relative Risk (95% Confidence Interval)	1.65 (1.26 to 2.14; P<0.001)	

- In KALM-1, the percent of patients with a decrease of at least 4 points in the weekly mean WI-NRS score was reported as 37.1% (observed 40.5%) with difelikefalin compared to 17.9% (observed 21.2%) of patients in the placebo group (P<0.001). The pre-specified secondary outcomes of mean change from baseline at week 12 in two itch-related quality-of-life instruments, the 5-D itch scale (duration, degree, direction, disability, distribution) total score (difelikefalin -5.0 vs. placebo -3.7) and the Skindex-10 scale (10 questions, rated 0 to 6) total score (difelikefalin -17.2 vs. placebo -12.0), were statistically significantly reduced with treatment compared to placebo.
- In KALM-2 (unpublished data), the percent of patients (observed data) with a decrease of at least 4 points in the weekly mean WI-NRS score was 37% with difelikefalin compared to 26% on placebo (adjusted P=0.01).[1,3]
- In KALM-1, mean baseline WI-NRS scores were 7.1±1.4 and 7.3±1.6 in the difelikefalin and placebo groups, respectively. At baseline, antipruritic medications were used in 38.1% of patients in the difelikefalin treatment group and 41.5% of patients on placebo, with diphenhydramine and hydroxyzine listed as the most commonly used medications. It was noted that the degree of treatment effect was consistent across subgroups stratified by baseline use of antipruritic medications.

Safety Results from Clinical Trials[1-3]

- In KALM-1, adverse events were reported in 68.8% of patients treated with difelikefalin compared to 62.2% on placebo. Serious adverse events occurred in 25.9% of patients on difelikefalin and 21.8% of patients in the placebo group. Discontinuation due to adverse reactions were reported in 7.9% of patients on difelikefalin and 4.8% of patients receiving placebo.
- The most common adverse events reported in KALM-1 and KALM-2 as noted in the product information are included in Table 2 below.

Table 2: Adverse reactions reported in >=2% on difelikefalin and >=1% higher than placebo[1]

Adverse Reactions[a]	Difelikefalin N=424	Placebo N=424
Diarrhea	38 (9.0%)	24 (5.7%)
Dizziness	29 (6.8%)	16 (3.8%)
Nausea	28 (6.6%)	19 (4.5%)
Gait disturbances	28 (6.6%)	23 (5.4%)
Hyperkalemia	20 (4.7%)	15 (3.5%)
Headache	19 (4.5%)	11 (2.6%)
Somnolence	18 (4.2%)	10 (2.4%)
Mental status changes	14 (3.3%)	6 (1.4%)

[a] most common adverse drug reactions

Safety Considerations[1]

- **Boxed warning:** None.
- **Contraindications:** None.
- **Warnings / precautions**:
  - Dizziness, Somnolence, Mental Status Changes, and Gait Disturbances: Dizziness, somnolence, mental 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 difelikefalin.
  - 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 difelikefalin on the patient's ability to drive or operate machinery is known.

Other Considerations[1-6]

- Abuse potential: Difelikefalin is a peripherally restricted, selective KOR agonist. In KALM-1, it was noted that there was no indication of abuse or physical dependence, and no reported adverse events related to withdrawal upon discontinuation of difelikefalin.[2]
- Special patient populations:[1]
    - Hepatic impairment: no clinically significant difference in the pharmacokinetics of difelikefalin were noted in patients with mild to moderate hepatic impairment. As patients with severe hepatic impairment were not evaluated, difelikefalin is not recommended in this population.
    - Geriatric use: patients 65 years of age and older treated with difelikefalin had a higher incidence of somnolence (7.0%) compared to patients less than 65 years (2.8%). The incidence of somnolence was comparable in both age groups receiving placebo (3.0% vs. 2.1%, respectively).
- Direct comparison trials: At this time, there are no direct comparison trials of difelikefalin and other potential treatments for uremic pruritus.[2,3] High quality evidence is available with the gamma-aminobutyric acid (GABA) analogues (primarily with gabapentin, also with pregabalin) in uremic pruritus with a large magnitude of effect.[4-6]

Other Therapeutic Options[1-6]

Difelikefalin and other potential therapies for uremic pruritus available on the VA National Formulary are listed in Table 3 below.

Table 3: Comparison of Available Agents Used for CKD Associated Pruritus

Treatment	Formulary status	Use in uremic pruritus	Other Considerations
Difelikefalin	Non-formulary	Labeled indication for moderate-to-severe pruritus associated with CKD on HD Efficacy:[1-3] decrease >= 4 points in WI-NRS score in 40.5% on difelikefalin vs. 21.2% on placebo	No direct comparison trials Dosing:[1] 0.5 mcg/kg bolus IV injection into venous line dialysis circuit at end of each HD treatment Side effects:[1] diarrhea, dizziness, nausea, gait disturbances, including falls, hyperkalemia, headache, somnolence, mental status change
Gabapentin, Pregabalin	VANF	Off-label use for uremic pruritus Efficacy in uremic pruritus:[4] 4.95 cm reduction on VAS vs. placebo (high certainty evidence); may also reduce uremic pruritus vs. antihistamines (low certainty evidence)	Dosing for uremic pruritus:[5] gabapentin (immediate release) initial 100 mg after dialysis on HD days; may increase per response and tolerability up to 300 mg after dialysis on HD days; pregabalin (immediate release) 50 mg every other day after dialysis on HD days or 25 mg daily, each increased per response and tolerability to 50 or 75 mg daily; 75 mg twice weekly given after dialysis on HD days also option Side effects:[4] somnolence, dizziness, fatigue
Topical analgesics (capsaicin, pramoxine)	VANF	Data in uremic pruritus:[4,5] capsaicin SMD -0.84 vs. vehicle (moderate certainty evidence); pramoxine -1.97 cm lower on VAS vs. vehicle (very low certainty evidence)	Apply to affected area 2 to 4 times daily
Oral antihistamines (e.g., hydroxyzine, diphenhydramine, loratadine)	VANF	Used in pruritus due to allergic conditions, histamine-mediated pruritus[5]	Dosing:[5] hydroxyzine 25 mg 3 to 4 times daily or diphenhydramine 25 mg 3 to 4 times daily. If daytime sedation is bothersome, use of a less sedating agent (e.g., loratadine) has been suggested during the day, with a more sedating agent at night. Side effects: drowsiness, dry mouth, dizziness, cognitive dysfunction, headache, nausea
Montelukast	VANF	Limited data in uremic pruritus;[4,5] SMD -1.40 lower vs. placebo (moderate certainty evidence)	Dosing:[4,5] 10 mg daily Side effects: most common per product information include upper respiratory infection, fever, headache, pharyngitis, cough, abdominal pain, diarrhea, otitis media, influenza, rhinorrhea, sinusitis, otitis
Sertraline	VANF	Limited data in uremic pruritus;[4,5] -1.80 cm lower on VAS vs. placebo (low certainty evidence)	Dosing:[4,5] 50 mg daily used in 8-week trial Side effects (not reported in clinical trial[4]): most common per product information include nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, decreased libido

CKD=chronic kidney disease; HD=hemodialysis; SMD=standardized mean difference; VANF=VA National Formulary; VAS=visual analog scale

Projected Place in Therapy[1-6]

- Uremic pruritis is noted to be common in patients with ESKD, affecting 22% to 57% of patients receiving dialysis.[4,5] It has been reported that 20% to 40% of patients on hemodialysis have moderate-to-severe pruritus associated with CKD.[2,3] Symptoms of pruritus may vary from generalized to more localized primarily affecting the back, or arms, head or abdomen.[5,6] Duration and intensity of symptoms are also variable, and may cause sleep disturbances, mood, and affect quality-of-life.[5,6] Most patients with uremic pruritus will have dry skin, with other skin manifestations as a result of repetitive scratching.[5]
- The cause of uremic pruritus has not been identified, although several possibilities have been proposed including metabolic abnormalities, dialysis technique, systemic inflammation and dysregulated immune system, mast cell hyperactivity, or an imbalance in the opioid system where it is thought that pruritus may be increased by mu-receptor activation and kappa-receptor blockade and decreased by kappa-receptor activation and mu-receptor blockade.[2,4-6] Initial therapy often includes optimization of dialysis, management of hyperparathyroidism and hyperphosphatemia, and use of topical emollients and/or analgesic agents.[3,5] A trial of oral antihistamines are often used,[2,3,5] although data are limited.[4] High quality evidence is available with the GABA analogues (primarily with gabapentin, also with pregabalin) in uremic pruritus with a large magnitude of effect.[4-6] Limited data are also available with montelukast[4-6] and sertraline.[5] Phototherapy may also be considered in refractory patients.[5]
- Difelikefalin is a selective kappa opioid receptor agonist and is thought to reduce uremic pruritus via the opioid receptor system.[1-3] Based on results from two placebo-controlled trials, difelikefalin demonstrated a modest reduction in itch intensity compared to placebo, with the percent of patients with a decrease of at least 4 points in the weekly mean WI-NRS score (recommended primary endpoint per FDA review) reported as 40.5% with difelikefalin compared to 21.2% of patients on placebo in the published U.S. clinical trial.[1-3] In this trial, it was noted that close to 40% of patients were using an antipruritic agent at baseline.[2] The most common side effects with difelikefalin included diarrhea, dizziness, nausea, gait disturbances, including falls, hyperkalemia, headache, somnolence, and mental status changes. In addition, somnolence may occur more frequently in patients over 65 years of age. Per the manufacturer labeling, it is recommended that difelikefalin not be used in patients with severe hepatic impairment.[1]
- Place in therapy:[1-6] As noted above, data are limited as to effective therapies for the management of uremic pruritis. Use of difelikefalin has been recommended in refractory uremic pruritis and may be considered on a limited basis in patients with a diagnosis of moderate-to-severe uremic pruritus after attempts to reduce symptoms through optimization of dialysis, management of hyperparathyroidism and hyperphosphatemia, use of topical emollients and/or analgesic agents (e.g., capsaicin, pramoxine), a trial of oral antihistamines (e.g., diphenhydramine, hydroxyzine, loratadine), and gabapentin (pregabalin if gabapentin not tolerated); due to the modest benefit and significant cost of difelikefalin as well as lack of direct comparison trials, alternate agents (e.g., montelukast, sertraline) may also be considered prior to difelikefalin on an individual basis. Phototherapy may also be considered as a treatment option. If it is determined that difelikefalin is appropriate, the patient should be reassessed for response to treatment (per the U.S. clinical trial, a treatment effect was noted by week 1, with persistence throughout the 12 weeks of treatment) and therapy discontinued if there is not a clinically meaningful reduction in itch intensity (e.g., at least a 3 to 4-point reduction on the WI-NRS) or improvement in itch-related sleep disturbance, mood, or quality of life, or if treatment is not tolerated.

References

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4. Hercz D, Jiang SH, Webster AC. Interventions for itch in people with advanced chronic kidney disease. Cochrane Database Syst Rev 2020, Issue 12. Art. No.: CD011393. DOI: 10.1002/14651858.CD011393.pub2.
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