CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761434Orig1s000

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	BLA
Application Number	761434
PDUFA Goal Date	November 28, 2025
TTT #	2025-14016
Reviewer Name	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Division Director	Suzanne Robottom, PharmD
Review Completion Date	November 19, 2025
Subject	Evaluation of Need for a REMS
Proper Name	sibeprenlimab
Trade Name	Voyxact
Name of Applicant	Otsuka Pharmaceutical Company, Ltd.
Therapeutic Class	A Proliferation Inducing Ligand (APRIL) blocker
Dosage Form	Injection
Dosing Regimen	400 mg administered by subcutaneous injection once every 4 weeks

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Voyxact (sibeprenlimab) is necessary to ensure the benefits outweigh its risks.

Otsuka Pharmaceutical Company, Ltd. submitted a Biologics License Application (BLA) 761434 for sibeprenlimab with the proposed indication (b) (4) in adults with primary immunoglobulin A nephropathy (IgAN). This application is under review in the Division of Cardiology and Nephrology (DCN). During the course of the review, DCN revised the indication to reduce proteinuria in adults with primary IgAN at risk for disease progression. This indication will be approved under accelerated approval based on the review team conclusions that the substantial reduction in proteinuria in the pivotal trial, Study 417-201-0007, was highly statistically persuasive and that substantial reduction in proteinuria was a reasonably likely surrogate endpoint for disease progression in IgAN.

The risks associated with sibeprenlimab include risk of immunosuppression leading to increased risk of infection, risk of interference with immune responses to vaccines, and increased risk of infection from live vaccines. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of sibeprenlimab outweigh its risks. FDA expects the likely prescribers to be familiar with managing the risks since other products for IgAN treatment have similar risks and the identified risks of concern did not rise to the level of a Boxed Warning.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Voyxact (sibeprenlimab) is necessary to ensure the benefits outweigh its risks. Otsuka Pharmaceutical Company, Ltd. submitted a Biologics License Application (BLA) 761434 for sibeprenlimab with the proposed indication (b) (4) (b) (4) in adults with primary immunoglobulin A nephropathy (IgAN). This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Voyxact (sibeprenlimab), a new molecular entity (NME) [a], is an A Proliferation-Inducing Ligand (APRIL) blocker, humanized immunoglobulin G2 (IgG2) monoclonal antibody, (b) (4)

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

[redacted] in adults with primary immunoglobulin A nephropathy (IgAN). Sibeprenlimab is proposed as a 400 mg dose administered by subcutaneous (SC) injection once every 4 weeks chronically.[b] Sibeprenlimab is proposed as a prefilled syringe intended for patient self-administration or for administration by a caregiver or healthcare practitioner. The proposed label includes language that this indication is approved under accelerated approval based on a substantial reduction in proteinuria as a surrogate endpoint, and slowing the loss of kidney function and reducing the risk of kidney failure in IgAN have not been demonstrated. Sibeprenlimab is not currently approved in any jurisdiction. Sibeprenlimab would be the first-in- class APRIL inhibitor approved for use in any indication.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA761434 relevant to this review:

- 11/2/2023: Breakthrough Therapy designation for the treatment of biopsy-confirmed IgAN was granted.
- 3/28/2025: NDA 761434 submission [redacted] in adults with primary immunoglobulin A nephropathy (IgAN) received.
- 7/14/2025: A 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 sibeprenlimab.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

IgAN is a serious kidney disease caused by buildup of immune complexes containing galactose-deficient immunoglobulin A1 (Gd-IgA1) in the kidneys, which leads to loss of kidney function[c]. IgAN is slowly progressive with a loss of glomerular filtration rate (GFR) of 1 to 3 mL/min/1.73m^2/year. IgAN predominantly affects East Asians and Caucasians and is estimated to affect around 200,000 individuals in the United States.[d] The population expected to use sibeprenlimab will likely be less than the estimated incidence since the drug is indicated for a portion of patients with IgAN: adults who are at risk of disease progression.[e] Though the rate of progression of IgAN is typically slow, 20-

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

[c] 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.*

[d] DeCongelio et al., 2025, The incidence and prevalence of immunoglobulin A nephropathy in the United States, Clin Nephrol, 103(1): 19-25.

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

30% of patients with IgAN progress to end-stage kidney disease (ESKD) 10 to 20 years after developing higher proteinuria levels and/or elevated serum creatinine levels. ESKD has high morbidity and mortality as well as a lower life expectancy. IgAN can have a significant impact on health-related quality of life with patients experiencing pain, fatigue, psychological effects, and functional limitations with symptom burden being higher in patients with higher proteinuria and lower estimated glomerular filtration rate (eGFR).[f]

3.2. Description of Current Treatment Options

The *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of IgAN*, updated in 2025, recommends initiating treatment with dual therapies that prevent or reduce pathogenic IgA production and IgA/IgA and IgA/IgG immune complex formation along with therapies to manage the consequences of existing IgAN-induced nephron loss.[g] To achieve the first aim, targeted-release budesonide (Nefecon), an oral corticosteroid, or reduced-dose systemic corticosteroid therapy is recommended. To manage the consequences of existing IgAN-induce nephron loss, recommendations include healthy lifestyle education and modifications, lowering blood pressure, and the use of renin-angiotensin system inhibitors (RASi) or a dual endothelin angiotensin receptor antagonists (DEARA) (eg. sparsentan), with or without sodium-glucose cotransporter-2 (SGLT2) inhibitors.[g] A RASi, such as an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocked (ARB), is first-choice drug intervention in all patients with IgAN. Patients at risk of progressive loss of kidney function with IgAN can be treated with sparsentan, a DEARA, replacing a RASi. The 2025 guidelines also suggest that patients at risk of progressive loss of kidney function be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i), used off-label.

Two medications have been granted accelerated approval to reduce proteinuria in adults with IgAN at risk of rapid disease progression: Fabhalta (iptacopan) and Vanrafia (atrasentan).

Fabhalta (iptacopan) was approved on December 5, 2023, with a REMS to ensure that the benefits of the drug outweigh the risk of serious infections caused by encapsulated bacteria. The most recently approved REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU consist of prescriber certification, pharmacy certification, and dispensing of Fabhalta with evidence or other documentation of safe-use conditions.

Filspari (sparsentan) was approved on February 17, 2023, with a REMS to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity and hepatotoxicity associated with Filspari. The Filspari REMS was modified August 27, 2025, to remove references to the risk of embryo-fetal

[f] Tang, 2025, Clinical and Humanistic Burden of IgA Nephropathy in Adult Patients, Kidney360, 6:121-132.

[g] Floege et al., 2025, KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), Kidney International, 108(Suppl 4S), S1-S71.

toxicity since it was determined that a REMS is no longer necessary to ensure the benefits of Filspari outweigh the risk of embryo-fetal toxicity.[h] The most recently approved REMS aims to ensure the benefits of Filspari outweigh the risk of hepatotoxicity and consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU consist of prescriber certification, pharmacy certification, dispensing of Filspari to patients with evidence or other documentation of safe-use conditions, and each patient is subject to certain monitoring.

Recommendations for the treatment of patients with IgAN are listed in Table 1. IgAN is now understood to be progressive if not adequately treated. There is still unmet need for effective treatments with improved safety profiles that can slow the loss of kidney function in patients with IgAN.

Table 1: Summary of Treatment Options Relevant to IgAN

Trade Name (Generic) Year of Approval	Place in Therapy	REMS	Boxed Warning
FDA Approved Treatments			
Tarpeyo [investigational name Nefecon] (budesonide) 2023	Targeted release budesonide to treat the immune aspect of IgAN	No	No
Filspari (sparsentan) 2024	In patients at risk of progressive loss of kidney function, sparsentan should replace a RASi	Yes (Hepatotoxicity)[i]	Yes (Hepatotoxicity)
Fabhalta (iptacopan) 2024	Not routinely used. Accelerated Approval; Phase 3 study in progress	Yes (Serious infections caused by encapsulated bacteria)	Yes (Serious infections caused by encapsulated bacteria)

[h] Caruth, B. DRM. REMS Modification Rationale Review for Endothelin Receptor Antagonists, Filspari (NDA 216403), March 6, 2025.

[i] The Filspari REMS was modified on August 27, 2025, because it was determined that a REMS is no longer necessary to ensure the benefits of the drug outweigh the risk of embryofetal toxicity.

Table 1 (continued): Summary of Treatment Options Relevant to IgAN

Trade Name (Generic) Year of Approval	Place in Therapy	REMS	Boxed Warning
FDA Approved Treatments (continued)			
Vanrafia (atrasentan) 2025	An endothelin receptor antagonist with Accelerated Approval based on a reduction of proteinuria; Phase 3 study in progress	No	Yes (Embryo-fetal toxicity)
Other Treatments			
ACEi or ARB	Initial supportive care in patients with proteinuria ≥ 0.5 grams per day (not to be given in addition to sparsentan)	No	Yes (fetal toxicity)
SGLT2i	Add-on therapy in patients at risk of progressive loss of kidney function. Also reduce incidence of adverse cardiovascular events.	No	No

4. Benefit Assessment

The pivotal trial (Study 417-201-00007, National Clinical Trial [NCT] 05248646) supporting this application consisted of an ongoing, phase 3, multicenter, randomized, double-blind, placebo-controlled trial which evaluated sibeprenlimab 400 mg SC every 4 weeks compared to placebo, for 26 doses, with the last dose on Week 100. Subjects were adults who had biopsy-proven IgAN at risk of progressive loss of renal function and were required to receive standard of care (maximally tolerated and stable dose of an ACEi and/or ARB throughout the trial; an SLGT2 was also allowed if stable dose and initiated at least 3 months prior to screening). Most subjects in the trial (n=510, main cohort) had a baseline eGFR ≥30 mL/min/1.73 m^2, but an exploratory cohort (n=20) consisted of subjects with an eGFR ≥20 and <29 mL/min/1.73 m^2. Study 417-201-00007 primary efficacy endpoint for the interim analysis was change from baseline in 24-hour urine protein-to-creatinine ratio (uPCR) to week 40 (9 months) achieved with Sibeprenlimab versus placebo in addition to standard of care. The Division accepted a substantial reduction in proteinuria as a reasonably likely surrogate endpoint for disease progression (loss of kidney function) in IgAN and as a basis for accelerated approval. [jk] The efficacy analysis to support accelerated approval was based on the first 320 subjects with an eGFR ≥30 mL/min/1.73 m^2 who had completed or

[j] 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.*

[k] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Cardiology and Nephrology. Integrated Review: Voyxact (Sibeprenlimab), BLA 761434 Draft as of October 20, 2025.

discontinued the trial prior to the Week 40 visit. The Review Team determined Study 417-201-00007 met its primary endpoint of change from baseline in 24-hour uPCR to Week 40 with a statistically persuasive p-value (one-sided p<0.0001).[k] At Week 40, uPCR was reduced 51% (95% CI: 43%, 58%) from baseline in subjects treated with Sibeprenlimab compared to placebo.

The Review Team accepted interim analysis results for a subgroup of subjects with IgAN enrolled in a phase 2 trial (Study VIS649-201, [NCT 04287985]) as confirmatory evidence of effectiveness.[k] Study VIS649-201 was a phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of sibeprenlimab 2, 4, and 8 mg/kg intravenous (IV) compared with placebo in adult subjects with biopsy-proven IgAN and a uPCR ≥0.75 gram/gram from a 24-hour urine sample. At Month 9, uPCR was reduced 50% (95% CI: 18%, 70%) from baseline in the sibeprenlimab 4 mg/kg IV dose (the dose most comparable to the 400 mg SQ dose) subjects (n=41) compared to placebo.

The Agency determined the (b) (4) slow kidney function decline over the long-term in patients with IgAN has not been established.[k] During the course of the review, DCN revised the indication to reduce proteinuria in adults with primary IgAN at risk for disease progression. This indication will be approved under accelerated approval based on a substantial reduction in proteinuria. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

5. Risk Assessment & Safe-Use Conditions

The primary safety population for sibeprenlimab consists of all subjects in the randomized population who received sibeprenlimab 400 mg SC or placebo in the pivotal phase 3 trial, Study 417-201-0007. Study VIS649-201, the phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of sibeprenlimab IV compared with placebo, provides additional supportive safety data.

The full primary safety population for Study 417-201-0007 includes 259 subjects randomized to sibeprenlimab 400 mg vs 251 subjects randomized to placebo (510 total subjects), with treatment duration range from 4 to 105 weeks. Serious adverse events (SAEs) occurred in 9 subjects (3.5%) in the sibeprenlimab group compared with 11 (4.4%) subjects in the placebo group. One subject in the sibeprenlimab group experienced an SAE (chromaturia) that resulted in discontinuation of the study drug. The Clinical Reviewer determined two subjects in the sibeprenlimab group experienced COVID-19, but no other SAE was reported in more than one subject, and there was not an imbalance in the incidence of SAEs between treatment groups.[k]

A safety analysis was also conducted on the subpopulation who completed the 9-month (Week 40) uPCR-24h evaluation by the data cutoff date of September 4, 2024 (interim analysis [IA] safety set: 320 total subjects, 152 sibeprenlimab, 168 placebo). Additionally, a safety analysis for the 20 subjects from the exploratory cohort (eGFR 20 to 29mL/min/1.73 m^2) was reviewed. The Clinical Reviewer determined these analyses did not reveal additional safety concerns.[k]

A study pool was used to evaluate the Applicant prespecified adverse events of special interest (AESIs) due to sibeprenlimab's mechanism of action as an APRIL inhibitor. The AESIs include infections, injection site reactions, and hypersensitivity. The pooled safety data consist of the first 9 months of the double-blind treatment periods of Study 417-201-0007 (of the IA safety set) and Study VIS649-201 (155 total subjects: 117 sibeprenlimab, 38 placebo) for subjects who received any amount of treatment. In the AESI analysis, the majority of infections were mild or moderate in severity and resolved without treatment interruptions or discontinuation and there were no important imbalances in the incidence of bacterial infections between treatment groups. Similarly, the majority of injection site reactions in Study 417-201-00007 were mild in severity and resolved on the same day as treatment administration and the incidence of infusion site reactions was low in Study VIS649-201. There were three hypersensitivity-related treatment emergent adverse events (TEAEs) in sibeprenlimab-treated patients. Two hypersensitivity events were mild in severity, and the third event was in one subject in Trial VIS649-201 that had an anaphylactic reaction, which appeared to be related to contrast agent and not related to sibeprenlimab.

There were no deaths observed in Study 417-201-00007 by the cutoff date (September 4, 2024). In Study VIS649-201 there was one death in the placebo group.

The labeling[l] will include warnings and precautions for the following risks: risk of immunosuppression leading to increased risk of infection, risk of interference with immune responses to vaccines, and increased risk of infection from live vaccines. These risks are known risks in the APRIL blockers due to their mechanism of action in modulating the immune system. While the study population was small, no other new or serious risks were identified; no other safety signals were identified for this product. The Clinical Reviewer concluded labeling is adequate to mitigate the potential risks and to ensure the benefits of sibeprenlimab outweigh the risks.[k]

6. Expected Postmarket Use

The likely prescribers for sibeprenlimab are nephrology specialists familiar with IgAN and treatment strategies that modulate immune response and currently prescribe other medications associated with increase of infection. If approved, sibeprenlimab will likely be dispensed from outpatient specialty pharmacy settings and primarily be self-administered by the patient at home. Based on the anticipated medication use process, monitoring for signs and symptoms of infection will be primarily handled by the patient/caregiver. Scheduling of live vaccines while taking sibeprenlimab should be a collaborative effort between the prescriber and the patient or patient's caregiver.

No concerning care gaps have been identified within the intended scope of practice. Labeling is sufficient to ensure the safe use of sibeprenlimab in the expected postmarket setting.

[l] Otsuka Pharmaceutical Company, Ltd. Voyxact (sibeprenlimab). NDA 761434 (sequence 0033). Draft Prescribing Information with Agency Edits as of November 5, 2025.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of sibeprenlimab outweigh the risks. FDA expects the likely prescribers to be familiar with managing the risks related to immunosuppression and infection because other products they prescribe (e.g., budesonide, systemic glucocorticoids, cyclophosphamide) also carry these similar risks. Furthermore, the severity of the risk of immunosuppression and increased risk of infections was not determined to rise to the level warranting a Boxed Warning.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sibeprenlimab beyond routine pharmacovigilance and labeling. The Applicant states that "no additional risk management or monitoring programs are warranted beyond routine labeling and risk mitigations."

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for sibeprenlimab 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRISTEN M LAMBERT
11/19/2025 02:21:06 PM

YASMEEN I ABOU-SAYED
11/19/2025 03:32:05 PM

SUZANNE B ROBOTTOM
11/19/2025 04:59:24 PM