New Drug Overview

Voyxact (sibeprenlimab-szsi)

PDL Category: Immunological Agents

Introduction

Disease Background:

- Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide, requiring a kidney biopsy for diagnosis (*Zhou et al 2026*).
  - It is described by changing degrees of glomerular hematuria, proteinuria, and progressive chronic kidney disease (*Zhou et al 2026*).
  - It is accompanied with a significant lifetime risk of kidney failure (*Heerspink et al 2025*).
    - It is estimated that approximately 25-30% of patients develop chronic kidney disease and end-stage renal disease (ESRD) about 20-25 years once diagnosed (*Zhou et al 2026*).
  - Of patients with higher proteinuria levels and/or elevated serum creatinine levels, ESRD progression is about 15% to 25% at 10 years and 20% to 30% at 20 years (*Cattran et al 2025*).
- While IgAN may occur at any age, a peak incidence is observed in the second and third decades of life. In North America and Western Europe, it occurs more in males than females for both adults and children; however, in East Asia, males and females are equally affected (*Cheung and Barratt 2024*).
- It is caused by deposits of IgA in the kidney (*Zhou et al 2026*).
- Patients with IgAN may exhibit a spectrum of clinical appearances. Most patients present with either gross hematuria (40% to 50% have one or recurrent episodes), often occurring with an upper respiratory infection, or microscopic hematuria with or without mild proteinuria (30% to 40%). Less than 10% of patients appear with either nephrotic syndrome or an acute, rapidly progressive glomerulonephritis depicted by edema, hypertension, hematuria, and renal impairment. Infrequently, acute kidney injury with or without oliguria may develop due to crescentic IgAN or to hematuria causing tubular occlusion and/or damage by red cells (*Cheung and Barratt 2024*).
- The main goal of therapy is prevention of disease progression to ESRD (*Cattran et al 2025*).
  - Goals include proteinuria reduction, stabilizing eGFR, and resolution of microscopic hematuria,
    - Proteinuria is a dominant risk for disease progression; the goal is reduction of proteinuria to < 0.5 g/day in adults.
- In general, all patients with IgA nephropathy should receive supportive care, which includes therapy to reduce proteinuria and glomerular hyperfiltration, controlling blood pressure, dyslipidemia treatment (if needed), and lifestyle modifications (which may include dietary sodium and protein restriction, smoking cessation, weight control, and exercise as appropriate) (*Cattran et al 2025*).
  - If diagnosed with IgAN and have proteinuria ≥0.5g/day, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) is recommended (*Cattran et al 2025*).
    - Reasonable alternatives in patients not able to tolerate an ACE inhibitor or an ARB may include a sodium-glucose cotransporter 2 (SGLT2) inhibitor, an endothelin receptor antagonist, or a dual endothelin angiotensin receptor antagonist (*Cattran et al 2025*).
- Voyxact was FDA approved in 2025.

Pharmacology/Usage

- Voyxact (sibeprenlimab-szsi) is an A Proliferation Inducing Ligand (APRIL) blocker and humanized immunoglobulin G2 (IgG2) monoclonal antibody produced by Chinese Hamster Ovary (CHO) cells. It is preservative free.
  - It binds to APRIL with a dissociation constant (K_D) of 0.95 pM, which blocks signaling at the B cell maturation antigen (BCMA) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptors. Inhibition of APRIL results in reduced levels of serum galactose-deficient immunoglobulin A1 (Gd-IgA1), which is implicated in the pathogenesis of IgAN.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Voyxact (sibeprenlimab-szsi)
• To reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for disease progression.*	✔

***This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether Voyxact slows kidney function decline over the long-term in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.**

(Prescribing information: Voyxact 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Voyxact (sibepren-limab-szsi)	Solution for Injection, in single-dose prefilled syringe	SC	Subcutaneous (SC) injection once every 4 weeks	• Intended for patient self-administration or administration by a caregiver after proper training. • Allow syringe to come to room temperature for 15-30 minutes before giving an injection. Do not use if it has been at room temperature for 7 days or longer. • For SC injection only, to be injected into the front of the thigh or abdomen. The back of the upper arm can also be used as an injection site if administered by a caregiver. • If a scheduled dose is missed, administer the dose as soon as possible and then

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				resume dosing every 4 weeks thereafter.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Voyxact was assessed in a randomized, double-blind, placebo-controlled, multicenter, global study (VISONARY) that included adults with biopsy-confirmed IgAN, an estimated glomerular filtration rate (eGFR) ≥30ml/min/1.73m^2, proteinuria (defined as either urine protein/creatinine ratio based on 24-hour urine collections [uPCR-24hr] ≥0.75g/g or urine protein ≥1.0g/day), and on a stable and maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) with or without a sodium-glucose co-transporter 2 inhibitor (SGLT2i).
  - Those with other glomerulopathies or those who had been treated with systemic immunosuppressants in the 16 weeks prior to screening were excluded.
- Patients (N=510) were randomized to receive either Voyxact or placebo SC.
  - An interim analysis for efficacy was conducted on the first 320 randomized patients (63%) who had the opportunity to reach the month 9 visit, 152 of whom were randomized to receive Voyxact while 168 were randomized to receive placebo.
    - Baseline demographics and disease characteristics were generally balanced between treatment groups.
      - At baseline, the median age of included patients was 42 years (range 18 to 83 years), while 63% were male and 59% were Asian.
      - At baseline, mean uPCR-24hr was 1.5g/g, mean eGFR was 63ml/min/1.73m^2, and 74% had hematuria (based on urine dipstick).
      - At baseline, 98% were treated with an ACEi and/or ARB and 40% of patients were also on an SGLT2i.
- The primary endpoint was the relative change from baseline in uPCR-24h at month 9.
  - The mean estimated percent change compared to baseline in uPCR-24h at month 9 was -50% in the Voyxact group vs 2% in the placebo group, with a treatment difference of 51% ($p<0.0001$).
- The treatment effect (percentage reduction in uPCR-24h between Voyxact and placebo) was consistent across the following subgroups and pre-specified stratification factors, including sex, age, race, ethnicity, geographic region, baseline proteinuria (uPCR-24h), baseline eGFR, and SGLT2i use.

Clinical guidelines

- Note that Voyxact was not included in this guideline as it was FDA approved after the guidelines were published.
- **Kidney Disease Improving Global Outcomes (KDIGO) 2025 clinical practice guideline for the management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)** (*KDIGO 2025*)
  - If proteinuria is ≥0.5g/day (or equivalent), then patients with IgAN are at risk of progressive kidney function loss, and treatment (or additional treatment) should be considered.
  - Treatment of IgAN in patients at risk of progressive kidney function loss and who do not have a variant form of primary IgAN:
    - Managing patients should include preventing or reducing IgA complex formation and governing the consequences of current IgAN-induced nephron loss. The latter should include.
      - Lifestyle modification, such as dietary sodium restriction, smoking cessation, control of weight, and exercise.
      - Blood pressure management, with a goal of ≤120/70mmHg.

- Using renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism (DEARA), either as monotherapy or in combination with a sodium-glucose cotransporter-2 inhibitor (SGLT2i).
  - It is recommended that all patients be treated with maximally tolerated doses of an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin II receptor blocker (ARB).
  - It is suggested if patients are at risk of progressive kidney function loss with IgAN, that they be treated with sparsentan (should not be combined with a RAS inhibitor).
  - It is suggested that if patients are at risk of progressive kidney function loss with IgAN, that they be treated with an SGLT2i.
- Addressing CV risk

○ It is not likely that drugs newly approved for IgAN will be used in resource-limited settings, due to accessibility and affordability.
○ Note that sibeprenlimab-szsi was listed in a table discussing phase 3 clinical trials and the status of the study was in follow-up as of July 2024 per the guidelines.
○ Antiplatelet agents, anticoagulants, azathioprine, cyclophosphamide, calcineurin inhibitors, rituximab, and fish oil are not recommended in IgAN.

Safety summary

- **Contraindications:**
  ○ In patients with serious hypersensitivity to sibeprenlimab-szsi or any of the excipients of the product.

- **Box Warning:** None.

- **Warnings and precautions:**
  ○ Voyxact suppresses the immune system by reducing antibody production, which may increase the risk of infections. Patients with chronic or recurring infections may have an increased risk of serious infection.
    - Before starting Voyxact, assess patients for active infections. During treatment, monitor patients for signs and symptoms of infection. If a serious infection develops, consider interrupting Voyxact until the infection is controlled.
    - There are limited clinical study data with concomitant use of Voyxact and systemic immunosuppressants. Consider the potential for increased immunosuppression when co-administering Voyxact and immunosuppressants or when starting Voyxact before or after immunosuppressive therapy.
  ○ Due to its mechanism of action, Voyxact may interfere with the immune responses to vaccines and increase the risk of infection from live vaccines. Live vaccines are not recommended within 30 days prior to initiation of Voyxact or during treatment with Voyxact as safety has not been established.
    - No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Voyxact or on the efficacy of immunizations administered while receiving Voyxact.

- **Common adverse drug reactions**: Listed % incidence for adverse drug reactions= reported % incidence for drug (Voyxact) minus reported % incidence for placebo (reported in ≥10% of patients treated with Voyxact and at a higher incidence than placebo). Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  ○ The most frequently reported adverse events included infections (4%) and injection site reactions (1%).
    - The most common infection was upper respiratory infection (1%), and the most common injection site reaction was injection site erythema (1%).
    - Most adverse reactions were reported as mild or moderate in severity and resolved without treatment interruption or discontinuation.

- **Drug interactions:** None.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.
    - Monoclonal antibodies, such as Voyxact, can be actively transported across the placenta as pregnancy progresses; thus, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy.
    - Pregnant women exposed to Voyxact, or their healthcare providers, should report Voyxact exposure by calling 1-833-869-9228 or visiting www.VOYXACT.com.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide, requiring a kidney biopsy for diagnosis (*Zhou et al 2026*).
  - It is described by changing degrees of glomerular hematuria, proteinuria, and progressive chronic kidney disease.
- Voyxact, a SC injection intended for self-administration, is an APRIL blocker indicated to reduce proteinuria in adults with primary IgAN at risk for disease progression.
  - This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether Voyxact slows kidney function decline over the long-term in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.
- Before starting treatment, assess patients for active infections. During treatment, monitor patients for signs and symptoms of infection. If a serious infection develops, consider interrupting Voyxact until the infection is controlled.
- The efficacy of Voyxact was assessed in a randomized, double-blind, placebo-controlled, multicenter study that included adults with biopsy-confirmed IgAN, an eGFR ≥30ml/min/1.73m^2, proteinuria, and who were on a stable and maximally tolerated dose of an ACEi and/or ARB with or without a SGLT2i.
  - The primary endpoint was the relative change from baseline in uPCR-24h at month 9.
    - Results suggested that the estimated percent change compared to baseline was significantly different between Voyxact and placebo, in favor of Voyxact.
- Current guidelines do not include Voyxact as they were published prior to Voyxact becoming FDA approved. A comparator with Voyxact may include Vanrafia.

- It is recommended that Voyxact should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

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