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Health Technology Briefing
July 2025

Iptacopan for Primary Immunoglobin (IgA) Nephropathy

Company/Developer	Novartis Pharmaceuticals UK Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27443	NICE ID: 10436	UKPS ID: 672385

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Iptacopan is being developed for the treatment of primary IgA Nephropathy (IgAN), a rare and progressive kidney disease that can lead to kidney failure (also known as Berger's disease). IgAN occurs when the IgA protein builds up in the kidneys, causing inflammation. This accumulation impairs the kidneys' ability to filter waste and fluids from the blood effectively, resulting in long-term damage. Symptoms of IgAN include blood and protein in the urine, high blood pressure, and elevated creatinine levels, which indicate reduced kidney function. Patients face health burden due to ongoing kidney damage, and limited treatment options which fail to slow disease progression, and result in further kidney damage, and the need for dialysis or transplant.

Iptacopan is a first-in-class (novel) orally administered drug that works by blocking a protein named factor B, which plays a key role in part of the immune system, called the alternative complement pathway. This pathway is known to be overactive in IgAN. Typically, this pathway protects the body by activating inflammation when needed, but in IgAN patients, it becomes overactive and leads to too much inflammation, which can damage the kidneys. Iptacopan blocks another protein, C3 convertase, from working. This is responsible for breaking down C3, which contributes to inflammation. By inhibiting factor B, iptacopan prevents the activity of C3 convertase. This is expected to reduce inflammatory responses, and kidney tissue injury. If approved, iptacopan could provide a new treatment option for adult patients with IgAN.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Treatment of adult patients with primary immunoglobulin A (IgA) nephropathy (IgAN).[1-4]

Technology

Description

Iptacopan is a proximal complement inhibitor that targets Factor B (FB) to selectively inhibit the alternative pathway. In PNH, inhibition of FB in the alternative pathway of the complement cascade prevents the activation of C3 convertase and the subsequent formation of C5 convertase to control both C3-mediated extravascular haemolysis (EVH) and terminal complement-mediated intravascular haemolysis (IVH).
In C3G, overactivation of the complement alternative pathway leads to deposition of C3 within the glomeruli, triggering inflammation, glomerular injury, and kidney fibrosis. Iptacopan selectively blocks the alternative pathway overactivation by inhibiting the alternative pathway related C3 convertase activity, leading to decreased cleavage of C3 and reduced C3 deposition in the kidney.[2,5-7]

Iptacopan is currently in clinical development for the treatment of IgAN in adults. In the phase III clinical trial (APPLAUSE-IgAN, NCT04578834), participants are given 200mg iptacopan orally twice daily.[2,4,6,8]

Key Innovation

Iptacopan is a first-in-class (novel) complement inhibitor, providing a key innovation in the treatment of IgAN. Iptacopan specifically targets the underlying immunological mechanisms contributing to IgAN progression.[5,9] Current therapies are predominantly non-specific immunosuppressants. Early phase clinical studies supports reductions in proteinuria and stabilisation of kidney function with iptacopan, and that it may offer a novel treatment approach for patients with a high risk of kidney function decline.[2]

Regulatory & Development Status

Iptacopan currently has Marketing Authorisation in the EU/UK for:

- monotherapy in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria who have haemolytic anaemia.[5]
- the treatment of adult patients with complement 3 glomerulopathy (C3G) in combination with a renin-angiotensin system (RAS) inhibitor, or in patients who are RAS-inhibitor intolerant, or for whom a RAS inhibitor is contraindicated.[5]

Iptacopan has the following regulatory designations/awards:

- an Orphan Drug Designation in the EU in October 2020 for the treatment of primary IgAN.[10]
- an Accelerated Approval by the US FDA for the reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression in August 2024.[11]

Iptacopan is also in Phase III/II clinical development for:[12]

- Atypical haemolytic uraemic syndrome
- Immune complex mediated membranoproliferative glomerulonephritis
- Anti-neutrophil cytoplasm antibodies associated vasculitis
- Generalised myasthenia gravis
- Age-related macular degeneration
- Lupus nephritis

Patient Group

Disease Area and Clinical Need

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IgAN is a chronic autoimmune kidney disorder, also known as Berger's disease.[13] It is characterised by the deposition of IgA in the glomeruli, the filtering units of the kidney. This abnormal IgA accumulation triggers inflammation and progressive scarring, leading to a gradual decline in kidney function.[13] While the exact cause is unclear, causal factors include genetic predisposition, abnormal mucosal immune responses, and environmental factors such as infections. Risk factors also include a family history of kidney disease, male sex, and certain ethnic backgrounds, typically East Asian or White European.[14] The condition typically presents in young adults and may be asymptomatic or manifest with haematuria (blood in urine), proteinuria (excess protein in urine), hypertension, and in some cases, progression to kidney failure.[13,15]

IgAN (N02.B1-N02.B6) is the most common glomerulonephritis worldwide, though its prevalence is hard to estimate as people with mild disease do not commonly receive a biopsy diagnosis.[16,17] A systematic review of biopsy-based studies spanning forty countries suggests an overall incidence of at least 2.5 per 100,000 a year in adults.[18] Based on high quality data from European national registries, IgAN point prevalence was estimated at 2.53 per 10,000 in patients of all ages. Prevalence was considerably lower in elderly populations.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends:

- Sparsentan (Filspari) for treating primary IgAN in adults with a urine protein-to-creatinine ratio (UPCR) of 0.75 g/g or more, if it is considered the most suitable treatment option.[20]

- Targeted-release budesonide for treating primary IgAN in adults with a UPCR of 1.5 g/g or more. This is recommended only if it is an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated.[21]

Current pharmacological standard of care includes:[22]

- Blood pressure medication, such as ACE inhibitors or ARBs.
- Sodium-glucose co-transporter 2 inhibitors.
- Immunosuppressants, such as steroids.

Clinical Trial Information

Trial	**APPLAUSE-IgAN; CLNP023A2301;** NCT04578834**; EudraCT** 2020-001049-38**;** (APPLAUSE-IgAN) A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy Patients **Phase III –** Active, not recruiting **Location(s):** 15 EU countries, UK, USA, Canada and other countries **Primary completion date:** October 2025
Trial Design	Randomised, parallel assign, double blind
Population	N=519 (actual); participants with IgAN; aged 18-100 years, with proteinuria (UPCR ≥1 g/g) due to IgA nephropathy, confirmed at screening. All patients must have received supportive care with a stable dose of ACEi or ARB at the locally approved maximum or maximally tolerated dose

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Intervention(s)	Iptacopan 200mg capsules taken orally twice a day
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: • Ratio to baseline in UPCR (sampled from 24h urine collection) at 9 months [Time frame: baseline and 9 months] • Annualised total estimated Glomerular Filtration Rate (eGFR) slope over 24 months). [Time frame: baseline and 24 months] See trial record for full list of other outcomes
Results (efficacy)	The main trial population included 222 patients in the iptacopan group and 221 in the placebo group. The interim efficacy analysis included the first 250 patients who were randomised (125 in each group) and, who either remained in the trial until month 9 or discontinued before month 9. At month 9, the adjusted geometric mean 24-hour UPCR was 38.3% lower with iptacopan compared to placebo (95% confidence interval, 26.0 to 48.6; P < 0.001). This reduction in proteinuria was supported by consistent findings in secondary endpoint analyses.[23]
Results (safety)	There were no unexpected safety findings with iptacopan. The incidence of adverse events during the treatment period was similar in both groups, with most events being mild to moderate in severity and reversible. Importantly, no increased risk of infection was observed.[23]

Trial	**CLNP023A2002B; NCT04557462; EudraCT 2020-002200-40;** A Multicenter Rollover Extension Program (REP) to Evaluate the Long-term Safety and Tolerability of Open Label Iptacopan in Adult Participants With Primary IgA Nephropathy Who Have Completed Study CLNP023X2203 or CLNP023A2301 **Phase III –** Active, recruiting **Location(s):** 12 EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2032
Trial Design	Non-randomised, open-label, single-arm interventional
Population	N=540 (estimated); participants with IgAN; aged 18-100 years
Intervention(s)	Iptacopan 200mg capsules taken orally twice a day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures are the number and percentage of participants [from date of first administration of study treatment (day 1) to 7 days after the date of the last actual administration of study treatment] with: • Serious adverse event • Adverse event • Adverse events of special interest • Abnormalities in vital signs • Abnormalities in electrocardiogram ECG

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	• Abnormalities in clinical laboratory evaluations See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**CLNP023X2203; NCT03373461; EudraCT 2017-000891-27;** An Adaptive Seamless Randomized, Double-blind, Placebo-controlled, Dose Ranging Study to Investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy Patients **Phase II -** Completed **Location(s):** 8 EU countries, UK, and other countries **Primary completion date:** June 2021
Trial Design	Randomised, parallel assignment, double blind
Population	N=112 (actual); participants with IgAN; aged 18-100 years
Intervention(s)	Iptacopan (LNP023) 10 mg, 50 mg, 100 mg or 200mg capsules taken orally twice a day
Comparator(s)	Iptacopan matching placebo
Outcome(s)	Primary outcome measure: • Ratio to baseline of UPCR [Time frame: baseline and day 90] See trial record for list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Trial	**CLNP023A2201; NCT06797518;** A Multicenter, Single Arm, Open Label Biopsy Study to Evaluate Structural and Functional Changes in Kidneys of Adult Patients With IgA Nephropathy Receiving Iptacopan on Top of Supportive Care **Phase II –** Not yet recruiting **Location(s):** No location data available **Primary completion date:** December 2027
Trial Design	Non-randomised, open label, single group assignment
Population	N=20 (estimated); participants with IgAN; aged 18-99 years
Intervention(s)	Iptacopan 200mg capsules taken orally twice a day
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure:

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	• Proportion of participants achieving a reduction of minimum one order of magnitude in complement C3 mesangial deposition. [Time frame: baseline, month 9] See trial record for list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price of iptacopan is £26,500 (Hospital only) for 56 x 200mg capsules (list price).[24]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Atrasentan for treating primary IgA nephropathy (ID6588). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Sibeprenlimab for treating IgA nephropathy (TSID12111). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Targeted-release budesonide for treating primary IgA nephropathy (review of TA937) (ID6485). Expected December 2025.
- NICE technology appraisal in development. Sparsentan for treating primary IgA nephropathy (ID6308). June 2025.
- NICE technology appraisal. Targeted-release budesonide for treating primary IgA nephropathy. (TA937). December 2023.

NHS England (Policy/Commissioning) Guidance

None identified.

Other Guidance

- Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. October 2021.[25]

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