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Health Technology Briefing
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Obinutuzumab for treating primary membranous nephropathy

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30811	NICE ID: Not Available	UKPS ID: 663138

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Obinutuzumab is being developed as a treatment for primary membranous nephropathy (pMN). Membranous nephropathy (MN) is an immune system condition that causes too much fluid to be retained in the body and too much protein to be lost in the urine (proteinuria). MN happens when the immune system mistakenly attacks the filters in the kidneys. This causes swelling or puffiness (oedema), high blood pressure and extreme tiredness. Most cases of pMN only affects the kidneys (primary) where as some cases happen along with other illnesses or triggers. Despite the treatments currently available, many people do not get better, about 20–40% of people do not respond to treatment. Therefore, there is a need for new treatments that are both more effective.

Obinutuzumab is given through a drip into the vein (intravenous infusion). It is a type of monoclonal antibody (a specifically designed protein with a specific attachment site). Obinutuzumab can attach to the protein CD20, which is found on B-cells (a type of white blood cell involved in the immune system). Obinutuzumab works by targeting and removing these B-cells, which helps lower the levels of harmful antibodies and reduces kidney damage. If licensed (approved), obinutuzumab will provide a new treatment option to pMN patients.

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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Proposed Indication

Treatment for primary membranous nephropathy (pMN).[1]

Technology

Description

Obinutuzumab (Gazyvaro, Gazyva) is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype.[1,2] It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies.[2]

Obinutuzumab is currently in clinical development for the treatment of pMN in adults. In the phase III clinical trial (MAJESTY, NCT04629248), participants are administered intravenous (IV) infusion of 1000 mg of obinutuzumab at week 0, week 2, week 24, and week 26.[1]

Key Innovation

Although current anti-CD20 monoclonal antibody therapy is favoured as part of the initial therapy in pMN, a subgroup of membranous nephropathy (MN) patients may be resistant to current therapies, necessitating the use of alternative agents such as cytotoxic therapies.[3] Therefore, there is an unmet need for well-tolerated, effective treatments of pMN.

Obinutuzumab has superior in vitro B-cell cytotoxicity compared with current anti-CD20 treatments. Obinutuzumab is directed at a different epitope on CD20 and can evoke a greater B-cell apoptotic response.[4] Obinutuzumab has shown to be an effective and safe treatment for patients resistant to current anti-CD20 therapy.[5] If licensed, obinutuzumab will provide a new treatment option for patients with pMN.

Regulatory & Development Status

Obinutuzumab is currently marketed in the EU/UK in combination with other technologies for the following indications for the following indications:[2]

- Previously untreated chronic lymphocytic leukemia (CLL) and with comorbidities making them unsuitable for full dose fludarabine based therapy
- Previously untreated advanced follicular lymphoma (FL)
- FL that has progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Obinutuzumab is also in phase III/II clinical development for:[6]

- Non-Hodgkin's lymphoma
- Lymphoma
- Richter syndrome
- Lupus nephritis
- Systemic lupus erythematosus
- Idiopathic nephrotic syndrome
- CLL
- FL

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- Diffuse large B-cell lymphoma
- Mantle cell lymphoma
- Graft vs. host disease

Patient Group

Disease Area and Clinical Need

Membranous nephropathy (MN) is a type of glomerulonephritis. Glomerulonephritis means inflammation of the filters in the kidney known as glomeruli. The glomeruli filter the blood as it passes through the kidneys and urine is made. Nephropathy means disease of the kidney. In membranous nephropathy, the glomeruli in the kidney are damaged and the membranes of the glomeruli become thickened. This results in large amounts of protein leaking from the blood into the urine. Healthy kidneys do not leak any protein in the urine.[7] About 80% of MN cases are renal limited (pMN) and 20% are associated with other systemic diseases or exposures (secondary MN).[8] Symptoms of MN include swelling or puffiness (odema) in different parts of the body, especially around the eyes and ankles. Additionally, high blood pressure, which can damage the structure of the kidney if left untreated, and extreme tiredness.[9] Left untreated, two-thirds of patients with MN can develop nonprogressive chronic kidney disease or progress to end-stage renal disease in 10 years.[4] Risk factors include age - it most commonly occurs above 40 years of age, with the peak incidence between 50 to 60 years. It is more common in males than females and tends to show a better outcome in females.[10] MN can occasionally run in families, although no genetic basis has yet been found.[9]

MN affects around 1 in 100,000 people in the UK.[9] MN is the second most common nephropathy in adults. The incidence is 8 to 10 cases per 1 million population worldwide.[10] In England, 2024-25, there were 844 finished consultant episodes (FCE) and 698 admissions for nephrotic syndrome - diffuse membranous glomerulonephritis(ICD-10 code N04.2) which resulted in 1254 FCE bed days and 576 day cases.[11]

Recommended Treatment Options

There is no treatment option recommended by NICE for pMN. However, NHS Clinical Priorities Advisory Group recommend rituximab as a routine commissioning treatment option for idiopathic MN in adults.[12]

Treatment for MN is based on the perceived risk of kidney damage. If there is minimal risk, a 'watch and wait' approach is used for around six months. Medication is still likely to be prescribed during this time. This may include:

- Angiotensin receptor blockers or angiotensin-converting enzyme (ACE) inhibitors to reduce the loss of protein in the urine.
- Diuretics (water tablets) to help the body get rid of excess water to control any swelling.

If further treatment is needed, immunosuppressants medicines may be prescribed. This may include steroids to dampen the immune system.[9]

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Clinical Trial Information

Trial	**MAJESTY;** NCT04629248, EudraCT 2020-003233-38, CTIS 2023-506525-11-00; A Phase III Randomized, Open-Label Active Comparator-Controlled Multicenter Study to Evaluate Efficacy and Safety of Obinutuzumab in Patients With Primary Membranous Nephropathy **Phase III** - Active, not recruiting **Location(s):** Four EU countries, USA and six other countries **Primary completion date:** December 2025 (Estimated)
Trial Design	Randomised, parallel assignment, open label
Population	N = 142; participants with diagnosis of pMN; aged 18 to 75 years old.
Intervention(s)	• Obinutuzumab 1000 mg (IV) • Methylprednisolone 80 mg (IV) • Acetaminophen (650-1000 mg, or equivalent dose of a similar agent) (IV) • Diphenhydramine (50 mg, or equivalent dose of a similar agent) (IV)
Comparator(s)	Oral tacrolimus
Outcome(s)	Primary outcome: Percentage of participants who achieve a Complete Remission (CR) at Week 104 [Time Frame: Week 104]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Obinutuzumab is already marketed in the UK for the treatment of CLL and FL; a 1000mg/40ml vial (25mg/ml) costs £3,312 (NHS indicative price).[13,14]

Relevant Guidance

NICE Guidance

There is currently no NICE guidance for pMN.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy. Rituximab for idiopathic membranous nephropathy (Adults) (2012). 201005P. October 2022.

Other Guidance

- Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the management of Glomerular Diseases. 2021.[15]

Additional Information

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