



**CLINICAL PRIORITIES ADVISORY GROUP
18 07 2022**

Agenda Item No	5.2
National Programme	Internal Medicine
Clinical Reference Group	Renal Services CRG
URN	2012

Title
Rituximab for idiopathic membranous nephropathy in Adults

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval at CPAG prioritisation

Proposition
<p>For routine commissioning.</p> <p>Rituximab to be available as a routine commissioning treatment option for adults with idiopathic membranous nephropathy who are intolerant or have contraindications to cytotoxic therapy.</p> <p>Some centres have offered Rituximab for this indication, so this policy proposition is to clarify the commissioning position and obtain the associated investment, if supported.</p>

Clinical Panel recommendation
<p>Rituximab to be prescribed as a first line routine commissioning treatment for adults with idiopathic membranous nephropathy and who are intolerant or have contraindications to cytotoxic therapy.</p>

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Head of Acute Programmes Programme confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of rituximab compared with current treatment (calcineurin inhibitors, alkylating agents, or no rituximab treatment)?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Remission of proteinuria	This outcome is important to patients because a remission of proteinuria is a strong predictor of reduced risk of decline in kidney function.
Certainty of evidence: Low to high	<p>In total 3 RCTs provided evidence relating to remission of proteinuria in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with ciclosporin (a calcineurin inhibitor), 1 study compared rituximab with cyclophosphamide (an alkylating agent) and corticosteroids, and 1 study compared rituximab with supportive therapy (no rituximab treatment).</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin.</p> <p>Complete or partial remission at 6 months:</p>

- *no statistically significant difference* in complete or partial remission in the rituximab group (23/65, 35%) compared with the ciclosporin group (32/65, 49%) (risk difference -14%, 95% CI -31 to 3%). **(MODERATE)**

Complete or partial remission at 12 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (39/65, 60%) compared with the ciclosporin group (34/65, 52%) (risk difference 8%, 95% CI -9 to 25%). **(MODERATE)**

Complete or partial remission at 18 months:

- *statistically significant increase* in complete or partial remission in the rituximab group (40/65, 62%) compared with the ciclosporin group (15/65, 23%) (risk difference 38%, 95% CI 23 to 54%). **(HIGH)**

Complete or partial remission at 24 months:

- *statistically significant increase* in complete or partial remission in the rituximab group (39/65, 60%) compared with the ciclosporin group (13/65, 20%) (risk difference 40%, 95% CI 25 to 55%, p<0.001). **(HIGH)**

Rituximab compared with cyclic cyclophosphamide and corticosteroid

One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.

Complete or partial remission at 6 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (19/37, 51%) compared with the cyclic cyclophosphamide and corticosteroid group (24/37, 65%) (OR 0.57, 95% CI 0.22 to 1.45). There was *no statistically significant difference* in complete remission in the rituximab group (3/37, 8%) compared with the cyclic cyclophosphamide and corticosteroid group (2/37, 5%) (OR 1.54, 95% CI 0.24 to 9.80). **(LOW)**

Complete or partial remission at 12 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (23/37, 62%) compared with the cyclic cyclophosphamide and corticosteroid group (27/37, 73%) (OR 0.61, 95% CI 0.23 to 1.63). There was *no statistically significant difference* in complete remission in the rituximab group (6/37, 16%) compared with the cyclic cyclophosphamide and corticosteroid group (12/37, 32%) (OR 0.40, 95% CI 0.13 to 1.23). **(LOW)**

Complete or partial remission at 18 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (21/32, 66%) compared with the cyclic cyclophosphamide and corticosteroid group (27/34, 79%) (OR 0.49, 95% CI 0.16 to 1.49). There was *no statistically significant difference* in complete remission in the rituximab group (10/32, 31%) compared with the cyclic cyclophosphamide and corticosteroid group (7/34, 21%) (OR 1.75, 95% CI 0.57 to 5.36). **(LOW)**

Complete or partial remission at 24 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (22/26, 85%) compared with the cyclic cyclophosphamide and corticosteroid group (25/31, 81%) (OR 1.32, 95% CI 0.33 to 5.29). There was *no statistically significant difference* in complete remission in the rituximab group (11/26, 42%) compared with the cyclic cyclophosphamide and corticosteroid group (11/31, 35%) (OR 1.33, 95% CI 0.46 to 3.89). **(LOW)**

Complete or partial remission at 36 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (17/20, 85%) compared with the cyclic cyclophosphamide and corticosteroid group (16/22, 73%) (OR 2.12, 95% CI 0.45 to 9.96). There was *no statistically significant difference* in complete remission in the rituximab group (6/20, 30%) compared with the cyclic cyclophosphamide and corticosteroid group (7/22, 32%) (OR 0.92, 95% CI 0.25 to 3.41). **(LOW)**

Rituximab compared with supportive therapy

One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy.

Complete or partial remission at 6 months:

- *no statistically significant difference* in complete or partial remission in the rituximab group (13/37, 35.1%) compared with the supportive therapy group (8/38, 21.1%) (OR 2.0, 95% CI 0.7 to 5.7, p=0.21). **(MODERATE)**

Complete or partial remission, post-RCT observational follow-up (median 17 months, IQR 12.5 to 24.0 months):

- *statistically significant increase* in complete or partial remission in the rituximab group (24/37, 64.9%) compared with the supportive therapy group (13/38, 34.2%) (p<0.01). There was a *statistically significant increase* in complete remission in the rituximab group (7/37) compared with the supportive therapy group (1/38) (p=0.03). **(LOW)**

	<p>Protein-to-creatinine ratio at 3 months:</p> <ul style="list-style-type: none"> <i>no statistically significant difference</i> in protein-to-creatinine ratio in the rituximab group (4814.4 mg/g, IQR 3205.5 to 7398.6 mg/g) compared with the supportive therapy group (4832.1 mg/g, IQR 2424.9 to 7911.9 mg/g) (p=0.94). (MODERATE) <p>Protein-to-creatinine ratio at 6 months:</p> <ul style="list-style-type: none"> <i>no statistically significant difference</i> in protein-to-creatinine ratio in the rituximab group (3531.2 mg/g, IQR 1796.6 to 6469.4mg/g) compared with the supportive therapy group (5265.8 mg/g, IQR 2500.1 to 7690.7 mg/g) (p=0.18). (MODERATE) <p>Protein-to-creatinine ratio, post-RCT observational follow-up (median 17 months, IQR 12.5 to 24.0 months):</p> <ul style="list-style-type: none"> <i>statistically significant increase</i> in protein-to-creatinine ratio in the rituximab group (2194.8 mg/g, IQR 1309.8 to 5310.0 mg/g) compared with the supportive therapy group (4701.1 mg/g, IQR 2027.8 to 8265.3 mg/g) (p=0.02). (MODERATE) <p>One study provided moderate to high certainty evidence that there was a significant benefit of rituximab compared with ciclosporin in complete or partial remission at 18 and 24 months, but not before 18 months. Two studies provided low to moderate certainty evidence that there was no difference between rituximab and cyclic cyclophosphamide and corticosteroids in complete or partial remission or complete remission at any time point up to 36 months, and a significant benefit of rituximab compared with supportive therapy alone in complete or partial remission, complete remission, and protein-to-creatinine ratio at a median of 17 months. However, there was no difference in remission or protein-creatinine ratio between rituximab and supportive therapy up to 6 months.</p>
<p>Excretory kidney function</p> <p>Certainty of evidence: Low to moderate</p>	<p>This outcome is important to patients because it is a measure of how well a patient's kidneys function.</p> <p>In total 3 RCTs provided evidence relating to excretory kidney function in adults with IMN, measured at different time points up to 3 years. One study compared rituximab with ciclosporin, 1 study compared rituximab with cyclophosphamide and corticosteroids, and 1 study compared rituximab with supportive therapy (no rituximab treatment).</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin.</p> <p>Number of adults with ≥50% decrease in creatinine clearance from baseline at 6 months:</p>

- number of adults who had $\geq 50\%$ decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (4/65, 6.2%) (risk difference -4.6% , 95% CI -11.2 to 1.9%). Confidence intervals could not be used to draw conclusions about treatment effects. **(LOW)**

Number of adults with $\geq 50\%$ decrease in creatinine clearance from baseline at 12 months:

- number of adults who had $\geq 50\%$ decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference -10.8% , 95% CI -19.3 to -2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)**

Number of adults with $\geq 50\%$ decrease in creatinine clearance from baseline at 18 months:

- number of adults who had $\geq 50\%$ decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference -10.8% , 95% CI -19.3 to -2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)**

Number of adults with $\geq 50\%$ decrease in creatinine clearance from baseline at 24 months:

- number of adults who had $\geq 50\%$ decrease in creatinine clearance from baseline in the rituximab group (1/65, 1.5%) compared with the ciclosporin group (8/65, 12.3%) (risk difference -10.8% , 95% CI -19.3 to -2.2%). Confidence intervals could not be used to draw conclusions about treatment effects. **(MODERATE)**

Rituximab compared with cyclic cyclophosphamide and corticosteroid

One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.

Serum creatinine at 6 months (n=73):

- mean serum creatinine in the rituximab group (1.00 mg/dl, SD 0.25 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (0.98 mg/dl, SD 0.47 mg/dl). No statistical analysis reported. **(MODERATE)**

Serum creatinine at 12 months (n=72):

- mean serum creatinine in the rituximab group (0.98 mg/dl, SD 0.29 mg/dl) compared with the cyclic cyclophosphamide and

corticosteroid group (0.98 mg/dl, SD 0.48 mg/dl). No statistical analysis reported. **(MODERATE)**

Serum creatinine at 18 months (n=66):

- mean serum creatinine in the rituximab group (0.98 mg/dl, SD 0.26 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.14 mg/dl, SD 0.90 mg/dl). No statistical analysis reported. **(MODERATE)**

Serum creatinine at 24 months (n=57):

- mean serum creatinine in the rituximab group (0.94 mg/dl, SD 0.20 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.12 mg/dl, SD 0.77 mg/dl). No statistical analysis reported. **(MODERATE)**

Serum creatinine at 36 months (n=42):

- mean serum creatinine in the rituximab group (0.97 mg/dl, SD 0.20 mg/dl) compared with the cyclic cyclophosphamide and corticosteroid group (1.22 mg/dl, SD 0.77 mg/dl). No statistical analysis reported. **(MODERATE)**

Rituximab compared with supportive therapy

One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy.

eGFR at 3 months:

- *no statistically significant difference* in eGFR in the rituximab group (66.7 ml/min/1.73m², IQR 57.2 to 87.1 ml/min/1.73m²) compared with the supportive therapy group (68.9 ml/min/1.73m², IQR 45.7 to 89.7 ml/min/1.73m²) (p=0.95). **(MODERATE)**

eGFR at 6 months:

- *no statistically significant difference* in eGFR in the rituximab group (65.6 ml/min/1.73m², IQR 51.0 to 89.0 ml/min/1.73m²) compared with the supportive therapy group (72.5 ml/min/1.73m², IQR 52.4 to 89.7 ml/min/1.73m²) (p=0.75). **(MODERATE)**

eGFR at last follow up (median 17 months, IQR 12.5 to 24.0 months):

- *no statistically significant difference* in eGFR in the rituximab group (61.1 ml/min/1.73m², IQR 48.7 to 83.4 ml/min/1.73m²) compared with the supportive therapy group (73.1 ml/min/1.73m², IQR 50.4 to 90.5 ml/min/1.73m²) (p=0.48). **(LOW)**

	<p>Serum creatinine at 3 months:</p> <ul style="list-style-type: none"> <i>no statistically significant difference</i> in serum creatinine in the rituximab group (94.6 µmol/litre, IQR 78.7 to 114.0 µmol/litre) compared with the supportive therapy group (100.8 µmol/litre, IQR 81.3 to 115.8 µmol/litre) (p=0.88). (MODERATE) <p>Serum creatinine at 6 months:</p> <ul style="list-style-type: none"> <i>no statistically significant difference</i> in serum creatinine in the rituximab group (94.6 µmol/litre, IQR 75.1 to 130.8 µmol/litre) compared with the supportive therapy group (97.2 µmol/litre, 76.0 to 126.4 µmol/litre) (p=0.67). (MODERATE) <p>Serum creatinine at last follow up (median 17 months, IQR 12.5 to 24.0 months):</p> <ul style="list-style-type: none"> <i>no statistically significant difference</i> in serum creatinine in the rituximab group (101 µmol/litre, IQR 87 to 135 µmol/litre) compared with the supportive therapy group (97.2 µmol/litre, 78.5 to 133.5 µmol/litre) (p=0.50). (LOW) <p>These studies provided low to moderate certainty evidence that there was no difference between rituximab and supportive therapy in excretory kidney function. One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin. However, no conclusions could be drawn because the confidence intervals were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No statistical analysis was reported for the difference between rituximab and cyclic cyclophosphamide and corticosteroids therefore no conclusions could be drawn.</p>
<p>End stage renal disease (ESRD)</p> <p>Certainty of evidence:</p> <p>Moderate to high</p>	<p>This outcome is important to patients because ESRD is the final, permanent stage of chronic kidney disease, where kidney function has declined to the point that the kidneys can no longer function on their own.</p> <p>In total 2 RCTs provided evidence relating to ESRD in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with ciclosporin and 1 study compared rituximab with cyclic cyclophosphamide and corticosteroids.</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <ul style="list-style-type: none"> 1 RCT (Fervenza et al 2019) (n=130) reported the number of adults with ESRD in the rituximab group (0/65) and the ciclosporin group (1/65). No statistical analysis was reported. (LOW) <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p>

	<ul style="list-style-type: none"> 1 RCT (Scolari et al 2021) (n=74) reported the number of adults with ESRD in the rituximab group (0/37, 0%) and the cyclic cyclophosphamide and corticosteroid group (2/37, 5.4%). No statistical analysis reported. The 2 adults in the cyclic cyclophosphamide and corticosteroid group who developed ESRD had eGFRs at baseline of 69 ml/min/1.73m² and 41 ml/min/1.73m², respectively. (LOW) <p><i>Rituximab compared with supportive therapy</i></p> <p>No evidence was identified for this comparator.</p> <p>These studies provided moderate to high certainty evidence on the effects of rituximab on ESRD compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No statistical analysis was provided and there were few events in both groups, therefore no conclusions could be drawn. No evidence was identified that compared rituximab with supportive therapy.</p>
Important outcomes	
<p>Quality of life</p> <p>Certainty of evidence:</p> <p>Low to moderate</p>	<p>This outcome is important to patients because IMN causes nephrotic syndrome which is associated with increased infections and thrombosis and may have a severe impact on quality of life.</p> <p>In total 1 RCT provided evidence relating to quality of life in adults with IMN, measured at different time points up to 2 years. The study compared rituximab with ciclosporin.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>1 RCT (Fervenza et al 2019) (n=130) reported quality of life in adults with complete or partial remission in the rituximab group compared with the ciclosporin group, measured using subscales of the KDQOL-SF.</p> <p>At 6 months:</p> <ul style="list-style-type: none"> SF-12 physical health composite subscale (modelled difference in means 2.0, 95% CI -3.5 to 7.5). (LOW) SF-12 mental health composite subscale (modelled difference in means 3.3, 95% CI -1.4 to 7.9). (LOW) Symptom/problem list subscale (modelled difference in means 7.4, 95% CI 0.8 to 14.1). (MODERATE) Effects of kidney disease subscale (modelled difference in means 0.1, 95% CI -7.0 to 7.2). (LOW) Burden of kidney disease subscale (modelled difference in means: 3.3, 95% CI -6.3 to 13.0). (LOW) <p>At 12 months:</p>

	<ul style="list-style-type: none"> • SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI -3.8 to 4.2). (LOW) • SF-12 mental health composite subscale (modelled difference in means 4.1, 95% CI 0.6 to 7.6). (MODERATE) • Symptom/problem list subscale (modelled difference in means 2.3, 95% CI -3.2 to 7.8). (LOW) • Effects of kidney disease subscale (modelled difference in means 3.3, 95% CI -4.0 to 10.6). (LOW) • Burden of kidney disease subscale (modelled difference in means -4.5, 95% CI -16.1 to 7.1). (LOW) <p>At 24 months:</p> <ul style="list-style-type: none"> • SF-12 physical health composite subscale (modelled difference in means 0.2, 95% CI -4.9 to 5.3). (LOW) • SF-12 mental health composite subscale (modelled difference in means 0.3, 95% CI -3.7 to 4.3). (LOW) • Symptom/problem list subscale (modelled difference in means 2.2, 95% CI -4.3 to 8.8). (LOW) • Effects of kidney disease subscale (modelled difference in means 6.9, 95% CI -2.4 to 16.3). (LOW) • Burden of kidney disease subscale (modelled difference in means 1.2, 95% CI -12.5 to 14.9). (LOW) <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p> <p>No evidence was identified for this comparator.</p> <p><i>Rituximab compared with supportive therapy</i></p> <p>No evidence was identified for this comparator.</p> <p>One RCT provided low to moderate certainty evidence on the effects of rituximab compared to ciclosporin on quality of life using 5 components of the KDQOL-SF questionnaire in adults with complete or partial remission. No conclusions could be drawn because the confidence intervals were not adjusted for multiple comparisons and could not be used for inference about treatment effects. No evidence was identified for rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids or supportive therapy.</p>
Anti-PLA2R level and positivity	This outcome is important to patients because PLA2R autoantibody levels are thought to correlate with disease activity (active disease, partial remission, complete remission) in patients treated with rituximab.

<p>Certainty of evidence:</p> <p>Moderate</p>	<p>In total 2 RCTs provided evidence relating to anti-PLA2R level in adults with IMN, measured at different time points up to 3 years. One study compared rituximab with cyclophosphamide and corticosteroids and 1 study compared rituximab with supportive therapy.</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>No evidence was identified for this comparator</p> <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p> <p>One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.</p> <p>Anti-PLA2R level at 6 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 44 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (13 RU/ml, IQR 0 to 86 RU/ml) (p=0.30). (MODERATE) <p>Anti-PLA2R level at 12 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in anti-PLA2R level in the rituximab group (2 RU/ml, IQR 0 to 44 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 73 RU/ml) (p=0.83). (MODERATE) <p>Anti-PLA2R level at 18 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 0 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 57 RU/ml) (p=0.21). (MODERATE) <p>Anti-PLA2R level at 24 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 0 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 53 RU/ml) (p=0.26). (MODERATE) <p>Anti-PLA2R level at 36 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in anti-PLA2R level in the rituximab group (0 RU/ml, IQR 0 to 18 RU/ml) compared with the cyclic cyclophosphamide and corticosteroid group (0 RU/ml, IQR 0 to 45 RU/ml) (p=0.49). (MODERATE) <p><i>Rituximab compared with supportive therapy</i></p>
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	<p>One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy.</p> <p>Anti-PLA2R level at 3 months:</p> <ul style="list-style-type: none"> • <i>statistically significant decrease</i> in anti-PLA2R level in the rituximab group (0.0 RU/ml, IQR 0.0 to 49.1 RU/ml) compared with the supportive therapy group (54.6 RU/ml, IQR 16.5 to 278.4 RU/ml) ($p < 0.001$). (MODERATE) <p>Anti-PLA2R level at 6 months:</p> <ul style="list-style-type: none"> • <i>statistically significant decrease</i> in anti-PLA2R level in the rituximab group (0.0 RU/ml, IQR 0.0 to 34.0 RU/ml) compared with the supportive therapy group (45.7 RU/ml, IQR 7.6 to 262.2 RU/ml) ($p = 0.002$). (MODERATE) <p>Number of adults PLA2R positive at 3 months:</p> <ul style="list-style-type: none"> • <i>statistically significant decrease</i> in the number of adults who were PLA2R positive in the rituximab group (11/37, 31.4%) compared with the supportive therapy group (25/38, 83.3%) ($p < 0.001$). (MODERATE) <p>Number of adults PLA2R positive at 6 months:</p> <ul style="list-style-type: none"> • <i>statistically significant decrease</i> in the number of adults who were PLA2R positive in the rituximab group (13/37, 36.1%) compared with the supportive therapy group (24/38, 75.0%) ($p = 0.001$). (MODERATE) <p>These studies provided moderate certainty evidence that there was no difference between rituximab and a cyclic regimen of cyclophosphamide and corticosteroids in anti-PLA2R levels, but that rituximab decreased anti-PLA2R levels compared supportive therapy. No evidence was identified that compared rituximab with ciclosporin.</p>
<p>The time interval to maximum reduction of anti-PLA2R antibodies and proteinuria following rituximab administration</p>	<p>This outcome is important to patients because it is thought to correlate with the speed of remission in patients treated with rituximab.</p> <p>No evidence was identified for this outcome.</p>
<p>Serum albumin</p> <p>Certainty of evidence:</p> <p>Low to high</p>	<p>This outcome is important to patients because the definition of complete or partial remission may be defined as a composite of proteinuria and serum albumin level.</p> <p>In total 2 RCTs provided evidence relating to serum albumin in adults with IMN, measured at different time points up to 2 years. One study compared rituximab with cyclophosphamide and</p>

	<p>corticosteroids and 1 study compared rituximab with supportive therapy.</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>No evidence was identified for this comparator.</p> <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p> <p>One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.</p> <p>Serum albumin at 6 months:</p> <ul style="list-style-type: none"> • in the rituximab group (34 g/litre, IQR 28 to 38 g/litre) and the cyclic cyclophosphamide and corticosteroid group (36 g/litre, IQR 28 to 38 g/litre). No statistical analysis reported. (MODERATE) <p>Serum albumin at 12 months:</p> <ul style="list-style-type: none"> • in the rituximab group (37 g/litre, IQR 29 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (37 g/litre, IQR 32 to 40 g/litre). No statistical analysis reported. (MODERATE) <p>Serum albumin at 18 months:</p> <ul style="list-style-type: none"> • in the rituximab group (39 g/litre, IQR 34 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (38 g/litre, IQR 33 to 41 g/litre). No statistical analysis reported. (MODERATE) <p>Serum albumin at 24 months:</p> <ul style="list-style-type: none"> • in the rituximab group (40 g/litre, IQR 35 to 42 g/litre) and the cyclic cyclophosphamide and corticosteroid group (38 g/litre, IQR 34 to 41 g/litre). No statistical analysis reported. (MODERATE) <p>Serum albumin at 36 months:</p> <ul style="list-style-type: none"> • in the rituximab group (38 g/litre, IQR 32 to 41 g/litre) and the cyclic cyclophosphamide and corticosteroid group (39 g/litre, IQR 33 to 43 g/litre). No statistical analysis reported. (MODERATE) <p><i>Rituximab compared with supportive therapy</i></p> <p>One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy.</p> <p>Serum albumin at 3 months:</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in serum albumin in the rituximab group (27 g/litre, IQR 21 to 31 g/litre) compared with the
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	<p>supportive therapy group (23 g/litre, IQR 19 to 27 g/litre) (p=0.10). (MODERATE)</p> <p>Serum albumin at 6 months:</p> <ul style="list-style-type: none"> • <i>statistically significant increase</i> in serum albumin in the rituximab group (30 g/litre, IQR 26 to 34 g/litre) compared with the supportive therapy group (24 g/litre, IQR 20 to 29 g/litre) (p=0.029). (MODERATE) <p>Serum albumin at last follow up (median 17 months, IQR 12.5 to 24.0 months):</p> <ul style="list-style-type: none"> • <i>statistically significant increase</i> in serum albumin in the rituximab group (32 g/litre, IQR 26 to 35 g/litre) compared with the supportive therapy group (27 g/litre, IQR 20 to 30 g/litre) (p=0.03). (LOW) <p>One study provided low to moderate certainty evidence that, compared with supportive therapy, rituximab increased serum albumin at 6 and 17 months but not at 3 months. One study provided moderate certainty evidence on the effects of rituximab compared with a cyclic regimen of cyclophosphamide and corticosteroids; however, no statistical analysis was provided therefore no conclusions could be drawn. No evidence was identified that compared rituximab with ciclosporin.</p>
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Safety

<p>Serious adverse events</p> <p>Certainty of evidence:</p> <p>Moderate to high</p>	<p>Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have long-term consequences.</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>One RCT (Ferverza et al. 2019, n=130) compared rituximab with ciclosporin.</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in the number of adults with serious adverse events in the rituximab group (11/65, 17%) compared with the ciclosporin group (20/65, 31%) (p=0.06). No incidences of cancer or death occurred during the trial. (HIGH) <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p> <p>One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in the number of adults with serious adverse events in the rituximab group (7/37, 19%) compared with the cyclic cyclophosphamide and corticosteroid group (5/37, 14%) (p=0.75). Three incidences of cancer (2 in the rituximab arm [lung and breast carcinoma] and 1 in the cyclic
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	<p>cyclophosphamide corticosteroid group [prostate carcinoma]). The patient with lung cancer died during follow-up. (MODERATE)</p> <p><i>Rituximab compared with supportive therapy</i></p> <p>One RCT (Dahan et al. 2017, n=75) compared rituximab with supportive therapy.</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in serious adverse events in the rituximab group (8 events) compared with the supportive therapy group (8 events) (p=0.87). One incidence of cancer occurred in the supportive therapy group. (MODERATE) <p>These studies provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, a cyclic regimen of cyclophosphamide and corticosteroids, or supportive therapy, in serious adverse events.</p>
<p>Adverse events</p> <p>Certainty of evidence:</p> <p>Moderate to high</p>	<p>Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have long-term consequences.</p> <p>No evidence was identified for children.</p> <p><i>Rituximab compared with ciclosporin</i></p> <p>One RCT (Fervenza et al. 2019, n=130) compared rituximab with ciclosporin.</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in the number of adults with adverse events in the rituximab group (46/65, 71%) compared with the ciclosporin group (51/65, 78%) (p=0.31). (HIGH) • <i>statistically significant increase</i> in the number of adults with infusion-related reactions in the rituximab group (16/65, 25%) compared with the ciclosporin group (0/65, 0%) (p<0.001). (MODERATE) <p><i>Rituximab compared with cyclic cyclophosphamide and corticosteroid</i></p> <p>One RCT (Scolari et al. 2021, n=74) compared rituximab with cyclic cyclophosphamide and corticosteroid.</p> <ul style="list-style-type: none"> • <i>no statistically significant difference</i> in the number of adults with adverse events in the rituximab group (16/37, 43%) compared with the cyclic cyclophosphamide and corticosteroid group (16/37, 43%) (p>0.99). (MODERATE) • <i>statistically significant increase</i> in the number of adults with drug infusion-related reactions or intolerance in the rituximab group (9/37, 24%) compared with the cyclic cyclophosphamide and corticosteroid group (1/37, 3%) (p=0.01). (MODERATE)

	<p><i>Rituximab compared with supportive therapy</i></p> <p>No evidence was identified for this comparator.</p> <p>These studies provided moderate to high certainty evidence that there was no difference between rituximab and ciclosporin, or a cyclic regimen of cyclophosphamide and corticosteroids, in adverse events, but rituximab increased infusion-related reactions compared with ciclosporin or cyclic cyclophosphamide and corticosteroids. No evidence was identified for rituximab compared with supportive therapy.</p>
<p>Abbreviations</p> <p>KDQOL-SF, Kidney Disease Quality of Life Short Form; PLA2R, phospholipase A2 receptor; RCT, randomised controlled trial</p>	

In the Population what is the cost effectiveness of rituximab compared with current treatment (alkylating agents, calcineurin inhibitors, or no rituximab treatment)?

Outcome	Evidence statement
Cost-effectiveness	<p>Cost effectiveness may not be a priority to individual patients, but it is an important outcome for decision makers. It reflects the incremental clinical effectiveness of rituximab compared with other available treatment options as well as the cost.</p> <p>One network meta-analysis (NMA) (Dai et al 2021) examined the cost effectiveness of different treatment options (rituximab, tacrolimus, chlorambucil, ciclosporin and cyclophosphamide) for IMN based on BNF 2019 prices and the clinical outcome of complete and partial remission rate.</p> <p>The cost-effectiveness compared with rituximab was calculated as:</p> <ul style="list-style-type: none"> • Tacrolimus: rituximab was dominated • Chlorambucil: £20,351.20 (ICER above the NICE threshold of £20,000) • Ciclosporin: rituximab was dominated • Cyclophosphamide: rituximab was dominated <p>The cost effectiveness outcomes modelled in this study should be treated with some degree of caution. The clinical effectiveness data used in the NMA come from 2 RCTs: 1 which is included in the clinical effectiveness section of this evidence review (Dahan et al. 2017) and another RCT (Jinling et al. 2019) which is not in publication.</p> <p>The NMA investigated multiple treatment options for IMN and included 75 RCTs, only 2 of these provided data on the clinical effectiveness of rituximab. The confidence intervals for all the pairwise comparisons of rituximab with other treatment options were very wide, which is likely to lead to a lack of certainty in the resulting cost-effectiveness estimate. Furthermore, the economic model only compares</p>

	<p>immunosuppressant therapies and it is unclear if other costs (for example supportive therapy) are included in the model.</p> <p>A cost-effectiveness analysis (Hamilton et al. 2018) examined the cost-effectiveness of rituximab compared with the modified Ponticelli regimen (rotating high-dose intravenous corticosteroids and immunosuppression, in this case with methylprednisolone and cyclophosphamide).</p> <p>ICER:</p> <ul style="list-style-type: none"> • 1 year: rituximab dominates • 5 years: £95 494.13 (primary outcome reported, above the NICE threshold of £20,000) • 10 years: £24 256.91 (above the NICE threshold of £20,000) • Lifetime: £10 246.09 <p>In terms of QALY gains, rituximab has a small benefit over the modified Ponticelli regimen at 1 year but this effect is reversed from 5 years onwards:</p> <ul style="list-style-type: none"> • 1 year: rituximab 0.954, modified Ponticelli regimen 0.952 • 5 years: rituximab 3.697, modified Ponticelli regimen 3.712 • 10 years: rituximab 6.513, modified Ponticelli regimen 6.603 • Lifetime: rituximab 13.650, modified Ponticelli regimen 14.162 <p>The authors reported that at 5 years after treatment, rituximab is cheaper than the modified Ponticelli regimen and that most of the modelled ICERs were below the £20,000 per QALY threshold set by NICE as the acceptable limit for cost-effectiveness. They reported that rituximab was cheaper over a lifetime but less effective than the modified Ponticelli regimen. Rituximab was associated with a QALY loss of 0.014 at 5 years after treatment.</p> <p>The authors noted that despite its efficacy, the modified Ponticelli regimen is associated with a significant side-effect profile, including an increased risk of infection, osteoporosis, diabetes mellitus, weight gain, hemorrhagic cystitis, infertility, and malignancy. Serious adverse events were included in the model.</p> <p>As with the study by Dai et al. 2021, these findings should be interpreted with caution. Firstly, the clinical effectiveness data are taken from 1 RCT and 1 observational study and may not be representative of the efficacy observed in recent RCTs. Secondly, while the costs for rituximab and the modified Ponticelli regimen included in the model were comprehensive and reflective of UK practice, these are now potentially out of date.</p>
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Abbreviations

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNF, British National Formulary; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year; RCT, randomised controlled trial

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Subgroup	Evidence statement
Adults/ children/ age	<p>No evidence was identified for children.</p> <p>1 RCT (Fervenza et al 2019) (n=130) found that the treatment effect of rituximab compared with ciclosporin in terms of complete or partial remission, was consistent across the pre-specified age-subgroups of ≤ 50 and > 50 years. Test for interaction $p=0.87$.</p> <p>1 RCT (Scolari et al 2021) (n=74) found a trend for lower complete remission rates at 12 months in the rituximab arm for adults < 55 years compared with people ≥ 55 years. However, statistical tests for interaction were nonsignificant.</p>
eGFR greater or less than 60ml/min/1.73m² at baseline	<p>No evidence was identified that compared outcomes in people with an eGFR greater or less than 60ml/min/1.73m².</p>
Proteinuria at baseline	<p>1 RCT (Scolari et al 2021) (n=74) found a trend for lower complete remission rates at 12 months in the rituximab group for adults with more severe proteinuria or lower serum albumin compared with less severe proteinuria or higher serum albumin. However, statistical tests for interaction were nonsignificant.</p>
Anti-PLA2R level at baseline	<p>1 RCT (Fervenza et al. 2019) (n=130) provided comparative evidence of complete or partial remission by anti-PLA2R level at baseline. In adults with a baseline anti-PLA2R level of ≤ 40 units/ml, 11/15 adults in the rituximab group were in complete or partial remission at 24 months compared with 7/19 adults in the cyclosporine group (risk difference 36.5%, 95% CI 5.3 to 67.7%). In adults with a baseline anti-PLA2R level of > 40 units/ml, 28/50 adults in the rituximab group were in complete or partial remission at 24 months compared with 6/46 adults in the ciclosporin group (risk difference 43.0%, 95% CI 26.1 to 59.8%). Test for interaction $p=0.72$.</p> <p>1 RCT (Scolari et al. 2021) (n=74) provided comparative evidence of complete or partial remission in adults who were anti-PLA2R positive at baseline by their baseline anti-PLA2R level. In adults with a baseline anti-PLA2R level > 58 units/ml 7/7 (100%) were in complete or partial remission at 24 months in the rituximab group compared with 9/12 (75%) in the cyclic cyclophosphamide and corticosteroid group, $p=0.74$. In adults with a baseline anti-PLA2R level ≤ 58 units/ml 6/8 (75%) were in complete remission at 24 months in the rituximab group</p>

	compared with 5/6 (83%) in the cyclic cyclophosphamide and corticosteroid group, p=1.00.
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<p>Patient Impact Summary</p> <p>The condition has the following impacts on the patient's everyday life:</p> <ul style="list-style-type: none"> • mobility: Patients have nil - severe problems in walking about • ability to provide self-care: Patients have nil - severe problems in washing or dressing • undertaking usual activities: Patients have slight - severe problems in doing their usual activities OR are unable to do their daily activities • experience of pain/discomfort: Patients have slight - extreme pain or discomfort • experience of anxiety/depression: Patients are moderately - extremely anxious or depressed
<p>Further details of impact upon patients: Patients with Idiopathic Membranous Nephropathy live with a constant threat of kidney failure. In many patients, despite treatment, the disease ultimately leads to kidney failure. In these patients the only treatment options are lifelong dialysis or transplantation with associated implications for quality of life, morbidity (including mental health) mortality and wider costs.</p> <p>Further details of impact upon carers: People with active nephrotic symptoms have a severe symptom burden (see above) and poor quality of life. This impacts significantly on the responsibility, caring burden, and quality of life for carers. For example, carers may have to take patient's to dialysis multiple times a week, they may need to help with activities of daily living, and in very severe disease they may donate a kidney to their loved one.</p>

Considerations from review by Rare Disease Advisory Group
Not Applicable

Pharmaceutical considerations
The drug is already used by NHS Providers for other autoimmune disorders, and specifically, is currently used for IMN by some NHS Providers.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine Programme of Care Clinical Chair and Senior manager on 9 June 2022 and by the full Internal Medicine Assurance Committee on the 21 st June 2022.

