CLINICAL PRIORITIES ADVISORY GROUP
06 October 2021

Agenda Item No	2.1
National Programme	Trauma
Clinical Reference Group	Neurosciences
URN	URN 1910

Title
Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning. The proposition is for Rituximab to be routinely commissioned as a treatment for adults with IgM paraproteinaemic demyelinating peripheral neuropathy within the criteria set out in the policy. The use of rituximab aims to produce a lifelong effect through a resetting phenomenon of the B cells leading to a lifelong remission. This should prevent the use of immunoglobulin. This treatment is expected to provide a net recurrent saving to the NHS compared to current alternative treatment.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes 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 patients with IgM paraproteinaemic demyelinating peripheral neuropathy, with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the clinical effectiveness and safety of rituximab versus conservative management, medical interventions or placebo?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Disability **Certainty of evidence:** Moderate to High	Disability is a critical outcome as the symptoms and signs of peripheral neuropathy result in patient disability which impacts of mobility, activities of daily living, independence and wellbeing. 1 systematic review with meta-analysis of two RCTs reported disability, as measured by INCAT score, for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • The number of participants with improved INCAT score at 8-12 months was statistically significantly greater with rituximab (12/33) compared to placebo (4/40) (RR 3.51, 95%CI 1.30 to 9.45, $I^2 = 0\%$, p=0.013, 73 participants). **HIGH**

	• Mean improvement in INCAT score at 8-12 months was statistically significantly greater with rituximab compared to placebo (MD -0.45, 95%CI -0.85 to -0.05, I^2 =0%; p=0.029, 73 participants). **HIGH** • There was no significant difference in the mean improvement in INCAT scores at 8-9 months (MD -0.33, 95%CI -0.73 to 0.07, I^2 = 0%, p=0.11, 70 participants). **MODERATE** **This study provides high certainty evidence that, in patients with IgM PDPN, at 8 to 12 months, rituximab improves disability, as measured by improvements in INCAT score, compared to placebo. However, there was no difference in mean improvement when assessed at a follow up range of 8-9 months (moderate certainly).**
Global impression of change **Certainty of evidence:** Moderate	Global impression of change is relevant to patients because the major disability of ataxic unsteadiness and tremor are poorly 'measured' in scores. This is a critical outcome/ treatment effect as a holistic measure of treatment, subjectively assessed by the patient and clinician that will not be captured by individual measures. 1 systematic review with meta-analysis of two RCTs reported global impression of change for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • At 8-12 months rituximab (27/32) statistically significantly improved participant's subjective impression of their condition as "stable or improved" compared to placebo (17/38) (RR 1.86, 95%CI 1.27 to 2.71, I^2 =0%, p=0.0014, 70 participants). **MODERATE** • At 8-12 months rituximab (12/32) statistically significantly improved participant's subjective impression of their condition as "improved" compared to placebo (1/38) (RR 9.67, 95%CI 1.84 to 50.85, I^2 = 0%, p=0.0074, 70 participants). **MODERATE** **This study provides moderate certainty evidence that, in patients with IgM PDPN, rituximab improves patient's subjective impression of change compared to placebo at a follow-up range of 8 to 12 months.**
Haematological response **Certainty of evidence:** Moderate	Haematological response is important to patients because these are direct, quantifiable measures of anti-CD20 treatment response and occur prior to clinically detectable change. Sustained reduction in pathological antibodies results in improved outcomes. 1 systematic review with meta-analysis of two RCTs reported haematological response for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016). Haematological response as measured by change in serum IgM level was reported by one of the RCTs included in the

	systematic review. Haematological response as measured by IgM anti-MAG titre was reported as meta-analysis of two RCTs: • Eight months after treatment, there was a statistically significant decrease in the level of serum IgM after rituximab compared to placebo (mean [SD] -254.4 [55] vs. 32.3 [55] MD -286mg/dL, 95%CI -329 to -244, 26 participants, p value not reported). **MODERATE** • At 8-12 months, there was a significant decrease in the titre of IgM anti-MAG activity (MD -17.79 units/mL, 95%CI -33.33 to -2.25, I^2 = 0%, p=0.025, 71 participants). **MODERATE** **This study provides moderate certainly evidence that, in patients with IgM PDPN, rituximab significantly improved haematological response compared with placebo, as measured by IgM serum level at eight months and IgM anti-MAG titre at 8-12 months.**
Important outcomes	
Sensory impairment **Certainty of evidence:** Low	Sensory impairment is an important outcome for patients as improvement to sensory impairment can improve independence and function 1 systematic review reported sensory impairment, as measured by changes in NIS, for rituximab compared to placebo in patients with IgM PDPN from 1 RCT (Lunn and Nobile-Orazio 2016): • There was no significant difference in NIS score at 12 months for rituximab (mean [SD] 1.1 [6] compared to placebo (mean [SD] 1.8 [5.1] (MD -0.70, 95%CI -4.03 to 2.63, 45 participants, p value not reported). **LOW** **This study provides low certainty evidence that, in patients with IgM PDPN, rituximab does not significantly improve sensory impairment, as assessed by NIS score, compared to placebo at 12 months.**
10 metre walk test **Certainty of evidence:** Low to Moderate	The 10 metre walk test is relevant to patients because it is an important outcome which crosses between impairment and disability. Imbalance, sensory dysfunction and weakness all contribute to altered walking times which improve after treatment. 1 systematic review with meta-analysis of two RCTs reported 10 metre walk test for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016). Improvement in 10 metre walk time was reported as meta-analysis of two RCTs. Number of participants who improved in 10 metre walk time was reported by one of the RCTs included in the systematic review: • There was no statistically significant difference in improvement in time to walk 10 metres for rituximab compared to placebo at 8-12 months (MD -0.35 seconds, 95%CI -1.89 to 1.19, I^2 = 0%, p=0.66, 68

	participants). **MODERATE** • There was no statistically significant difference in the number of participants who improved in 10 metre walk at six months (rituximab 9/13 vs. placebo 5/13 RR 1.80, 95%CI 0.83 to 3.92, 26 participants). No p value was reported. **LOW** **This study provides moderate certainty evidence that, in patients with IgM PDPN, rituximab does not significantly improve 10 metre walk time compared to placebo. It also provides low certainty evidence that, compared to placebo, rituximab does not significantly affect the number of patients with an improved 10m walk time.**
Quality of life **Certainty of evidence:** Moderate to High	Quality of life is an important outcome in these patients as neuropathy impacts on patient's function and activities of daily living. Improvement in quality of life, especially physical functioning, is a marker of successful treatment. 1 systematic review reported quality of life, as measured by mean changes in the physical and mental health subscores of the SF-36, for rituximab compared to placebo in patients with IgM PDPN from 1 RCT (Lunn and Nobile-Orazio 2016): • There was a statistically significant improvement in SF-36 physical subscores (mean [SD] rituximab 11.6 [19.6] vs. placebo -3.9 [9.8], MD 15.50, 95%CI 5.24 to 25.76, 37 participants) for rituximab compared to placebo at 12 months. No p value was reported. **HIGH** • There was no statistically significant difference in SF-36 mental health subscores between rituximab and placebo at 12 months (mean [SD] rituximab 4.5 [9.9] vs. placebo -2.1 [12.8], MD 6.60, 95%CI 0.35 to 13.55, 41 participants). No p value was reported. **MODERATE** **This study provides high certainly evidence that, in patients with IgM PDPN, rituximab significantly improved quality of life on the physical subscale compared with placebo at 12 months. There was no significant difference in the mental health subscale (moderate certainly).**
Motor impairment **Certainty of evidence:** Low to Moderate	Motor impairment occurs late in PDPN probably representing failure to treat early or effectively enough. It contributes greatly to imbalance but is less likely to show a therapeutic effect. It is an important indicator of permanent impairment. The two RCTs included in the systematic review (Lunn and Nobile-Orazio 2016) reported motor impairment, as measured by MRC score. As this outcome was not reported in the systematic review the data were taken from the individual RCT papers: • One RCT (Léger et al 2013) provided evidence for the mean change in MRC score at 12 months. The study reported no significant difference in the median change in

	MRC score at 12 months between rituximab 0.0 (95%CI -3 to 0.0) and placebo 0.0 (95%CI -1.5 to 1.5) p=0.17. **MODERATE** • The second RCT (Dalakas et al 2009) also reported no significant changes in the MRC score, but no measure of statistical significance was recorded. **LOW** **This study provides moderate certainty evidence that in patients with IgM PDPN, at 12 months, rituximab does not significantly improve MRC scores compared to placebo.**
Safety	
Adverse events **Certainty of evidence:** Low to Moderate	Adverse events are relevant to patients because they may reduce quality of life and require additional treatments. Serious adverse events may negate the expected health improvement associated with treatment. 1 systematic review with meta-analysis of two RCTs reported adverse events for rituximab compared to placebo in patients with IgM PDPN (Lunn and Nobile-Orazio 2016): • At 12 months, there was no statistically significant difference in the occurrence of any adverse event between rituximab (26/39) and placebo (23/41) (RR 1.18, 95%CI 0.84 to1.66, I^2 =0%, p=0.34, 80 participants). **MODERATE** • At 12 months, there was no statistically significant difference in the occurrence of severe adverse events between rituximab (2/39) and placebo (0/41) (RR 3.11, 95%CI 0.34 to 28.54, I^2 =0%, p=0.32, 80 participants). **LOW** **This study provided low to moderate certainty evidence that in patients with IgM PDPN, rituximab does not significantly worsen adverse effects compared with placebo.**

Abbreviations: Anti-MAG - anti-myelin-associated glycoprotein; CI - confidence interval; I^2 - Study heterogeneity (a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity); IgM - immunoglobulin M; INCAT – inflammatory Neuropathy Cause and Treatment; IQR – inter-quartile range; ISS – INCAT sensory score; LPL - lymphoplasmacytic lymphoma; MA - meta-analysis; MAG - myelin-associated glycoprotein; MD - mean difference; MGUS - monoclonal gammopathy of undetermined significance; MRC – Medical Research Council; NIS - Neuropathy Impairment Score; PDPN - paraproteinaemic demyelinating peripheral neuropathy; RCT - randomised controlled trial; RR - risk ratio; SD – standard deviation, SF-36 - Short Form 36 Health Survey; WM - Waldenstrom's macroglobulinemia

In patients with IgM paraproteinaemic demyelinating peripheral neuropathy with MGUS, LPL, WM or low-grade Non-Hodgkin lymphoma, what is the cost effectiveness of rituximab versus conservative management, medical interventions or placebo?

Outcome	Evidence statement
Cost Effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients with IgM paraproteinaemic demyelinating peripheral neuropathy who would benefit more from treatment with rituximab?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with rituximab.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients may have severe difficulty with walking about or are unable to walk about.
- **ability to provide self-care:** Patients may have severe problems in washing or dressing or are unable to wash or dress
- **undertaking usual activities:** Patients may have severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients may have pain or discomfort**.**
- **experience of anxiety/depression:** Patients may be anxious or depressed.

Further details of impact upon patients: Patients diagnosed with PDPN develop a slowly progressive distal sensorimotor neuropathy with disabling ataxia and a prominent tremor. Sensory loss, imbalance, tremor and eventual loss of distal power and muscle wasting are the source of progressive impairment, disability and decline in quality of life. Simple day-to-day tasks and occupational roles become difficult or even impossible. Approximately 50% of patients have significant difficulty in walking and with balance and may have falls.

Further details of impact upon carers: The impact on carers is significant. Carers may have to spend time assisting the patient with mobility aids and with personal care and activities of daily living. Carers may have to make sacrifices in their own lives to assist with the care and managing the patient's financial affairs and this, together with the burden of caring for the patient, may impact on their physical and mental wellbeing.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations
The Clinical Commissioning Policy Proposition recommends rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults. This is an off label use of rituximab which is not licensed for use in children. It is excluded to tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Trauma PoC on the 8th September 2021.