South East London Integrated Medicines Optimisation Committee
Formulary recommendation

Reference	**140**
Intervention:	**Rituximab intravenous injection for the treatment of autoimmune haemolytic anaemia in adults** (Rituximab is an anti-lymphocyte monoclonal antibody)
Date of Decision	**November 2022**
Date of Issue:	**December 2022**
Recommendation:	**RED – suitable for prescribing, supply and administration by hospital only**

Further Information	• Autoimmune haemolytic anaemia (AIHA) is a very rare condition where acquired haemolysis is caused by the destruction of red blood cells through autoimmune mechanisms. AIHA is a common term for several types of autoimmune haemolytic anaemias.
	• Rituximab intravenous injection is accepted for use in South East London for the treatment of the following types of AIHA:
	  ○ **First line treatment** in cold haemagglutinin disease (CHAD) with:
	  - symptomatic anaemia
	  - transfusion dependence
	  - severe circulatory symptoms
	  ○ **First line treatment alongside intravenous (IV) prednisolone** in severe or atypical AIHA:
	  - Severe AIHA is defined as haemoglobin <80g/dL
	  - Atypical AIHA is defined as IgA-mediated, mixed, or DAT-negative cases
	  ○ **Second line treatment** in warm AIHA which has:
	  - failed to respond to IV prednisolone 1mg/kg/day for at least 3 weeks or
	  - has relapsed during or after steroid reduction
	• For all types of AIHA, rituximab is recommended at a dose of 375mg/m^2 weekly for 4 doses as a **single course**. This is in line with guidance from the British Society for Haematology and First International Consensus Group. Repeat courses are not supported by this recommendation.
	• Rituximab is **not licensed** for use in this setting (off-label use). Informed consent should be gained from the patient before treatment is initiated.
	• This recommendation only supports use of the best value rituximab product for AIHA, taking into account any locally negotiated prices.
	• The Committee reviewed evidence for the use of rituximab at a lower dose of 100mg/m^2 weekly for 4 doses as a single course. However due to the limited evidence of benefit in comparison to standard dosing (375mg/m^2), the lower dosing schedule (100mg/m^2 weekly for 4 doses) **is not recommended** for use in South East London in this setting.

Shared Care/ Transfer of care required:	N/A

Cost Impact for agreed patient group	• It is estimated 16 patients across SEL will be eligible for treatment with rituximab in this setting each year. Approximately 80-90% of these patients will be from SEL (13 -14 patients). • Treatment is based on one 500mg rituximab vial of best value rituximab preparation (biosimilar) and an average body surface area of 1.75m^2 and costs approximately ~£1,131 per patient per year (based on a dose rounded to 700mg). • Assuming approximately 13 patients overall for SEL are treated annually with rituximab in this setting, this equates to ~ £14,700 (£774 per 100,000 population). • The costs of using rituximab could potentially be offset by a reduction in transfusion requirements for this patient cohort and an associated reduction in patient risks

	from repeated blood transfusions. The approval will also reduce the need for individual funding requests to be submitted.
Usage Monitoring & Impact Assessment	**Acute Trusts:** • Monitor and audit usage and outcomes from use of rituximab in this setting (against criteria in this recommendation) and report back upon request of the Committee.
	SEL Borough Medicines Teams: • Monitor exception reports from GPs if inappropriate prescribing requests are made to primary care
Evidence reviewed	**References (from evidence review)** 1. Hill QA, Stamps R, Massey E, Grainger JD, Provan D et al. Jäger U, Barcellini W, Broome CM, et al. The diagnosis and management of primary autoimmune haemolytic anaemia. British Journal of Haematology 2016; 176(3):395-411 2. Berentsen S, Barcellini W. Autoimmune haemolytic anaemia. New England Journal of Medicine 2021;385:1407-19 3. Jager U, Barcellini W, Broome CM, Gertz MA, Hill A et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: recommendations from the First International Consensus Meeting. Blood Rev 2020;41:100648 4. Go RS, Winters JL, Kay NE (2017) How I treat autoimmune hemolytic anemia. Blood; 129(22):2971-2979 5. Kawata E, Chin-Yee I, Hsia C, Solh Z. IgA-mediated autoimmune haemolytic anemia. Am J Hematol 2020; 95:129-130 6. Birgens, H., Frederiksen, H., Hasselbalch, H.C., Rasmussen, I.H., Nielsen, O.J. et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br.J Haematol 2013; 163, 393– 399. 7. Roche Products Limited. MabThera 100 mg Concentrate for Solution for Infusion - Summary of Product Characteristics [Online]. Available here [Accessed 8 November 2022] 8. Michel M, Terriou L, Roudot-Thoraval F, Hamidou M, Ebbo M et al. A randomized and double-blind controlled trial evaluating the safety and efficacy of rituximab for warm auto-immune hemolytic anemia in adults (the RAIHA study). American Journal of Hematology; 92(1):23-27 9. Reynaud Q, Durieu I, Dutertre M, Ledochowski S, Durupt S et al. Efficacy and safety of Rituximab in auto-immune haemolytic anemia: A meta-analysis of 21 studies. Autoimmunity Reviews 2015;14(4): 304-313. 10. National Institute for Health and Care Excellence. Autoimmune haemolytic anaemia: rituximab. Evidence summary [ESUOM39] Published 10th February 2015 [Online]. Available here [Accessed 8 November 2022] 11. Berentsen S, Ulvestad E, Gjertsen BT, Hjorth-hansen H, Langholm R et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. Blood 2004; 103(8):2925-2928 12. Schollkopf C, Kjeldsen L, Bjerrum OW, Mourits-Andersen HT, Nielsen JL et al. Rituximab in chronic cold agglutinin disease: a prospective study of 20 patients. Leuk Lymphoma 2006; 47(2):253-60 13. Berentsen S, Randen U, Oksman M, Birgens H, Tvedt THA et al. Bendamustine plus rituximab for chronic cold agglutinin disease: results of a Nordic prospective multicenter trial. Blood 2017;130(4):537-541 14. Berentsen S, randen U, Vagan AM, Hjorth-Hansen H, Vik A et al. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. Blood 2010; 116(17):3180-3184 15. Barcellini, W., Zaja, F., Zaninoni, A., Imperiali, F.G., Di Bona E et al. Sustained response to low-dose rituximab in idiopathic autoimmune hemolytic anemia. European journal of Haematology 2013;91(6):546-551 16. Fattizzo B, Zaninoni A, Pettine L, Cavallaro F, Di Bona E, Barcellini W. Low-dose rituximab in autoimmune hemolytic anemia: 10 years after. Blood 2019; 133(9):997-998

NOTES:

a) SEL IMOC recommendations and minutes are available publicly via the website.

b) This SEL IMOC recommendation has been made on the cost effectiveness, patient outcome and safety data available at the time. The recommendation will be subject to review if new data becomes available, costs are higher than expected or new NICE guidelines or technology appraisals are issued.

c) **Not to be used for commercial or marketing purposes. Strictly for use within the NHS**