Medicine Guideline

Rituximab

Areas where Protocol/Guideline applicable	SESLHD
Authorised Prescribers:	SESLHD Medical Officers
Indication for use	• Non-Hodgkin's lymphoma (NHL) e.g., primary CNS lymphoma and Waldenstrom's Macroglobulinaemia • Chronic lymphocytic leukaemia (CLL) • Rheumatoid arthritis (RA) • Granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) • Antibody mediated rejection • Myasthenia gravis • Paraneoplastic and autoimmune encephalitis • Nephrotic syndrome • Pemphigus • ANCA associated vasculitis • Systemic lupus erythematosus • Idiopathic thrombocytopenic purpura • Neuromyelitis Optica • Polymyositis/dermatomyositis • Autoimmune haemolytic anaemia When rituximab is to be prescribed for an indication that is not list on the formulary, Individual Patient Use (IPU) approval is required as outlined in SELSHDPD/183 *Medicine: Drug Formulary Policy*.
Adjunctive Therapy	**Premedications** • For cancer indications refer to eviQ. • Premedication is required prior to administration of rituximab to reduce the risk of hypersensitivity reactions. • Premedication should consist of an antipyretic and an antihistamine. An addition of a glucocorticoid should also be considered. • Premedication should be given 30-60 minutes prior to commencing rituximab therapy.
Contra-indications	• Known hypersensitivity to rituximab, murine proteins, or to any component of the product. • Rituximab should **not** be administered to patients with an active infection or severely immunocompromised patients (e.g., in hypogammaglobinaemia or where CD4 or CD8 levels are very low).
Precautions	• Severe infusion related reaction – usually occur within one to two hours of commencing the first rituximab infusion. • Patients with a history of pulmonary insufficiency should be monitored closely due to the risk of pulmonary events (e.g., hypoxia, severe bronchospasm, dyspnoea, and acute respiratory failure). • In patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before rituximab treatment. Pre-existing ischaemic cardiac conditions may become symptomatic, such as angina pectoris and cardiac arrhythmias such as atrial fibrillation and flutter. Cardiac patients require a pre infusion ECG as determined by Medical Officer.

	• Patients should be assessed for a history of hepatitis B infection (either HbsAg +ve or HbcAb +ve) before the first administration of rituximab. • Live vaccines should be avoided in immunosuppressed patients unless the medical officer considers it necessary. • Signs of progressive multifocal leucoencephalopathy (PML) • Pregnancy • Lactation • Exercise caution in patients with a history of recurring or chronic infections.
Important Drug Interactions	There is limited data on possible drug interactions with rituximab. • Avoid combination with other cytokine modulators (e.g., TNF-alpha antagonists, belimumab, tocilizumab, tofacitinib); may increase risk of infection. • Consider withholding antihypertensives for 12 hours before and during administration to reduce hypotension.
Dosage	Dependent on indication, refer to appropriate reference text (e.g., MIMs, eTG, eviQ).
Duration of therapy	Dependent on indication, refer to appropriate reference text (e.g., MIMs, eTG, eviQ).
Prescribing Instructions	• Obtain patient consent. • Before prescribing, complete pre-screening of Hepatitis B (including Hepatitis B core antibody), C, and HIV (+/- Mycobacterium tuberculosis and Strongyloides stercoralis infection. • Rituximab and associated premedications must be prescribed on the eMR (eFluids), eRIC, or in Mosaiq/ARIA, with administration rates clearly specified. In the absence of eMM systems, the appropriate paper medication chart may be used.
Administration Instructions	**Administer premedications as prescribed 30 to 60 minutes prior to commencing rituximab infusion.** Refer to SESLHDPR/368 Safe Handling and Management of Monoclonal Antibodies for PPE and other requirements. Rituximab doses will either be supplied from Pharmacy Services as a pre-made IV infusion bag (outpatients) or as vials for dilution (inpatients). Handle gently and avoid foaming as protein may precipitate. <u>Preparing rituximab vials for administration:</u> 1. Perform hand hygiene and don PPE 2. Aseptically withdraw the necessary amount of rituximab and add into an infusion bag containing Sodium Chloride 0.9% to give a concentration between 1 mg/mL to 4 mg/mL of rituximab. Each vial should be used once only, and any residue discarded. 3. To mix the solution, gently invert the bag to avoid foaming. 4. The bag should be inspected visually for particulate matter and discolouration prior to administration. Note: For rituximab doses less than 700mg, remove 100mL from the 500mL Sodium Chloride 0.9% bag first and then add rituximab to give a final concentration of 1 mg/mL to 4 mg/mL.

Rituximab

Administering rituximab

Rituximab is given as an intravenous infusion (IV). There are a number of infusion related events associated with the infusion of rituximab requiring careful monitoring of the patient. Adverse reactions are most likely to occur during the first 30 minutes and up to 2 hours after the initial infusion of IV rituximab. To reduce the risk of adverse reactions infusions are commenced slowly and administered with an increasing rate as tolerated. Future infusions may be given at a faster rate if no adverse events are experienced with the initial infusion

- Infuse Rituximab via infusion pump with Y-line IV giving set. The IV line is to be primed with reconstituted drug.
- The post-infusion 0.9% sodium chloride flush is to be administered at the same rate of infusion for minimum of 15 minutes.
- Administer Rituximab solution as per appropriate infusion rate schedule.

Infusion time	First 30 mins	0.5 – 1 hr	1 – 1.5 hrs	1.5 – 2 hrs	2 – 2.5 hrs	2.5 – 3 hrs	3 – 3.5 hrs	3.5 hrs onwards
First infusion#	50 mg/hr	100 mg/hr	150 mg/hr	200 mg/hr	250 mg/hr	300 mg/hr	350 mg/hr	400 mg/hr (MAX rate)
Subsequent infusions – if nil adverse events during first infusion	100 mg/hr	200 mg/hr	300 mg/hr	400 mg/hr (MAX rate)	➔			
Rapid infusion protocol€	20% of dose (i.e., 200 mL/hr for dose loaded in 500 mL bag	Remaining 80% of dose to be given over approx. 60 mins (i.e., 400 mL/hr (MAX rate) for dose loaded in 500 mL bag)						

 # Patients who experienced infusion reactions to the first infusion will receive the second infusion as per the first infusion schedule. The rate of the infusion should not exceed half that associated with the prior reactions.

€ The rapid infusion regimen is ONLY to be used in patients who meet the following criteria: (1) receiving their second or subsequent infusion of rituximab (2) previous infusion/s received without grade 3 or 4 infusion-related toxicities AND (3) circulating lymphocyte count < 5.0 x 10/L
Use with caution in patients with clinically significant cardiovascular disease, congestive heart failure (New York Heart Association [NYHA] grade II or higher), ventricular arrhythmia requiring medication within 1 year, or peripheral vascular disease (NYHA grade II or higher)

For example:
Rapid Infusion Protocol for a dose of 700 mg added to a 500 mL Sodium Chloride 0.9% bag:
final concentration 700 mg in 600 mL (including approximate bag overage of 30 mL):

Infusion time	First 30 mins	0.5 – 1 hr	1 – 1.5 hrs
Rapid infusion protocol	20% of dose	Remaining 80% of dose to be given over approx. 60 mins	
	140 mg (120 mL) over 30 minutes (infusion rate 240 mL/hr)	560 mg (480 mL) over 60 minutes (infusion rate 480 mL/hr)	

For rheumatoid arthritis ONLY, if their first and second infusions are well tolerated a faster rate of 250 mg/hour for 30 minutes followed by 600 mg/hour for 90 minutes can be used (for doses of 1000 mg in 250 mL). Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid 2 hour-infusion.

Monitoring requirements	• Full Blood Count (FBC), Electrolyte, Urea and Creatinine (EUCs), Liver Function Test (LFTs) and Lactate Dehydrogenase (LDH) at baseline and regularly throughout treatment as clinically indicated. • Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus (HIV) screening is recommended prior to commencing treatment with rituximab due to the risk of reactivation. • Consider risk-based screening for Mycobacterium tuberculosis and Strongyloides stercoralis infection in high-risk groups. • Patients receiving rituximab are at an increased risk of progressive multifocal leucoencephalopathy (PML), an opportunistic viral infection of the brain. PML can lead to severe disability or death, and therefore the patient should be monitored for new or worsening neurological changes (confusion, disorientation, motor weakness, hemiparesis, altered vision and speech, poor motor co-ordination, seizures). • Monitor temperature, pulse, BP, respirations, and oxygen saturation at baseline, then every 30 minutes until completion of the infusion, and then one hour post completion of the infusion. Always check observations immediately prior to a rate increase. **Do not increase the rate if there is any concern with patient's vital signs/condition**

Management of Complications

	Toxicity grade			
	1	**2**	**3**	**4**
Allergic reaction/ Hypersensitivity	• Transient flushing • Transient rash • Fever <38°C • Mild Rhinitis	• Rash • Flushing • Urticaria • Dyspnoea • Fever >38°C • Rigor or chills • Moderate Rhinitis	• Symptomatic bronchospasm with or without urticaria. • Allergy related oedema or angioedema • Hypotension	Anaphylaxis
Other infusion related side effects		• Transient hypotension • Throat irritation	• Cytokine release syndrome	
Management	Slow or stop the infusion. Notify Medical Officer. Refer to Hypersensitivity management guidelines. Once symptoms have resolved and following Medical Officer review, the infusion may be recommenced at half the rate prior to the reaction and then increased as tolerated. Document all side effects actions and effect in the patient medical record (EMR/eRIC/Mosaiq/ARIA).		Stop the infusion immediately. Call for medical assistance immediately – (CR/RR or Medical Emergency depending on patient's condition). Administer oxygen if required, prime fresh IV line with 0.9% Sodium Chloride and administer appropriate emergency treatment. Document all side effects actions and effect in the patient medical record (EMR/ eRIC/Mosaiq/ARIA). Update the patient's ADR profile in eMR. Complete IMS+ notification for grade 3-4, or <3 if treatment is not able to continue on the day.	

Basis of Protocol/Guideline:	1. Roche Australia. 2021. Mabthera (rituximab) IV Product Information. 2. UpToDate. 2021. Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy. 3. Vo, K., Waddell, J. A. & Suda, K. J. 2011, Rapid development of Infusion-Related Severe Hypotension during Rituximab Therapy. The Annals of Pharmacotherapy. Vol. 45, p. e29. doi: 10.1345/aph.1P733 4. Cancer Institute NSW (eviQ). 2020. Rituximab Rapid Infusion. 5. MIMs Online. MIMs Full Prescribing Information – Riximyo (rituximab). 2020. 6. Australian Government Department of Health. n.d. PBS Rituximab. Accessed 14/03/2022. 7. Cancer Institute NSW (eviQ). 2020. Non-Hodgkin Lymphoma Rituximab Protocol. 8. Alexander, M., King, J., Bajel, A., Doecke, C., Fox, P., Lingaratnam, S., Mellor, J.D., Nicholson, L., Roos, I., Saunders, T., Wilkes, J., Zielinski, R., Byrne, J., MacMillan, K., Mollo, A, Kirsa, S., and Green, M. 2014. Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. Internal Medicine Journal, 44. doi: 10.1111/imj.12564 9. U.S. Department of Health & Human Services – National Cancer Institute. 2017. Common Terminology Criteria for Adverse Events, Version 5.0. Accessed 16/03/2022. Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf 10. Cancer Institute NSW (eviQ). 2019. Hypersensitivity Reaction 11. ASHM (Australian Society for HIV, Viral Hepatitis, and Sexual Health Medicine). 2020. Indications for HIV testing. 12. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol. 2013 Jul;59(1):169-77. 13. Gea-Banacloche. J.C. 2010. Rituximab-Associated Infections. Seminars in Haematology, 47,2. Pages 187-198. doi: https://doi.org/10.1053/j.seminhematol.2010.01.002 14. Baxter Compounding. (2021). Additive volumes to Baxter diluent solutions (V7). 15. Davis, J.S., Currie, B.J., Fisher, D.A., Huffam, S.E., Anstey, N.M., Price, R.N., Krause, V.L., Zweck, N., Lawton, P.D., Snelling, P.L., Selva-nayagam, S. 2003. Prevention of opportunistic infections in immunosuppressed patients in the tropical Top End of the Northern Territory. Commun Dis Intell, 27(4): 526-532. Available: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-2003-cdi2704-pdf-cnt.htm/$FILE/cdi2704s.pdf
Groups consulted in development of this guideline	SGH Ambulatory Care Unit (CNE) POWH Haematology (CNC) POWH ESCM Respiratory & IC (CNC)

AUTHORISATION	
Author (Name)	Erica Wales
Position	Quality Use of Medicines, Lead Pharmacist
Department	SESLHD Clinical Governance Unit
Position Responsible (for ongoing maintenance of Protocol)	Quality Use of Medicines, Lead Pharmacist
GOVERNANCE	
Enactment date	April 2023
Expiry date:	March 2025
Ratification date by SESLHD DTC	2nd November 2023
Chairperson, DTC	Dr John Shephard
Version Number	1.2