Ballarat Health Services

DRUG GUIDELINE

Rituximab (intravenous infusion in MDU)

SCOPE (Area): **FOR USE IN:** Medical Day Unit
EXCLUSIONS: Paediatrics (seek Paediatrician advice), other areas
SCOPE (Staff): Medical, Nursing and Pharmacy

BRAND NAMES
Mabthera®.

PHARMACOLOGY AND PHARMACOKINETICS
Rituximab is a chimeric anti-CD20 antibody that binds with high affinity to the CD20 antigen located on the membrane of precursor and mature B cells resulting in lysis of these cells. B lymphocytes are an important mediator in the pathogenesis of rheumatoid arthritis via production of autoantibodies, their role as antigen-presenting cells, and in activation of T lymphocytes. The resultant reduction in T cell activation and cytokine production is thought to mediate its effects. The terminal half-life is around 21 days.

INDICATIONS
- Severe rheumatoid arthritis in patients with inadequate response, or intolerance, to a TNF-alpha antagonist. To be given in conjunction with weekly oral methotrexate, unless contraindicated.
- Other indications for rituximab are not covered in this guideline.

CONTRAINDICATIONS
- Severe immunosuppression.
- Serious or untreated infection (e.g. sepsis, abscess, hepatitis B, active TB - before treatment completed).
- Live vaccines are not to be administered with rituximab.
- Known hypersensitivity to rituximab, any of its excipients or to murine proteins.

PRECAUTIONS
- Before commencing treatment with rituximab all patients should be screened for past or current tuberculosis (TB) and hepatitis B and C (with complete hepatitis B and C serology including both antibodies and antigen).
- Rituximab may reactivate inactive hepatitis B and latent TB (begin TB treatment before starting rituximab).
- Use of rituximab may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of rituximab should be immediately suspended until a diagnosis of PML has been excluded. If a diagnosis of PML is confirmed rituximab must be permanently discontinued.

- Cardiac disease - monitor closely; angina, arrhythmias, heart failure and MI have occurred with rituximab. Patients with any of these conditions require careful assessment prior to prescribing rituximab and close monitoring during the infusion.
- Renal or hepatic impairment – safety and efficacy is not established. Requires Specialist review.
- Pulmonary disease or lung metastases - increases the risk of severe dyspnoea, bronchospasm and hypoxia with rituximab.
- Surgery - consider the increased risk of perioperative infections with rituximab.
- Women - ensure effective contraception during and for 1 year after stopping treatment.

PREGNANCY AND BREASTFEEDING

Not recommended. Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

- Vaccines – for live vaccines see Contraindications. Non-live vaccines may be administered, however the response may be reduced.
- Antihypertensive medications – consider withholding 12 hours prior to rituximab as hypotension may occur.
- Treatment with another cytokine modulator (TNF-alpha antagonists, abatacept, anakinra, belimumab, tocilizumab) - avoid combination with rituximab, may increase risk of infection.
- Disease Modifying Anti-Rheumatic Drugs (other than methotrexate) – if used concomitantly or following rituximab, monitor for signs of infection.
- Myelosuppressive drugs - rituximab causes myelosuppression, combinations with other drugs that also have this effect may result in additional myelosuppression.

DOSAGE AND ADMINISTRATION

Emergency treatment for anaphylaxis (adrenaline, antihistamine, corticosteroid and resuscitative equipment) must be readily available, as well as oxygen and bronchodilators for other possible infusion reactions. See below for more information.

Check Contraindications and Precautions (above) and Monitoring (below) before prescribing. For patients on antihypertensive medications, prior to admission Medical staff must decide if they are to be withheld 12 hours prior to (and during) the infusion – see Drug Interactions.

Ensure contraception for women (where appropriate) during treatment and for 12 months after the final dose.

Administer via CVC or peripheral line.

Immunisation status requires review prior to commencement with rituximab, and any vaccinations required are to be administered at least 4 weeks prior to starting rituximab.

A response to treatment is usually seen within 16 weeks.

Caution: When handling rituximab, wear protective clothing including a mask/respirator, safety glasses/face shield, gown and gloves. Rituximab is not a cytotoxic, but is a non-cytotoxic antineoplastic monoclonal antibody.

1.) Dose and prescribing:

All patients receive 1000mg in 500 mL sodium chloride 0.9% (rate as outlined below). A course of treatment is 1000 mg for 2 doses, given 2 weeks apart. Patients who respond to the initial course, may have the course repeated (usually after 6–12 months, and no less than 16 weeks) if there is deterioration. Prescribe on the BHS IV orders chart (MR/645.0).

2.) Ascertain if any previous adverse reaction to rituximab:

NOTE: If an adverse event was experienced with the previous infusion, the initial infusion rate as outlined below must be followed.

3.) Administer premedications to reduce the severity and frequency of infusion reactions:

To be prescribed on the Medication Chart (MR/700.2).

Administer 30 to 60 minutes prior to rituximab administration:

- paracetamol 1000 mg (500mg x TWO) orally AND
- cetirizine 10 mg orally

Administer 30 minutes prior to rituximab administration:

- methylprednisolone 100 mg IV

4). Determine if initial or second infusion rate is to be used:

Some patients may develop antibodies after the first course of rituximab which may be associated with the worsening of infusion or allergic reactions in subsequent courses. **The first infusion of each course must be treated as an initial infusion.**

a.) Initial IV infusion (or if previous reaction):

Only to be administered in MDU. Use a dedicated line with a 3 way tap. Wear gown, gloves, goggles and face mask

Prime the line with sodium chloride 0.9%.

Use premixed rituximab 1000 mg in 500 mL (2 mg/mL) sodium chloride 0.9% IV bags.

Use a light protective over bag during storage and when hanging

Take observations (blood pressure, heart rate, temperature, respirations, SaO_2 and conscious state) as outlined below.

Start Rate: Take baseline observations and commence at 50 mg/hr (25 mL/hr) for 30 mins. See Initial Infusion table below.

Increase Rate: If no adverse reaction, increase by 50 mg/hr (25 mL/hr) every 30 mins, to a maximum of 400 mg/hr (200 mL/hr). Repeat observations at each rate change or every 30 minutes.

End of infusion: Flush line with sodium chloride 0.9% 100 mL at the same rate the infusion finished at. No observations are required once the infusion is complete.

Infusion reaction: If an infusion reaction occurs, temporarily discontinue the infusion and notify the medical officer

- **For mild reactions (chills, shivering, pruritis, urticaria, headache, throat irritation, flushing, mild shortness of breath)** - if an infusion-related reaction occurs stop the infusion immediately and contact HMO for specific advice. Infusion-related reactions are usually reversible with a reduction in rate, or interruption of the infusion, and administration of appropriate symptomatic treatment, if required. In most cases, the infusion can be resumed at a 50% reduction rate (e.g. from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved.

- **For severe reactions including angioedema, hypotension with systolic BP <90 mmHg - stop** infusion and call a MET call.

Initial Infusion (or previous reaction) for rituximab 2 mg/mL		
Time (min)	**Infusion rate (mL/hr)**	**Volume to be infused (mL)**
0-30	25	12.5
30-60	50	25
60-90	75	37.5
90-120	100	50
120-150	125	62.5
150-180	150	75
180-210	175	87.5
210-240	200	100
240-255	200	50

b.) Second IV infusion (if no adverse reaction to initial infusion):

**Only to be administered in MDU. Use a dedicated line with a 3 way tap. Wear gown, gloves, goggles and face mask **

Prime the line with sodium chloride 0.9%.

Use premixed Rituximab 1000 mg in 500 mL (2 mg/mL) sodium chloride 0.9% IV bags.

Use a light protective outer bag during storage and when hanging.

Take observations (blood pressure, heart rate, temperature, respirations, SaO_2 and conscious state) as outlined below.

Start Rate: Take baseline observations and commence at 100 mg/hr (50 mL/hr) for 30 mins. See Second Infusion table below.

Increase Rate: If no adverse reaction, increase by 100 mg/hr (50 mL/hr) every 30 mins, to a maximum of 400 mg/hr (200 mL/hr). Repeat observations at each rate change or every 30 mins.

End of infusion: Flush line with sodium chloride 0.9% 100 mL at the same rate the infusion finished at. No observations are required once the infusion is complete.

Infusion reaction: If an infusion reaction occurs, temporarily discontinue the infusion and notify the medical officer

- **For mild reactions (chills, shivering, pruritis, urticaria, headache, throat irritation, flushing, mild shortness of breath)** - if an infusion-related reaction occurs stop the infusion immediately and contact HMO for specific advice. Infusion-related reactions are usually reversible with a reduction in rate, or interruption of the infusion, and administration of appropriate symptomatic treatment, if required. In most cases, the infusion can be resumed at a 50% reduction rate (e.g. from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved.
- **For severe reactions including angioedema, hypotension with systolic BP <90 mmHg - stop** infusion and call a MET call.

Second Infusion (if NO previous reaction) for rituximab 2 mg/mL		
Time (min)	**Infusion rate (mL/hr)**	**Volume to be infused (mL)**
0-30	50	25
30-60	100	50
60-90	150	75
90-120	200	100
120-150	200	100
150-180	200	100
180-195	200	50

5). Monitor for infusion related reactions:

- Reactions typically occur 30–120 minutes after starting infusion and commonly (>1 %) include fever, chills and/or rigors, nausea, vomiting, urticaria, itch, headache, rash, flushing, throat irritation, bronchospasm, dyspnoea, angioedema, rhinitis, hypotension, hypertension, dizziness, anxiety, tachycardia, AF, chest pain, myalgia. Severe reactions may be indistinguishable from hypersensitivity reactions (e.g. anaphylaxis) or cytokine release syndrome; severe pulmonary and cardiac events (e.g. acute respiratory distress syndrome, MI) and acute reversible thrombocytopenia have also occurred.
- Anaphylaxis or other hypersensitivity reactions can occur.
- Generally the reaction rate is higher with the first infusion than the second.
- Most reactions are mild to moderate in severity, with less than 1% of patients having a severe reaction. However, fatalities have occurred.
- Closely monitor patients with pre-existing cardiac conditions (see Precautions).

General Administration Information

- **Infusion preparation:** Premixed
- **Final concentration:** 2 mg/mL
- **Infusion pump:** Alaris PC with LVP and Guardrails
- **Routes of administration:**

  IV injection: No
  IV intermittent infusion: No
  IV continuous infusion: Yes
  IM injection: No
  Subcut injection: No
- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook ('Yellow book') in your ward area. **Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.**

MONITORING (INCLUDING BLOOD TESTS)

- Measure complete blood count, ALT, AST and creatinine before treatment.
- **Check patients for infections before, during and after treatment;** time to recovery of B lymphocytes is variable (greater than 2 years after last dose in about 8% of patients). Patients taking rituximab are more vulnerable to infectious diseases such as atypical pneumonia, listeriosis and tuberculosis.
- Surveillance for malignancy, particularly skin cancers, is also important.

NURSING PRACTICE POINTS

- **Patients should be asked to report symptoms suggestive of infection, including fever or persistent cough.**

- **Patients require close monitoring and regular observations as outlined above. Ask the patient to immediately report fever, chills, rash, difficulty breathing or swollen lips, tongue or face.**
- All infusions are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.
- Infusions require an independent double check by 2 Registered Nurses prior to commencement.
- All lines, IV bags and protective equipment (except goggles and respirator) require disposal in a cytotoxic waste container.

ADVERSE EFFECTS

- Generally the frequency and severity of adverse effects for rheumatoid arthritis are less than those seen with rituximab for antineoplastic indications.
- **Common (>1%)**
  Infusion related reactions (see Dosage and Administration above), infections (may be severe or even fatal), neutropenia (may be up to a year delayed onset), lymphopenia (see below), decreased immunoglobulin levels, arrhythmias, musculoskeletal pain, weakness.
- **Infrequent (0.1–1%)**
  Thrombocytopenia, anaemia, angina, MI, heart failure.
- **Rare (<0.1%)**
  Haemolytic anaemia, aplastic anaemia, serum sickness, severe skin conditions days to months after treatment (including Stevens-Johnson syndrome, toxic epidermal necrolysis, vesiculobullous dermatitis), pulmonary infiltrates, pneumonitis, cranial neuropathy (vision or hearing loss), progressive multifocal leukoencephalopathy.
- **Lymphopenia** - rituximab induces a rapid loss of B lymphocytes. Recovery usually begins about 6 months after stopping treatment; full recovery often occurs within 12 months but may take longer.

DRUG PRESENTATIONS, LOCATION AND STORAGE

Premixed bag: Rituximab 1000 mg in 500 mL sodium chloride 0.9% IV bags. Stable for 90 days from date of manufacture.
Imprest Locations (at the time of guideline development): Pharmacy only.
Refrigerate between 2-8°C. Protect from light.

RELATED DOCUMENTS

SOP0001 Clinical Care
CPP0022 Labelling of Injectable Medicines and Lines

REFERENCES

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