Rituximab for induction or re-induction (not maintenance of remission) treatment of ANCA-associated vasculitis

South Australian Medicines Evaluation Panel
**Summary of SAMEP review**

<table>
<thead>
<tr>
<th>Receipt of High Cost Medicine (HCM) formulary application:</th>
<th>11 February 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of SAMEP meetings:</td>
<td>13 March 2013, 8 May 2013 &amp; 10 July 2013</td>
</tr>
</tbody>
</table>

**Name of medicine**  
Rituximab (Tradename: MabThera®)

**Dosage form**  
Injection, concentrated

**Strength**  
500mg and 100mg vials

**Requested Statewide HCM Formulary Listing**  
‘ANCA-associated vasculitis (AAV) including granulomatosus with polyangiitis (GPA; Wegener’s granulomatosus), microscopic polyangiits (MPA) and eosinophilic granulomatosus with polyangiitis (Churg-Strauss syndrome)

Average cost of medicine per treatment course  

<table>
<thead>
<tr>
<th>BSA</th>
<th>Dose</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.33m²</td>
<td>500mg weekly</td>
<td>4 weeks</td>
<td>$9,054</td>
</tr>
<tr>
<td>1.6m²</td>
<td>600mg weekly</td>
<td>4 weeks</td>
<td>$10,865</td>
</tr>
<tr>
<td>1.87m²</td>
<td>700mg weekly</td>
<td>4 weeks</td>
<td>$12,676</td>
</tr>
<tr>
<td>2m²</td>
<td>750mg weekly</td>
<td>4 weeks</td>
<td>$13,581</td>
</tr>
</tbody>
</table>

(A 180cm tall person weighing 80kg has a body surface area of 2m²)

The proposed dose in the application is 1g every two weeks for 2 doses, costing $9,054 per treatment. (NB. Patients enrolling in the observational RITAZAREM trial are required to be treated at 375mg/m², which is a more expensive regimen, at a cost to SA Health, not the manufacturer).

Projected future usage for the proposed indication  

In the 2011-2012 financial year, there were 69 separations (for 38 patients) from SA health public hospitals that included ANCA-associated vasculitis as a primary or a secondary diagnosis. The average length of stay was 6.4 days (range: 1-53 days). Based on available IPU data, Rituximab is being used by 9 patients per year for this indication across SA Health. Assuming all patients who received rituximab were admitted to hospital, this correlates to 24% of patients (9/38) with disease severe enough for admission, receiving rituximab. However, the actual proportion is likely to be much lower as many patients with AAV are treated solely as outpatients.
SAMEP recommendations

Following the review of the current available evidence (Appendix 3) and consideration of formal feedback from the heads of public hospital rheumatology departments and respiratory departments and the Statewide Renal Clinical Network, SAMEP recommend the following:

- Rituximab is listed on the Statewide High Cost Medicines Formulary for the following indications:

  Induction OR re-induction\(^1\) (NOT maintenance of remission) of ANCA-associated vasculitis (AAV), including:
  - Granulomatosis with polyangiitis (GPA or ‘Wegener’s granulomatosis’);
  - Microscopic polyangiitis (MPA); or
  - Eosinophilic granulomatosis with polyangiitis (‘Churg-Strauss syndrome’).

  With:
  - ANCA positive serology;
  - Generalised or severe disease, defined as including a minimum of one of the following:
    - Acute severe glomerulonephritis with progressive renal failure
    - Risk to sight including scleritis/episcleritis, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudates/haemorrhage)
    - Bronchial/subglottic obstruction
    - Pulmonary haemorrhage
    - Parenchymal lung disease
    - Sensory neural hearing loss
    - Recurrent sinonasal disease requiring recurrent surgical interventions
    - Meningitis, organic confusion, seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex

  and
  - The patient is contraindicated to cyclophosphamide, defined as including a minimum of one of the following:
    - Previous treatment with cyclophosphamide and cumulative dose ≥ 20g.
    - Previous severe hypersensitivity to cyclophosphamide.
    - History of bladder cancer.
    - Pregnant or breastfeeding.
    - Female of reproductive age who has been counselled about the fertility risks associated with cyclophosphamide and wishes to retain fertility.

  - Contraindications to cyclophosphamide:
    - For patients who respond well to cyclophosphamide, but relapse at a later date, there is no immediate reason not to reconsider using cyclophosphamide again for re-induction, except where the cumulative dosage ≥20g (Mahr, Heijl et al. 2013). 2 courses of cyclophosphamide for an average patient is ≈20g, therefore most patients would be eligible for rituximab after ≥2 relapses.

\(^1\) Re-induction must be after ≥2 relapses ≥1 year after remission
For initial treatment, very few patients would be contraindicated to treatment with cyclophosphamide. Intolerances can be generally be managed (eg severe nausea), and should not be considered the same as contraindications.

The risk of bladder cancer is increased by Cyclophosphamide administration in relation to cumulative dose. There seems to be limited data concerning the risk of recurrence or progression of bladder cancer caused by cyclophosphamide in patients with pre-existing disease; however it would seem prudent to avoid its use in this context.

Cyclophosphamide increases the risk of infertility and so rituximab is a preferable alternative in women wishing to maintain fertility. The anticipated number of women having this contraindication is likely to be small as the median age of onset of these diseases is approximately in the mid-40s.

- The Clinical Pathway developed by SAMEP, in consultation with rheumatologists and nephrologists specialising in vasculitis, be adopted statewide, including formulary listing of all medicines included in the pathway (Appendix 1)
  - Mycophenolate mofetil is considered the appropriate standard of care in the treatment of patients with less severe AAV who are contraindicated to cyclophosphamide and methotrexate. Mycophenolate mofetil is not currently listed on the statewide formulary for this indication; however it proposed for the treatment of less severe AAV as there is evidence to support its effectiveness for this indication. Evidence suggests that Mycophenolate mofetil is at least as effective as cyclophosphamide for induction of remission, and is significantly cheaper (cost for mycophenolate mofetil at usual dose of 1000mg BD is ~$250 per year) (Jones, Harper et al. 2013).
  - It is proposed that mycophenolate is added to the statewide formulary for this indication.

- Prescribing of rituximab for patients qualifying under this formulary listing is restricted to consultant rheumatologists, immunologists, nephrologists or respiratory physicians.
  - Prescribing should only be by the appropriate consultant specialist to ensure that rituximab is used for the appropriate indication and to minimise leakage.

- Prescribers are required to complete the rituximab eligibility form prior to dispensing of the initial dose (Appendix 2).
  - A rituximab eligibility form has been developed to ensure that prescribing is for the listed indications and to make prescribers aware of the requirements for provision of written patient consent and data collection. This will also assist with monitoring of indications of use, as this data is not captured by current prescribing and dispensing systems for formulary-listed medicines.

- Prescribers must provide objective measures of patient outcomes at 3 months to their local DTC. A collated report of rituximab treatment for SAMEP-approved non-PBS indications should be forwarded to SAMEP from the local DTCs annually. If outcome
data is not received by the DTC within 4 months of dispensing, no further rituximab will be allowed for patients that qualify under this formulary listing and who are managed within that non-compliant clinical unit.

- Outcome data is required for all patients who receive rituximab for the listed indications. Prescribers are required to state at the time of initial prescription which patient-specific objective measures will be used to monitor response to treatment.
- There is no single test or scoring system to reliably determine new active AAV, remission or relapse. The Birmingham Vasculitis Activity Score (BVAS) and the Disease Extent Index are increasingly being used as validated clinical assessment tools to accurately measure the effect of treatment of AAV in clinical trials (Luqmani 2013). In clinical practice however, the BVAS is rarely used due to limitations in the daily clinical setting, especially as the score alone does not give an indication as to which organs are involved.
- The applicants recommended that no further rituximab should be provided to a clinical unit if outcome data is not received after 4 months.

- **Written information on the estimated effectiveness and possible risks of treatment with rituximab is provided to patients/carers prior to the administration of the initial dose of the drug.**
NOTES:

1. Treatment algorithm is for the induction of remission in patients with active generalised or severe ANCA-associated vasculitis, including:
   - Granulomatosis with polyangiitis (Wegener’s granulomatosis)
   - Microscopic polyangiitis
   - Eosinophilic granulomatosis with polyangiitis

2. Patient must have ANCA positive serology and generalised or severe disease, defined as including a minimum of one of the following:
   - Acute severe glomerulonephritis with progressive renal failure
   - Risk to sight incl. scleritis/episcleritis, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudates/haemorrhage)
   - Bronchial/subglottic obstruction
   - Pulmonary haemorrhage
   - Parenchymal lung disease
   - Sensory neural hearing loss
   - Recurrent sinonasal disease requiring recurrent surgical interventions
   - Meningitis, organic confusion, seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex

3. Trial of cyclophosphamide to be considered six IV pulses or 3 months of oral therapy.

4. In localised/early disease, methotrexate can be used for induction instead of cyclophosphamide, however if relapse occurs cyclophosphamide must be considered (unless contra-indicated) in patients with localised disease prior to considering rituximab. Mycophenolate mofetil is considered the appropriate standard of care in the treatment of patients with less severe AAV who are contraindicated to cyclophosphamide and methotrexate.

5. Contra-indications to cyclophosphamide:
   - Previous treatment with cyclophosphamide and cumulative dose ≥ 20g.
- Previous severe hypersensitivity to cyclophosphamide.
- History of bladder cancer.
- Pregnant or breastfeeding.
- Female of reproductive age who has been counselled about the fertility risks associated with cyclophosphamide and wishes to retain fertility.

6. Remission – defined as resolution and/or absence of **active** disease
7. Relapse – evidence of recurrent active disease following remission.
8. Outcomes to be provided following rituximab therapy:
   - Objective measures of patient outcomes at 3 months to be reported to the local DTC.
Appendix 2: Pharmacy checklist form

Statewide High Cost Medicines Formulary

Rituximab

Injection, concentrated

**Rituximab** is listed on the Statewide High Cost Medicines Formulary for the following indications:

- ANCA-associated vasculitis (AAV), including:
  - Granulomatosis with polyangiitis (GPA or ‘Wegener’s granulomatosis’)
  - Microscopic polyangiitis (MPA)
  - Eosinophilic granulomatosis with polyangiitis (‘Churg-Strauss syndrome’)

The following information is required to be provided by the **prescriber** prior to dispensing of the high cost medicine:

**Hospital:**

**UR number:**

**Prescriber eligibility for rituximab:** (*both* criteria must be ticked)

1. **Approved consultant. ie one of the following:** (please tick one)
   - Consultant Rheumatologist
   - Consultant Immunologist
   - Consultant Nephrologist
   - Consultant Respiratory Physician

   **and**

2. **Prescriber agrees to provide objective measures of outcome at 3 months to the DTC**. Please provide patient-specific objective measures by which you intend to monitor response to treatment:

**Patient eligibility for rituximab:** (*all six* criteria must be ticked)

1. **ANCA-associated vasculitis**

   **and**

2. **ANCA positive serology**

   **and**

3. **For induction of remission OR re-induction of remission after ≥2 relapses (NOT maintenance of remission)**

   **and**

---

2 If outcome data is not received by the DTC after 4 months no further rituximab will be allowed for treatment of AAV within that clinical unit.
4. □ Generalised or severe disease, defined as including a minimum of one of the following: (please tick as applicable)
   - □ Acute severe glomerulonephritis with progressive renal failure
   - □ Risk to sight including scleritis/episcleritis, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudates/haemorrhage)
   - □ Bronchial/subglottic obstruction
   - □ Pulmonary haemorrhage
   - □ Parenchymal lung disease
   - □ Sensory neural hearing loss
   - □ Recurrent sinonasal disease requiring recurrent surgical interventions
   - □ Meningitis, organic confusion, seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex

   and

5. □ Contraindicated to cyclophosphamide (tick one of the following):
   - □ Previous treatment with cyclophosphamide and cumulative dose ≥ 20g.
   - □ Pregnant or breastfeeding
   - □ Previous severe hypersensitivity to cyclophosphamide
   - □ History of bladder cancer
   - □ Female of reproductive age has had counselling about fertility risks associated with cyclophosphamide and wishes to retain fertility

6. □ Patient has been provided with written information about the intended treatment with the rituximab.

I certify that the above information is correct: ______________________________________
(Prescriber’s signature)
Date:
Name:
Position:
Department:
Contact/pager number:

Please return completed form to Pharmacy

Information for pharmacy
This form should be retained in the pharmacy department and a copy forwarded to:
- The Executive Officer
  South Australian Medicines Evaluation Panel
  Medicines and Technology Policy and Programs
  Level 8, CitiCentre
  11 Hindmarsh Sq
  Adelaide 5000
- 8226 7083
- SAMEP@health.sa.gov.au

For more information: http://www.sahealth.sa.gov.au/samep

© Department for Health and Ageing, Government of South Australia. All rights reserved.
Version: 11 Nov 2013
Appendix 3: Review of the evidence

Comparator
Treatment without rituximab, including cyclophosphamide, azathioprine, methotrexate and mycophenolate (in combination with corticosteroids) and/or plasma exchange.

Clinical Practice Guidelines
A Clinical practice guideline based on a systematic review was published in 2012 (Guerry, Brogan et al. 2012).

Evaluations by other Jurisdictions

<table>
<thead>
<tr>
<th>Regulatory Authority/Committee</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>No</td>
</tr>
<tr>
<td>Canadian Agency for Drugs and Technologies in Health (CADTH) / Canadian Expert Drug Advisory Committee (CEDAC)</td>
<td>Rituximab has been evaluated for induction of remission in GPA (Wegener’s) and Microscopic polyangiitis by CADTH in July 2012 (CADTH 2012)</td>
</tr>
<tr>
<td>Scottish Medicines Consortium (SMC)</td>
<td>No</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence (NICE)</td>
<td>No. However, NICE is currently preparing guidance entitled “Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis” which is due to be published in 2013.</td>
</tr>
<tr>
<td>All Wales Medicines Strategy Group (AWMSG)</td>
<td>No</td>
</tr>
<tr>
<td>North Yorkshire Primary Care Trust (NYPCT)</td>
<td>Rituximab for treatment of vasculitis – including Wegener’s Granulomatosis (Fell 2011)</td>
</tr>
<tr>
<td>Food and Drug Administration (FDA)</td>
<td>Extended the registered indications of rituximab in the US to include GPA (Wegener’s) and Microscopic Polyangiitis (MPA), in combination with corticosteroids, in April 2011</td>
</tr>
</tbody>
</table>

The Clinical practice guideline and reviews by CADTH and NYPCT recommend rituximab for AAV patients contraindicated, intolerant or refractory to conventional therapy (Fell 2011; CADTH 2012; Guerry, Brogan et al. 2012). NYPCT restricted patient group to those with severe AAV. Guerry et al and NYPCT also recommend use in frequently relapsing patients despite either 3 months of use of conventional therapy or when there are concerns regarding cumulative glucocorticoid and/or CYC toxicity. Information on cost included in CADTH and NYPCT reviews but none of the three reviews conducted a cost-effectiveness analysis.

Evidence provided by applicant
The submission presented 2 randomised controlled trials, 1 epidemiological review (non-systematic), 1 perspective (opinion) and 2 retrospective case-series:

Randomised Controlled Trials (RCTs):
Epidemiological review:

Perspective / Opinion:

Retrospective case series:

Search strategy for additional evidence

Population
- Adult patients with ANCA-associated small vessel vasculitis, including:
  - granulomatosis with polyangiitis (GPA or Wegener’s granulomatosis)
  - microscopic polyangiitis (MPA)
  - eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Intervention
- Rituximab (Tradename: Mabthera®)

Comparator
- Treatment without rituximab, including cyclophosphamide, azathioprine, methotrexate and mycophenolate (in combination with corticosteroids).

Outcome(s)
- Mortality
- Remission rate and duration of remission
- Number and severity of relapses
- Change in renal function
- Cumulative dose of immunosuppressants
- Adverse effects of treatment
- Health-related quality of life

Databases searched (refer to appendix 5 for search terms)
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Medline
- Embase

Selection criteria: Randomised controlled trials, Systematic reviews. No language restrictions.

Clinical Trials Registries searched
- Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
- US National Institutes of Health Trial Registry www.clinicaltrials.gov
- European Clinical Trials Register www.clinicaltrialsregister.eu

Refer to appendix 5 for identified ongoing trials.
SUMMARY OF EVIDENCE

Evidence Statement Matrices

Evidence Statement Matrices using the NHMRC Rating Scale (appendix 6) are provided below for the clinical scenarios proposed by the applicant for listing of rituximab on the formulary:

1. **Rituximab in combination with IV/oral corticosteroids for induction treatment of generalised or severe AAV in patients contraindicated to cyclophosphamide**

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>B</td>
<td>2 systematic reviews but no meta-analysis: 1 including 2 RCTs (CADTH report 2012); other (Guerry et al 2012) including same two 2 RCTs plus 41 observational/uncontrolled (predominantly refractory/relapsed population)</td>
</tr>
<tr>
<td>Consistency</td>
<td>B</td>
<td>RCTs consistent that remission rates are similar between rituximab &amp; cyclophosphamide trial arms; however remission rates varied between trials. RITUXVAS was a more severely diseased population (renal involvement) and yet had higher remission rates in both arms (82% RTX/CYC, 91% CYC) than RAVE trial (64% rituximab, 53% CYC). Likely due to 12 months follow-up of RITUXVAS patients and 6 months follow-up in RAVE patients, combination of RTX/CYC in RITUXVAS and that RAVE sample included relapsed patients.</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>C</td>
<td>Moderate therapeutic impact, depending on length of follow-up or population characteristics (see above). RAVE was a non-inferiority trial and rituximab was found to be no-worse than cyclophosphamide regimen for induction/relapsed patients. RITUXVAS also found similar remission and relapse rates between rituximab/CYC and cyclophosphamide regimens for induction. Need longer term follow-up data. Similar safety between rituximab and CYC regimens in RITUXVAS may be because in rituximab regimen patients also received cyclophosphamide with 1st and 3rd rituximab infusions. Similar safety in RAVE but again perhaps because relapsing patients had been previously exposed to cyclophosphamide and other medications. However, no real evidence to indicate safety benefits from rituximab and some concern re malignancies (although cannot disentangle from carcinogenic medication hx). Therapeutic impact of rituximab relative to usual care for patients contraindicated to cyclophosphamide unknown.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>C</td>
<td>The 2 RCTs available are for induction therapy but not for patients contraindicated to CYC. Unclear how patients contraindicated to CYC would perform on rituximab compared those not contraindicated to CYC. Populations are likely to have considerable cross-over with the target population of generalised or severe AAV in SA receiving induction treatment, although 30% of cases with Churg-Strauss Syndrome or localised Wegener’s Granulomatosis may be ANCA negative (Lapraik et al 2007). Majority of AAV is WG or MPA, with WG more likely in SA, given the latitude and majority Caucasian population (Koldingsnes &amp; Nossent 2008)</td>
</tr>
<tr>
<td>Applicability</td>
<td>C</td>
<td>RITUXVAS = 44 patients in 8 centres in Europe and Australia. RAVE = 197 patients in 9 centres in the US. Proposed rituximab dosing/delivery in application differs from that in the trials.</td>
</tr>
</tbody>
</table>

2. **Rituximab in combination with IV/oral corticosteroids as rescue therapy for management of treatment-resistant (refractory) AAV or in patients who are intolerant to cyclophosphamide**

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>D</td>
<td>41 observational/uncontrolled (predominantly refractory/relapsed populations) studies of small sample size (Ns ranged from 4-65)</td>
</tr>
<tr>
<td>Consistency</td>
<td>B</td>
<td>Complete/partial remission and relapse rates fairly similar across observational studies.</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>C</td>
<td>Moderate. In observational studies complete remission rates varied from 25-100% with follow-up usually longer than a year and up to 4 years. Mean complete or partial remission was 91%. Relapse rates ranged from 0-100%. Mean relapse was 32%. Large range in rates due to small sample sizes. Relative effectiveness of rituximab compared to usual care in...</td>
</tr>
</tbody>
</table>
cyclophosphamide-intolerant patients is unknown.

<table>
<thead>
<tr>
<th>Generalisability</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>Large number of observational studies in refractory/relapsed populations. Unclear what proportion of observational studies included refractory, as opposed to relapsed populations. Majority of studies were WG or MPA with ANCA positivity. Populations will have some cross-over with the target population of treatment-resistant (refractory) AAV in SA, although 30% of cases with Churg-Strauss Syndrome or localised Wegener’s Granulomatosis may be ANCA negative (Lapraik et al 2007). Majority of AAV is WG or MPA, with WG more likely in SA, given the latitude and majority Caucasian population (Koldingsnes &amp; Nossent 2008). Unknown what proportion of patients were intolerant to cyclophosphamide in these studies.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Applicability</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Observational studies are likely to be from many different countries [although have not cross-checked this]. Proposed dosing regimen was used in some of the observational studies.</td>
</tr>
</tbody>
</table>

3. **Rituximab in combination with IV/oral corticosteroids as therapy for AAV patients who frequently relapse (≥2) despite maintenance therapy with prednisolone combined with azathioprine, methotrexate or alkylating agents, or after successful weaning of an adequate course of maintenance therapy**

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>B</td>
<td>1 double-blind RCT (RAVE) in mixed induction/relapsed population plus 41 observational/uncontrolled (predominantly refractory/relapsed populations)</td>
</tr>
<tr>
<td>Consistency</td>
<td>B</td>
<td>Complete/partial remission and relapse rates fairly similar across observational studies, given the small sample sizes. Complete remission rates consistent with RCT. Remission rates of 67% vs 42% (p=0.01) for rituximab vs CYC, respectively, in RAVE for patients with relapse history.</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>B</td>
<td>Substantial. Relapsed (at baseline) patients in RAVE had 1.4 times the odds of remission when receiving rituximab, as opposed to CYC (ie odds 40% higher), albeit only measured over 6 months. 95% CI=1.03, 1.91 (95% probability that results would fall within range from slight effect ie 3% increase in odds up to very large effect ie 91% increase in odds); p=0.03. Observational studies had longer follow-up – most of these studies had follow-up longer than a year.</td>
</tr>
<tr>
<td>Generalisability</td>
<td>B</td>
<td>The double-blind RCT (RAVE) included patients with Wegener’s Granulomatosis and Microscopic Polyangiitis with positive ANCA assays, manifestations of severe disease and a BVAS score of ≥3 (scores=0-63, higher scores = more active disease). This population was mixed induction/relapsed. Large number of observational studies in refractory/relapsed populations. Unclear what proportion of observational studies included relapsed, as opposed to refractory populations. Majority of studies were WG or MPA with ANCA positivity. Populations will have some cross-over with the target population of relapsing AAV in SA, although 30% of cases with Churg-Strauss Syndrome or localised Wegener’s Granulomatosis may be ANCA negative (Lapraik et al 2007). Majority of AAV is WG or MPA, with WG more likely in SA, given the latitude and majority Caucasian population (Koldingsnes &amp; Nossent 2008).</td>
</tr>
<tr>
<td>Applicability</td>
<td>C</td>
<td>RAVE = 197 patients in 9 centres in the US. Proposed rituximab dosing/delivery differs from that in the trial, although used in some observational studies. Observed dosing are likely to be from many different countries [although have not cross-checked this].</td>
</tr>
</tbody>
</table>

As the majority of studies included mixed populations for the three clinical scenarios above, the evidence for all three scenarios is summarised together.

**Quality of the Evidence**

**Systematic reviews**

Two relevant systematic reviews were identified but neither included a meta-analysis: 1 including 2 RCTs - 1 moderate quality open-label (induction), 1 good quality double-blind (induction/relapsed) (CADTH report 2012);

In 2012 the Canadian Agency for Drugs and Technologies in Health (CADTH) published their review and recommendation of rituximab for the induction of remission in GPA and MPA(CADTH 2012). The CADTH
recommendation for listing rituximab was restricted to patients who had severe intolerance or other contraindication to cyclophosphamide, or who had failed an adequate trial of cyclophosphamide. CADTH considered an 'adequate trial' of cyclophosphamide to be six IV pulses or 3 months of oral therapy. Their recommendation was based upon one double-blind RCT, the RAVE trial (n=197), where rituximab was reported to be non-inferior, but not superior, to oral cyclophosphamide for inducing remission in patients with severely active GPA or MPA, based on the percentage of patients who achieved complete remission at six months, defined as a zero score on BVAS plus discontinuation of prednisone (Stone, Merkel et al. 2010; CADTH 2012).

The other systematic review included the same two RCTs plus 41 observational/uncontrolled studies, predominantly in the refractory/relapsed population (Guerry, Brogan et al. 2012).

**Randomised controlled trials**

There were two published randomised controlled trials (RCTs) investigating rituximab compared to cyclophosphamide in AAV. The RCTs are consistent that remission rates are similar between rituximab and cyclophosphamide trial arms; however remission rates varied between trials.

1. The RAVE trial included 197 patients with active, severe GPA and MPA, however patients with Churg-Strauss syndrome and/or renal impairment were specifically excluded from the trial (Stone, Merkel et al. 2010). Ninety-six (49%) of patients were newly diagnosed, and 101 (51%) of patients had relapsing disease. Patients who had received oral or IV cyclophosphamide within 4 months of enrolment for the RAVE trial were also excluded; however no patients in the rituximab arm were contraindicated to cyclophosphamide. The RAVE trial was double-blinded, however the method of randomisation is not provided and it is unclear whether allocation was concealed. In addition it is also unclear if all outcome assessors were blinded to treatment groups. 6 patients randomised to the rituximab group crossed over to the cyclophosphamide group, and 7 patients in the cyclophosphamide group crossed over to the rituximab group. Analysis however was based upon intention-to-treat. Results were only available for the mixed population or the relapsing population alone, not for the induction population alone.

The second published randomised trial, the RITUXVAS trial, investigated the use of rituximab in ANCA-associated renal vasculitis (Jones, Cohen Tervaert et al. 2010). The number of patients enrolled was small (n=44) and therefore the trial was not adequately powered to detect an effect with any precision and the baseline characteristics of patients were significantly different. In addition, it was open-label with 3 of the 4 outcome assessors being unblended to treatment group, providing a risk of measurement bias. For ethical reasons patients randomised to the rituximab arm also received two infusions of cyclophosphamide, with a third dose being allowed within the first six months in non-responders. The number of patients requiring a third dose was not provided by the authors.

Both the RAVE and RITUXVAS trials used the Birmingham Vasculitis Activity Scores (BVAS) to measure disease activity; however neither trial made it clear which clinical indicators of AVV accounted for the differences in scores.

Follow-up periods for both trials was short: 6 months for RAVE and 12 months for RITUXVAS. Longer follow-up is required to determine relapse rates with rituximab and to investigate safety concerns.

**Data Extraction Table from RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Grant Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVE  (Stone, Merkel et al. 2010)</td>
<td>Grant from the National Institute of Allergy &amp; Infectious Diseases to the Immune Tolerance Network. Genentech &amp; Biogen provided study</td>
</tr>
<tr>
<td>RITUXVAS (Jones, Cohen Tervaert et al. 2010)</td>
<td>Cambridge University Hospitals National Health Service Foundation Trust. Hoffmann-La Roche provided study medication &amp; a research grant</td>
</tr>
</tbody>
</table>
medication & partial funding. Other independent grants/awards.

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicentre, randomised, double-blind, double-dummy, non-inferiority trial</th>
<th>Open-label, multicentre, randomised trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Patient population</td>
<td>ANCA-positive adults with either Wegener’s granulomatosis or microscopic polyangiitis. Birmingham Vasculitis Activity Score for Wegener’s granulomatous (BVAS/WG) of 3 or more. Trial included a mixed induction/relapsing population and patients with Churg-Strauss syndrome and/or renal impairment were excluded.</td>
<td>Newly-diagnosed adult patients with AAV who were ANCA positive and had renal involvement (evidenced by biopsy or haematuria)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Rituximab 375mg/m² IV infusion weekly for four weeks + daily placebo tablet. If remission between 3-6 months, switched from placebo (cyclophos) to placebo (azathioprine). 1-3 IV doses of methylprednisolone 1000mg, followed by prednisone 1mg/kg/day, tapered so that at 5 months all patients in remission had ceased steroids.</td>
<td>Plasma exchange or 2g IV methylprednisolone</td>
</tr>
<tr>
<td>No. of patients on intervention</td>
<td>99 (24 microscopic polyangiitis, 74 Wegener’s granulomatosis, 1 unknown)</td>
<td>33</td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo infusion + daily cyclophosphamide 2mg/kg/ day (adjusted for renal insufficiency). If remission between 3-6 months, switched from cyclophosphamide to azathioprine 2mg/kg/day. 1-3 IV doses of methylprednisolone 1000mg, followed by prednisone 1mg/kg/day, tapered so that at 5 months all patients in remission had ceased steroids.</td>
<td>Plasma exchange or 2g IV methylprednisolone</td>
</tr>
<tr>
<td>No. of patients on comparator</td>
<td>98 (24 microscopic polyangiitis, 74 Wegener’s granulomatosis)</td>
<td>11</td>
</tr>
<tr>
<td>Primary efficacy outcome(s)</td>
<td>BVAS/WG of 0 and successful tapering off prednisone at 6 months</td>
<td>Sustained remission (BVAS/WG of 0 for at least 6 months) &amp; rates of severe adverse events</td>
</tr>
<tr>
<td>Secondary outcome(s)</td>
<td>Rates of disease flares (↑in BVAS/WG of 1 point of more) BVAS/WG of 0 during prednisone treatment (at less than 10mg/day) Adverse events Cumulative glucocorticoid dose SF-36 scores</td>
<td>Time to remission (BVAS/WG of 0 maintained for 2 months) Change in BVAS between 0 and 3 months Change in GFR Prednisolone dose at 12 months SF-36 scores Score on Vasculitis Damage Index</td>
</tr>
<tr>
<td>Blinding of patients</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blinding of outcome assessors</td>
<td>Unclear</td>
<td>3 unblinded, 1 blinded</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Withdrawals from intervention arm of study</td>
<td>1 withdrew and 6 switched to comparator arm</td>
<td>0</td>
</tr>
</tbody>
</table>

*3* Scores range from 0 to 63 with higher scores indicating more active disease.
Withdrawals from placebo arm of study

<table>
<thead>
<tr>
<th>Primary Outcome: BVAS/WG of 0</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 withdrew and 7 switched to intervention arm</td>
<td>63/99 (64%)</td>
<td>52/98 (53%)</td>
<td>25/33 (76%)</td>
<td>9/11 (82%)</td>
</tr>
</tbody>
</table>

Secondary Outcomes

<table>
<thead>
<tr>
<th>BVAS/WG of 0 on &lt; 10mg prednisone Disease flares (increase of BVAS/WG of ≥ 1pt)</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>70/99 (71%)</td>
<td>61/98 (62%)</td>
<td>70/99 (6%)</td>
<td>10/98 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Median time to remission (days) (IQ range)

<table>
<thead>
<tr>
<th>Cumulative steroid dose</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.095 ± 0.018</td>
<td>0.082 ± 0.019</td>
<td>0.095 ± 0.018</td>
<td>0.082 ± 0.019</td>
<td></td>
</tr>
</tbody>
</table>

Mean prednisolone dose at 12 months (mg/kg/day) ± Standard error of mean

<table>
<thead>
<tr>
<th>Median BVAS at entry (IQ range)</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 (14-24)</td>
<td>18 (12-25)</td>
<td>20 (5-44)</td>
<td>12 (9-33)</td>
<td></td>
</tr>
</tbody>
</table>

Mean BVAS at 3 mo (IQ range)

<table>
<thead>
<tr>
<th>Median BVAS at 3 mo (IQ range)</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.9 (10.4)</td>
<td>7.9 (12.6)</td>
<td>6.0 (10.4)</td>
<td>5.3 (12.9)</td>
<td></td>
</tr>
</tbody>
</table>

Mean improvement in SF-36 physical summary scores (SD)

<table>
<thead>
<tr>
<th>Mean improvement in SF-36 mental summary scores (SD)</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux+cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 (20-45)</td>
<td>27 (12-47)</td>
<td>0 (0-1.5)</td>
<td>0 (0-0)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Ritux + cyclophos</th>
<th>Cyclophos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (all causes)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>6/33 (18%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6/99 (6%)</td>
<td>1/98 (1%)</td>
<td>2/33 (6%)</td>
</tr>
<tr>
<td>Serious events requiring hospitalisation</td>
<td>8/99 (8%)</td>
<td>2/98 (2%)</td>
<td>27 in 12/33 patients</td>
</tr>
<tr>
<td>Infection</td>
<td>Grade 3: 7/99 (7%)</td>
<td>Grade 3: 7/98 (7%)</td>
<td>19 infections in 12/33 patients</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>Not reported</td>
<td>2/33 (6%)</td>
<td>0/11 (0%)</td>
</tr>
</tbody>
</table>

Recommended dose

No dose-ranging studies have been conducted in AAV, therefore the optimal dose, dose interval and duration of rituximab therapy is unknown.
The dose for induction proposed by the applicant(s) is two 1g IV infusions, administered two weeks apart. Although this is a different regimen to that used in the two randomised controlled trials, it has been recommended elsewhere (Fell 2011). This is the same dosing protocol as used in the treatment of rheumatoid arthritis.

The dose used in the two multicentre RCTs published to date (the RAVE and RITUXVAS trials) was 375mg/m² per week for four weeks (Jones, Cohen Tervaert et al. 2010; Stone, Merkel et al. 2010). Jones et al 2009 found similar remission rates between the two protocols in retrospective case series of 65 patients (81% for 375 mg/m²/week for 4 weeks; 75% for 1000mg 2 weeks apart) (Jones, Cohen Tervaert et al. 2010).

**Effectiveness**

*Induction Treatment of Generalised or Severe AAV In Patients Contraindicated To Cyclophosphamide*

RAVE was a non-inferiority trial and rituximab was found to be no-worse than cyclophosphamide regimen for induction/relapsed patients, based on the percentage of patients achieving complete remission at six months (64% versus 53% respectively)(Stone, Merkel et al. 2010). RITUXVAS also found similar remission and relapse rates between rituximab/CYC and cyclophosphamide regimens for induction. In the RITUXVAS trial, the percentage of sustained remission at 12 months was not statistically significantly different between the rituximab group compared to the control (76% versus 82%) (Jones, Cohen Tervaert et al. 2010).

There were no statistically significant between-treatment differences in the percentage of patients having either a severe flare or a limited flare in the RAVE trial, or in the percentage of patients having a major relapse in the RITUXVAS trial. In both trials there were no statistically significant between-treatment differences in corticosteroid use or in irreversible damage as measure by VDI. There were no reported differences in quality of life between treatments in either trial (CADTH 2012).

The therapeutic impact of rituximab relative to usual care for patients contraindicated to cyclophosphamide is unknown as the 2 RCTs available are for induction therapy but not for patients contraindicated to cyclophosphamide.

*Rescue Therapy For Management Of Treatment-Resistant(Refractory) AAV Or In Patients With AAV Who Are Intolerant To Cyclophosphamide*

There is limited evidence in relation to refractory patients. There is a systematic review of 41 small observational studies including relapsing and refractory patients which showed a favourable risk/benefit ratio, although there is a lack of long-term data pertaining to adverse events (Guerry, Brogan et al. 2012). Complete remission rates varied from 25-100% and mean complete or partial remission was 91%, with follow-up usually longer than a year and up to 4 years. Relapse rates ranged from 0-100%, with mean relapse of 32%.

*Patients Who Frequently Relapse (2 Or More) Despite Maintenance Therapy Or After Successful Weaning Of An Adequate Course Of Maintenance Therapy*

For patients with relapsing disease, the percentage of patients achieving complete remission at six months was statistically significantly higher in the rituximab group compared with the control group (67% versus 42%); however there may be selection bias with this subgroup as recurrences were probably due to cyclophosphamide failures. The subgroup of newly diagnosed AAV showed no difference in complete remission rates (61% versus 63%)(Stone, Merkel et al. 2010). Therefore considering rituximab in the context of relapse disease is reasonable, particularly where the maximum cumulative dose of cyclophosphamide has been reached.
Safety

The FDA have added a black box warning to the registered prescribing information in the United States. The black box warning alerts prescribers to the risk of fatal infusion reactions, tumour lysis syndrome (TLS), severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML) with rituximab (FDA 2012).

Severe infusion reactions typically occurred during the first infusion with time to onset between 30 and 120 minutes. Reactions include urticarial, hypotension, angioedema, hypoxia, bronchospasm, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylaxis or death. In clinical trials, the observed incidence of infusion reactions was ≥ 25% (FDA 2012).

JC virus infection resulting in PML can occur in rituximab-treated patients with autoimmune diseases who have had prior or concurrent immunosuppressive treatment, with most cases diagnosed within 12 months of the last infusion of rituximab (FDA 2012).

In both the RAVE and RITUXVAS trials, the incidence of adverse events and serious events was not statistically significantly different between treatment groups (CADTH 2012). Similar safety between rituximab and cyclophosphamide regimens in RITUXVAS may be because in rituximab regimen patients also received cyclophosphamide with 1st and 3rd rituximab infusions. Similar safety in RAVE may also be because relapsing patients had been previously exposed to cyclophosphamide and other medications.

In the RITUXVAS trial there appeared to be a doubling of the rate of early death in the rituximab group compared with the control group (18% to 9%) although the trial is insufficiently powered for this to reach statistical significance (Jones, Cohen Tervaert et al. 2010). In the RAVE trial 5% of patients who received rituximab developed malignant conditions during the six month trial duration, compared to 1% in the control group (Stone, Merkel et al. 2010).

A recent Cochrane review of adverse effects of biologic drugs found that in short-term RCTs (median duration 6 months) the use of rituximab was associated with a statistically significantly higher risk of total adverse events, withdrawals due to adverse events, serious infections and tuberculosis reactivation compared with control (Singh, Wells et al. 2012). The authors highlighted the urgent need for research into long term safety of rituximab and other biologic drugs. The observational prospective cohort, which is a long-term extension to the RAVE study will help provide an estimate of the long-term risk in patients with AAV.

Summary of Safety and Effectiveness

The evidence suggests that rituximab is effective in the treatment of AAV and no increased toxicity when rituximab is used with glucocorticoids as part of induction therapy. As such they support the use in this context where standard therapy is thought not to be appropriate. The lack of long term data means that safety and effectiveness in relation to repeated dosing and maintenance is unknown.

Conflict of interest declaration

The applicants declared no conflicts of interest.

The Chair of the South Australian Medicines Evaluation Panel (SAMEP) declared that as this formulary application refers to her specific area of clinical practice, there may be a perceived or potential conflict of interest. For this reason, the deputy chair of SAMEP led the review.
Appendix 4: Search strategy

Cochrane Database of Systematic Reviews

Search strategy:  
1. rituximab.mp. [mp=title, abstract, full text, keywords, caption text]
2. mabthera.mp. [mp=title, abstract, full text, keywords, caption text]
3. 1 or 2
4. wegener.mp. [mp=title, abstract, full text, keywords, caption text]
5. polyangiitis.mp. [mp=title, abstract, full text, keywords, caption text]
6. vasculitis.mp. [mp=title, short title, abstract, full text, keywords, caption text]
7. 4 or 5 or 6
8. 3 and 7

*Date of Search: 11 Feb 2013*
*Citations returned: 4 (none applicable)*

Cochrane Central Register of Controlled Trials

Search strategy:  
1. rituximab.mp.
2. Vasculitis/ or exp Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ or exp Systemic Vasculitis/
3. 1 and 2

*Date of Search: 20 Feb 2013*
*Citations returned: 3 citations (all applicable)*

Medline

Search strategy:  
1. rituximab.mp.
2. clinical trial.mp.
3. clinical trial.pt.
4. random$.mp.
5. tu.xs.
6. randomised clinical trial.mp.
7. randomized.ab.
8. placebo.ab.
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Systemic Vasculitis/ or exp Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ or Vasculitis/
11. exp Wegener Granulomatosis/
12. exp Churg-Strauss Syndrome/
13. Microscopic Polyangiitis/
14. 10 or 11 or 12 or 13
15. 1 and 9
16. 14 and 15
17. limit 16 to randomized controlled trial

*Date of Search: 11 Jan 2013*
*Citations returned: 6 (2 applicable)*
Appendix 5: Identified on-going trials

1. ClinicalTrials.gov identifier: NCT01697267
   Trial name: Rituximab Vasculitis Maintenance Study (RITAZAREM)
   Official title: An International, Open Label, Randomised Controlled Trial Comparing Rituximab With Azathioprine as Maintenance Therapy in Relapsing ANCA-associated Vasculitis
   Primary outcome: Time to disease relapse from randomisation
   Estimated completion: December 2016

2. ClinicalTrials.gov identifier: NCT01731561
   Trial name: Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN 2)
   Official title: Maintenance of Remission Using Rituximab in Systemic ANCA-associated Vasculitis II
   Primary outcome: Number of relapses (BVAS>0) majors and minors in each group at the end of the maintenance treatment (18 months treatment + 16 months follow-up)
   Estimated completion: February 2018

3. ClinicalTrials.gov identifier: NCT01586858
   Official title: Rituximab for ANCA-associated Vasculitis (RAVE) Long-Term Follow-Up Study
   Design: Observational prospective cohort

4. ClinicalTrials.gov identifier: NCT00748644
   Official title: Maintenance of Remission Using Rituximab in Systemic ANCA-associated Vasculitis
   Design: Prospective, multicenter, controlled, open-label randomized comparative study of rituximab versus azathioprine
   Estimated completion: December 2013

5. ClinicalTrials.gov identifier: NCT01750697
   Trial name: A study of intravenous MabThera/Rituxan in Pediatric Patients with severe Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis (Wegener s) or microscopic polyangiitis
   Official title: A phase 2 international, multicenter, open-label, uncontrolled study to evaluate the safety and pharmacokinetics of 4 x 375 mg/m2 intravenous rituximab in pediatric patients with severe granulomatosis with polyangiitis or microscopic polyangiitis
   Estimated completion: March 2017

6. ClinicalTrials.gov identifier: NCT01613599
   Trial name: An Observational Study Of The Safety Of MabThera/Rituxan (Rituximab) In Patients With Granulomatosis With Polyangiitis (Wegener's) Or Microscopic Polyangiitis
   Official title: Prospective, Observational Safety Study of Patients With Granulomatosis With Polyangiitis (Wegener's) or Microscopic Polyangiitis Treated With Rituximab
   Primary outcome measures: Safety: Incidence of serious infections
   Secondary outcomes: Safety: Incidence of serious adverse events
   Estimated completion: April 2018

7. EudraCT Number: 2008-002846-51
   Trial name: Etude de l'efficacité du Rituximab versus Azathioprine en traitement d'entretien au cours des vascularites associées aux ANCA : Etude prospective, multicentrique, contrôlée, randomisée (Study of the efficacy of Rituximab versus Azathioprine in maintenance treatment in ANCA-associated vasculitis: prospective, multicenter, controlled, randomized study)
   Primary outcome measures: Number of major relapse (BVAS > 10) in each arm at the end of the 28-month period of maintenance (18 months of treatment + 10 months of follow-up).
## Appendix 6: NHMRC evidence rating guide

### 1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td>
</tr>
<tr>
<td>B</td>
<td>One or two Level II studies with a low risk of bias or SR/ several Level III studies with a low risk of bias</td>
</tr>
<tr>
<td>C</td>
<td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td>
</tr>
<tr>
<td>D</td>
<td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td>
</tr>
</tbody>
</table>

### 2. Consistency (if only one study was available, rank this component as ‘not applicable’)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>All studies consistent</td>
</tr>
<tr>
<td>B</td>
<td>Most studies consistent and inconsistency can be explained</td>
</tr>
<tr>
<td>C</td>
<td>Some inconsistency, reflecting genuine uncertainty around question</td>
</tr>
<tr>
<td>D</td>
<td>Evidence is inconsistent</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable (one study only)</td>
</tr>
</tbody>
</table>

### 3. Clinical impact (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Very large</td>
</tr>
<tr>
<td>B</td>
<td>Substantial</td>
</tr>
<tr>
<td>C</td>
<td>Moderate</td>
</tr>
<tr>
<td>D</td>
<td>Slight / restricted</td>
</tr>
</tbody>
</table>

### 4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Formulary Submission?)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence directly generalisable to target population</td>
</tr>
<tr>
<td>B</td>
<td>Evidence directly generalisable to target population with some caveats</td>
</tr>
<tr>
<td>C</td>
<td>Evidence not directly generalisable to the target population but could be sensibly applied</td>
</tr>
<tr>
<td>D</td>
<td>Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply</td>
</tr>
</tbody>
</table>

### 5. Applicability (Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence directly applicable to <em>South Australian public hospital</em> context</td>
</tr>
<tr>
<td>B</td>
<td>Evidence applicable to <em>South Australian public hospital</em> context with few caveats</td>
</tr>
<tr>
<td>C</td>
<td>Evidence probably applicable to <em>South Australian public hospital</em> context with some caveats</td>
</tr>
<tr>
<td>D</td>
<td>Evidence not applicable to <em>South Australian public hospital</em> context</td>
</tr>
</tbody>
</table>

Source: Adapted from NHMRC 2009
Appendix 7: References


FDA (2012). Rituximab (Rituxan) Full Prescribing Information. Silver Spring, Maryland, Food and Drug Administration [Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5362lbl.pdf].


Disclaimer: This review was produced as an advisory note for the SA Medicines Advisory Committee. The data used to compile the report comes from various sources. The Department is not able to guarantee that different sources have compiled or reported data in a consistent way. The Department uses its best endeavours to ensure the quality of the information available in this report. Before relying on the information within this report, users should carefully evaluate its accuracy, currency, completeness and relevance for their purposes, and should obtain any appropriate professional advice relevant to their particular circumstances. The Department cannot guarantee and assumes no legal liability or responsibility for the accuracy, currency or completeness of the information.