Rheumatology Subcommittee of PTAC

Meeting held 13 October 2015

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Rheumatology Subcommittee meeting; only the relevant portions of the minutes relating to Rheumatology Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Rheumatology Subcommittee may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes have been reviewed by PTAC at its meeting on 11 & 12 February 2016.

Record of the Rheumatology Subcommittee of PTAC meeting held at PHARMAC on 13 October 2015

1. Febuxostat

1.1. The Subcommittee noted the August 2015 PTAC minutes for febuxostat, noting that the Committee had recommended removing the requirement to trial probenecid prior to accessing funded febuxostat.

1.2. The Subcommittee considered that two of the biggest barriers to treatment success in patients with gout were underdosing of allopurinol and lack of adherence to urate-lowering therapy.

1.3. The Subcommittee noted that there was no evidence that febuxostat would improve treatment compliance compared with allopurinol and, given the difference in cost between the two treatments, resources would be better used encouraging appropriate allopurinol use rather than widening access to febuxostat. The Subcommittee noted that there was a research assay used in Christchurch to measure oxypurinol concentrations, which can be performed to ensure that patients are taking allopurinol. However, members noted that this test was not currently widely used across the country or available in primary care.

1.4. The Subcommittee noted PTAC's comments regarding probenecid and considered that removing the requirement to trial probenecid prior to febuxostat would be pragmatic despite the difference in price. The Subcommittee considered that removing the requirement to trial probenecid prior to accessing febuxostat would result in an increased use of febuxostat as it would make it easier for patients to move from allopurinol to febuxostat. The Subcommittee considered that potentially up to 10% of allopurinol patients could switch to febuxostat if the requirement to trial probenecid prior to febuxostat was removed. The Subcommittee considered that there would be unlikely to be any changes in lab testing or frequency of GP visits if patients moved from allopurinol to febuxostat without trialling probenecid.

1.5. Taking into account PTAC's August 2015 review and recommendations, the Subcommittee **recommended** the following changes be made to the febuxostat Special Authority (and hospital restrictions as applicable):

> Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1 Patient has been diagnosed with gout; and
> 2 ~~Any of the following~~ **Either**:
> 2.1 The patient has a serum urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses of at least 600 mg/day **and up to 900 mg/day (see Note)** ~~and addition of probenecid at doses of up to 2 g per day or maximum tolerated dose~~; or
> 2.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required**.** ~~and serum urate remains greater than 0.36 mmol/l despite use of probenecid at doses of up to 2 g per day or maximum tolerated dose; or~~
> 2.3 ~~The patient has renal impairment such that probenecid is contraindicated or likely to be ineffective and serum urate remains greater than 0.36 mmol/l despite optimal treatment with allopurinol (see Note).~~

Renewal from any relevant practitioner. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefitting from treatment.

Note: ~~In chronic renal insufficiency, particularly when the glomerular filtration rate is 30 ml/minute or less, probenecid may not be effective.~~ The efficacy and safety of febuxostat have not been fully evaluated in patients with severe renal impairment (creatinine clearance less than 30 ml/minute). No dosage adjustment of febuxostat is necessary in patients with mild or moderate renal impairment. Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/l, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.

2. Review of Biologic Treatment Restrictions for Rheumatology Indications

2.1. The Subcommittee noted a request from PHARMAC staff to review the current funding restrictions for first-line access to biologic treatments in rheumatology indications to ensure they are clear and clinically appropriate.

2.2. The Subcommittee also noted a submission from a supplier requesting changes to the criteria for ankylosing spondylitis and rheumatoid arthritis.

2.3. The Subcommittee noted that recommendations in the following paragraphs were for changes to the criteria that currently apply to etanercept; however, the intention is that any recommended changes would apply to any biologic treatment that was subject to the relevant access criteria at the time any changes were made.

General

2.4. The Subcommittee considered that the requirement for renewal applications to be made every 6 months was unnecessarily burdensome on rheumatology clinics as it was inconsistent with usual practice of reassessing stable patients every 12 months. The Subcommittee **recommended** that renewal periods for all rheumatology indications be increased to 12 months. The Subcommittee considered that there would be no clinical or financial impact if the renewal time was increased to 12 months, but it would free up clinic time.

Juvenile idiopathic arthritis

2.5. The Subcommittee considered that there was no particular reason not to include a maximum dose restriction to the renewal criteria for juvenile idiopathic arthritis that matched the current maximum dose restriction for other indications (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), although members considered that these doses were unlikely to be exceeded currently.

2.6. The Subcommittee noted that the initial approval period for juvenile idiopathic arthritis was inconsistent with the initial approval period for other rheumatology indications and **recommended** that the initial approval period for biologic treatments for juvenile idiopathic arthritis be increased from 4 months to 6 months.

Rheumatoid arthritis

2.7. The Subcommittee noted that a supplier had requested removal of the word “erosive” from criterion 2.1 and that PHARMAC staff had received other queries around the definition of “erosive rheumatoid arthritis” in this criterion. The Subcommittee

considered that if the word “erosive” was removed from the criterion, approximately 100-150 patients per year would access biologic treatment at least 6 months to 2 years earlier than they would otherwise, which would be associated with a significant cost to the Combined Pharmaceutical Budget. The Subcommittee considered that the intent of the criterion could be clarified by stating that the patient must have cyclic citrullinated peptide (CCP) antibody positive rheumatoid arthritis or rheumatoid arthritis with erosions confirmed by imaging (plain radiology, MRI, CT or ultrasound). The Subcommittee considered that the words “severe” and “active” in criterion 2.1 were unnecessary given the disease-specific requirements in other criteria, and could be removed.

2.8. The Subcommittee considered that criterion 2.2 was somewhat unnecessary as it covered all possibilities; however, members considered that it was a useful reminder that the tumour necrosis factor (TNF) alpha inhibitor treatments were more effective when used with methotrexate.

2.9. The Subcommittee noted that few patients were accessing biologic treatments after methotrexate/ciclosporin or methotrexate/intramuscular gold combinations. The Subcommittee considered that these criteria could be removed without significant clinical impact; however, members considered there was no particular need to remove them, noting that they provide an alternative option for the few patients who cannot take leflunomide.

2.10. The Subcommittee **recommended** changing the initial criteria for etanercept for rheumatoid arthritis as follows (additions in bold, deletions in strikethrough):

> **Initial application - (rheumatoid arthritis)** only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> Either:
> 1 Both:
> 1.1 The patient has had an initial Special Authority approval for adalimumab for rheumatoid arthritis; and
> 1.2 Either:
> 1.2.1 The patient has experienced intolerable side effects from adalimumab; or
> 1.2.2 The patient has received insufficient benefit from adalimumab to meet the renewal criteria for adalimumab for rheumatoid arthritis; or
> 2 All of the following:
> 2.1 Patient has had ~~severe and active~~ erosive rheumatoid arthritis **(confirmed by radiology imaging, or the patient is cyclic citrullinated peptide (CCP) antibody positive)** for six months duration or longer; and
> 2.2 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
> 2.3 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and
> 2.4 Patient has tried and not responded to at least three months of oral or parenteral methotrexate in combination with sulphasalazine and hydroxychloroquine sulphate (at maximum tolerated doses); and
> 2.5 Any of the following:
> 2.5.1 Patient has tried and not responded to at least three months of oral or parenteral methotrexate in combination with the maximum tolerated dose of ciclosporin; or
> 2.5.2 Patient has tried and not responded to at least three months of oral or parenteral methotrexate in combination with intramuscular gold; or
> 2.5.3 Patient has tried and not responded to at least three months of therapy at the maximum tolerated dose of leflunomide alone or in

combination with oral or parenteral methotrexate; and

2.6 Either:

2.6.1 Patient has persistent symptoms of poorly controlled and active disease in at least 20 swollen, tender joints; or

2.6.2 Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and

2.7 Either:

2.7.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or

2.7.2 C-reactive protein levels not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

Ankylosing spondylitis

2.11. The Subcommittee noted that a supplier had requested removal of the requirement for sacroiliitis to be bilateral in criterion 2.3, noting that modified New York criteria for ankylosing spondylitis include both bilateral (grade ≥2) and unilateral (grade 3-4) sacroiliitis. The Subcommittee considered that the requested change was unnecessary, noting that it was extremely unusual to see grade 3-4 unilateral sacroiliitis on plain radiographs and in the odd instance where this occurred there was almost always bilateral sacroiliitis seen on MRI.

2.12. The Subcommittee noted that the ankylosing spondylitis renewal requirement to measure BASDAI after 12 weeks of treatment was out of sync with the 6-monthly renewal period. Therefore, the Subcommittee **recommended** amending the renewal criteria for etanercept for ankylosing spondylitis as follows (deletions in strikethrough, additions in bold):

> **Renewal - (ankylosing spondylitis)** only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 Either:
> 1.1 Applicant is a rheumatologist; or
> 1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with etanercept treatment; and
> 2 ~~Following 12 weeks of etanercept treatment,~~ **Following 12 weeks' initial treatment and for subsequent renewals, treatment has resulted in an improvement in** BASDAI ~~has improved by~~ **of** 4 or more points from pre-treatment baseline on a 10 point scale, or **an improvement in BASDAI of** ~~by~~ 50%, whichever is less; and
> 3 Physician considers that the patient has benefited from treatment and that continued treatment is appropriate; and
> 4 Etanercept to be administered at doses no greater than 50 mg every 7 days.

Psoriatic arthritis

2.13. The Subcommittee noted a suggestion from a clinician that a trial of leflunomide should be required (rather than either/or with sulphasalazine) prior to accessing biologic treatments for psoriatic arthritis, because it is more effective than previously thought in this indication.

2.14. The Subcommittee considered that the available evidence supported similar efficacy of methotrexate, leflunomide and sulphasalazine in psoriatic arthritis. The Subcommittee considered that it would be reasonable to require a trial of all three

agents, alone or in combination, prior to accessing a biologic treatment for psoriatic arthritis. However, the Subcommittee considered that there was no particular reason to make the change to the criteria, noting that it would be unlikely to have a significant impact on biologic treatment usage.

2.15. The Subcommittee noted that dactylitis is a predictor of adverse outcome/erosions in patients with psoriatic arthritis and considered that this could be added to the list of major active joints in criterion 2.4.2. The Subcommittee considered that this would result in more patients with psoriatic arthritis accessing biologic treatment, although it was difficult to estimate the additional number.

2.16. The Subcommittee considered that the words "severe" and "active" in criterion 2.1 were unnecessary and could be removed.

Adult-onset Still's disease

2.17. The Subcommittee considered that it would be reasonable to include a maximum dose restriction to the renewal criteria for Adult-onset Still's disease that matched the current maximum dose restriction for other indications (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), although members considered that these doses were unlikely to be exceeded currently.

2.18. The Subcommittee **recommended** adding "at a dose of at least 0.5 mg/kg" after the word "glucocorticosteriods" in criterion 2.2 of the initial application for etanercept for Adult-onset Still's disease.

3. TNF-alpha inhibitors for Inflammatory Bowel Disease-Associated Arthritis (IBD-A)

3.1. The Subcommittee noted that in February 2015, PTAC recommended that access to at least one of adalimumab or infliximab should be widened to include inflammatory bowel disease-associated arthritis (IBD-A) with a low priority and also recommended seeking further advice from the Rheumatology Subcommittee on appropriate Special Authority criteria. In particular, PTAC requested advice on potential first-line disease-modifying antirheumatic drugs (DMARDs) (eg methotrexate) that could be reasonably tried prior to a TNF-alpha inhibitor in IBD-A-axial, and the Committee also requested the Subcommittee's advice on the use of cyclooxygenase-2 (COX-2) inhibitors prior to TNF-alpha inhibitors in IBD-A, should these become funded.

3.2. The Subcommittee considered that there was insufficient evidence to recommend a trial of any DMARD in axial IBD-A. The Subcommittee noted that it had previously suggested the use of sulfasalazine at its meeting in October 2014. However, this was not evidence based.

3.3. The Subcommittee noted a Cochrane review of the tolerability of COX-2 inhibitors used for the treatment of rheumatological manifestations of IBD (Miao et al. Cochrane Database Syst Rev 2014;10:CD007744) in which the two included studies suggested no exacerbation of IBD symptoms from celecoxib or etoricoxib; however, the authors stated that no definitive conclusions could be drawn from the review.

3.4. The Subcommittee noted that patients with IBD-A are often unable to take NSAIDs as these can cause colitis flare. However; the Subcommittee considered that if a patient was in remission from their IBD and still had axial symptoms, it would be reasonable

to require a trial of non-steroidal anti-inflammatory agent (NSAID) or a COX-2 inhibitor unless the patient has previously experienced a colitis flare from these treatments.

3.5. The Subcommittee considered that it would be unreasonable to require a trial of NSAIDs or COX-2 inhibitors in patients with active IBD, which was the group under consideration for funded treatment with TNF alpha inhibitors. The Subcommittee considered that this should be clarified in the proposed criteria.

3.6. The Subcommittee **recommended** that the following funding criteria should apply to the use of adalimumab or infliximab in IBD-A (changes from the criteria previously proposed by the Subcommittee are marked up with additions in bold and deletions in strikethrough):

> **Initial application — (inflammatory bowel arthritis – axial)** only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both
> 1 Patient has a confirmed diagnosis of **active** ulcerative colitis or **active** Crohn's disease made by a gastroenterologist; and
> 2 All of the following:
> 2.1 Patient has ~~severe~~ axial inflammatory pain for six months or more; and
> 2.2 Patient is unable to take non-steroidal anti-inflammatory drugs (NSAIDs); and
> 2.3 Patient has bilateral sacroiliitis demonstrated by plain radiographs, CT or MRI scan; and
> 2.4 Patient's inflammatory bowel arthritis has not responded adequately to prior treatment consisting of at least 3 months of an exercise regime supervised by a physiotherapist~~ and concomitant sulphasalazine (unless contraindicated)~~; and
> 2.5 A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 6 on a 0-10 scale (see Note).
>
> Notes: The BASDAI must have been determined at the completion of the 3 month exercise trial, but prior to ceasing any previous pharmacological treatment. The BASDAI measure must be no more than 1 month old at the time of initial application.
>
> **Initial application — (inflammatory bowel arthritis – peripheral)** only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both
> 1 Patient has a confirmed diagnosis of **active** ulcerative colitis or **active** Crohn's disease made by a gastroenterologist; and
> 2 All of the following:
> 2.1 Patient has active peripheral joint arthritis in at least four joints from the following: hip, knee, ankle, subtalar, tarsus, forefoot, wrist, elbow, shoulder, sternoclavicular; and
> 2.2 Patient has tried and not responded to at least three months of oral or parenteral methotrexate (unless patient is on azathioprine) at a dose of at least 20 mg weekly or a maximum tolerated dose; and
> 2.3 Patient has tried and not responded to at least three months of sulphasalazine (or sulphasalazine is contraindicated); and
> 2.4 Any of the following:
> 2.4.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
> 2.4.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
> 2.4.3 ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

Renewal — (inflammatory bowel arthritis – axial) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for **12** ~~6~~ months for applications meeting the following criteria:
All of the following:

1 Either:
  1.1 Applicant is a rheumatologist; or
  1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with TNF-alpha inhibitor treatment; and
2 ~~Following 12 weeks of etanercept treatment,~~ **Following 12 weeks' initial treatment and for subsequent renewals, treatment has resulted in an improvement in** BASDAI ~~has improved by~~ **of** 4 or more points from pre-treatment baseline on a 10 point scale, or **an improvement in BASDAI of** ~~by~~ 50%, whichever is less; and
3 Physician considers that the patient has benefited from treatment and that continued treatment is appropriate; and
4 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 5 mg/kg every 8 weeks for infliximab]

Renewal — (inflammatory bowel arthritis – peripheral) only from a rheumatologist or Practitioner on the recommendation of a rheumatologist. Approvals valid for **12** ~~6~~ months for applications meeting the following criteria:
All of the following:

1 Either:
  1.1 Applicant is a rheumatologist; or
  1.2 Applicant is a Practitioner and confirms that a rheumatologist has provided a letter, email or fax recommending that the patient continues with TNF-alpha inhibitor treatment; and
2 Either:
  2.1 Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
  2.2 The patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to prior TNF-alpha inhibitor treatment in the opinion of the treating physician; and
3 TNF-alpha inhibitor to be administered at doses no greater than x dose every x days. [40 mg per 14 days for adalimumab and 5 mg/kg every 8 weeks for infliximab]

4. Tocilizumab Amendment of RA criteria

Application

4.1. The Subcommittee reviewed a clinician application with support from the New Zealand Rheumatology Association to remove of requirement to try rituximab prior to accessing tocilizumab (Actemra) for patients with rheumatoid arthritis seronegative for both anti-cyclic citrullinated peptide [CCP] antibodies and rheumatoid factor.

Recommendation

4.2. The Subcommittee **recommended** amending the hospital restrictions for tocilizumab to remove the requirement to trial rituximab in patients with rheumatoid arthritis seronegative for both anti-cyclic citrullinated peptide [CCP] antibodies and rheumatoid factor (RF) only if this would be cost-neutral to the status quo hospital expenditure on rituximab and tocilizumab for this patient group.

4.3. The Decision Criteria particularly relevant to this recommendation are: (*i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

4.4. The Subcommittee noted the following supporting information provided in the application:

- A multicenter, randomised, double-blind, placebo-controlled, phase III trial of rituximab plus methotrexate (n=311) versus methotrexate ("placebo" arm, n=209) in patients with rheumatoid arthritis refractory to tumour necrosis factor (TNF) alpha inhibitor treatment (the "REFLEX" trial, Cohen et al. Arthritis Rheum 2006;9:2793-2806). The primary endpoint was American College of Rheumatology (ACR)20 response at week 24, using a Cochran-Mantel-Haenszel analysis and stratifying by RF status (positive versus negative) and geographic region (US versus non-US) at baseline. The authors reported that fewer RF-negative patients than RF-positive patients achieved an American College of Rheumatology (ACR)20 response at week 24, both in patients treated with placebo (12% versus 19%) and in patients treated with rituximab (41% versus 54%). Differences in the ACR20 response rates between the placebo and rituximab groups were significant for both RF-positive patients ($p < 0.0001$) and RF-negative patients ($p < 0.0009$). However, there was no significant interaction between treatment and RF status ($p = 0.9$), indicating that the effect of treatment on the ACR response was not dependent on baseline RF status.

- A poster presentation of a subgroup analysis of the same study (Tak et al. Poster presented at 2006 ACR/ARHP Annual Scientific Meeting in Washington DC) found that the subgroup of patients who were seronegative for both RF and anti-CCP antibodies still derived benefit from rituximab compared with placebo as measured by European League Against Rheumatism (EULAR) and ACR20 responses, although higher-level ACR responses (ACR50 and ACR70) were not observed in the subgroup of patients who were seronegative for both autoantibodies. The authors noted the low patient numbers in this subgroup (n=25 for rituximab and n=14 for placebo).

- A retrospective analysis of a pooled cohort from two phase III studies including patients with active rheumatoid arthritis where rituximab was added to existing methotrexate (Isaacs et al, Ann Rheum Dis 2009;68(Suppl3):442). A total of 670 pts were included: 554 (82.6%) seropositive and 116 seronegative. The authors reported that seropositivity was significantly associated with an increased probability of patients achieving ACR20 and ACR50 at week 24, and significantly increased probably of achieving ACR20, 50 and 70 at week 48.

- An analysis of datasets from 10 European registries to assess the 6-month effectiveness of the first rituximab course in rheumatoid arthritis and to identify possible predictors of response (Chatzidionysiou et al. Ann Rheum Dis 2011;70:1575–1580). The study found that significantly better results were seen as measured by Disease Activity Score based on 28 joint counts (DAS28) after 6 months for RF-positive patients than for RF-negative patients, but also for anti-CCP-positive versus negative individuals and double-positive

versus double-negative patients. However, the authors note that seronegative patients also responded well to rituximab, and the difference between groups was not as strong at 6 months as at 3 months. The authors speculate that seronegative patients may respond more slowly to rituximab. The authors note limitations of the study and note that prospective data collection is needed for more robust conclusions.

- A retrospective evaluation of 235 patients with rheumatoid arthritis who were observed through 52 weeks of follow-up after infliximab or tocilizumab treatment in a Japanese hospital (presented in abstract form only: Sato et al. Arthritis Rheum 2013;65(Suppl 10):S1010-1; Sato et al. Arthritis Rheum Dis 2014;73(Suppl 2):FRI0023). Clinical efficacy was assessed based on a 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) remission and achievement of Boolean-based remission criteria and its components (≤1) at 52 weeks after initiating treatment. The authors reported that anti-RF positivity and anti-CCP positivity appear to affect response to infliximab but not tocilizumab. The Subcommittee queried the applicability of this study to the New Zealand setting, noting that there are possible ethnic differences in response to biologic treatments.

- A review article (Jones and Ding. Clin Med Insights Arthritis Musculoskelet Disord 2010;3:81-89) which noted results of the AMBITION trial showing that ACR20 response to tocilizumab was higher than methotrexate in patients who were RF-positive (73% vs 57%) and RF-negative (64% vs 37%).

4.5. The Subcommittee noted the following additional publications provided by PHARMAC staff:

- A meta-analysis of the effect of baseline RF and anti-CCP antibody serotype on rituximab clinical response in 2,177 patients from four phase II or III placebo-controlled trials (Isaacs et al. Ann Rheum Dis 2013;72:329–336). The efficacy end point in all analyses was change from baseline in DAS28-ESR at 24 weeks. The authors report that the overall-effect model indicated evidence of a modest additional treatment benefit with rituximab in seropositive patients: reduction in DAS28-ESR at week 24 was on average 0.35 units (95% CI 0.12 to 0.84; n=1394) greater than in seronegative patients; this effect was not seen in placebo patients.

- A systematic review and meta-analysis of RF as a predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis (Maneiro et al. Semin Arthritis Rheum 2013;43:9-17). A total of 23 studies were included in the review. RF positivity at starting predicted better ACR20, ACR50 and EULAR with rituximab and tocilizumab but not with abatacept.

4.6. The Subcommittee considered that there was reasonably good quality evidence to suggest that seropositive patients are more likely to achieve a response to rituximab, although the effect size did not appear to be large in the meta-analysis. The Subcommittee considered that it would be reasonable to use the response rates from the REFLEX trial for the purposes of PHARMAC's analyses.

4.7. The Subcommittee noted that there was also some evidence to suggest that baseline seropositivity is associated with higher response rates from tocilizumab treatment, although the evidence appeared somewhat conflicting. The Subcommittee considered that it would be reasonable to assume a smaller effect size for tocilizumab compared with rituximab, with respect to the impact of seropositivity on response to treatment.

Members suggested that it would be reasonable for the analysis to assume that approximately 10% more seronegative patients would response to tocilizumab versus rituximab.

4.8. The Subcommittee considered that response to rituximab and tocilizumab is likely to be independent, meaning that failure to respond to one treatment did not necessarily mean that the patient would not respond to the other. Further, members noted that seronegative patients still received benefit from rituximab, albeit not as great as seropositive patients. For these reasons, the Subcommittee considered that if the requirement for rituximab to be trialled prior to tocilizumab in seronegative patients was removed, patients should still be able to move to rituximab if they received insufficient benefit from tocilizumab.

4.9. The Subcommittee noted that it was necessary to wait 4 months before assessing response to rituximab (as opposed to 12 weeks with tocilizumab) so there would be a longer time between switching treatments in non-responders for those who try rituximab first.

4.10. The Subcommittee considered that, for these patients, the key benefit of trialling tocilizumab first would be achieving remission sooner. The Subcommittee noted that a long-term advantage of early remission on disease progression was not demonstrated in the Behandel Strategieen (BeSt) trial (Goekoop-Reuiterman et al. Arthritis Rheum 2008;58(2 Suppl):S126-35). However, members considered that patients feel better with early remission and quality of life is improved.

4.11. The Subcommittee considered that there was no safety issue concerning starting one of the drugs before the other. However, there could be an issue for patients who did not respond to rituximab and subsequently their initiation of treatment on tocilizumab was delayed by 4 months during that trial period.

4.12. The Subcommittee considered that there would be no change in adverse affects by altering the order of treatment with the two agents.

4.13. The Subcommittee considered that the size of the relevant patient group estimated in the application (10 patients per year) was reasonable. The Subcommittee noted that a proportion of patients in this group would currently move to tocilizumab anyway after the four-month assessment of rituximab.

4.14. The Subcommittee noted that some patients would prefer a longer acting treatment rather than having to have monthly infusions and this could be a factor in deciding which treatment was tried first if the requirement to try rituximab first was removed for seronegative patients.

4.15. The Subcommittee considered that removing the requirement to trial rituximab prior to tocilizumab in seronegative patients was unlikely to result in a large clinical benefit given that a reasonable proportion of such patients would derive benefit from rituximab. Therefore, the Subcommittee considered that the criteria should be changed only if it would not result in an increased cost, noting that the price difference between the biologic treatments was the primary reason for the current funded treatment order.

4.16. The Subcommittee considered that if the requirement to trial rituximab was removed, this should be only for patients who were both RF-negative and anti-CCP antibody negative.