**Rheumatology Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)**

**Meeting held on 17 October 2017**

## (minutes for web publishing)

Rheumatology Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.*

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 will be reviewed by PTAC at its meeting on 8 & 9 February 2018, the record of which will be available in due course.

**Record of the Rheumatology Subcommittee of the PTAC meeting held at PHARMAC on 17 October 2017**

## 1 Record of the Previous Rheumatology Subcommittee Meeting

1.1 The Subcommittee noted and accepted the record of its previous meeting held on 13 October 2015.

## 2 Previous recommendations and action points

2.1 The Subcommittee noted a summary of the outstanding Rheumatology Subcommittee recommendations and action points.

2.2 The Subcommittee noted that in October 2014 it had recommended PHARMAC staff conduct a review of the available options for the treatment of dry mouth in patients with Sjögren's syndrome and that this had not yet been progressed. The Subcommittee considered that while there remains a need for such treatments, no suitable treatments are available. The Subcommittee considered that this action point should be removed.

## 3 Factors for Consideration presentation

3.1 The Subcommittee noted a presentation by PHARMAC staff outlining PHARMAC's new decision-making criteria, the Factors for Consideration (FFC), which replaced the previous nine Decision Making Criteria on 1 July 2016. Members noted that all recommendations made by the Subcommittee should be now provided in the context of the FFC.

## 4 Therapeutic Group Review

### Named Patient Pharmaceutical Assessment (NPPA) applications

4.1 The Subcommittee noted a summary of NPPA initial applications in the rheumatology therapeutic area. The Subcommittee considered it would be useful to also review renewal applications and those that did not meet NPPA prerequisites. The Subcommittee asked that at the next meeting the NPPA report include all applications, and that staff consider how best to report trends in the data.

### Non-steroidal anti-inflammatories (NSAIDs)

*Sulindac*

4.2 The Subcommittee noted that the supplier of sulindac has notified discontinuation of sulindac (Aclind) 100 mg and 200 mg tablets from November 2018 and February 2019 respectively. The Subcommittee considered that celecoxib is an alternative treatment, however, noted that this may not be the case for gastrointestinal patients.

## Antirheumatoid agents

*Adalimumab audit*

4.3 The Subcommittee noted a recent audit of adalimumab Special Authorities had been undertaken and that follow-up to this was currently being undertaken with clinicians who had shown significant non-compliance. The Subcommittee considered that as a result of this process there was an increased understanding about the Special Authority waiver application process.

## Hyperuricaemia and antigout

*Febuxostat*

4.4 The Subcommittee noted that PTAC, at its meeting in August 2015, had recommended removing the requirement to trial probenecid prior to accessing febuxostat with a medium priority.

4.5 The Subcommittee noted that PHARMAC staff had requested advice regarding the comparators and assumptions in the analysis of this proposal.

4.6 The Subcommittee considered that most prescribers do not prescribe probenecid and considered that this was a barrier to people accessing febuxostat under the current Special Authority criteria.

4.7 The Subcommittee considered that if the requirement to trial probenecid was removed, the majority (perhaps 70-80%) of new febuxostat patients would have switched from allopurinol. Members considered that allopurinol is a complicated treatment to effectively prescribe with dose titration taking 6-9 months. Members considered that this could be leading to poorer access to treatment for some patient groups with reduced access to medical services, such as Māori.

4.8 Members considered that prescriber education around how to titrate allopurinol may be beneficial to encourage appropriate use of allopurinol.

4.9 Members considered an audit of febuxostat Special Authorities may be useful to ascertain if allopurinol intolerance or efficacy was being misrepresented when applying for other treatments.

4.10 The Subcommittee considered it likely that monotherapy febuxostat is more effective than monotherapy probenecid in patients intolerant or contraindicated to allopurinol, but that there is poor evidence of this comparison, including no head to head trials.

4.11 The Subcommittee considered that while some patients might use febuxostat in combination with probenecid, this would not be in any significant numbers and those that did use combination treatment, it would be more likely to be in combination with benzbromarone.

4.12 The Subcommittee considered that if all gout treatments were open-access, then febuxostat would be the most commonly used.

**Muscle relaxants**

*Orphenadrine citrate*

4.13 The Subcommittee noted that use of orphenadrine citrate (Norflex) had been increasing. Members considered that there was little evidence for the use of orphenadrine citrate. The Subcommittee asked PHARMAC to investigate what is causing this rise in use and whether there was any regional variation.

**Treatments relating to rheumatology but falling outside the Musculoskeletal System therapeutic group**

*Oral pilocarpine*

4.14 The Subcommittee noted there was some use of oral pilocarpine, for which there is not currently a registered product, but considered that it could be compounded from funded eye drops. The Subcommittee considered that the number of patients seeking access to a specifically oral pilocarpine form would be very small and it was appropriate for funded access to be managed by NPPA.

*Mycophenolate mofetil*

4.15 The Subcommittee noted that generic non-enteric coated mycophenolate brands are now available. The Subcommittee considered there were no specific concerns regarding switching patients to a generic product.

*Methotrexate*

4.16 The Subcommittee noted that clinicians and patients had reported issues with the current brand of methotrexate 2.5 mg tablet (Trexate). Members considered the 2.5 mg tablet was very small and hard to remove from the blister packaging, which caused trouble for patients who are elderly, have arthritis, or otherwise have limited hand function.

4.17 The Subcommittee noted that methotrexate was proposed for inclusion in the 2017/18 Tender. The Subcommittee considered it was important that evaluation of bids for methotrexate 2.5 mg tab consider suitability for people with arthritis or similar with reference to both tablet size and blister packaging. The Subcommittee also considered that the methotrexate 10 mg tablet must be scored to facilitate 5 mg increment dose adjustments.

*Triamcinolone acetonide*

4.18 The Subcommittee noted a request from a GP to make triamcinolone acetonide inj 10 mg per ml, 1 ml ampoule and inj 40 mg per ml, 1 ml ampoule available on a Practitioners Supply Order (PSO). Members considered this would be more convenient for the patient as currently a patient has to leave the practice, get the prescription filled then return.

4.19 The Subcommittee considered that a typical patient would receive one or two injections, which must be given by a doctor, but do not need to be refrigerated. For

this reason, the Subcommittee considered triamcinolone differed to other injections which were administered by a nurse.

4.20 The Subcommittee considered that it was not common for patients to be dispensed additional injections to be stored and injected at subsequent visits.

4.21 The Subcommittee considered that if triamcinolone were available on a PSO this would likely result in clinicians performing more injections as the product would be more easily available.

4.22 The Subcommittee **recommended** that PHARMAC make up to 5 injections of triamcinolone acetonide available on a PSO.

*Belimumab*

4.23 The Subcommittee noted that the supplier of belimumab, GSK, had been running a compassionate access program in New Zealand but that this was ending. The Subcommittee considered that PHARMAC should seek an application for belimumab from its supplier.

*Secukinumab*

4.24 The Subcommittee noted that PTAC had recently considered secukinumab for severe plaque psoriasis. The Subcommittee considered that PHARMAC should request an application for secukinumab for ankylosing spondylitis from the supplier.

## 5 Tofacitinib

### Application

5.1 The Subcommittee considered an application from the supplier, Pfizer New Zealand, for the funding of tofacitinib for moderate to severe rheumatoid arthritis in adults who have had an inadequate response, or are intolerant, to methotrexate.

### Recommendation

5.2 The Subcommittee **recommended** that tofacitinib be funded for patients with moderate to severe rheumatoid arthritis who were not adequately responding to TNF inhibitors with a high priority, subject to the following Special Authority criteria:

> **Initial application** only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 The patient has had an initial Special Authority approval for adalimumab and/or etanercept for rheumatoid arthritis; and
> 2 Either:
> 2.1 The patient has experienced intolerable side effects from a reasonable trial of adalimumab and/or etanercept; or
> 2.2 Following at least a four month trial of adalimumab and/or etanercept, the patient did not meet the renewal criteria for adalimumab and/or etanercept; and

3 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance.

**Renewal** only from a rheumatologist or medical practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1 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 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 treatment in the opinion of the physician.

5.3 The Subcommittee **recommended** that tofacitinib be funded with a medium priority for patients with rheumatoid arthritis under the same Special Authority criteria in place for adalimumab and etanercept.

**Discussion**

5.4 The Subcommittee noted that the applicant had proposed tofacitinib be funded for rheumatoid arthritis (RA) under the same restrictions currently in place for adalimumab and etanercept on the basis that tofacitinib provides similar efficacy as the TNF-alpha inhibitors.

5.5 The Subcommittee noted that the current restrictions for adalimumab and etanercept relate to patients whose RA is severe, active and erosive and has not responded to several other treatments. The Subcommittee considered that such patients have significant pain, difficulty working or carrying out normal day to day activities, have higher mortality and greater likelihood of requiring joint surgery.

5.6 The Subcommittee noted that, while effects on family and whanau is not well described, a Dutch study (Jacobi et al Arthritis & Rheumatism 2003; 49: 567-73) noted about 40% of RA patients received care from their partners which disrupted schedules. The Subcommittee noted no good evidence for disparities in subgroups.

5.7 The Subcommittee noted that currently funded first-line biologic treatments for RA are adalimumab and etanercept, and second and third-line biologic options are infliximab, tocilizumab, and rituximab.

5.8 The Subcommittee considered that most clinical trials report ACR20 response rates of around 70% with currently funded agents, so a significant number of patients do not respond, and success rates fall with each line of treatment to 40% at fourth-line. Further, the treatment target of remission or low disease activity are achieved in even fewer patients, so members considered there is an unmet need for those receiving an inadequate response to TNF-inhibitors.

5.9 The Subcommittee considered that the health need was less for patients who had not yet tried a TNF-inhibitor as such patients may not have poor treatment response or adverse events to the funded agents.

5.10 The Subcommittee considered that prevalence of RA is between 2.4 and 3.5%, with 20% of those being eligible for biologic treatment and an estimated 30% of those receiving such a treatment.

5.11 The Subcommittee estimated that, if tofacitinib were funded with the same restrictions as adalimumab and etanercept, around 20% of patients treated with a biologic would switch to tofacitinib, noting that some people would prefer a twice daily oral agent over a weekly or fortnightly injection. Members considered that convenience of administration may drive clinician preference, but also considered that familiarity with TNF-inhibitors may mean clinicians continue to use them earlier in the treatment algorithm.

5.12 The Subcommittee considered that adherence to biologics would likely be greatest for infused biologics, but it was unclear how adherence would differ between a twice daily oral and a weekly or fortnightly self-administered injection.

5.13 The Subcommittee noted the applicant's statement that there is wastage with biologics due to refrigeration issues that do not apply to tofacitinib. The Subcommittee acknowledged the possibility of wastage, but noted the application did not provide evidence to support the assertion and have not heard of it being reported.

The Subcommittee noted that the evidence for the use of tofacitinib for the treatment of RA:

- ORAL-STANDARD (Trial 1064; van Vollenhoven et al N Engl J Med 2012;367:508-19)
- ORAL-STEP (Trial 1032; Burmester et al Lancet 2013)
- ORAL-SYNC (Trial 1046 Kremer et al Ann Intern Med 2013;159(4):253-261)
- ORAL-SOLO (Trial 1045; Fleischmann et al N Engl J Med 2012b;367(6):495-507), and
- Trial 1035 (Fleischmann et al Arthritis & Rheumatism Vol 64 No 3 March 2012 pp 617-629).

5.14 The Subcommittee considered the strength and quality of the evidence to be high, though noted that long-term registry data on safety is currently lacking.

5.15 The Subcommittee considered that the trials demonstrated around 50-60% success rate in achieving the measure ACR20, though also considered that this measure only demonstrated a weak benefit, which also explained high rates of success in the placebo arms.

5.16 The Subcommittee considered that the infection rate in patients receiving tofacitinib appears to be less than or similar to that seen in TNF inhibitor studies

but may be higher than with methotrexate, however considered that further long-term data was needed.

5.17 Members considered that tofacitinib can lead to reactivation of Herpes zoster in around 10-15% of patients and that it would be clinically appropriate for patients being treated with tofacitinib to receive a Herpes zoster vaccine. Members noted that the budget impact of this could be significant.

5.18 The Subcommittee considered that tofacitinib appeared to be more effective than TNF-inhibitors when used as monotherapy, for example where methotrexate was contraindicated.

5.19 The Subcommittee considered that tofacitinib appeared to be as effective as a TNF-inhibitor when each was used with methotrexate.

5.20 Members also considered that as tofacitinib was orally administered there were benefits in avoiding the discomfort of injection therapy or local injection site reactions.

5.21 The Subcommittee noted that treatment with tofacitinib would also reduce the time and costs associated with intravenous infusions for patients and hospitals. Members considered that, if tofacitinib were to be funded, some patients may switch from infliximab for this reason.

5.22 The Subcommittee considered that the optimal sequencing of these agents was unclear based on currently available evidence, but considered that tofacitinib would likely be used after TNF-inhibitor treatment as another line of treatment, mainly due to clinician familiarity with anti-TNF treatments and better evidence for long term safety.

5.23 The Subcommittee considered that, based on currently available evidence, it would be appropriate to fund tofacitinib as a first-line treatment for use with or without methotrexate or as a second-line agent for patients who have not responded adequately to TNF inhibitors. The Subcommittee considered that the health need for another treatment option with a different mechanism of action was greater in patients who were not adequately responding to TNF inhibitors.

## 6 Biologics rheumatology criteria

6.1 The Subcommittee reviewed a paper from PHARMAC staff regarding a number of requests for changes to the access criteria for biologics for rheumatology indications.

*Removal of C-reactive Protein (CRP)-related Criteria from the Rheumatoid Arthritis and Psoriatic Arthritis Criteria*

6.2 The Subcommittee estimated that removing the requirement for CRP greater than 15 mg/L may increase the prevalence of patients on biologics by about 30 people. The Subcommittee considered that these patients would have what is considered an abnormal level but their CRP is less than 15 mg/L. The Subcommittee

considered that 15 mg/L was not a clinically relevant threshold and patients with any abnormally elevated level of CRP might benefit from treatment with biologics.

6.3 Members considered that many of these patients may already be getting access to funded treatment via the criterion that specifies CRP levels were "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", even if the patient does not strictly meet this requirement.

6.4 The Subcommittee considered that Disease Activity Score (DAS) better predicts response to treatment than CRP.

6.5 The Subcommittee **recommended** that the Special Authorities for biologics for RA be amended as follows (where appropriate):

> Either:
> 1. Patient has a**n abnormal** C-reactive protein level ~~greater than 15 mg/L~~ measured no more than one month prior to the date of this application; or
> 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.

6.6 The Subcommittee considered that for patients with psoriatic arthritis, CRP was not an appropriate biomarker and **recommended** that the Special Authorities for biologics for psoriatic arthritis remove requirements relating to CRP entirely. The Subcommittee considered that this may widen access to around 70 patients per year.

*Removal of the Term "Erosive" from the Rheumatoid Arthritis Criteria*

6.7 The Subcommittee considered that the current criterion, below, was unclear, as it could be interpreted that the RA had to have been severe, active and erosive for at least six months, or that the RA had to have been known for six months and was now severe, active and erosive.

> Patient has had severe and active erosive rheumatoid arthritis (either confirmed by radiology imaging, or the patient is cyclic citrullinated peptide (CCP) antibody positive) for six months duration or longer.

6.8 The Subcommittee considered it was inappropriate to require that a patient who had severe, active and erosive RA wait six months without treatment. It was also considered that RA that is erosive will remain erosive. The Subcommittee considered that removal of the term erosive would represent a large budget impact, and that this term was sometimes interpreted to mean 'has the potential to erode'. The Subcommittee considered that it would be more appropriate to amend the criteria to specify cyclic citrullinated peptide (CCP) antibody positive rather than use the term 'erosive'.

6.9 The Subcommittee **recommended** that the Special Authority for biologics for rheumatoid arthritis be replaced with the following:

1. Patient has rheumatoid arthritis and has been diagnosed for at least 6 months; and
2. Either:
   2.1. Patient has erosions; or
   2.2. Patient is cyclic citrullinated peptide (CCP) antibody positive;

6.10 The Subcommittee considered that this was a tidying up of the language and expected this would not result in a change in uptake.

*Amendment of Rheumatoid Arthritis Indication Definition*

6.11 The Subcommittee noted a request from a supplier that the definition of 'erosive rheumatoid arthritis' be amended to include elevated rheumatoid factor, as follows:

> Patient has had severe and active erosive rheumatoid arthritis (either confirmed by radiology imaging, or the patient is cyclic citrullinated peptide (CCP) antibody positive, **or the patient has a rheumatoid factor greater than 3 times the upper limit of normal**) for six months duration or longer.

6.12 The Subcommittee considered that this change would make the restrictions more complicated than was needed, that excluding the requirement for CCP weakened the restrictions, and that clinicians had not been seeking this change. The Subcommittee considered that this amendment should not be made.

*Amendment of the Ankylosing Spondylitis Disease Severity Criteria*

6.13 The Subcommittee noted a request to amend or remove the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) requirements from the ankylosing spondylitis criteria. The criteria currently require a BASDAI score of at least 6 on a 0-10 scale.

6.14 The Subcommittee considered that it was reasonable to require a measure of severity to access biologics, and that a severity cut-off of a BASDAI score of 6 was reasonable. The Subcommittee considered that amendment to the BASDAI score criterion was not required.

*Amendment of the Tocilizumab Systemic Juvenile Idiopathic Arthritis (sJIA) Criteria*

6.15 The Subcommittee noted a proposal to amend restrictions on tocilizumab to create access criteria for patients with active systemic features.

6.16 The Subcommittee considered that the changes proposed in the submission were reasonable, although considered that the proposed limitation that the patient had tried ciclosporin was not necessary. The Subcommittee noted the De Benedetti et al trial (De Benedetti et al N Engl J Med 2012; 367:2385-2395), which suggested this patient group may have more benefit from tocilizumab than currently funded sJIA patients, and that evidence for this was of good strength and quality.

6.17 The Subcommittee considered that there was a very small number of patients affected by this change who present with sJIA without active systemic disease and who do not respond to other currently funded treatment. The Subcommittee noted

that only 2-3 NPPAs were received in the last two years that could have met Schedule access with this change. The Subcommittee considered that widened access for this proposal would mean that tocilizumab use would increase, at most, by 5 extra patients.

6.18 The Subcommittee considered that it was not appropriate to require patients to have trialled ciclosporin, cytotoxics (such as vincristine), or anakinra (which is not currently registered) prior to accessing tocilizumab.

6.19 The Subcommittee **recommended** that the access criteria for tocilizumab for systemic juvenile idiopathic arthritis be amended as follows (additions in bold):

> Initiation – systemic juvenile idiopathic arthritis **with active arthritis and without active systemic features**
> Rheumatologist
> *Re-assessment required after 6 months*
> Both:
> 1 Patient diagnosed with systemic juvenile idiopathic arthritis; and
> 2 Patient has tried and not responded to a reasonable trial of all of the following, either alone or in combination: oral or parenteral methotrexate; non-steroidal anti-inflammatory drugs (NSAIDs); and systemic corticosteroids.
>
> **Initiation – systemic juvenile idiopathic arthritis with active systemic features**
> **Rheumatologist**
> ***Re-assessment required after 6 months***
> **Both:**
> 1 **Patient diagnosed with systemic juvenile idiopathic arthritis presenting with active systemic features; and**
> 2 **Patient has tried and not responded to a reasonable trial of the following, either alone or in combination: non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.**

*Addition of COX-2 Inhibitors to Criteria Requiring a Trial of NSAIDs*

6.20 The Subcommittee noted a request that "funded cyclooxygenase (COX)-2 inhibitors' be included as part of the definitions of NSAIDs which occur throughout the biologic restrictions. The Subcommittee noted that this request follows PHARMAC's funding of celecoxib in June 2017.

6.21 The Subcommittee noted that celecoxib is an NSAID, but considered that some clinicians might not consider it as such and so it would be an appropriate clarification to add.

6.22 The Subcommittee considered this change would have little to no effect on biologic use as the efficacy of COX-2 was similar to other NSAIDs but some may tolerate them more.

6.23 The Subcommittee **recommended** amending the restrictions on biologics by replacing "NSAIDs" with "NSAIDs, including funded cyclooxygenase (COX)-2 inhibitors" as appropriate.