Rheumatology Subcommittee of PTAC
Meeting held 4 October 2013

(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 2008*.

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 were reviewed by PTAC at its meeting on 13 & 14 February 2014, the record of which will be available in April 2014.

Record of the Rheumatology Subcommittee of PTAC meeting held at PHARMAC on 4 October 2013

1. Benzbromarone

1.1 The Subcommittee noted that benzbromarone has been funded since 1 April 2013 subject to the Special Authority criteria. The funded brand (Benzbromaron AL 100) is supplied by Link Pharmaceuticals under section 29 of the Medicines Act 1981 and must be prescribed in accordance with section 25 of the Medicines Act.

1.2 The Subcommittee noted that, as at 31 August 2013, there were 104 Special Authority approvals for benzbromarone, including 14 patients transferred from NPPA funding, although members noted that less than half of the people with approvals appear to have received funded benzbromarone on an ongoing basis since it was funded.

1.3 The Subcommittee noted that the supplier of febuxostat, TeArai BioFarma, had raised concerns with PHARMAC about the safety of benzbromarone and that PHARMAC staff were seeking the Subcommittee's advice in this regard.

1.4 The Subcommittee reviewed the following information provided by PHARMAC staff:

- The information provided to PTAC at its November 2010 meeting in relation to benzbromarone.
- Previous PTAC and Subcommittee minutes relating to benzbromarone.
- A letter from the Centre for Adverse Reactions Monitoring (CARM) regarding a patient who was hospitalised 'about a month after commencing benzbromarone'.
- Letters to the Editor regarding benzbromarone published in the New Zealand Medical Journal (NZMJ) (2013;126(1382):116-126).
- The May 2013 PTAC minute for febuxostat.
- A submission from TeArai BioFarma (5 September 2013).
- A case report provided by TeArai BioFarma (Tausche et al. Case Rep Med 2011).
- A further submission from TeArai BioFarma (12 September 2013).
- A paper discussing the frequency of fulminant hepatic failure in patients taking benzbromarone (Matsumoto et al. Japanese Journal of Clinical Pathology 2011;59:1117-22, translated into English on 9 September 2013).
- Best Practice Journal 51 gout treatment article.

1.5 The Subcommittee considered that the available information did not raise any new safety concerns with benzbromarone. However, members considered that there were a number of steps that could be taken to reduce the risk of harm from benzbromarone, as discussed below.

1.6 The Subcommittee supported the continued funding of benzbromarone under the current Special Authority criteria (with one amendment as recommended below). The Subcommittee considered that benzbromarone should continue to be funded in the event that febuxostat was funded, noting that it was an important treatment option and was of particular use as a second-line treatment in patients with moderate renal impairment,

increased cardiovascular risk, organ transplant recipients and other patients taking azathioprine.

Interaction between benzbromarone and other treatments

1.7 The Subcommittee considered that there was good evidence to suggest that there was an interaction between warfarin and benzbromarone such that the anticoagulant effect of warfarin is increased in patients taking benzbromarone.

1.8 The Subcommittee considered that it was difficult to estimate the frequency of benzbromarone/warfarin co-prescribing. Members considered that the prevalence of cardiovascular disease was not a good proxy for warfarin prescribing. Members suggested that PHARMAC staff could look at the frequency of warfarin and allopurinol co-prescribing if an estimate was needed.

1.9 The Subcommittee noted that, given its known interaction with the CYP2C9 liver isoenzyme, benzbromarone had the potential to interact with other pharmaceuticals commonly prescribed in patients with gout, for example most NSAIDs.

1.10 The Subcommittee considered that it would not be practical or appropriate to amend the benzbromarone Special Authority to alert prescribers to all the possible drug-drug interactions. The Subcommittee considered that it would be more appropriate to ensure that prescribers had better access to benzbromarone prescribing information (see below).

Risk of hepatotoxicity

1.11 The Subcommittee noted that the submissions from TeArai BioFarma suggested that the incidence of life-threatening hepatotoxicity from benzbromarone in the 2008 publication (Lee et al. Drug Saf 2008;31:643-665) was underestimated because the publication omitted some of the reported cases.

1.12 The Subcommittee noted that the Pharma Letter (February 2000) reported six deaths in Japan from fulminant hepatitis in patients using benzbromarone between 1997 and 2000, and that the same document referred to 300,000 users of benzbromarone in Japan since 1979. The Subcommittee noted that the Japanese Pharmaceutical and Medical Devices communication in November 2011 (translated to English) reported approximately 20 cases per year of hepatic disorder in patients taking benzbromarone.

1.13 The Subcommittee considered that it was not of material importance that some cases had been missed from the Lee 2008 publication – the risk was known, the incidence range was approximately correct, and the risk appears acceptable in the context of known risks of adverse reactions from other gout treatments.

1.14 The Subcommittee noted that benzbromarone was introduced in the 1970s but the first death was not reported until the mid 1990s, so it would not be possible to say with confidence that febuxostat – which was only relatively recently introduced – had a lower incidence of serious liver reactions than benzbromarone as there is a lack of longer-term safety data for febuxostat.

Prescriber and patient information

1.15 The Subcommittee considered that, due to the fact that benzbromarone is not registered in New Zealand and is currently only registered in non-English-speaking countries, there was no good source of benzbromarone prescribing information or patient information for New Zealand prescribers and patients.

1.16 The Subcommittee **recommended** that the New Zealand Rheumatology Association (NZRA) be approached to develop, and make available on its website, prescriber and patient information sheets for benzbromarone, which would include information about the risks of hepatotoxicity and adverse interactions with other medicines. The Subcommittee **recommended** that PHARMAC include a link to this information on the benzbromarone Special Authority form once it was available.

1.17 The Subcommittee noted that it appeared that prescriber software did not alert prescribers to the fact that certain funded medicines are not registered. Members considered that this was a particular issue for Special Authority medicines as there may be a perception from some prescribers that these are registered. Therefore, the Subcommittee **recommended** that the following criterion be added to all Special Authority forms where the medicine is not registered:

> 1 The applicant acknowledges that this medicine is not registered for use in New Zealand and must be prescribed and supplied in accordance with section 25 and section 29, respectively, of the Medicines Act 1981.

1.18 The Subcommittee **recommended** that PHARMAC work with the Best Practice Advocacy Coalition (BPAC) to develop more prescriber education on the use of benzbromarone.

2 Febuxostat

2.1 The Subcommittee noted that PTAC had reviewed an application to fund febuxostat (Adenuric) at its May 2013 and had recommended that it be funded with a medium priority, subject to Special Authority criteria. The Subcommittee supported the funding of febuxostat and agreed with PTAC's recommendation and made the following additional comments below.

2.2 The Subcommittee considered that recent publication of a population-based cohort study of hospitalisation for severe cutaneous adverse reactions in allopurinol initiators (Kim et al. Arthritis Care Res 2013;65:578-584) suggests that the incidence of allopurinol hypersensitivity may be more common than the 1 in 56,000 figure noted by PTAC, with an estimated 1 additional hospitalisation for severe cutaneous adverse reactions for each 1,540 patients newly initiated on allopurinol.

2.3 The Subcommittee noted that there was a lack of longer-term safety data for febuxostat. The Subcommittee noted that there was an on-going trial (the CARES trial) investigating the cardiovascular safety of febuxostat versus allopurinol in patients with gout who have increased cardiovascular risk.

2.4 The Subcommittee noted that most studies of febuxostat were conducted in patients with normal renal function or mild renal impairment so it is not clear if febuxostat would be safer than allopurinol in patients with renal impairment (or vice versa).

2.5 The Subcommittee considered that until further published evidence of febuxostat in renal impairment became available it would be appropriate to include a requirement that the patient has a rate of creatinine clearance greater than or equal to 30 ml/min, as there was no compelling evidence that febuxostat was safe to prescribe in patients with a glomerular filtration rate (GFR) <30.

2.6 The Subcommittee considered that it would be necessary to perform liver function monitoring with febuxostat as recommended on its Medsafe datasheet. Members

considered that liver function testing would be needed prior to initiation of treatment and at least every 3 months thereafter.

2.7 The Subcommittee noted that it could have been helpful for PTAC to have had some input from rheumatologists in reviewing the application and requested that, in future, new funding applications be reviewed by the Subcommittee as well as PTAC.

2.8 The Subcommittee noted that the supplier (TeArai BioFarma) had proposed that PHARMAC include a proportion of patients (24.3%) on 40 mg febuxostat (gained by halving an 80 mg tablet, as TeArai does not have access to a 40 mg tablet) in its cost analysis, because lower doses will be taken in the ~27% of gout patients with moderate-to-severe renal impairment. The Subcommittee considered that this would not be appropriate, noting that evidence suggests that 40 mg febuxostat at 40 mg per day is not more effective than allopurinol at doses up to 300 mg per day. The Subcommittee considered that most prescribers would aim to gradually increase the febuxostat dose in such patients. Members noted that it was possible that patients would simply discard the other half of the 80 mg tablet.

3 Baclofen

3.1 The Subcommittee noted that PTAC had previously advised that it would not be appropriate for baclofen intrathecal injection to be funded in the community because there are considerable safety risks associated with its use, including the risk of fatalities and withdrawal syndrome related to pump malfunction or failure to provide refill doses. The Subcommittee noted that baclofen injection is listed in the HML without restrictions and can be dispensed into the community in up to 30-day lots according to the HML rules. However, the Subcommittee considered that lack of community funding was providing a barrier to the use of intrathecal baclofen and **recommended** that PHARMAC list baclofen intrathecal injection in Section B of the Pharmaceutical Schedule, restricted to use in a programmable pump.

4 .Tocilizumab (Actemra) for the treatment of rheumatoid arthritis

3.1 The Subcommittee noted that it had reviewed an application from Roche to list tocilizumab on the HML for rheumatoid arthritis and systemic juvenile idiopathic arthritis (sJIA) at its meeting in October 2011 and the application had also been reviewed by PTAC at its November 2011 meeting.

3.2 The Subcommittee noted that PTAC had recommended that tocilizumab be listed on the HML for patients with sJIA who have not responded to prior treatment with NSAIDs, methotrexate and systemic corticosteroids, with a high priority, and that this had been implemented from 1 July 2013.

3.3 The Subcommittee noted that PTAC had recommended that tocilizumab be listed on the HML for patients with rheumatoid arthritis who have not responded to prior treatment with standard disease modifying anti-rheumatic drugs (DMARDs) and at least one TNF inhibitor, with a low priority, and that this had not been progressed by PHARMAC.

3.4 The Subcommittee noted that Roche had submitted a response to the November 2011 PTAC minutes, including longer-term safety and efficacy data and an application (including a commercial proposal) to list tocilizumab on the HML for use as a first-line

biologic treatment option, as monotherapy, in patients with rheumatoid arthritis who cannot use methotrexate.

3.5 The Subcommittee considered that the phase 4 randomised, double-blind controlled-phase trial of tocilizumab monotherapy versus adalimumab monotherapy for the treatment of rheumatoid arthritis (ADACTA) (Gabay et al. Lancet 2013;381(9877):1541-50) provided good quality evidence that tocilizumab was more effective than adalimumab as monotherapy after 24 weeks' treatment in patients with rheumatoid arthritis who were intolerant to methotrexate or in whom continued treatment with methotrexate was considered inappropriate. The Subcommittee noted that the evidence was limited to a single relatively small-scale, short-term, supplier-sponsored trial. The Subcommittee noted that the publication did not provide an explanation of why nearly 30% of the screened patients were considered ineligible to be enrolled. Members noted that the response rates in the adalimumab monotherapy arm appeared lower than might have been expected from previous adalimumab monotherapy trials.

3.6 The Subcommittee noted that the primary outcome measure in ADACTA was the change in disease activity score using 28 joints (DAS28) from baseline to week 24. Members considered that the statistically significant difference in change in DAS28 between tocilizumab (-3.3) and adalimumab (-1.8) at week 24 would be clinically significant. The Subcommittee considered that the side effect profile for both treatments was generally in line with previous studies.

3.7 The Subcommittee noted that there was only a small difference in Health Assessment Questionnaire (HAQ) score in favour of tocilizumab at week 24 (difference of 0.2, p=0.0653); however, members noted that the longer-term aim of treatment was primarily to treat active disease (as measured by DAS) and prevent HAQ increasing, so it would be possible to show an improvement in DAS without significant changes in HAQ over a period of 24 weeks. Members noted that there was a lack of tocilizumab monotherapy data beyond 24 weeks so it was not possible to estimate the duration of benefit, although there was no particular reason not to assume that the early benefit would be sustained.

3.8 The Subcommittee noted the supplier's assumption that approximately 18% of patients eligible for treatment with a biologic agent in New Zealand would be intolerant to methotrexate, based on a telephone survey of 20 rheumatologists. The Subcommittee noted that this was a small number and may not be representative of the view of the larger rheumatologist community. The Subcommittee noted that PHARMAC's data show that approximately one-third of patients on adalimumab or etanercept use these biologic treatments without methotrexate. The Subcommittee considered that the supplier's estimate of the number of patients likely to take a biologic without methotrexate was likely an underestimate, and that one-third was probably closer to reality.

3.9 The Subcommittee noted that patients who couldn't take methotrexate could take a TNF inhibitor or rituximab with leflunomide or other DMARDs – i.e. TNF-inhibitor monotherapy was not the only treatment option for these patients. However, the Subcommittee considered that compared with the rheumatoid arthritis population as a whole, the group of patients who cannot take methotrexate (due to intolerance or because it is contraindicated) have fewer treatment options available to them. Members considered that tocilizumab was unlikely to be used in combination with leflunomide in patients who couldn't take methotrexate, noting that data on this combination are lacking.

3.10 The Subcommittee considered that most patients would prefer to self-inject a community biologic versus a hospital infusion of tocilizumab, unless the community biologic wasn't working. This would mean that, in practical terms, even if tocilizumab was available as a first-line option it would more likely be used as a second-line option, at least in the short-term. Members considered that this situation would likely change over time as clinicians' experience with tocilizumab increases, especially if clinicians consider that tocilizumab is more effective than TNF inhibitors in methotrexate intolerant patients.

3.11 The Subcommittee considered that if tocilizumab was available as proposed by the supplier there would likely be an initial rapid switch from a proportion of the patients taking community-funded TNF inhibitors without methotrexate who were doing less well than might be expected from tocilizumab treatment. Members considered that the availability of tocilizumab for this patient group was unlikely to significantly grow the biologic market, but would likely extend the duration of biologic treatment.

3.12 The Subcommittee considered that the availability of tocilizumab for patients with rheumatoid arthritis who cannot take methotrexate could place a considerable burden on the hospital infusion services, although this was not a reason not to progress the proposal.

3.13 The Subcommittee noted that as tocilizumab dosage is calculated by weight there is potential for wastage as some patients would require a dose not summing exactly to a vial. The Subcommittee noted that wastage could be reduced if multiple patients were infused on the same day; however this would require a certain degree of organisation on the part of the DHB hospital infusion services and it is not clear whether or not this would actually occur in practise.

3.14 The Subcommittee **recommended** that access to tocilizumab on the HML be widened to include treatment of rheumatoid arthritis as monotherapy in patients who cannot take methotrexate, subject to the following restrictions, with a medium priority.

Initiation —Rheumatoid Arthritis - rheumatologist
Re-assessment required after 6 months
All of the following:
1 Patient has had severe and active erosive rheumatoid arthritis for six months duration or longer; and
2 Tocilizumab is to be used as monotherapy; and
3 Either:
  3.1 Treatment with methotrexate is contraindicated; or
  3.2 Patient has tried and did not tolerate oral or parenteral methotrexate; and
4 Either:
  4.1 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of cyclosporine alone or in combination with another agent; or
  4.2 Patient has tried and not responded to at least three months therapy at the maximum tolerated dose of leflunomide alone or in combination with another agent; and
5 Either:
  5.1 Patient has persistent symptoms of poorly controlled and active disease in at least 20 active, swollen, tender joints; or
  5.2 Patient has persistent symptoms of poorly controlled and active disease in at least four active joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and
6 Either:
  6.1 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
  6.2 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.

Continuation – rheumatologist or practitioner on recommendation of a rheumatologist
Re-assessment required after 6 months
All of the following:
1 Tocilizumab is to be used as monotherapy; and
1.1 Either:
1.1.1 Treatment with methotrexate is contraindicated; or
1.1.2 Patient has tried and did not tolerate oral or parenteral methotrexate; and
2 Either:
2.1 Following 6 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 On subsequent reapplications, 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.