Ad-Hoc Rheumatology Subcommittee of PTAC meeting held 8 March 2011

(minutes for web publishing)

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

The Ad-Hoc 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 5 & 6 May 2011, the record of which is available on the PHARMAC website.

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1 Benzbromarone

1.1 The Subcommittee noted that PTAC had recommended that benzbromarone be funded for gout, subject to Special Authority criteria, with a high priority. The Subcommittee reviewed the Special Authority criteria proposed by PTAC and **recommended** that the following changes be made (additions in bold, deletions in strikethrough):

Initial application from any relevant practitioner. Applications valid for six months for applications meeting the following criteria:
Both:
1 Any of
- 1.1 The patient has a serum ~~uric acid~~ **urate** level greater than 0.36 mmol/l despite treatment with allopurinol at doses ~~up to~~ **of** at least 600 mg/day and appropriate doses of probenecid; or
- 1.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and satisfactory control of serum ~~uric acid~~ **urate** (to less than or equal to 0.36 mmol/l) could not be achieved by probenecid; or
- 1.3 Both:
  - 1.3.1 The patient has renal impairment and serum ~~uric acid~~ **urate** remains greater than 0.36 mmol/l ~~with an adjusted dose of~~ **despite optimal treatment with** allopurinol **(see Note)**; and
  - 1.3.2 The patient has a rate of creatinine clearance **greater than or equal to** ~~>30~~ **20** ml/min; or
- 1.4 **All of the following:**
  - **1.4.1** The patient has had a ~~renal~~ **solid organ** transplant and requires urate-lowering therapy[1]; and
  - **1.4.2 Allopurinol is contraindicated; and**
  - **1.4.3 Appropriate doses of probenecid are ineffective or probenecid cannot be used due to reduced renal function.**

2 The patient is receiving monthly liver function tests.

Note: 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.

1.2 Reasons for the recommended changes are as follows:

Criterion 1.1: The Subcommittee considered that the dose of allopurinol was too loosely defined, as the criterion would allow patients on much lower (potentially subtherapeutic) doses of allopurinol, eg 200 mg, to access benzbromarone when increased doses of allopurinol may be effective.

Criterion 1.3.1: The Subcommittee considered that although it was appropriate to adjust the initial dose of allopurinol in patients with renal impairment, current evidence suggests that it is safe to subsequently increase the dose of allopurinol in these patients if the target serum urate level is not reached. The Subcommittee noted that this is now

[1] Please refer to the updated proposed Special Authority criteria located in the minutes of the Ad-hoc Rheumatology Subcommittee meeting held on 14 October 2011.

becoming common clinical practice. The Subcommittee noted that it is important to closely monitor patients in this situation.

Criterion 1.3.2: The Subcommittee acknowledged that the evidence suggested that the efficacy of benzbromarone decreases with reducing renal function; however, members considered that benzbromarone can still be effective in patients with creatinine clearance between 20 and 30 ml/min.

Criterion 1.4: The Subcommittee considered that allopurinol may be inappropriate in patients undergoing any solid organ transplant (ie not just renal) who are also taking azathioprine and that benzbromarone should be available for these patients if probenecid is ineffective or cannot be used.

1.3 The Committee considered that the available treatments for gout were suboptimally used in New Zealand and that more education in this area is needed. The Subcommittee considered that education about the use of higher doses of allopurinol, benzbromarone and the treatment of gout generally would be important if benzbromarone were to become funded.

2 Baclofen injection

2.1 The Subcommittee noted that PTAC had recommended that baclofen intrathecal injection be included on the Discretionary Community Supply (DCS) list, restricted to patients with severe chronic spasticity of cerebral origin or due to multiple sclerosis, spinal cord injury or spinal cord disease, where oral antispastic agents have failed or have caused unacceptable side effects. The Subcommittee noted that this had not been implemented, largely because PHARMAC staff considered the need to be low based on only one Hospital Exceptional Circumstances (HEC) application being made in the past five years. The Subcommittee considered that the usage was possibly higher than indicated by the HEC applications because there are patients who are funded by ACC for baclofen injection. The Subcommittee considered that listing baclofen injection on the DCS list would remove some of the barriers to hospitals funding insertion of the pump needed for baclofen injection delivery. Therefore, the Subcommittee **recommended** that baclofen injection be listed on the DCS list as recommended by PTAC.

3 Non-steroidal anti-inflammatory drug (NSAID) subsidies

3.1 The Subcommittee noted that PHARMAC staff were seeking advice around the possibility of fully funding some or all of the NSAID presentations that are currently partly funded (ketoprofen, mefenamic acid, sulindac and tiaprofenic acid).

3.2 The Subcommittee noted that there were currently four fully funded oral NSAIDs (diclofenac, ibuprofen, naproxen and tenoxicam), three of which (diclofenac, naproxen and ibuprofen) could be given in variable dose schedules. The Subcommittee considered that the ability to give NSAIDs in variable dosing schedules was important for use in the elderly and in patients with comorbidities such as reduced renal function. Of the NSAIDs that are currently partly funded, only sulindac and tiaprofenic acid can be given in variable dose schedules.

3.3 The Subcommittee considered that the majority of patients could be managed adequately using the fully funded NSAIDs. The Subcommittee considered that the order in which the fully funded NSAIDs were used was a matter of clinical judgement; however, members considered that naproxen and diclofenac are generally preferred as first-choice agents, followed by ibuprofen.

3.4 The Subcommittee reiterated its previous comments about the idiosyncratic nature of patient responses to NSAIDs both in terms of efficacy and side effects, and that it is important to have as large a range of fully funded agents as possible as there is a small proportion of patients who are not able to be managed on the fully funded agents. For these patients the only funded option is to try paracetamol in combination with an NSAID; however, this was unlikely to produce an optimal clinical response. The Subcommittee noted that patient management had become more problematic recently due to the withdrawal of indomethacin and piroxicam from the New Zealand market and the removal of the Special Authority for full subsidy of NSAIDs (for new patients).

Diclofenac 50 mg dispersible tablets

3.5 The Subcommittee considered that there could be some benefit from diclofenac 50 mg dispersible tablets in children as there was currently no fully funded dispersible alternative to ibuprofen oral liquid and, as such, it would be desirable for this presentation to be available fully funded for children. However, the Subcommittee considered that there was insufficient benefit of the 50 mg dispersible tablets over the regular 50 mg tablets to justify the increased cost for the adult population. Therefore, when considering the NZ population as a whole, the Subcommittee **recommended** against increasing the subsidy to match the current price of diclofenac 50 mg tablets.

Ibuprofen 400 mg and 600 mg tablets

3.6 The Subcommittee considered that while the higher strength ibuprofen tablets could reduce the pill burden for patients taking ibuprofen, there was not any particular problem with patients taking 2 of the 200 mg tablets given that this was a standard dose that patients are used to taking and the tablets are film coated and relatively small. The Subcommittee considered that the increased cost of the higher strengths versus multiples of the 200 mg strength would not be outweighed by the benefits of reducing pill burden and, therefore, **recommended** against increasing the subsidy to match the current price of ibuprofen 400 mg and 600 mg tablets.

Ketoprofen 100 mg and 200 mg long-acting capsules, mefenamic acid 250 mg capsules, sulindac 100 mg and 200 mg tablets and tiaprofenic acid 300 mg tablets

3.7 The Subcommittee considered that the clinical benefits and risks of ketoprofen, mefenamic acid, sulindac and tiaprofenic acid were essentially similar to each other and to the fully funded NSAIDs. The Subcommittee considered that any of these agents would be useful to trial in patients who had not responded adequately to, or could not tolerate, naproxen, diclofenac and ibuprofen.

3.8 The Subcommittee considered that the main use of ketoprofen, sulindac and tiaprofenic acid would be in osteoarthritis, whereas mefenamic acid is mainly used in women with menstrual cramps and, therefore, is outside the area of the Subcommittee's expertise.

3.9 The Subcommittee considered that, as fourth-line treatments, ketoprofen, sulindac and tiaprofenic acid would be given in daily doses equivalent to diclofenac 150 mg (2x 75 mg long-acting tablets) and ibuprofen 1600 mg (2x 800 mg long acting tablets) as follows: ketoprofen 200 mg (one 200 mg long-acting capsule); sulindac 400 mg (2x 200 mg tablets); tiaprofenic acid 600 mg (2x 300 mg tablets).

3.10 The Subcommittee **recommended** increasing the subsidy for at least one of, but preferably all of, ketoprofen, sulindac and tiaprofenic acid to match the current price of these treatments so they become fully funded.

4 Review of the access criteria for TNF alpha inhibitors

4.1 Members noted that they had noticed a decrease in frequency of rheumatology hospital beds filled following the availability of adalimumab for inflammatory arthritides.

Rheumatoid arthritis access criteria

4.2 The Subcommittee reviewed the adalimumab Special Authority criteria for rheumatoid arthritis and **recommended** that the following changes be made (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 etanercept for rheumatoid arthritis; and
- 1.2 Either:
  - 1.2.1 The patient has experienced intolerable side effects from etanercept; or
  - 1.2.2 The patient has received insufficient benefit from etanercept to meet the renewal criteria for etanercept for rheumatoid arthritis; or

2 All of the following:
- 2.1 Patient has had severe and active erosive rheumatoid arthritis 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 ~~at least two of the following (triple therapy):~~ sulphasalazine~~, prednisone at a dose of at least 7.5 mg per day, azathioprine, intramuscular gold, or~~ **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 ~~therapy at~~ the maximum tolerated dose of cyclosporin ~~alone or in combination with another agent~~; 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** ~~another agent~~; and

2.6 Either:

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

2.6.2 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

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.

Renewal - (rheumatoid arthritis) 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 adalimumab treatment; and

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

3 Either:

3.1 Following ~~4~~ **3** 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

3.2 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; and

4 Either:

4.1 Adalimumab to be administered at doses no greater than 40 mg every 14 days; or

4.2 Patient cannot take concomitant methotrexate and requires doses of adalimumab higher than 40 mg every 14 days to maintain an adequate response.

4.3 The Subcommittee **recommended** that the same changes be made to the relevant portion of the etanercept Special Authority for rheumatoid arthritis.

4.4 The Subcommittee considered that the proposed changes to the initial approval criteria are in line with the current evidence for methotrexate combination treatment in rheumatoid arthritis, summarised in Katchamart et al. Ann Rheum Dis 2009;68:1105-1112. The Subcommittee considered that the current evidence suggests that there is no evidence of increased efficacy from adding azathioprine to methotrexate, only increased toxicity.

4.5 The Subcommittee considered that it would be unreasonable to expect patients to try all of the combinations in the proposed criterion 2.5 in the initial approval criteria because of the toxicity of these regimens.

4.6 The Subcommittee considered that the proposed changes to the initial approval criteria would have no effect on patient numbers as they essentially reflect what is currently being done in clinical practice.

4.7 The Subcommittee noted that the current 4 months initial treatment trial period required by the renewal criteria is problematic from a practical perspective due to difficulties in synchronising clinic visits and prescriptions. The Subcommittee considered that changing this to 3 months would align better with prescriptions and would not have any appreciable effect on patients accessing treatments as it is very unlikely that any patients who would have shown a response at 4 months would not show a response at 3 months.

Ankylosing spondylitis access criteria

4.8 The Subcommittee reviewed the adalimumab Special Authority criteria for ankylosing spondylitis and **recommended** that the following changes be made (additions in bold, deletions in strikethrough):

Initial application - (ankylosing spondylitis) 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 etanercept for ankylosing spondylitis; and
- 1.2 Either:
  - 1.2.1 The patient has experienced intolerable side effects from etanercept; or
  - 1.2.2 The patient has received insufficient benefit from etanercept to meet the renewal criteria for etanercept for ankylosing spondylitis; or

2 All of the following:
- 2.1 Patient has a confirmed diagnosis of ankylosing spondylitis for more than six months; and
- 2.2 Patient has low back pain and stiffness that is relieved by exercise but not by rest; and
- 2.3 Patient has bilateral sacroiliitis demonstrated by plain radiographs, CT or MRI scan; and
- 2.4 Patient's ankylosing spondylitis has not responded adequately to treatment with two or more non-steroidal anti-inflammatory drugs (NSAIDs), in combination with anti-ulcer therapy if indicated, while patient was undergoing at least 3 months of an exercise regime supervised by a physiotherapist; and
- 2.5 Either:
  - 2.5.1 Patient has limitation of motion of the lumbar spine in the sagittal and the frontal planes as determined by **the following** ~~a score of at least 1 on each of the lumbar flexion and lumbar side flexion measurements of the~~ Bath Ankylosing Spondylitis Metrology Index (BASMI) **measures: a modified Schober's test of less than or equal to 4 cm and lumbar side flexion measurement of less than or equal to 10 cm (mean of left and right)**; or
  - 2.5.2 Patient has limitation of chest expansion by at least 2.5 cm below the following average normal values corrected for age and gender (see Notes); and
- 2.6 A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 6 on a 0-10 scale.

4.9 The Subcommittee **recommended** that the same changes be made to the relevant portion of the etanercept Special Authority for rheumatoid arthritis.

4.10 The Subcommittee noted that the BASMI was not commonly used by clinicians and there was more than one table that could be used to derive a BASMI score. The

Subcommittee considered that the proposed changes would avoid potential confusion without changing the number of patients who would be able to access adalimumab or etanercept under this criterion.

Psoriatic arthritis criteria

4.11 The Subcommittee reviewed the adalimumab Special Authority criteria for psoriatic arthritis and **recommended** that the following changes be made (additions in bold, deletions in strikethrough):

Initial application - (psoriatic 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 etanercept for psoriatic arthritis; and
  - 1.2 Either:
    - 1.2.1 The patient has experienced intolerable side effects from etanercept; or
    - 1.2.2 The patient has received insufficient benefit from etanercept to meet the renewal criteria for etanercept for psoriatic arthritis; or

2 All of the following:
  - 2.1 Patient has had severe active psoriatic arthritis for six months duration or longer; and
  - 2.2 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
  - 2.3 Patient has tried and not responded to at least three months of sulphasalazine at a dose of at least 2 g per day or leflunomide at a dose of up to 20 mg daily (or maximum tolerated doses); and
  - 2.4 Either:
    - 2.4.1 Patient has persistent symptoms of poorly controlled and active disease in at least ~~20~~ **10** active, swollen, tender joints; or
    - 2.4.2 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
  - 2.5 Any of the following:
    - 2.5.1 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
    - 2.5.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
    - 2.5.3 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 - (psoriatic arthritis) 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 adalimumab treatment; and

2 Either:
  - 2.1 Following ~~4~~ **3** 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 ~~50%~~ **30%** improvement in active joint count from baseline and a clinically significant response to prior adalimumab treatment in the

opinion of the treating physician; and

3 Adalimumab to be administered at doses no greater than 40 mg every 14 days.

4.12 The Subcommittee **recommended** that the same changes be made to the relevant portion of the etanercept Special Authority for rheumatoid arthritis.

4.13 The Subcommittee considered that, unlike patients with rheumatoid arthritis, patients with psoriatic arthritis often have patchy asymmetric involvement of small joints of the hands and feet. The Subcommittee considered that the requirement for 20 active, swollen, tender joints in criterion 2.4.1 in the initial approval was preventing patients who would otherwise meet the criteria from accessing treatment. The Subcommittee was unsure as to how many more patients would access treatment if the criterion was changed as proposed, but thought perhaps there would be a 5%–10% increase in psoriatic arthritis applications.

4.14 The Subcommittee considered that there was no justification for the renewal requirement in criterion 2.2 to be more stringent than the equivalent requirement in the renewal for rheumatoid arthritis (which requires a continuing 30% improvement).

4.15 The change to renewal criterion 2.1 was proposed for the same reason as the same proposed change to the rheumatoid arthritis renewal approval.

Juvenile idiopathic arthritis criteria

5.1 The Subcommittee reviewed the etanercept Special Authority criteria for juvenile idiopathic arthritis and **recommended** that the following changes be made (additions in bold, deletions in strikethrough):

Initial application - (juvenile idiopathic arthritis) only from a named specialist or rheumatologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1 To be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
2 Patient diagnosed with Juvenile Idiopathic Arthritis (JIA); and
3 Patient has had severe active polyarticular course JIA for 6 months duration or longer; and
4 **Either**
  4.1 Patient has tried and not responded to at least three months of oral or parenteral methotrexate (at a dose of 10-20 mg/m² weekly or at the maximum tolerated dose) in combination with oral corticosteroids (prednisone 0.25 mg/kg or at the maximum tolerated dose); ~~and~~ **or**
  4.2 **Patient has tried and not responded to at least three months of oral or parenteral methotrexate (at a dose of 10-20 mg/m² weekly or at the maximum tolerated dose) in combination with a full trial of serial intra-articular corticosteroid injections; and**
~~5 Patient has tried and not responded to at least three months of oral or parenteral methotrexate (at a dose of 10-15 mg/m² weekly or at the maximum tolerated dose) in combination with one other disease-modifying agent; and~~
6 Both:
  6.1 Either:
    6.1.1 Patient has persistent symptoms of poorly-controlled and active disease in at least 20 active, swollen, tender joints; or
    6.1.2 Patient has persistent symptoms of poorly-controlled and active disease in at least four active joints from the following: wrist, elbow, knee, ankle, shoulder,

cervical spine, hip; and

6.2 Physician's global assessment indicating severe disease.

Renewal - (juvenile idiopathic arthritis) only from a named specialist, rheumatologist or Practitioner on the recommendation of a named specialist or rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1 Either:
  - 1.1 Applicant is a named specialist or rheumatologist; or
  - 1.2 Applicant is a Practitioner and confirms that a named specialist or rheumatologist has provided a letter, email or fax recommending that the patient continues with etanercept treatment; and

2 Subsidised as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and

3 Either:
  - 3.1 Following ~~4~~ **3** months initial treatment, the patient has at least a 50% decrease in active joint count and an improvement in physician's global assessment from baseline; or
  - 3.2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count and continued improvement in physician's global assessment from baseline.

4.16 In relation to the proposed changes to criterion 4 in the initial application, he Subcommittee considered that clinical practise was moving away from the use of systemic corticosteroids in favour of intra-articular steroids, because of the side effects associated with systemic corticosteroids.

4.17 In relation to the proposed deletion of criterion 5 in the initial application, the Subcommittee considered that there is no other disease modifying agent that has been shown to be effective in juvenile idiopathic arthritis. The Subcommittee noted that hydroxychloroquine was currently prescribed so that patients could meet this criterion; however, it was not an effective treatment.

4.18 The change to renewal criterion 2.1 was proposed for the same reason as the same proposed change to the rheumatoid arthritis renewal approval.