Ad-Hoc Rheumatology Subcommittee of PTAC meeting held 14 October 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 16 & 17 February 2012, the record of which will be available on the PHARMAC website in March 2012.

Contents

1 Record of the previous Subcommittee meeting

1.1 The Subcommittee noted and accepted the record of its previous meeting held on 8 March 2011.

1.2 The Subcommittee noted that one of its recommendations had been to amend criterion 2.4.1 of the Special Authority criteria for adalimumab and etanercept in psoriatic arthritis to allow patients to meet this criterion if they had 10, rather than 20, active, swollen, tender joints. However, members noted that when PTAC reviewed the Subcommittee minutes at its May 2011 meeting, PTAC considered that there was no compelling evidence to support this change and instead recommended that the number of active, swollen, tender joints be changed from 20 to 15, noting that this more closely reflected the patient populations in the clinical trials. The Subcommittee noted that this change had subsequently been made to the Special Authority from 1 September 2011.

1.3 The Subcommittee disagreed with PTAC's view, noting that 15 was the average number of active, swollen, tender joints across all patients enrolled in the trials, not the entry criterion for the trials, which was 5. Therefore, members considered that there would have been many patients in the trials with fewer than 15 active, swollen, tender joints who benefited from treatment. Members considered that limiting funding to patients with at least 15 active, swollen, tender joints instead of at least 10 was purely a cost-containment exercise rather than a reflection of the trial data as suggested by PTAC.

1.4 The Subcommittee considered that there would be patients who did not currently meet all the necessary criteria for an initial Special Authority approval for adalimumab and/or etanercept who would qualify for, and potentially benefit from, treatment if the number of active joints in criterion 2.4.1 was changed to 10. Members agreed to provide PHARMAC staff with an estimate of the number of additional patients who would be eligible for treatment if the required number of active joints in this criterion was altered from the current 15 to 10.

1.5 The Subcommittee noted that subsequent to publication of its 8 March 2011 minutes on PHARMAC's website, a patient had written to a Subcommittee member concerned that they would not meet the proposed criteria for benzbromarone because they were taking azathioprine for a non-transplant-related condition. The Subcommittee noted that the intent of the proposed criterion 1.4.1 ("The patient has had a solid organ transplant and requires urate-lowering therapy") was to cover patients on azathioprine, and that the possibility that there would be patients on azathioprine for other conditions (e.g. systemic lupus erythematosus) who might also meet the other criteria had not been considered at the time. Therefore, the Subcommittee **recommended** that its proposed Special Authority criteria for benzbromarone be amended as follows (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 urate level greater than 0.36 mmol/l despite treatment with allopurinol at doses 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 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 urate remains greater than 0.36 mmol/l despite optimal treatment with allopurinol (see Note); and

1.3.2 The patient has a rate of creatinine clearance greater than or equal to 20 ml/min; or

1.4 All of the following:

1.4.1 The patient **is taking azathioprine** ~~has had a solid organ transplant~~ and requires urate-lowering therapy; 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.

2 Therapeutic group review update

2.1 The Subcommittee noted the update of funded Anticholinesterases, Non-steroidal Anti-inflammatory Drugs (NSAIDs), Antirheumatoid Agents, Hyperuricaemia and Antigout agents and Muscle Relaxants provided by PHARMAC staff.

2.2 The Subcommittee noted that supply of naproxen oral liquid in New Zealand appeared unfeasible but that diclofenac oral suspension 10 mg/ml is fully funded if compounded using the Ora-products according to the compounding rules. Members commented that it would be preferable for diclofenac dispersible tablets to be fully funded for children; however, it appeared that the oral suspension could be more palatable to children than the dispersible tablets dispersed in water.

2.3 The Subcommittee noted that, as for other compounded oral liquids, prescriptions for diclofenac oral suspension only need to state the strength, dose/frequency and length of treatment, not the actual compounding formula. Members noted that the components needed to make diclofenac oral suspension (diclofenac tablets and relevant suspending agent i.e. Ora-products) are fully funded on the Pharmaceutical Schedule without restriction. The Subcommittee noted that an oral liquid formulation does not need to be published on the www.pharminfotech.co.nz website to receive a subsidy.

2.4 The Subcommittee reiterated its previous desire for funded access to adalimumab to be widened to include juvenile idiopathic arthritis.

2.5 The Subcommittee noted the August 2011 PTAC minutes in relation to cevimeline for the treatment of dry mouth (xerostomia) associated with Sjögren's syndrome. The Subcommittee noted that PTAC had recommended that cevimeline be funded for this use with a low priority. Members commented that the main benefit of cevimeline over

pilocarpine appears to be reduced side effects rather than better efficacy; however, members agreed that the evidence is poor. The Subcommittee noted that cevimeline was currently not available in New Zealand (irrespective of its funding status). The Subcommittee supported consideration of funding pilocarpine tablets should this formulation become registered in New Zealand.

2.6 The Subcommittee considered that preservative-free tear substitutes would be preferable to the currently funded preservative-containing eye drops for treating dry eyes associated with Sjögren's syndrome. Members requested an update from PHARMAC staff regarding the possibility of funding preservative-free eye drops.

2.7 The Subcommittee noted PTAC's May 2011 minutes in relation to an application to widen access to funded mycophenolate mofetil (MMF) to include induction and maintenance treatment of patients with lupus nephritis (LN) or vasculitis. The Subcommittee noted that PTAC had recommended that MMF should be funded for a maximum of 24 weeks' induction treatment in patients with LN (with a high priority) or vasculitis (with a low priority) who have not responded to cyclophosphamide or in whom cyclophosphamide use is not tolerated or is contraindicated and that the application for funding of MMF for maintenance treatment in LN or vasculitis be declined. The Subcommittee noted that there would be a proportion of patients who receive MMF induction treatment followed by azathioprine maintenance who then relapse. The Subcommittee considered that MMF re-induction and maintenance treatment should be an option for these patients, noting that this was a different patient group from that considered by PTAC for MMF maintenance treatment. The Subcommittee **recommended** that the Special Authority criteria proposed by PTAC for MMF be amended as follows (additions in bold, deletions in strikethrough):

Mycophenolate mofetil - Special Authority for Subsidy

Initial application – (Lupus Nephritis and Vasculitis Induction) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
All of the following:
1 Either:
1.1 The patient has newly diagnosed active proliferative (class III/IV) and/or membranous (class V) lupus nephritis, or
1.2 The patient has newly diagnosed ANCA-associated vasculitis; and
2 Either:
2.1 Cyclophosphamide has been trialled and discontinued because of unacceptable side effects or inadequate clinical response; or
2.2 Cyclophosphamide treatment is contraindicated; and
3 Mycophenolate induction treatment to be given in combination with corticosteroids for a maximum of 24 weeks.

Renewal application - – (Lupus Nephritis and Vasculitis) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
All of the following:
1 Either:
1.1 The patient has lupus nephritis, or
1.2 The patient has ANCA-associated vasculitis; and
2 The patient has responded to mycophenolate induction treatment; and

3 Azathioprine maintenance treatment has been trialled and discontinued because of unacceptable side effects or inadequate clinical response.

Initial application – Other Diseases – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Either:
1 Transplant recipient; or
2 Both:
Patients with diseases where:
2.1 Steroids and azathioprine have been trialled and discontinued because of unacceptable side effects or inadequate clinical response; and
2.2 Either:
Patients with diseases where:
2.2.1 Cyclophosphamide has been trialled and discontinued because of unacceptable side effects or inadequate clinical response; or
2.2.2 Cyclophosphamide treatment is contraindicated.

2.8 The Subcommittee **recommended** that PHARMAC staff seek further input from nephrologists on this issue and regarding potential patient numbers if MMF was funded for LN and vasculitis as proposed (both for induction and azathioprine-failure maintenance treatment).

2.9 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).

3 Review of topical products for joint and muscular pain

Capsaicin 0.025% cream

3.1 The Subcommittee noted that in November 2002 PTAC considered an application to fund capsaicin 0.025% cream (Zostrix) for the symptomatic relief of pain associated with osteoarthritis and that, following a recommendation from PTAC to decline the application, it was declined by PHARMAC in March 2005. The Subcommittee noted that capsaicin 0.075% cream is currently funded only for post-herpetic neuralgia or diabetic peripheral neuropathy.

3.2 The Subcommittee noted that, like topical NSAIDs, capsaicin was frequently recommended in international guidelines as a treatment option for symptom management in patients with osteoarthritis.

3.3 The Subcommittee considered that evidence from 5 randomised controlled trials, one of which used a higher strength preparation (0.075%), suggested that capsaicin cream was more efficacious than placebo in reducing tenderness and pain in osteoarthritis

(Deal et al, Clin Ther 1991;13:383-95; McCarthy and McCarty, J Rheumatol 1992;19:604-7; Altman et al, Semin Arthritis Rheum 1994;23(6 Suppl 3):25-33; Gemmell et al, J Manipulative Physiol Ther 2003;26:315-23; McCleane G. Eur J Pain 2000;4:355-60). Of note, in a 12-week study patients with osteoarthritis treated four times daily with capsaicin cream 0.025% reported a 53% reduction in pain compared with 27% of placebo-treated patients at week 12 (Altman et al, 1994); in another study patients with rheumatoid arthritis and osteoarthritis treated with capsaicin cream 0.025% or placebo four times daily demonstrated mean reductions in pain of 57% and 33%, respectively, at four weeks (Deal et al, 1991). The Subcommittee considered that the quality of the evidence was moderate, noting that it is difficult to conduct a placebo controlled trial with an agent such as topical capsaicin. The Subcommittee noted that PTAC appeared to have reviewed only two of these studies in 2002 (Altman et al, 1994 and Deal et al, 1991).

3.4 The Subcommittee noted that the mechanism of action of capsaicin (primarily related to depletion of substance P at the application site) is different from other funded agents so there is a possibility that topical capsaicin could have an additive effect on the efficacy of other currently funded options such as NSAIDs and paracetamol. However, the Subcommittee noted that there appeared to be no evidence to support this, nor were members aware of any studies comparing topical capsaicin with other treatment options such as NSAIDs and paracetamol.

3.5 The Subcommittee considered that if it was funded, capsaicin 0.025% cream would be used mainly as an add-on/supplementary treatment and would not replace the use of any currently funded treatment to any significant degree.

3.6 The Subcommittee considered that the patient population that would benefit the most from capsaicin 0.025% cream would be patients with osteoarthritis who could not tolerate oral treatment options (including paracetamol, non-topical NSAID preparations and intra-articular corticosteroids) although, as noted previously, the Subcommittee considered that this was not a high unmet clinical need.

3.7 The Subcommittee considered that any restrictions placed on the use of capsaicin 0.025% cream would be for financial rather than clinical reasons, noting that if it was funded without restrictions it would likely be used in a wide range of indications, potentially including neuropathic pain and sports injuries.

3.8 The Subcommittee considered that the need to apply capsaicin 0.025% cream four times daily may limit compliance. Members also noted that capsaicin causes irritation to mucous membranes (e.g. in eyes and mouth) which could cause problems if patients were not careful about washing their hands after applying the cream.

3.9 Overall, the Subcommittee considered that the level of evidence in support of funding capsaicin 0.025% cream warranted further investigation and **recommended** that PHARMAC staff take the application back to PTAC for an updated review.

4 Tocilizumab (Actemra) for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis

General

4.1 The Subcommittee reviewed an application from Roche Products (NZ) Ltd for the funding of tocilizumab (Actemra) on the Pharmaceutical Schedule for the treatment of patients with rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis (sJIA).

4.2 The Subcommittee noted that tocilizumab is a monoclonal antibody to both soluble and membrane-bound interleukin (IL)-6 receptors which is administered in-hospital as a 1-hour intravenous infusion.

4.3 The Subcommittee noted that tocilizumab is currently registered by Medsafe for use in RA in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) or as monotherapy in case of intolerance to MTX. The Subcommittee noted that the supplier was intending to seek registration for its use in sJIA in the coming months.

Rheumatoid arthritis

4.4 The Subcommittee noted that the supplier was requesting that tocilizumab be funded for RA subject to the same access criteria as adalimumab and etanercept (i.e. as a first-line biologic treatment option but after other non-biologic treatments have been tried and provided insufficient benefit).

4.5 The Subcommittee reviewed the findings from nine key clinical trials of tocilizumab in patients with active RA despite prior treatment with non-biologic DMARDs; these trials are summarised as follows:

- CHARISMA (Maini et al, Arthritis Rheum 2006;54:2817-2829) was a phase 2 dose-finding study in which 359 patients with active RA on MTX were randomised to 16 weeks of treatment with tocilizumab 2, 4 or 8 mg/kg every 4 weeks with or without MTX, or MTX plus placebo, following a 4-week MTX-only stabilisation period.

- TOWARD (Genovese et al, Arthritis Rheum 2008;58:2968-2980) was a phase 3 double-blind randomised controlled trial in which 1,220 patients with active RA on conventional DMARD treatment were randomised to receive tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks, in addition to their DMARD treatment.

- OPTION (Smolen et al, Lancet 2008;371:987-97) was a phase 3 double-blind, randomised controlled trial in which 623 patients with active RA on MTX were randomised to receive tocilizumab 4 or 8 mg/kg or placebo every 4 weeks for 24 weeks, in addition to MTX at stable pre-study doses.

- SATORI (Nishimoto et al, Mod Rheumatol 2009;19:12-19) was a multicenter, double-blind, randomised controlled trial in which 125 patients with active RA on low-dose MTX were randomised to receive either tocilizumab 8 mg/kg every 4 weeks or MTX 8 mg/week for 24 weeks.

- AMBITION (Jones et al, Ann Rheum Dis 2010;69:88-96) was a double-blind, randomised controlled trial in which 673 patients with active RA in whom previous treatment with MTX or biologic agents had <u>not</u> failed were randomised to receive 24 weeks' treatment with either tocilizumab 8 mg/kg every 4 weeks, MTX starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by

tocilizumab 8 mg/kg every 4 weeks. An extension to AMBITION with 2 and 3-year data has been published in abstract form (Jones et al, Ann Rheum Dis 2010;69(suppl 3):386).

- STREAM (Nishimoto et al, Arthritis Rheum 2004;50:1761-1769; Nishimoto et al, Ann Rheum Dis 2009;68:1580-1584) evaluated the safety and efficacy of 5 years of tocilizumab monotherapy (8 mg/kg every 4 weeks) in 143 patients who were originally enrolled in a 3-month randomised phase 2 trial – in which 164 patients with active RA who had received at least one prior DMARD were randomised to receive tocilizumab 4 mg/kg or 8 mg/kg or placebo every 4 weeks.

- RADIATE (Emery et al, Ann Rheum Dis 2008;67:1516-1523) was a phase 3, randomised controlled trial in which 499 patients on MTX who had had inadequate response to one or more tumour necrosis factor (TNF) inhibitors were randomised to receive tocilizumab 4 mg/kg or 8 mg/kg or placebo every 4 weeks for 24 weeks, in addition to MTX.

- SAMURI (Nishimoto et al, Ann Rheum Dis 2007;66:1162-1167) was a multi-centre, x-ray reader-blinded, randomised controlled trial in which 306 patients with active RA were randomised to receive tocilizumab 8 mg/kg every 4 weeks or conventional DMARDs for 52 weeks.

- LITHE (Kremer et al, Arthritis Rheum 2011;63:609-621) was a 2-year double-blind, placebo-controlled trial in which 1,196 patients were randomised to receive tocilizumab 4 mg/kg or 8 mg/kg or placebo every 4 weeks, in addition to MTX. Rescue treatment was available from week 16.

4.6 The Subcommittee considered that the results of CHARISMA, TOWARD and OPTION supported the efficacy of tocilizumab 8 mg/kg (and, to a lesser extent, 4 mg/kg) every 4 weeks in combination with MTX versus MTX in patients with active rheumatoid arthritis despite prior DMARD therapy, with typical American College of Rheumatology (ACR) response rates of approximately 38%–49% vs 9%–29%, respectively for ACR50 and 20%–37% versus 2%–18%, respectively for ACR70 at 24 weeks. In general, members considered that tocilizumab appeared to produce 28-joint Disease Activity Score (DAS28) remission (defined as DAS28 <2.6) in approximately 30% of patients. Tocilizumab also appeared to result in normalisation of c-reactive protein (CRP) and produce a consistent increase in haemoglobin, particularly at the 8 mg/kg dose.

4.7 The Subcommittee considered that the results of AMBITION supported the efficacy of tocilizumab monotherapy (8 mg/kg every 4 weeks) compared with MTX in patients with RA, with a higher ACR20 response in the tocilizumab group at week 24 compared with MTX (69.9% vs 52.5%, respectively; $p<0.001$). Significant differences were also seen for ACR50 (44.1% for tocilizumab and 33.5% for MTX, $p<0.002$) and ACR70 (28.0% for tocilizumab and 15.1% for placebo, $p<0.001$) at week 24.

4.8 The Subcommittee considered that the results of RADIATE supported the efficacy of tocilizumab in combination with MTX in patients who had previously received an inadequate response from TNF inhibitors, with ACR50 and ACR70 responses in 28.8% and 12.4% of patients in the tocilizumab 8 mg/kg plus MTX group versus 3.8% and 1.3% of patients in the placebo plus MTX group. DAS28 remission rates at 24 weeks were 30.1% and 1.6% in the tocilizumab 8 mg/kg plus MTX and placebo plus MTX groups, respectively.

4.9 The Subcommittee considered that the results of the longer-term/extension studies (STREAM and the extension to AMBITION) appeared to support the sustained efficacy of tocilizumab.

4.10 The Subcommittee considered that the radiologic data from SAMURI and LITHE showed a reduction in radiologic deterioration with tocilizumab 8 mg/kg (and 4 mg/kg in LITHE).

4.11 The Subcommittee considered that the safety data from the clinical trials (also reviewed in Campbell et al, Rheumatology 2011;50:552-62 and Nishimoto et al, Mod Rheumatol 2010;20:222-232) showed that tocilizumab is associated with an increase in the rate of serious infections (generally similar to other biologics for RA), frequent transaminase rises which are generally transient but occasionally require withdrawal, occasional grade 3 neutropenia which usually spontaneously reverses, and a rise in cholesterol in about 25% of patients. The Subcommittee speculated that the rise in cholesterol may simply reflect unmasking of underlying hypercholesterolemia following the reduction in CRP produced by tocilizumab; however, it is possible that this may result in more patients requiring cholesterol-lowering therapy. The Subcommittee noted that thus far there appeared to be no safety signals relating to tuberculosis reactivation or malignancy; however, it may be too soon to tell given the relative absence of longer-term data.

4.12 The Subcommittee noted that there were no trials directly comparing tocilizumab to any other biologic treatment for RA. The Subcommittee considered that the findings from three publications attempting to draw indirect comparisons with different biologic agents suggest that tocilizumab provides similar efficacy to TNF inhibitors in RA. However, the Subcommittee noted that there are a number of weaknesses associated with such comparisons, particularly relating to potential differences in trial populations.

4.13 Overall, the Subcommittee considered that the strength and quality of the evidence was high and generally suggest that tocilizumab 8 mg/kg given every 4 weeks is effective in the treatment of RA, with a similar efficacy and safety profile to other currently available biologic treatments for RA. The Subcommittee considered that the evidence suggests that tocilizumab is slightly more effective when given in combination with MTX; however, it may be useful as monotherapy in patients who are intolerant to MTX or in whom MTX is contraindicated.

4.14 The Subcommittee noted that tocilizumab administration would be associated with resource impacts for hospitals relating to the intravenous infusion, which would include at least 15 minutes prior to the infusion to set it up, the 1 hour needed for the infusion, and monitoring of the patient afterwards.

4.15 The Subcommittee considered that the patient populations that would most benefit from tocilizumab would be patients with RA who had not responded adequately to TNF inhibitors, those in whom TNF inhibitors are contraindicated, and those who develop systemic lupus erythematosus (SLE) while taking TNF inhibitors. The Subcommittee considered that given the current lack of longer-term safety data, and the need for hospital infusion resources, tocilizumab should not be used as a first-line biologic treatment option except for patients in whom TNF inhibitors are contraindicated. The Subcommittee noted that TNF inhibitors in combination with leflunomide (or, potentially, sulphasalazine) could be used in patients who are intolerant to methotrexate. The Subcommittee noted that rituximab would be an option for patients in whom TNF inhibitors are contraindicated and that the relative cost of tocilizumab versus rituximab,

including the cost of infusions, would need to be taken into account when determining which should be used first in this situation.

4.16 The Subcommittee **recommended** that tocilizumab be funded as a first-line biologic treatment option for patients with RA, subject to restrictions similar to those currently applying to adalimumab and etanercept, only in patients for whom TNF inhibitors are contraindicated and only if it was cost-neutral to the health sector (including possible overall biologic market growth and taking into account the relative price of alternative biologic treatment options and the costs associated with the infusions).

4.17 The Subcommittee further **recommended** that if the cost of tocilizumab was such that it would result in an overall cost to the health sector, tocilizumab should be funded for RA only as a second-line treatment option (following a trial of one TNF inhibitor) in patients intolerant to MTX or as a third-line treatment option following trials of a TNF inhibitor and rituximab. The Subcommittee considered that, within the context of the rheumatology therapeutic area, this recommendation should be considered a high priority.

4.18 The Decision Criteria particularly relevant to these recommendations 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Systemic juvenile idiopathic arthritis

4.19 The Subcommittee noted that sJIA is a severe form of JIA, accounting for approximately 10%–20% of JIA cases, and is typically very difficult to treat.

4.20 The Subcommittee considered that there was little available evidence in support of the efficacy of MTX in sJIA and although sJIA does respond to high-dose corticosteroids these are associated with significant side effects in children such as growth retardation and osteoporotic fractures.

4.21 The Subcommittee noted that the age of diagnosis of sJIA was typically 2–3 years. The Subcommittee considered that sJIA often resolves after about 5–6 years but during the active phase it is very debilitating and approximately 20%–30% of patients will require ongoing longer-term treatment.

4.22 The Subcommittee considered that there was little evidence of benefit of etanercept in sJIA. The Subcommittee noted that while many children with sJIA ultimately end up being treated with etanercept, this is because their disease progresses and they develop arthritis and so meet the articular criteria for etanercept for JIA (i.e. they are not being treated with etanercept for the systemic features of JIA). This explains why patients originally diagnosed with sJIA typically start etanercept treatment at around 7–10 years rather than closer to their age at diagnosis when the systemic features are present but the arthritis has not yet developed.

4.23 The Subcommittee noted that patients with sJIA have high levels of IL-6, which provides a rationale for using an IL-6 inhibitor in the treatment of this disease. In contrast, there appears to be little evidence for a role of IL-6 in other JIA subtypes.

4.24 The Subcommittee noted that the supplier had provided one published randomised controlled trial (Yokota et al, Lancet 2008;371:998-1000) and two abstract reports of another randomised controlled trial (the TENDER trial) which is still in progress (De Benedetti et al, Arthritis Rheum 2010;62(Suppl 10):1434 and De Benedetti et al, Ann Rheum Dis 2011;70(Suppl 3):67), as well as unpublished data from TENDER and some earlier dose-finding studies, in support of its application for tocilizumab in sJIA.

4.25 In the published trial (Yokota et al, 2008), 56 sJIA patients aged 2–19 years (mean age 8.5 years) with active disease despite more than three months' treatment with corticosteroids were given tocilizumab 8 mg/kg every 2 weeks during a 6-week open-label lead-in phase. Forty-three patients achieving an ACR Paediatric (ACR Pedi) 30 response and a CRP of less than 5 mg/L were then randomly assigned to receive placebo or to continue tocilizumab treatment for 12 weeks. This was followed by an open-label extension to 48 weeks in 48 patients who had responded to tocilizumab and required further treatment. At the end of the open-label lead-in phase, the ACR Pedi 30, 50, and 70 response rates were 91%, 86% and 68%, respectively. At the end of the double-blind phase 80% of patients in the tocilizumab group and 17% of patients in the placebo group had maintained ACR Pedi 30 and CRP <5 mg/L. By the end of the open-label extension phase, ACR Pedi 30, 50, and 70 responses were seen in 98%, 94% and 90% of patients, respectively. Adverse events included two anaphylactoid reactions and one grade 3 neutropenia.

4.26 In the TENDER trial, 112 sJIA patients aged 2–17 years with active disease for at least 6 months and an inadequate response to previous NSAIDs and corticosteroids were randomly assigned in a 2:1 ratio to receive tocilizumab every 2 weeks (8 mg/kg for patients ≥30 kg; 12 mg/kg for patients <30 kg) or placebo for 12 weeks (Part I), followed by an open-label extension in which all patients received tocilizumab (Part II). At the end of Part I, the primary outcome measure of ACR Pedi 30 and absence of fever was achieved by 85% of tocilizumab-treated patients and 24% of placebo-treated patients, respectively ($p<0.0001$) (De Benedetti et al, 2010). The ACR Pedi 50, 70 and 90 responses were 85%, 71% and 37% in the tocilizumab group and 11%, 8% and 5% in placebo-treated patients. A total of 88%, 89% and 65% of 88 patients who had continued tocilizumab in Part II of the study and had reached 52 weeks of tocilizumab treatment by May 2010 had ACR Pedi 30 plus absence of fever, ACR Pedi 70 and ACR Pedi 90, respectively (De Benedetti et al, 2011). Adverse events associated with tocilizumab in Part II included 6 serious infections, all of which resolved and did not lead to discontinuation.

4.27 The Subcommittee considered that the limited available efficacy data appeared to be of good quality, noting that sJIA was a difficult patient population to study in clinical trials. The Subcommittee noted that there is limited short-term safety data and no long-term safety data in this patient population.

4.28 The Subcommittee considered that given the benefits of tocilizumab, the risks associated with corticosteroids, and the relative lack of evidence of efficacy of MTX, tocilizumab would most benefit sJIA patients if used as a first-line treatment.

4.29 The Subcommittee considered that, if used as a first-line treatment, tocilizumab could reduce costs associated with managing the adverse effects of corticosteroids as well as reducing the costs associated with suboptimally treated disease (e.g. surgery, wheelchairs, long-term disability). The Subcommittee considered that tocilizumab would also reduce the use of corticosteroids and could avoid the need for a proportion of patients to start etanercept.

4.30 The Subcommittee considered that if tocilizumab was funded as a first-line treatment option for sJIA, the average age of patients starting on treatment would be approximately 3 years.

4.31 Members considered that it may be possible to decrease the treatment frequency over time in responding patients.

4.32 The Subcommittee considered that, if funded, tocilizumab should be subject to criteria requiring discontinuation of treatment in non-responding patients, defined as those patients who have not achieved at least ACR Pedi 30 at 28 weeks.

4.33 The Subcommittee **recommended** that tocilizumab be funded for patients with sJIA as a first-line treatment option (i.e. with no requirement for any prior treatment to be trialled). The Subcommittee considered that, within the context of the rheumatology therapeutic area, this recommendation should be considered a high priority.

4.34 The Decision Criteria particularly relevant to this recommendation is: (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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.