Ophthalmology Subcommittee of PTAC
Meeting held 30 October 2014

(minutes for web publishing)

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

The Ophthalmology 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 7 & 8 May 2015, the record of which is available on our website.

1 Matters arising and correspondence

Infliximab criteria for chronic eye inflammation

1.1 The Subcommittee noted that PHARMAC had received several queries regarding the infliximab HML restrictions for ophthalmic indications. The Subcommittee considered that the final wording in the HML listing for ocular inflammation was not what was intended and the restrictions should be reviewed.

1.2 The Subcommittee noted the continuation restrictions are not practical and should include the duration of approval for continuing treatment and timing of the requirement to trial a withdrawal. Criteria for level of improvement and withdrawal are also necessary.

1.3 The Subcommittee noted feedback from clinicians that the restrictions should also be reviewed to accommodate appropriate treatment in paediatric patients. The Subcommittee supported reducing the requirement to have tried at least two other immunomodulatory agents to only one agent in children with chronic ocular inflammation. Members considered this was clinically appropriate and different from adult presentation due to the increased morbidity in this population, risk of early cataracts in children and more severe presentation. There is a clinical need to stabilise these patients more quickly and also to reduce steroid use to prevent cataract formation. There is also less evidence available regarding efficacy of other agents such as cyclosporin or mycophenolate in childhood uveitis. There is published evidence supporting use of infliximab in children and trials with adalimumab are in progress.

1.4 The Subcommittee **recommended** the HML restrictions for infliximab for ocular inflammation be amended as follows (additions in bold, deletions in strike through):

Initiation - severe ocular inflammation
Re-assessment required after 3 doses
Both:

1. Patient has severe, vision-threatening ocular inflammation requiring rapid control; and
2. Either:
   - 2.1 **Treatment with** ~~Patient has failed to achieve control of severe vision threatening ocular inflammation following~~ high-dose steroids (intravenous methylprednisolone) followed by high dose oral steroids **has proven ineffective at controlling symptoms**; or
   - 2.2 Patient developed new inflammatory symptoms while receiving high dose steroids.

Initiation- chronic ocular inflammation
Reassessment required after 3 doses
Both:

1. Patient has severe uveitis uncontrolled with treatment of steroids and other immunosuppressants with a severe risk of vision loss; and
2. **Either;**

a. Patient **is 18 years or older and treatment with** ~~has tried~~ at least two other immunosuppressant agents **has proven ineffective**; or
b. **Child is under 18 years and treatment with methotrexate has proven ineffective.**

Continuation- ocular inflammation

~~Both:~~
~~1. Patient has had a good clinical response to initial treatment; and~~
~~2. Either:~~
~~a. A trial withdrawa of infliximab has been trialled and patient has relapsed after trial withdrawal; or~~
~~b. Patient has Behcet's disease~~

Reassessment required after 12 months ongoing treatment, and every 12 months thereafter
Both
1. Either:
1.1 Following 3 initial doses, the patient has had a good clinical response and must be reassessed for continuation at 12 months; or
1.2 Following 12 months treatment, and every 12 months thereafter, the patient must be reassessed for continuation and meet one of the following:
a. Sustained reduction in inflammation (Standardisation of Uveitis Nomenclature (SUN) criteria < ½+ anterior chamber or vitreous cells, absence of active vitreous or retinal lesions, or resolution of uveitic cystoid macular oedema); or
b. Reduction in frequency of ocular attacks to ≤1/ year in patients with Behcet's disease; or
c. Sustained steroid sparing effect, allowing reduction in prednisone to <10mg daily, or steroid drops less than twice daily if under 18 years old; and

2. A trial withdrawal should be considered after every 24 months of stability, unless the patient is deemed to have extremely high risk of irreversible vision loss if infliximab is withdrawn.

2 Aflibercept

2.1 The Subcommittee reviewed an application from Bayer NZ Ltd and a clinician for the listing of aflibercept on the Hospital Medicines List (HML) for the treatment of neovascular (wet) age-related macular degeneration (wAMD).

Recommendation

2.2 The Subcommittee **recommended** that aflibercept be listed on the HML with a high priority subject to the following restriction criteria:

Initiation
Re-assessment required after 3 doses
Both:
1. Either
    1.1 Wet age-related macular degeneration (AMD); or
    1.2 Polypoidal choroidal vasculopathy; or
    1.3 Choroidal neovascular membrane from causes other than wet AMD; and
2. Either:
    2.1 The patient has had a severe ophthalmic inflammatory response following bevacizumab; or
    2.2 Treatment with bevacizumab has proven ineffective following at least three intraocular injections.

Continuation
Re-assessment required at 6 months, 12 months and 24 months from initiation of treatment, then 2 yearly thereafter.
Both:
1. Documented benefit must be demonstrated to continue; and
2. In the case of previous non-response to bevacizumab, a retrial of at least one dose of bevacizumab is required at 6 months, 12 months and 24 months to confirm non-response before continuing with aflibercept.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services,*

Discussion

2.3 The Subcommittee noted that in New Zealand, patients were often being treated for wAMD with either intravitreal bevacizumab or ranibizumab using a 'treat and extend' protocol where treatment intervals were extended out as long as possible while at the same time ensuring that the disease remained controlled. Members considered this typically meant that patients received treatment on average every 6 to 8 weeks. Some patients require more frequent administration with dosing every 2 weeks.

2.4 The Subcommittee noted an internal DHB hospital audit quoted in the clinician application had indicated that approximately 8% of patients treated with intravitreal bevacizumab had an inadequate response to treatment. The Subcommittee considered that this rate was quite low and that 10% would be a more reasonable estimate, but with a range of 10 to 40%. The Subcommittee considered that this patient group would likely have been switched to ranibizumab but this could vary depending on DHB. Members estimated 2 to 3% of patients would likely progress to require a third-line treatment option or rescue therapy.

2.5 The Subcommittee noted that the access criteria for ranibizumab currently do not define the meaning of 'non-response' or 'benefit'. Therefore, patients could remain on treatment for a long time despite requiring more frequent injections because slowing of disease progression could be regarded as a benefit of

treatment. Members noted the majority of current patients receive ongoing treatment.

2.6 The Subcommittee noted there is another small group of patient with polypoidal choroidal vasculopathy (PCV) that already receive treatment with bevicizumab or ranibizumab. Members noted these patients do not have not true choroidal neovascular membranes, nor wAMD, but they are grouped under the AMD banner. For clarification and completeness, the Subcommittee considered this group should be added to existing and new criteria. Members noted this subgroup is particularly responsive to aflibercept. The Subcommittee considered approximately 10 – 15% of New Zealanders being treated for wAMD will have PCV.

2.7 The Subcommittee noted the results from two Phase III head-to-head multicentre randomised controlled trials of aflibercept and ranibizumab, VIEW 1 and VIEW 2 (Schmidt-Erfurth et al. Ophthalmology 2014;121:193-201; Heier et al. Ophthalmology 2012;119:2537-48). Patients were randomized to intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, 2 mg every 2-months after 3 initial monthly doses, or ranibizumab 0.5 mg monthly. The Subcommittee noted that these studies indicated that aflibercept given every 8-weeks was as effective as ranibizumab given 4-weekly in improving visual acuity outcomes, but with an average of 5.3 fewer injections after 96 weeks. The proportion of subjects with maintained vision at week 52 was >94% in all four treatment groups; largely similar proportions of patients (91.5% to 92.4%) maintained visual acuity across all treatment groups at week 96. All aflibercept treatment groups were numerically similar, and proven to be non-inferior to ranibizumab every 4-weeks, in the proportion of subjects maintaining vision.

2.8 The Subcommittee also noted additional evidence supplied by the clinician: Patel et al (Eye 2013;27:663-8) a case-series of three patients describing the efficacy of aflibercept in patients with wAMD refractory or with tachyphylaxis to bevacizumab and ranibizumab treatments; and Kumar et al (Retina 2013; 33:1605-12), a retrospective study of 33 patients assessing the efficacy of intravitreal aflibercept in patients with neovascular age-related macular degeneration resistant to ranibizumab. The Patel case series reported that all three patients had complete resolution of subretinal fluid and complete or near-complete resolution of retinal pigment epithelial detachment after treatment with aflibercept over 3-months. The Subcommittee noted that the Kumar study reported that aflibercept resulted in improvement in visual and anatomical outcomes in patients with persistent subfoveal fluid despite previous treatment with ranibizumab and bevacizumab (for some patients).

2.9 The Subcommittee noted that there was good quality evidence to support that aflibercept was non-inferior to ranibizumab in the treatment of wAMD but there was some lower quality evidence to suggest that it is more efficacious than bevacizumab and ranibizumab. The Subcommittee however noted that in the third-line setting, it would be likely that aflibercept would need to be administered more frequently than 2-monthly and likely monthly. From its clinical experience to date, the Subcommittee indicated that approximately 50% of patients who do not respond to bevacizumab and ranibizumab would respond to aflibercept.

2.10 The Subcommittee considered that the risks with the different treatments were similar but like bevacizumab, aflibercept would be associated with the same concerns of greater systemic exposure which is relevant in patients who are pregnant and who have recently had a stroke. Ranibizumab would be the preferred treatment in these patients.

2.11 The Subcommittee considered that bevacizumab would likely remain the first-line treatment option given its good cost-effectiveness relative to aflibercept and ranibizumab.

2.12 The Subcommittee considered that based on the available evidence and if the cost of the treatment was reasonable, aflibercept would be the better second-line treatment option when compared to ranibizumab as it would involve less injections and it is likely to be more efficacious. Members considered it would be appropriate to have less strict continuation criteria.

2.13 The Subcommittee considered that there is a clinical need for a third-line treatment option regardless of whether aflibercept or ranibizumab was available as a second-line treatment option.

2.14 The Subcommittee noted that depending on the access criteria decided for aflibercept, the access criteria for ranibizumab would need to be amended accordingly and **recommended** the following restriction criteria if ranibizumab was to be used as a third line agent:

Initiation
Re-assessment required after 3 doses
Both:
1.Either
1.1 Wet age related macular degeneration; or
1.2 Polypoidal choroidal vasculopathy; or
1.3 Choroidal neovascular membrane from causes other than wet AMD; and

2. Either

2.1 Treatment with bevacizumab and aflibercept has proven ineffective following at least 3 intraocular injections of each agent; or
2.2 The patient has had a myocardial infarction or stroke within the last 3 months; or
2.3 The patient is of childbearing age and has not yet completed a family

Continuation
Re-assessment required at 6 months, 12 months and 24 months from initiation of treatment, then 2 yearly thereafter.
Both:
1. Documented benefit from treatment must be demonstrated to continue; and
2. In the case of previous non-response to bevacizumab and aflibercept, a retrial of bevacizumab is required after 6 months, 12 months and then 24 months, to confirm non-response before continuing with ranibizumab.

3 TNF inhibitors for Behçet's disease

Application

3.1 The Subcommittee noted an application from the New Zealand Rheumatology Association for funding TNF inhibitors for patients with Behçet's disease and who are refractory to conventional therapy.

Recommendation

3.2 The Subcommittee **recommended** infliximab continue to be available on the HML as the first line TNF inhibitor for patients with ocular Behçet's disease who were refractory to conventional therapy. The Subcommittee noted this patient group is already accessing infliximab on the HML through the ocular inflammation criteria.

3.3 The Subcommittee **recommended** that funded access to adalimumab be widened to include patients with Behçet's disease and who were refractory to conventional therapy if cost neutral to infliximab. The Subcommittee **recommended** funding adalimumab for patients with Behçet's disease and who were refractory to conventional therapy as a second-line TNF treatment if infliximab had failed, with a high priority, subject to Special Authority criteria.

3.4 The Subcommittee **recommended** that the application to fund etanercept for Behçet's disease be declined due to weak evidence and reduced efficacy compared to infliximab and adalimumab.

3.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services,*

Discussion

3.6 The Subcommittee noted that the evidence supplied with this application was limited to etanercept and infliximab studies. PHARMAC staff however had also identified a small number of studies using adalimumab, another TNF inhibitor, and had sourced evidence on this drug.

3.7 The Subcommittee noted that PTAC reviewed TNF inhibitors for patients with Behçet's disease at its meeting in August 2012 and recommended the application be referred to the Dermatology and Ophthalmology Subcommittees for advice on specific Special Authority criteria and if there were any preferences for the specific TNF(s) to be funded.

3.8 The Subcommittee noted that the primary goal of Behçet's treatment was symptom control, early suppression of inflammation and prevention of organ damage. Treatments were frequently used in combination in order to maximise efficacy while minimising side effects. The Subcommittee also noted that

treatment options for Behçet's included corticosteroids and/or immunosuppressants (e.g. methotrexate, azathioprine, cyclosporin, tacrolimus and thalidomide) and oral colchicine. PHARMAC staff noted that tacrolimus and thalidomide were not currently funded in the community for Behçet's disease and none of these treatments were indicated for this condition. Most current treatment approaches were established primarily by extrapolation of their use and efficacy in other inflammatory conditions, such as rheumatoid arthritis.

3.9 The Subcommittee noted that infliximab was administered by intravenous infusion in hospital. Infliximab use in DHBs hospitals was mainly used for GI conditions; Crohn's disease and ulcerative colitis. The Subcommittee also noted that since July 2013 infliximab has been listed on the Hospital Medicines List (HML) for severe and chronic ocular inflammation for patients who met certain criteria, including Behçet's disease.

3.10 The Subcommittee noted ophthalmic manifestations of Behçet's disease often drive treatment decisions due to the severity of disease. Behçet's eye disease is fulminant and relapsing, often with limited response to conventional immunosuppressants.

3.11 The Subcommittee noted that there are number of prospective observational studies and retrospective case series suggesting efficacy of infliximab for the treatment of inflammatory eye disease, major organ involvement, and other symptoms in Behçet's disease.

3.12 The Subcommittee noted a review of by Arida et al (Semin Arthritis Rheum 2011;41:61-70) which analysed published data for anti-TNF agents their efficacy and safety for 369 patients with Behçet's disease. This review identified 14 prospective studies (through to 2010) on infliximab use for posterior uveitis, reporting on 158 patients who were refractory to immunosuppressive therapy. A rapid and dramatic improvement of visual acuity and decrease of ocular inflammation starting 24 hours after infliximab was almost always reported. Infliximab induced a sustained response in 89% of these patients (follow up of 28 days to 3 years, median 15.9 months), and 65% achieved complete remission. Similarly, a 89% response rate was seen in all of the 262 patients with Behçet's disease and ocular involvement treated with infliximab that were identified in this review. Members noted that a combination of infliximab with azathioprine and/or ciclosporin and/or methotrexate appeared superior to monotherapy for sustained ocular remission in prospective studies.

3.13 The Subcommittee noted an uncontrolled series (Ohno et al. J Rheumatol 2004;31:1362-8) of 13 patients treated with infliximab (5 or 10 mg/kg intravenously for four doses at weeks 0, 2, 6, and 10) observed a decrease in the frequency of episodes of uveitis during the 14 weeks of treatment (one episode versus a mean of approximately four episodes in the 14 weeks prior to treatment).

3.14 The Subcommittee noted that in an open prospective study (Sfikakis et al, Ann Intern Med. 2004;140(5):404-6) of 25 patients with relapsed Behçet's ocular inflammation who were given a single infliximab infusion of 5 mg/kg while continuing their prior therapy. Most patients responded rapidly and all improved

by day 28. By day 28, vitritis and retinitis had resolved in 100%, retinal vasculitis in 94%, cystoid macular oedema in 90%, and visual acuity in 100%. Fifteen of these patients subsequently received infliximab at 4, 8, 16, and 24 weeks. Complete remission occurred in 60%; mild relapses responded to increased steroid therapy; three patients with retinitis responded to repeat infusion and subsequent increased frequency of infusions every 6 weeks. Visual acuity was improved.

3.15 The Subcommittee noted that a small number case reports had shown benefit with adalimumab treatment. A retrospective review (Bawazeer et al, Ocul Immunol Inflamm 2010;18(3):226-32) of eleven male patients with ocular Behçet's disease. Of the 21 eyes, 17 had improvement of visual acuity after the average follow-up of 10.8 months and 10 out of 11 patient showed completed remission of inflammation by 4 weeks. Olivieri et al (Clin Exp Rheumatol 2011;29(4 Suppl 67):S54-7) reported seventeen patients where treatment with infliximab had failed and were subsequently treated with adalimumab, and 12 had a good response, 9 of which achieved sustained remission. Adria et al (Semin Arthritis Rheum 2011;41:61-70) identified 16 patients who had responded to adalimumab treatment for ocular Behçet's disease (100% response rate) and switching from infliximab to adalimumab in two patients, due to hypersensitivity and to avoid delayed infusion reactions, was also successful.

3.16 The Subcommittee noted that the randomised controlled study evidence for use of etanercept in Behçet's disease was limited to one, small, short duration study (Melikoglu et al, J Rheum 2005;32(1):98-105). In this study, 40 Behçet's patients with mucocutaneous disease and/or arthritis were randomised 1:1 to receive either etanercept (25 mg subcutaneously twice a week) or placebo injections for four weeks. Members noted this study did not address ophthalmic complications of Behçet's disease because this was an exclusion criteria.

3.17 The Subcommittee noted the evidence for the use of etanercept for ocular Behçet's disease is limited to case reports and overall seems to be inferior to infliximab and adalimumab for this indication. Arida et al identified 10 patients treatment with etanercept for Behçet's disease with ocular involvement, of which 6 patients (60%) achieved complete remission.

3.18 There are no head to head studies currently available comparing TNF inhibitors for Behçet's disease in controlled trials and the majority of evidence has historically been for infliximab. The Subcommittee noted some centres use infliximab or adalimumab first line for ophthalmic manifestations of Behçet's disease. Whilst infliximab, adalimumab and etanercept all inhibited TNF-α, they had significant differences, for example, infliximab had a much longer half-life than etanercept and could bind surface-bound TNF-α, lysing cells expressing this molecule by complement fixation, whereas etanercept did not. The Subcommittee also noted that there were reports of differences in responses to etanercept and infliximab. Estrach C et al (Rheumatology 2002; 41:1213-4) reported a patient with refractory Behçet's disease where treatment with etanercept was ineffective after 3 months, however responded dramatically to infliximab in combination with methotrexate. The Subcommittee noted that there was sufficient evidence supporting infliximab and adalimumab for Behçet's

disease but there was a lack of evidence supporting etanercept, particularly for ophthalmic complications.

3.19 The Subcommittee noted that adalimumab is usually used as a single agent but infliximab was used alongside methotrexate. The Subcommittee noted is would be helpful to have adalimumab available as a first line TNF-inhibitor in addition to infliximab as it is self-administered by the patient at home and does not require a hospital visit. This would be particularly helpful for school aged children.

3.20 The Subcommittee considered it would be appropriate for patients to continue to access infliximab for ocular Behçet's disease through the severe ocular inflammation and uveitis restrictions currently included in the HML for infliximab for consistency and safety. The Subcommittee considered it would be inappropriate to include ocular Behçet's disease into a separate Behçet's disease HML restriction because a diagnosis of Behçet's disease may not be clear initially and rapid treatment may be necessary.

3.21 The Subcommittee **recommended** Special Authority criteria for ocular involvement be included in separate Behçet's disease criteria for adalimumab as this agent is not currently funded for other uveitis indications (however an application is expected) and would likely be a second line TNF inhibitor for this patient group.

3.22 The Subcommittee considered approximately 20% of patients treated with infliximab would need to switch to an alternative TNF inhibitor due to hypersensitivity, adverse effects or inadequate response.

3.23 The Subcommittee considered that there were approximately 40 patients with Behçet's disease in New Zealand and the numbers included in the application were likely an underestimate. Members considered at least 20 of these patients had uveitis.

3.24 If adalimumab was to be funded as a first line TNF inhibitor for Behçet's disease, the Subcommittee **recommended** the Special Authority include criteria similar to the infliximab.

3.25 The Subcommittee **recommended** the following be incorporated into Special Authority criteria if adalimumab was to be funded as a second line TNF-inhibitor treatment for Behçet's disease. The Subcommittee did not discuss non-ocular criteria.

> <u>Initial application- (Behçet's disease with severe ocular inflammation)</u>
> Only from an ophthalmologist or Practitioner on the recommendation of an ophthalmologist. Approvals valid for 3 months for applications meeting the following criteria
> All of the following:
> 1. Patient has Behçet's disease and severe, vision-threatening ocular inflammation requiring rapid control; and
> 2. Either:
> 2.1 Patient has experienced intolerable side effects from a reasonable trial of infliximab; or

2.2 Treatment with infliximab has proven ineffective in controlling symptoms.

Initial application - Behçet's disease with chronic ocular inflammation
Only from an ophthalmologist or Practitioner on the recommendation of an ophthalmologist. Approvals valid for 3 months for applications meeting the following criteria
All of the following:

1. Patient has Behçet's disease and severe uveitis uncontrolled with treatment of steroids and other immunosuppressants with a severe risk of vision loss; and
2. Treatment with 3 doses of infliximab has proven ineffective in controlling symptoms.

Renewal – (Behçet's disease with ocular inflammation)
Only from an ophthalmologist or Practitioner on the recommendation of an ophthalmologist. Approvals valid for 12 months for applications meeting the following criteria
All of the following:

1. Either:
   - 1.1 Following 3 months initial treatment patient had a good clinical response to treatment; or
   - 1.2 Following 12 months of ongoing treatment and every 12 months thereafter, the patient has had a reduction in frequency or maintains a frequency of ocular attacks to ≤1/ year; and
2. A trial withdrawal should be considered after every 24 months of stability, unless the patient is deemed to have extremely high risk of irreversible vision loss if adalimumab is withdrawn

4 Biosimilar infliximab

Application

4.1 The Subcommittee reviewed an application from Hospira (New Zealand) Ltd for the listing of its biosimilar infliximab (CT-P13, Inflectra/Remsima) in Section H of the Pharmaceutical Schedule.

Recommendation

4.2 The Subcommittee **recommended** that, subject to Medsafe approval, Hospira's biosimilar infliximab should be listed in Section H of the Pharmaceutical Schedule subject to the same restrictions as the Remicade (Janssen) brand of infliximab if cost saving to Remicade.

The decision criteria relating to this application were: *(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; (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; (vii) the direct cost to health service users;*

Discussion

4.3 The Subcommittee noted a presentation from PHARMAC staff regarding biosimilars, including the development and regulatory process.

4.4 The Subcommittee noted the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) guideline on biosimilar monoclonal antibodies and their discussion regarding indication extrapolation.

4.5 The Subcommittee noted that infliximab (Remicade, Janssen) is currently listed in Section H of the Pharmaceutical Schedule for use in DHB hospitals subject to restrictions for a range of inflammatory conditions including rheumatoid arthritis, Crohn's disease, ulcerative colitis, ocular inflammation and uveitis. Members noted ophthalmic use of infliximab (Remicade, Janssen) for ocular inflammation is off-label.

4.6 The Subcommittee noted the recommendation from PTAC and the Gastrointestinal and Rheumatology Subcommittees who have already reviewed Hospira's application for biosimilar infliximab earlier in 2014. Members also noted advice from PTAC that running a sole supply process for infliximab would be reasonable and that PHARMAC recently issued a Request for Tender (RFT) for the sole supply of infliximab to DHB hospitals. The Subcommittee noted PHARMAC staff advised a consultation letter on a proposal as a result of the RFT would be be issued soon, however no decision has been made regarding any changes to infliximab (Remicade) funding at this time.

4.7 The Subcommittee noted that Hospira's biosimililar infliximab (Inflectra/Remsima) was not currently approved by Medsafe but that it was approved by the European Medicines Agency (EMA), had been launched in some European countries and Medsafe is currently considering a submission. Members noted that in order to satisfy the EMA for approval a biosimilar must demonstrate that its variability in any parameter falls within the range of variability for the reference product and that any differences between it and the reference product have no clinically meaningful differences in quality, safety or efficacy compared with the reference product, Remicade.

4.8 The Subcommittee reviewed evidence comparing Hospira's biosimilar infliximab with Remicade including evidence from two comparative clinical studies in patients with ankylosing spondylitis (AS) (Study CT-P13 1.1, PLANETAS, Park et al Ann Rheum Dis. 2013;72(10):1605-12) and rheumatoid arthritis (RA) (Study CT-P13 3.1, PLANETRA, Yoo et al Ann Rheum Dis. 2013;72(10):1613-20) and unpublished data in patients with inflammatory bowel diseases (IBDs). The Subcommittee noted that there was no evidence for use of the biosimilar infliximab forophthalmic use for ocular inflammation and Behçet's disease. Members also noted there was no evidence for use of the biosimilar infliximab in children. The Subcommittee noted some minor differences in analytic characteristics of biosimilar infliximab and Remicade but considered these to be of no clinical significance. Members considered that overall the evidence indicated that Hospira's biosimilar infliximab demonstrated same or similar quality, safety and efficacy to Remicade.

4.9 The Subcommittee noted that process changes in the production of innovator biologic prodctus, including Remicade, result in variations between commercial lots (Schiestl et al Biotechnology Nature Biotechnology 2011, 29,310–312). Members considered that the Remicade product on the market was not exactly the same, but comparable to, thus be considered to be biosimilars of–the originally produced batches of Remicade.

4.10 The Subcommittee noted that sole supply funding contracts allow for a Discretionary Variance (DV) limit which allows the use of a small proportion of an alternative brand.

4.11 The Subcommittee noted that switching between products could be minimised through use of a longer tender period. Members considered most patients requiring infliximab for an ophthalmic indication would require a two to five year treatment periodThe Subcommittee considered a 5 year sole supply period would be appropriate.