PUBLIC SUMMARY DOCUMENT

Products and Sponsors: abatacept (Orencia®), Bristol-Myers Squibb Pharmaceuticals Pty Ltd;
anakinra (Kineret®), PharmaLink Pty Ltd;
adalimumab (Humira®), Abbott Australasia Pty Ltd;
etanercept (Enbrel®), Wyeth Australia Pty Limited;
infliximab (Remicade®), Schering-Plough Pty Ltd; and
rituximab (Mabthera®), Roche Products Pty Ltd),

Date of PBAC Consideration: December 2009

1. Purpose

To review the clinical and cost-effectiveness data of the biological disease-modifying antirheumatic drugs (bDMARDs): abacept, anakinra, adalimumab, etanercept, infliximab and rituximab, currently subsidised via the Pharmaceutical Benefits Scheme (PBS) for the treatment of severe, active rheumatoid arthritis.

2. Background

There are six biological disease modifying anti-rheumatic drugs (bDMARDs) subsidised via the PBS for the treatment of rheumatoid arthritis. These are adalimumab, etanercept, infliximab, rituximab, abatacept and anakinra. These bDMARDs have different mechanisms of action: three tumour necrosis factor (TNFα) inhibitors (adalimumab, etanercept, infliximab), a CD20-specific monoclonal antibody (rituximab), a T-cell co-stimulation modulator (abatacept) and an interleukin-1 (IL-1) inhibitor (anakinra).

Etanercept was the first bDMARD to receive a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) in December 2002. Adalimumab and infliximab were listed on a cost-minimisation basis compared to etanercept, while abatacept was listed on a cost-minimisation basis compared to infliximab. Rituximab was listed on a cost-minimisation basis compared to etanercept and adalimumab, with the proviso that to be eligible for treatment with rituximab, patients must have already failed to demonstrate a response to at least one course of treatment with a PBS-subsidised TNF-α inhibitor (adalimumab, etanercept, infliximab). Anakinra was listed on the basis of acceptable cost-effectiveness compared with a subsequent TNF-α inhibitor in patients who are unresponsive to, or intolerant of one or more prior TNF-α inhibitors, or in whom one or more prior TNFα-inhibitors are contra-indicated.

Access to PBS subsidised treatment with one of the bDMARDs listed on the PBS is limited to patients who meet certain eligibility criteria including having severe, active rheumatoid arthritis and failing to respond to non-biological disease modifying anti-rheumatic drugs (DMARD) used to treat rheumatoid arthritis. If a patient fails to achieve a preset response to a bDMARD, they cannot continue with PBS subsidised treatment with that bDMARD. If a patient fails to respond to bDMARD treatment three times they must have a minimum break of five years from biologic therapy before they are allowed to receive further subsidised bDMARDs.

The data considered by PBAC when it recommended the bDMARDs be subsidised through the PBS included estimates of the number of patients who would initiate and continue treatment in clinical practice. These estimates were based on factors including the incidence

and prevalence of severe active rheumatoid arthritis and the percentage of patients who continued treatment in the clinical trials conducted with each agent.

In December 2008, the Department of Health and Ageing asked PBAC for advice on the higher than estimated usage of the TNFα-inhibitors in rheumatoid arthritis. At that time the Committee considered that there were several factors which could account for the higher continuation rates observed in Australian clinical practice compared to those from clinical trials, including:

- higher doses of methotrexate and combination therapy are used in clinical practice which may lead to better patient responses to bDMARD therapy;
- the efficacy endpoint for the restrictions is a "hybrid" of the endpoints used in clinical trials which may be a factor in the higher continuation rates seen in practice;
- it is possible for prescribers to assess a patient's response more favourably to avoid a treatment failure being recorded; and
- better management of nuisance adverse effects such as injection site reactions, abnormalities of liver function tests and haematology.

The PBAC also considered that the impact on the clinical and cost-effectiveness of bDMARD treatment of more Australian patients remaining on treatment and for longer periods than was observed in clinical trials was unknown and requested that a review of cost-effectiveness of the bDMARDs be conducted.

3. Summary of Review and Findings:

Results of the randomised controlled trials:

With the exception of one trial comparing abatacept and infliximab (Schiff et al. 2008) there are no head-to-head trials comparing any of the bDMARDs. Therefore, the systematic review of efficacy and of adverse events considered by PBAC involved meta-analyses of indirect comparisons using Mixed Treatment Comparisons (MTC), based on the methods used by Nixon et al. (2007)[1].

The following table lists the key, randomised trials considered in the comparison of the bDMARDs. All trials were included in the Mixed Treatment Comparison, with the exception of Klareskog et al. (2004) which had patients who did not fail DMARD treatment.

[1] Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Stat Med* 2007;26(6):1237-54.

Publication details of the trials included in the efficacy Mixed Treatment Comparison

Trial	Publications
Etanercept	
Moreland *et al* (1999)	Moreland LW, Schiff MH, Baumgartner SW, *et al*. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130(6):478-86.
Weinblatt *et al* (1999)	Weinblatt ME, Kremer JM, Bankhurst AD, *et al*. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340(4):253-9.
Klareskog *et al* (2004) (TEMPO)	Klareskog L, van der Heijde D, de Jager JP, *et al*. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363(9410):675-81 van der Heijde D, Klareskog L, Singh A, *et al*. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006;65(3):328-34. van der Heijde D, Klareskog L, Rodriguez-Valverde V, *et al*. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54(4):1063-74.
Combe *et al* (2006) (Study 309)	Combe B, Codreanu C, Fiocco U, *et al*. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis* 2006;65(10):1357-62.
Adalimumab	
Furst *et al* (2003) (STAR)	Furst DE, Schiff MH, Fleischmann RM, *et al*. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;30(12):2563-71.
Weinblatt *et al* (2003) (ARMADA)	Weinblatt ME, Keystone EC, Furst DE, *et al*. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48(1):35-45.
Keystone *et al* (2004) (DE019)	Keystone EC, Kavanaugh AF, Sharp JT, *et al*. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50(5):1400-11. Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. *Clin Rheumatol* 2009;28(4):413-9.
van de Putte *et al* (2004)	van de Putte LB, Atkins C, Malaise M, *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;63(5):508-16.
Infliximab	
Maini *et al* (1999) (ATTRACT)	Maini R, St Clair EW, Breedveld F, *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354(9194):1932-9. Lipsky PE, van der Heijde DM, St Clair EW, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343(22):1594-602.

Trial	Publications
Westhovens *et al* (2006) (START)	Westhovens R, Yocum D, Han J, *et al*. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006;54(4):1075-86.
Abatacept	
Genovese *et al* (2005) (ATTAIN)	Genovese MC, Becker JC, Schiff M, *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353(11):1114-23.
Kremer *et al* (2006) (AIM)	Kremer JM, Genant HK, Moreland LW, *et al*. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144(12):865-76. Russell AS, Wallenstein GV, Li T, *et al*. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* 2007;66(2):189-94.
Anakinra	
Cohen *et al* (2004)	Cohen SB, Moreland LW, Cush JJ *et al*. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. *Ann Rheum Dis* 2004;63:1062-68.
Infliximab + abatacept	
Schiff *et al* (2008) (ATTEST)	Schiff M, Keiserman M, Codding C, *et al*. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67(8):1096-103.
Rituximab	
Edwards *et al* (2004)	Edwards JC, Szczepanski L, Szechinski J, *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350(25):2572-81. Strand V, Balbir-Gurman A, Pavelka K, *et al*. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. *Rheumatology (Oxford)* 2006;45(12):1505-13.
Cohen *et al* (2006) (REFLEX)	Cohen SB, Emery P, Greenwald MW, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54(9):2793-806. Keystone E, Burmester GR, Furie R, *et al*. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. *Arthritis Rheum* 2008;59(6):785-93.
Emery *et al* (2006) (DANCER)	Emery P, Fleischmann R, Filipowicz-Sosnowska A, *et al*. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54(5):1390-400.

The odds ratios (OR) for achieving a response compared with the control groups from the Mixed Treatment Comparison are presented in the table below.

Odds ratios from the mixed treatment comparison

Drug	ACR20 OR (95% CI)	ACR50 OR (95% CI)	LDAS OR (95% CI)	EULAR good/moderate OR (95% CI)
Abatacept	**4.22 (2.54, 6.63)**	**5.58 (3.39, 9.16)**	**4.41 (1.25, 16.66)**	NA
Adalimumab	**3.02 (2.13, 5.13)**	**3.66 (2.46, 5.60)**	NA	1.01 (0.00, $5.3x10^6$)
Anakinra	2.05 (1.00, 4.31)	**2.11 (1.05, 4.44)**	NA	NA
Etanercept[a]	**10.03* (5.23, 18.15)**	**15.88* (7.42, 36.15)**	1.56 (0.13, 23.84)	NA
Infliximab	**3.29 (1.80, 5.78)**	**4.90 (2.67, 9.25)**	9.61 (0.28, 382.0)	10.94 (0.00, 4410.0)
Rituximab	**4.22 (2.47, 7.30)**	**4.57 (2.67, 8.33)**	3.26 (0.11, 88.14)	**4.84 (1.35, 17.23)**

[a] Excluding Klareskog et al. (2004).
* the PBAC considered that there was uncertainty with the outcome of the Mixed Treatment Comparison with regard to etanercept being superior to adalimumab and infliximab
ACR = American College of Rheumatology; LDAS = low disease activity score, defined as a DAS28 of <3.2; EULAR = European League Against Rheumatism response; NA=not available
Bolded results are statistically significant

All of the bDMARDs demonstrated an advantage compared to the control arm for both the ACR20 and ACR50 response.

Although between-drug comparisons revealed a statistically significant advantage for etanercept versus all other drugs for ACR50, the PBAC agreed that there was uncertainty with the outcome of the Mixed Treatment Comparison indicating that etanercept is superior to adalimumab and infliximab. Other published analyses suggest that there are no differences in efficacy between the anti-TNFs. The superiority of etanercept shown in the Mixed Treatment Comparison could be attributed to the selection of data used, in particular the use of only trial arms with PBS-listed drug doses. Further possible reasons are the differences in covariates included in analyses. In the Mixed Treatment Comparison approach, treatments are compared at the same value of the study-level covariates. Other analyses may have ignored potentially significant study-level covariates which may partly explain the estimated differences in efficacy between the bDMARDs.

The PBAC noted that the Mixed Treatment Comparison showed anakinra to be inferior to the other bDMARDs. The PBAC further noted that the UK National Institute of Clinical Excellence (NICE) treatment guidelines do not recommend anakinra for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study.

Comparative toxicity:
Overall, there was no statistically significant difference between the bDMARDs for the occurrence of serious adverse events, withdrawals due to serious adverse events, serious infections and malignancies. PBAC considered that although it appears that the newer agents, rituximab and abatacept, may have better safety profiles than the TNF inhibitors, long term data are lacking.

4. Economic Analysis

Model and assumptions

The Committee considered the results from a deterministic semi-Markov model developed to model five different treatment sequences for the three anti-TNF drugs (etanercept, adalimumab and infliximab), rituximab and abatacept. Each treatment sequence used in the base case and scenario analyses included three treatments as allowed under the current PBS bDMARD subsidy arrangements that allow patients to trial three treatments in sequence and if they fail all three treatments, requires a five year break from bDMARD therapy.

Anakinra was excluded from the modelled economic analysis because the Mixed Treatment Comparisons revealed that anakinra was inferior to the other bDMARDs and because it has relatively small usage under the PBS.

For the base-case analysis, the continuation rates (i.e. response rates) for the bDMARDs were derived from Medicare Australia data from March 2003 to 31 May 2009. The PBAC considered that it was appropriate to use Medicare data to inform the response rates in the base-case economic model as this data is specific to the outcome criteria specified in the PBS restrictions. Scenario analyses were undertaken using the trial-based outcomes.

The continuation rates for the initial period (the proportion of patients continuing with the same bDMARD after the initial assessment) and the mean continuation rates for subsequent periods which were used to model the base case are presented in the following table.

Continuation (response) derived from Medicare data

bDMARD	Initial period	Subsequent periods
Etanercept	0.761	0.787
Infliximab	0.722	0.746
Adalimumab	0.707	0.726
Mean TNFs *	0.733	0.725
All bDMARDs	0.716	0.706

*this value is the mean for the three TNF alpha inhibitors and was used as an estimate for the continuation rates for rituximab and abatacept in the economic evaluation given the later listings of these agents.

It was noted that the continuation rates for rituximab and abatacept were lower than for the other agents (initial period: 0.490 and 0.588; subsequent periods 0.393 and 0.437 respectively). The PBAC agreed that these lower continuation rates were likely due to these being the last two drugs listed on the PBS but could also reflect that these drugs may be used in more treatment resistant patients. The PBAC noted that the use of the response rates for rituximab and abatacept based on Medicare data may not reflect the true efficacy of these agents, hence the economic evaluation used the mean continuation rates for the three TNF alpha inhibitors as an estimate for the continuation rates for rituximab and abatacept.

The key assumptions used in the model considered by PBAC and the impact on the incremental cost effectiveness ratio (ICER) that occurs if adjustments are made to this model are listed below.

Key assumptions

<table>
<tr><th>Issue</th><th>Comment</th><th>Direction</th><th>Approx magnitude</th></tr>
<tr><td>Under-calculation of Medicare ‘Ongoing Continuations’ rates</td><td>An identical time period (inception to May 2009) has been used when counting initial applications and continuing applications (or subsequent continuations following previous continuations). This underestimates the real continuation rate as a delay of approx 3 months following initiation to first continuation is required to enable all patients the time to have their initial therapy and have an assessment of eligibility for bDMARD continuation and have their subsequent application for continuing treatment made. If the continuation rates following initial treatment are re-estimated allowing for this lag time (ie using data only up to February 2009 to obtain a denominator of patient usage, but counting data up to May 2009 to estimate the numerator of continuing patients) the following continuation rates are obtained:
<table>
<tr><th></th><th>Medicare Rate in Review</th><th>Revised Medicare Rate</th></tr>
<tr><td>Etanercept</td><td>0.761</td><td>0.800</td></tr>
<tr><td>Infliximab</td><td>0.722</td><td>0.751</td></tr>
<tr><td>Adalimumab</td><td>0.707</td><td>0.756</td></tr>
<tr><td>Rituximab</td><td>0.490</td><td>0.599</td></tr>
<tr><td>Abatacept</td><td>0.588</td><td>0.726</td></tr>
<tr><td>TNFs</td><td>0.733</td><td>0.777</td></tr>
<tr><td>All bDMARDs</td><td>0.716</td><td>0.767</td></tr>
</table></td><td>Increase ICER</td><td>>$2,000/ QALY</td></tr>
<tr><td>Under-calculation of Medicare ‘Initial Continuations’ rates</td><td>As described above, the same methodological issue is present in calculations of the percentage of patients with an initial Medicare continuation. These values proxy for initial effectiveness in the base case.</td><td>Increase ICER</td><td>≈$2,000/ QALY</td></tr>
<tr><td>Quality of life in bDMARD responders is assumed to be maintained indefinitely while responding.</td><td>Australian Rheumatology Association Database (ARAD) data (beyond 36 months) shows that Quality of Life (QoL) appears to diminish gradually over time, even in responders continuing on treatment. Given the progressive nature of the disease and the ability for partial response etc, this would seem more realistic than indefinitely maintained utility.</td><td>Increase ICER</td><td>≈$5,000/ QALY</td></tr>
<tr><td>Administration costs do not include hospital admissions or home nursing.</td><td>Infusions of rituximab, infliximab and abatacept require day stay hospital admission costs and will attract higher administration costs than the MBS fee included in the model**. Some patients on etanercept or adalimumab need assistance with injecting, therefore some home nursing costs should be included.</td><td>Increase ICER</td><td>≈$25,000/ QALY</td></tr>
</table>

Issue	Comment	Direction	Approx magnitude
DMARD response of 15% in previously refractory patients.	The base case estimate of 15% appears reasonable, but highly uncertain given its non-evidentiary source. Alternatives were tested in sensitivity analyses. - Decrease response rate to 5% - Increase response rate to 40%	Decrease or Increase ICER	- ≈$2,000 to + ≈$20,000/ QALY
Unreasonable assumption that surgery is utility neutral	As an accurate estimate of utility benefit was not easily obtained, but benefits must be considered to exceed risks and should be of acceptable cost-effectiveness for surgery to proceed, excluding this completely may be more reasonable than including only costs.	Increase ICER	<$2,000/ QALY
Timeframe is long	Likely changes in treatment methods etc over time increase likelihood of irrelevance of model over time, consideration to shorter timeframes would be reasonable.	Increase ICER	ICER increases as time horizon decreases.
Long-term adverse events excluded	No specific adverse event rates or costs available.	Increase ICER	Unknown
Monitoring costs are incomplete	The recommendations and usual clinical practice with respect to monitoring (eg blood tests [ESR,CRP,FBC,Cr,LFT etc] and screening, GP and specialist review visits) were revised. The full costs of screening for TB, HIV, hepatitis etc are still not included, favouring bDMARDs, but unlikely to be of consequence.	ICER may remain slightly under-estimated	Unlikely to have substantial impact on ICER.
The bDMARD naive treatment effect in $2^{nd}/3^{rd}/4^{th}$ treatments is maintained.	This is tested in the sensitivity analyses with assumptions of decreased efficacy diminished by 10% and 25% for each additional bDMARD. The assumption of decreasing response is supported by literature and may be considered appropriate in the base case.	Decrease ICER	≈$2,000 to ≈$6,500/ QALY
Effect size of etanercept (MTC)	The relatively large initial effect size of etanercept derived from the MTC may be an artefact associated with the duration of treatment selected for this Review. The Cochrane review found a similar result at 6 months which had disappeared by 12 months.	Decrease ICER	≈$10,000 to ≈$20,000/ QALY

** The Committee did not accept the argument presented at the meeting hearing that the provision by an individual sponsor of an infusion service for one of the bDMARDs negates the need to include any costs associated with the administration of these agents. The PBAC considered that as a minimum, the cost claimed by medical practitioners for the administration of an IV infusion would be the MBS fee.

In particular, the PBAC discussed the following issues raised by the Australian sponsors of bDMARDs:

- that the model assumed that the bDMARD treatment effect in the second, third and fourth bDMARDs is maintained which was favourable to the bDMARDs. This assumption was tested in sensitivity analyses presented in the final report, with a 10% and 25% reduction in efficacy for each additional bDMARD resulting in only a minor reduction in the ICER from approximately $2,000 to $6,500 per QALY.
- The economic analysis assumed that 15% of patients in the usual care arm (non-biologic) of the model have a period of remission of rheumatoid arthritis without bDMARD treatment. The PBAC noted that the rates of response from the DMARD arms of the trials estimated by the Mixed Treatment Comparisons were: ACR20 = 26.1%; ACR50 =

8.6%; LDAS = 4.4%; and EULAR = 33.9% which gave a crude overall mean of 18.2% and a crude mean of 17.3% for the ACR measures. Based on the results of the Mixed Treatment Comparison, the PBAC considered that the assumption of 15% for the remission of rheumatoid arthritis was reasonable. The PBAC further noted that when tested in sensitivity analysis, reducing the remission rate to 5% gave a minor reduction in the ICER in the order of $2,000 per QALY.

- The model assumed that in the usual care arm and in non-responders to bDMARDs there would be disease progression and an associated decline in utility. The model therefore imposed a rate of diminishing utility of 2% per annum which was based on the midpoint of values obtained from the literature, as shown in the table below. This was accepted by the PBAC.

Estimating utility in non-responders to bDMARDs and patients receiving usual care

CUA study	Based on	HAQ progression	Utility decline per annum*
Brennan et al 2004	Functional grade III and IV	0.13 per annum	-0.03
Brennan et al 2007	Conventional DMARDs	0.042 per annum	-0.01
Chen et al 2006	Palliation	0.06 per annum	-0.01
Kielhorn et al 2008	Palliation	0.065 per 6 mth cycle	-0.03
Kobelt et al 2005	"Standard treatment"	0.03 per annum	-0.01
Lindgren et al 2009	Off treatment	0.03 per annum	-0.01
Spalding et al 2006	"Natural progression"	0.155 per 5 years	-0.01
Tanno et al 2006	Conventional DMARDs	0.067 per 6 mths	-0.02
Vera-Llonch et al 2008	Conventional DMARDs	0.065 per annum	-0.01
Wailoo et al 2008	After withdrawal from bDMARDs	0.02 per annum	0.00

*Utility estimated using AQoL = 0.85 - 0.23HAQ from Hawthorne et al, 2000

One sponsor questioned the multiplicative approach used in the model to apply the 2% decline in utility in non-responders and in patients receiving usual care, which used a log function. The sponsor argued that the decrement should have been applied as an absolute reduction in utility rather than a relative reduction each year (i.e. a linear decay versus a multiplicative decay). The PBAC considered that a multiplicative decline was more appropriate as this approach results in an eventual asymptote in utility at a value greater than zero. The PBAC also noted that for a linear decay, the entire quality of life benefit would be driven only by rheumatoid arthritis which ignores other factors which influence QALY measures.

Of those patients who no longer remain on the initiated bDMARD, some switch to another bDMARD and a minority cease bDMARDs in favour of DMARDs. The table below provides the percentages of patients who switch to another bDMARD as a result of failure (i.e. a lack of response) or an adverse event.

Percentage of patients discontinuing one bDMARD who switch to another bDMARD

TNFs	Etanercept	Adalimumab	Infliximab	Rituximab	Abatacept	ALL
0.804	0.789	0.704	0.918	0.804	0.804	0.804

In the absence of specific Medicare data, this information was extracted from the Australian Rheumatology Arthritis Database (ARAD). The figures for switching were derived by analysing ARAD data over a 36 month period, dividing the total number of patients discontinuing a given bDMARD by the total number of patients who switched to another bDMARD. For example, over 36 months 299 ARAD participants discontinued etanercept, and of these, 236 switched to another bDMARD (78.9%). The sample of patients recorded in the ARAD had not switched from rituximab or abatacept due to the relatively late entry to market of these drugs and hence the numbers of patients using these drugs were small and the opportunities for switching from these drugs was limited. Therefore, it was assumed in the economic modelling that the rate of switching from these latter drugs would be the same as the mean rate of switching from the TNFα inhibitors.

Results of the economic analysis

The base case incremental cost effectiveness ratio (ICER) for a representative treatment sequence of three bDMARDs with differing mechanisms of action exceeded $100,000. The corresponding ICER for the treatment sequence etanercept-adalumimab-infliximab most commonly observed in the analysed Medicare data also exceeded $100,000. These ICERs are above the range normally considered by PBAC to represent acceptable cost-effectiveness.

According to the semi-Markov model that was used, there were considerable differences in total costs, total quality adjusted life years (QALYs) and ICERs depending on the drug sequence and response measure used.

For example, using the ACR20 (American College of Rheumatology 20) as the outcome measure resulted in higher ICERs than in the base case. On the other hand, the ICER with the ACR50 (American College of Rheumatology 50) used as the continuation criteria was lower than the base-case. This is due to fewer responders to bDMARDs and therefore lower costs. Nevertheless, there are also fewer QALYs gained when ACR50 is used.

The LDAS (low disease activity score, defined as a DAS28 of <3.2) was the most stringent criteria – or at least had the lowest rate of responders. The total costs for treatment with bDMARDs were lowest for this outcome measure and QALYs were also lower. The PBAC agreed with its economics subcommittee that while the ICERs based on the LDAS are lower than the other response measures, in practice this outcome could not be adopted for the purpose of PBS restrictions.

The EULAR (European League Against Rheumatism) good/moderate response criteria resulted in ICERs similar to the base-case using Medicare continuation rates.

The PBAC also noted the results of an analysis of single administration of each agent based on different utility instruments (AQoL, SF-6D and EQ-5D) as presented in the Late Papers to the meeting Agenda.

While the use of the EQ-5D resulted in lower ICERs compared to the AQoL which was used in the base case analysis, the PBAC considered that the AQoL was a more appropriate outcome in the current circumstances, because it provides more detail about the quality of life

compared to the EQ-5D. The EQ-5D has only five dimensions and three levels in each dimension, therefore this outcome measure is sensitive to significant changes in one domain and there is more potential for one dimension to overstate the effect of clinical measures. The PBAC noted the variability in the baseline EQ-5D scores which suggested that this measure was less sensitive than the AQoL. The PBAC further noted that around a third of the health states in the EQ-5D have negative values which leads to a tendency for a larger difference in utility values between health states than with other instruments. Overall, the PBAC considered that the ICERs based on the EQ-5D are more uncertain compared to those based on the AQoL due to the EQ-5D being less sensitive and could not be accepted in preference to the AQoL derived ICERs. However, the EQ-5D results could form the lower boundary of an acceptable ICER.

The PBAC considered that the five year break in therapy required under the PBS restrictions after failure to respond to three bDMARDs was no longer clinically appropriate given the existence of multiple drugs with different mechanisms of actions and recommended that this requirement be removed from the restrictions. PBAC recalled it had settled on this exclusion period during its early considerations of the bDMARDs when only a limited number of these medicines were available. At that time, the five year period was seen as a reasonable timeframe to allow sponsors to obtain new data about the efficacy of one bDMARD following failure of another bDMARD.

The Committee considered that revising the restriction to allow patients to trial up to five bDMARDs would be appropriate to enable patients to try more treatments with different modes of action. The PBAC therefore examined the cost-effectiveness of trialing five bDMARDs in sequence, with no further bDMARD therapy after the fifth bDMARD treatment. When using AQoL utility values, this resulted in ICERs which exceeded $100,000 and were higher than in the base case reported above. The ICERs based on the EQ-5D results were lower than in the base case. Overall, the ICERs for this scenario remained unacceptably high to the Committee.

The Committee noted that examining the cost-effectiveness of a sequence of therapy in the management of a disease was not usual as part of its decision making and recommended that a policy framework be developed to address this issue. The Committee then agreed that the appropriate and consistent decision context for assessing the cost effectiveness of bDMARDs is the incremental cost-effectiveness ratio of a single administration of an agent. This is compatible with other medicine classes where different agents are used sequentially e.g. cytotoxic agents.

The ICERs for single administration of each agent using AQoL utility values were similar to those reported for the base case modelled economic evaluation. Using EQ-5D utility values, the ICERs were lower than in the base case. The PBAC again considered these ICERs unacceptably high and that a significant price reduction is required so that the ICERs fall within a range representing acceptable cost-effectiveness when these agents are used for the treatment of RA.

5. Recommendation and Reasons

The PBAC noted that there are a large number of patients with rheumatoid arthritis and acknowledged that there is a high clinical need for the bDMARDs.

The Committee was satisfied with the process followed in the conduct of the review. The Committee accepted the structure of the economic modelling used in the review and was satisfied with the rigour of the evidence used to inform the models assumptions. The use of Medicare Australia continuation rates in the base case economic model was accepted. The Committee noted that the approach used in the economic modelling did not disadvantage the bDMARDs as it assumes that there is no loss of response when a patient tries another bDMARD.

The PBAC agreed that, with the exception of anakinra, which appears inferior, there were no differences between the other five bDMARDs in terms of efficacy and safety.

The Committee considered that their decision context for cost effectiveness would be single administration of an agent. This is compatible with other medicine classes where different agents are used sequentially e.g. many cytotoxic agents.

Based on its overall considerations of the review, the PBAC recommended the following changes to the PBS subsidy arrangements for the bDMARDs.

- The current eligibility criteria for the bDMARDs be revised to ensure that they are consistent with the latest evidence for best practice with regard to the initiation of non-biological medicines in patients with rheumatoid arthritis. This reconsideration of the initiation rules should involve interaction with clinical experts and sponsors.
- The five year exclusion period between bDMARD treatments (after failure of three treatments) can no longer be justified. In its place, PBAC recommended the development of a new PBS restriction which allows patients to try a maximum of five bDMARDs within a life-time.
- The current continuation rules be maintained.
- The PBAC is minded to recommend removal of anakinra from the PBS. The sponsor should be given the opportunity to provide input to the Committee on this proposal prior to the Committee making a final recommendation.
- A significant price reduction is necessary to reduce the incremental cost-effectiveness ratio so that it falls within a range considered to represent acceptable cost-effectiveness when these agents are used for the treatment of rheumatoid arthritis.

6. Context for Decision

Cost-effectiveness reviews are an ongoing part of the management of the PBS. The outcomes of this review into the cost-effectiveness of the bDMARDs subsidised via the PBS for the treatment of rheumatoid arthritis provide a basis for changes to the current funding arrangements, including patients' eligibility criteria and/or price.

7. Sponsor Comments

PharmaLink Pty Ltd [anakinra (Kineret®)]

Pharmalink is working collaboratively with the PBAC to clarify the clinical need for anakinra in the treatment of rheumatoid arthritis and identify the subpopulation of patients who respond to anakinra.

Pharmalink will work with the PBAC to address the uncertainties identified in the review, with the goal of retaining PBS-subsidised access for those patients who respond only to anakinra or for whom TNF-a inhibitors are contraindicated and for whom no other therapeutic options are available.