

6.04 ETANERCEPT

**injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringes solvent 1 mL; injections 50 mg in 1 mL single use pre-filled syringes; injection 50 mg in 1 mL single use auto-injector;
Enbrel[®], Pfizer Australia Pty Ltd**

1 Purpose of Application

1.1 The major submission sought to extend etanercept’s current listing by adding a new general schedule Authority Required indication for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA).

2 Requested listing

2.1 The submission’s requested listing is shown in abbreviated form below:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
ETANERCEPT				
Initial treatment:				
etanercept 25 mg injection [4 x 25 mg vials] (& inert substance diluent [4 x 1 mL syringes], 1 pack	2	2	\$ [REDACTED]	Enbrel FZ
Injections 50 mg in 1 mL single use pre-filled syringes, 4, 1	1	3	\$ [REDACTED]	Enbrel FZ
Injection 50 mg in 1 mL single use auto-injector, 4, 1	1	3	\$ [REDACTED]	Enbrel FZ
Continuing treatment				
etanercept 25 mg injection [4 x 25 mg vials] (& inert substance diluent [4 x 1 mL syringes], 1 pack	2	2	\$ [REDACTED]	Enbrel FZ
Injections 50 mg in 1 mL single use pre-filled syringes, 4, 1	1	5	\$ [REDACTED]	Enbrel FZ
Injection 50 mg in 1 mL single use auto-injector, 4, 1	1	5	\$ [REDACTED]	Enbrel FZ

*Effective price = \$ [REDACTED]

Abbreviated restriction

Treatment phase: Initial 1 (new patients) & Initial 2 (re-commencement after a break in therapy) combined	
PBS category/program	General Schedule (Code GE)
Condition	Non-radiographic axial spondyloarthritis (new patients or patients recommencing after 24 months)
Restriction level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency

Public Summary Document – March 2015 PBAC Meeting

	<input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Clinical criteria	<p>Patient must be diagnosed with active non-radiographic axial spondyloarthritis who has experienced chronic back pain for 3 months or more and had an age of onset of less than 45 years AND Patient must not have failed treatment on PBS-subsidised etanercept within the last 24 months, AND (a) Patient must have one of the following: (i) Sacroiliitis on MRI plus one or more spondyloarthritis features (listed below) OR (ii) HLA-B27 positive test plus two or more spondyloarthritis features: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to NSAIDs, family history of SpA, HLA-B27, elevated CRP*</p> <p>*(Note that patients qualifying based on criteria (a)(ii) must meet “elevated CRP” as one of the two or more spondyloarthritis features). AND (b) Patient must have a BASDAI of ≥ 4 AND (c) Patient must have failed to achieve an adequate response following treatment with at least 2 NSAIDs for a total period of 3 months.</p>
Population Criteria	Patient must be an adult.
Treatment Criteria	<p>Patient must be treated by a rheumatologist</p> <p>The application must include details of the NSAIDs trialed, their doses and duration of treatment.</p> <p>Patients may re-trial etanercept after a minimum of 24 months have elapsed between the date the last prescription for PBS-subsidised etanercept was approved in this cycle and the date of the first application under a new cycle.</p> <p>-----</p>

Treatment phase: Continuing	
PBS category/program	General Schedule (Code GE)
PBS Indication	Non-radiographic axial spondyloarthritis
Restriction level/ Method	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic <input type="checkbox"/> Streamlined
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Clinical Criteria	<p>Patient must have a documented history of active non-radiographic spondyloarthritis, AND Patient must have received PBS-subsidised etanercept in this treatment cycle, AND</p>

	Patient must have demonstrated an adequate response to treatment with this drug.
Population Criteria	Patient must be an adult.
Treatment Criteria	Must be treated by a rheumatologist. An adequate response is defined as an improvement from baseline of at least 2 on the BASDAI and 1 of the following: -----

3 Background

- 3.1 This was the first consideration by the PBAC of etanercept for the treatment of nr-axSpA.
- 3.2 Etanercept is currently PBS-listed for severe chronic plaque psoriasis, severe active juvenile idiopathic arthritis, severe active rheumatoid arthritis, active ankylosing spondylitis and psoriatic arthritis. These various listings are spread across the general schedule and the Section 100 (Highly Specialised Drugs Program) parts of the PBS Schedule.
- 3.3 This submission was made under TGA/PBAC parallel process provisions.
- 3.4 The May 2014 TGA Clinical Evaluation Report initially did not support the approval of etanercept for the nr-axSpA indication for the following reasons:
- Efficacy was only seen on symptoms and signs of disease and not disease progression.
 - The proposed indication covers all adults when data are only available for adults under 50 years of age.
 - The indication is too broad for a positive benefit-risk balance to be achieved. Consideration should be given to limiting treatment to populations in which a higher treatment response was found.
 - The lack of efficacy and safety data beyond 24 weeks of treatment duration.
 - The need for further elucidation on how the proposed population would be identified in clinical practice so that inappropriate patients are not exposed to the risks of treatment.
 - Revisions are required on the product information.
- 3.5 After evaluation of the sponsor's response to the Clinical Evaluation Report, the clinical evaluator concluded that although the clinical benefit was marginal, the benefit-risk balance was favourable.
- 3.6 The TGA Delegate's Summary was received by the Department on 28 January 2015. The TGA Delegate's pre-ACPM preliminary assessment was that the Delegate was not in a position to say, at the time, that the application for etanercept should be approved for registration. The primary issues with the registration submission identified by the TGA Delegate were:

- 1) Whether the duration of the clinical trial experience, that is 12 weeks double-blind trial and 12 weeks extension is sufficient to support the extension of indication for a condition requiring long-term treatment; and
 - 2) Whether the proposed indication that includes the objective criteria of an increased CRP and/or MRI evidence of inflammation is sufficient to define the population of patients most likely to have positive benefit-risk profile.
- 3.7 At its February 2015 meeting, the Advisory Committee on Prescription Medicines resolved to approve an extension of etanercept's indications to include the following:

Non-radiographic Axial Spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and MRI change who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 .*

4 Clinical place for the proposed therapy

- 4.1 Axial spondyloarthritis (axSpA) is a group of related immune mediated diseases with the shared feature of axial inflammatory arthritis. This categorisation encompasses both ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Nr-axSpA is differentiated from AS by the absence of radiological evidence of sacroiliitis. The DUSC advice identified a potential risk in over-diagnosis and use outside the restriction in patients with back pain unrelated to spondyloarthritis. The DUSC also made note of the variable disease progression of nr-axSpA.
- 4.2 Etanercept is not likely to replace any pharmaceutical therapies.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

- 5.1 The submission nominated placebo as the main comparator. The evaluation considered this appropriate, although it was noted that as most patients would be expected to be on treatment with background NSAIDs. Therefore, the most relevant comparison would be between etanercept with NSAID background treatment versus placebo with NSAID background treatment. These were the treatment combinations that were included in the economic evaluation.
- 5.2 Adalimumab and certolizumab pegol were not nominated as comparators, but secondary indirect comparisons of efficacy were conducted against these drugs in the submission's clinical evaluation. Considering that none of these treatments are TGA approved or PBS-listed for nr-axSpA and there was no comparative safety data presented, the evaluation considered these supplementary comparisons had limited relevance.

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented a case study of a 19 year old patient indicating how etanercept treatment had benefited this patient in the context of his daily living activities. The clinician cited evidence from the literature that the progression rate of nr-axSpA to ankylosing spondylitis is slow and that early treatment of nr-axSpA is important in delaying the likelihood of progression to ankylosing spondylitis. The clinician was of the view that compared to the short duration of the clinical trial presented in the submission (i.e. 12 weeks), over a longer period TNF-alpha inhibitors are able to alter disease progression. In terms of the ability of clinicians to identify patients more likely to respond to treatment, the clinician was of the view that use of both the ASAS (assessment of spondyloarthritis international society) disease severity classification system and magnetic resonance imaging/C-reactive protein measurement can identify a moderate number of nr-axSpA patients more likely to respond to treatment. The clinician was of the view that there remains a clinical need for treatments of nr-axSpA to be PBS-subsidised.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 The submission was based on one head-to-head trial, Trial 1031, comparing etanercept to placebo (n=215).
- 6.4 Details of Trial 1031 are provided in the table below.

Trials and associated reports presented in the submission

Trial ID/Frist Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Trial 1031	Clinical trial report. A Multicentre, 12-Week Double Blind Placebo Controlled Randomized Study of Etanercept on a Background NSAID in the Treatment of Adult Subjects With Non Radiographic Axial Spondyloarthritis With a 92-Week Open Label Extension.	October 2013
Dougados	Symptomatic Efficacy of Etanercept and Its Effects on Objective Signs of Inflammation in Early Non-Radiographic Axial Spondyloarthritis - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial.	<i>Arthritis Rheum</i> , 2014; 66(8):2091–2102.

Source: Table 4, p. B.17 of the submission

- 6.5 The key features of Trial 1031 are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes	Use in modelled evaluation
Etanercept vs. placebo						
Trial 1031	215	R, MC, DB, 12 weeks	Low	Non-radiographic ax-SpA	ASAS 40	EQ-5D scores
Trial 1031 OL period	208	MC, OL 92 weeks	High	Non-radiographic ax-SpA	ASAS 40	EQ-5D scores

* The submission did not indicate whether the EQ-5D 3-level or EQ-5D 5-level value set was used.

ASAS= assessment of spondyloarthritis international society; Ax-SpA= axial spondyloarthritis; DB=double blind; EQ-5D= Euroqol 5D; MC=multi-centre; OL=open label; R=randomised.

Source: compiled during the evaluation

6.6 Assessment of Spondyloarthritis international Society (ASAS) response 40 (ASAS 40) is a composite outcome calculated as a 40% improvement and at least 2 units from baseline in at least 3 of 4 ASAS domains on a scale from 1 to 10. The domains consist of:

- Patient global assessments (visual analogue scale)
- Pain
- Function
- Inflammation

Comparative effectiveness

6.7 The submission claimed superior efficacy and inferior safety against placebo. A summary of the efficacy results of Trial 1031 are presented in the table below.

Results of primary endpoint ASAS 40 in Trial 1031

Trial ID	Etanercept n/N	Placebo n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)
Double blind period				
Week 2	16/105 (15.2)	4/108 (3.8)	0.11 (0.04, 0.19) p=0.004	4.04 (1.40, 11.68) p=0.010
Week 4	21/105 (20.0)	16/108 (14.8)	0.05 (-0.05, 0.15) p=0.318	1.35 (0.75, 2.44) p=0.321
Week 8	30/105 (28.6)	17/108 (15.7)	0.13 (0.02, 0.24) p=0.023	1.82 (1.07, 3.09) p=0.028
Week 12	34/105 (32.4)	17/108 (15.7)	0.17 (0.05, 0.28) p=0.004	2.06 (1.23, 3.45) p=0.006
Open label period – proportion with response				Pooled arms n/N (%)
Week 16	42/100 (42.0)	40/105 (38.1)	NR	82/205 (40.0)
Week 24	44/100 (44.0)	54/105 (51.4)	NR	98/205 (47.8)
Week 32	47/100 (47.0)	55/105 (52.4)	NR	102/205 (49.8)
Week 40	55/100 (55.0)	56/105 (53.3)	NR	111/205 (54.1)
Week 48	52/100 (52.0)	56/105 (53.3)	NR	108/205 (52.7)

Source: Table 17 and 46, p B.45 and B.89 of the submission, respectively. ASAS=Assessment in Ankylosing Spondylitis;

6.8 The ESC considered that whilst symptomatic improvement would be important to patients, a comparison of etanercept's effect on disease progression (from nr-axSpA to ankylosing spondylitis) would also be of importance but the trial evidence did not report on this outcome.

- 6.9 In response to the evaluation’s concern that the time period of the trial, 12 weeks, was unlikely to provide a reliable estimate of the incremental benefit over a longer time period, the Pre-Sub-Committee Response (PSCR) presented a graph plotting the proportion of patients achieving the ASAS 40 response for the double-blind and open label periods of study B1801031. The ESC advised that this graph would be more informative if it disaggregated the open label period to show those originally in the placebo group and those originally in the intervention group. This was provided in the sponsor’s pre-PBAC response.
- 6.10 The submission included secondary indirect comparisons of the efficacy of etanercept versus adalimumab and etanercept versus certolizumab pegol. A summary of efficacy results from the indirect comparisons are presented in the table below.

Results of the indirect comparisons (ASAS 40)

	Etanercept	Placebo	Adalimumab	RR (95% CI)	RD (95% CI)	NNT
ASAS 40						
Trial 1031	34/105 (32.4)	17/108 (15.7)	-	2.06 (1.23, 3.45) p=0.0062	0.17 (0.05, 0.28) p=0.0038	7 (4, 19)
ABILITY-1	-	14/94 (14.9)	33/91 (36.3)	2.44 (1.40, 4.24) p=0.0017	0.21 (0.09, 0.34) p=0.0006	5 (3, 11)
Haibel 2008	-	3/24 (12.5)	12/22 (54.5)	4.36 (1.42, 13.44) p=0.0103	0.42 (0.17, 0.67) p=0.0008	3 (2, 6)
ABILITY-1 & Haibel 2008 (pooled)	-	17/118 (14.4)	45/113 (39.8)	2.73 (1.66, 4.49) p<0.0001	0.29 (0.09, 0.48) p=0.0037	4 (3, 11)
Indirect comparison: Trial 1031 versus ABILITY-1 and Haibel 2008 pooled				0.75 (0.37, 1.54) p=0.4398	-0.12 (-0.35, 0.10) p=0.2885	-
	Etanercept	Placebo	Certolizumab	RR (95% CI)	RD (95% CI)	NNT
ASAS 40						
Trial 1031	34/105 (32.4)	17/108 (15.7)	-	2.06 (1.23, 3.45) p=0.0062	0.17 (0.05, 0.28) p=0.0038	7 (4, 19)
RAPID (200 mg)	-	8/50 (16.0)	22/46 (47.8)	2.99 (1.48, 6.04) p=0.0023	0.32 (0.14, 0.50) p=0.0004	4 (3, 8)
RAPID (400 mg)	-	8/50 (16.0)	24/51 (47.1)	2.94 (1.46, 5.92) p=0.0025	0.31 (0.14, 0.48) p=0.0004	4 (3, 8)
Indirect comparison: Trial 1031 versus RAPID 200mg				0.69 (0.29, 1.65) P=0.4012	-0.15 (-0.36, 0.06) p=0.1554	-
Indirect comparison: Trial 1031 versus RAPID 400mg				0.70 (0.29, 1.67) p=0.4200	-0.14 (-0.35, 0.06) p=0.1670	-

Source: Table 84 and 89, p. 145 and 156 of the submission. ASAS=Assessment of Spondyloarthritis International Society; CI= confidence interval; RD= risk difference; RR= risk ratio

- 6.11 No statistically significant differences were reported in the indirect analyses, but the comparators had superior efficacy in terms of point estimates.

Comparative harms

- 6.12 Statistical comparisons between etanercept and placebo in Trial 1031 were calculated during the evaluation. As would be expected, there were statistically significant differences in injection site reactions and injection site erythema. In light of

the short (12 week) duration of the randomised trial period, other important considerations would be increased risks of malignancy, and opportunistic infections mentioned in the latest periodic safety update report.

- 6.13 The ESC noted the initial negative pre-ACPM assessments contained within the Clinical Evaluation Report and the absence of a recommendation to approve in the TGA Delegate’s Summary. The ESC further noted that etanercept’s safety profile is well established in the treatment of rheumatoid arthritis and includes effects such as hepatotoxicity, serious infections and sepsis, demyelinating CNS disorders, haematological reactions including pancytopenia, new onset psoriasis. The ESC considered that there is no reason to expect a different adverse event profile in non-radiographic axial spondyloarthritis (nr-axSpA). The ESC commented that the trial data available so far support the expectation that etanercept’s safety profile is not substantially different in nr-axSpA compared to its existing registered indications.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Benefits/harms

- 6.14 A summary of the comparative benefits and harms for etanercept versus placebo is presented in the table below.

Summary of comparative benefits and harms for etanercept and placebo

Trial	Etanercept	Placebo	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Etanercept	Placebo	
Benefits						
ASAS 40 – proportion with response						
Week 2	16/105 (15.2)	4/108 (3.8)	4.04 (1.40, 11.68)	15.2	3.8	0.11 (0.04, 0.19)
Week 4	21/105 (20.0)	16/108 (14.8)	1.35 (0.75, 2.44)	20.0	14.8	0.05 (-0.05, 0.15)
Week 8	30/105 (28.6)	17/108 (15.7)	1.82 (1.07, 3.09)	28.6	15.7	0.13 (0.02, 0.24)
Week 12	34/105 (32.4)	17/108 (15.7)	2.06 (1.23, 3.45)	32.4	15.7	0.17 (0.05, 0.28)
Harms						
	Etanercept	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Etanercept	Placebo	
Eye disorder						
Trial 1031	4/111 (3.6)	0	9.16 (1.08, ∞)	3.6	0	0.04 (0.00, 0.09)
Injection site erythema						
Trial 1031	7/111 (6.3)	1/113 (0.9)	7.13 (1.17, 44.07)	6.3	0.9	0.05 (0.01, 0.12)
Injection site reaction						
Trial 1031	6/111 (5.4)	0	13.23 (1.62, ∞)	5.4	0	0.05 (0.02, 0.11)

CI = confidence interval; RD = risk difference; RR = risk ratio

*Over 12 weeks in the double blind period.

Source: Compiled during the evaluation

- 6.15 On the basis of Trial 1031 presented by the submission, for every 100 patients treated with etanercept in comparison to placebo:
- Approximately 17 additional patients would have experienced response, in terms of the ASAS 40, over 12 weeks.
 - Between 0 and 9 additional patients would have experienced an eye disorder over 12 weeks.
 - Between 1 and 12 additional patients would have experienced injection site

erythema over 12 weeks.

- Between 2 and 11 additional patients would have experienced an injection site reaction over 12 weeks.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Clinical claim

- 6.16 The submission claimed that etanercept was superior in terms of efficacy and inferior in terms of safety in comparison to placebo.
- 6.17 Though the efficacy claim was supported by statistically significant differences in ASAS measures and other composite instrument scores, these were generally restricted to the signs and symptoms of the disease and hence it was difficult to assess the clinical benefit of such differences. Additionally this was based on 12 weeks of randomised evidence, which, considering how little is known about the natural history of nr-axSpA, was insufficient to make conclusions on efficacy.
- 6.18 The safety claim was supported by 12 week Trial 1031 evidence and current clinical experience with etanercept.
- 6.19 In its secondary comparisons, the submission claimed non-inferior efficacy versus adalimumab as well as certolizumab pegol. The submission made no claims on safety. Though no statistically significant differences were found across major outcomes, the comparators had superior efficacy in the point estimates. Given the lack of defined minimum clinically important differences in nr-axSpA, the claim was not well justified.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Economic analysis

- 6.20 The submission sought listing on the basis of a cost-utility analysis comparing etanercept and background non-steroidal anti-inflammatory drugs (NSAIDs) to placebo and background NSAIDs.
- 6.21 The submission proposed an effective price of \$ [REDACTED] for all doses and presentations of etanercept in the requested nr-axSpA listing. This effective price was a result of a Special Pricing Arrangement (SPA) requested by the sponsor, to be offered as a [REDACTED]% rebate from the public price. This price was applied in the economic evaluation and the financial estimates.
- 6.22 The following table presents a summary of the structure and rationale of the model.

Summary of model structure and rationale

Time horizon	2 years in the model base case versus 12 weeks of comparative randomised data, and 2 years of follow-up in Trial 1031
Outcomes	LYs, QALYs
Methods used to generate results	Cohort expected value analysis
Cycle length	5 cycles of varying lengths (12 weeks; 24 weeks; 28 weeks), half cycle correction applied.

Public Summary Document – March 2015 PBAC Meeting

Transition probabilities	Transition to death based on AIHW mortality tables; etanercept treatment discontinuation based on Trial 1031 data.
Discount rate	5% for costs and outcomes
Cohort size	1,000 subjects (arbitrarily set).
Software package	Excel 2010

Source: compiled during the evaluation. LY = life years; QALY- Quality-adjusted life year.

- 6.23 The model extrapolated 12 week EQ-5D utilities from Trial 1031 over a 2 year period for a cohort of 1,000 subjects, assuming that etanercept treatment effect would remain constant beyond the 12 week period, and that patients receiving NSAIDs only would not improve from baseline. These assumptions were not supported by the trial evidence and significantly over-estimated the incremental effect.
- 6.24 The ESC advised that a time horizon of greater than 2 years would have been more realistic given the chronic nature of the condition. However, the ESC noted that the submission and pre-sub-committee response (p.2) "...acknowledged that a 2-year model timeframe was short... [and] did not involve a longer time horizon simply because there were no data to inform necessary data inputs...[I]n the absence of robust (long term) data to inform reliable assumptions about longer-term outcomes, lengthy extrapolations would lead to excess uncertainty." Therefore, the ESC considered that even if a longer time horizon was modelled, for the reasons acknowledged by the submission, the economic model would still have remained unreliable.
- 6.25 The table below presents a summary of the key drivers of the model.

Key drivers of the model

Description	Method/Value	Impact
Time horizon	2 years, assumed from 12 week randomized control evidence, and 2 year OL extension data	High, dependent on potential extrapolation assumptions
EQ-5D utilities	Trial based EQ-5D responses,	Moderate, favours etanercept.

Source: compiled during the evaluation. EQ-5D = Euroqol 5D; OL = open label.

- 6.26 The results of the submission's economic evaluation are presented in the table below:

Results of the economic evaluation

Component	Etanercept	Usual Care	Increment
Costs	\$ [REDACTED]	\$528,856	\$ [REDACTED]
LYs	1,940.1	1,940.1	0
QALYs	1,276.7	959.9	316.8
Incremental cost/QALY			\$ [REDACTED]

Source: Table 8, p D.29 of the submission. LY= life year; QALY= quality-adjusted life year.

- 6.27 The sensitivity analyses presented in the submission did not demonstrate great variation in the ICER, with the exception of certain assumptions regarding utilities. A model with a longer time horizon would be expected to have much greater sensitivity to changes in several variables.
- 6.28 The table below presents EQ-5D utilities derived from Trial 1031 and the model inputs. The submission assumed that utility values for subjects in the placebo arm beyond week 12 were not relevant because subjects had been crossed over to the

etanercept arm. The model inputs for utility for each cycle after initiating treatment (weeks 12, 40, 68, 92 and 104) were based on week 12 derived utilities. For the etanercept arm this meant the effect at 12 weeks was assumed to continue for 2 years, for the placebo arm the model assumed no benefit.

EQ-5D utilities from Trial 1031 and model inputs

Time period	Evaluable sample	Mean (SD)	Change from baseline, mean (SE)	Model input
Baseline/ Week 0				
Etanercept	70	0.47 (0.34)	N/A	0.4948
Placebo arm	69	0.52 (0.32)	N/A	0.4948
All subjects	139	0.49 (0.33)	N/A	NA
Week 12				
Etanercept arm, met cont. criteria	30	0.82 (0.12)	+0.40 (0.07)	0.8947
Etanercept arm, did not meet cont. criteria	38	0.57 (0.30)	+0.07 (0.04)	0.4948
Placebo arm	67	0.65 (0.29)	+0.11 (0.04)	0.4948
Week 40				
Etanercept arm, met cont. criteria	24	0.83 (0.18)	+0.45 (0.06)	0.8947
Etanercept arm, did not meet cont. criteria	3	0.41 (0.38)	-0.23 (0.22)	0.4948
Week 68				
Etanercept arm, met cont. criteria	16	0.86 (0.13)	+0.45 (0.08)	0.8947
Etanercept arm, did not meet cont. criteria	0	N/A	N/A	0.4948
Week 92				
Etanercept arm, met cont. criteria	10	0.86 (0.13)	+0.36 (0.11)	0.8947
Etanercept arm, did not meet cont. criteria	0	N/A	N/A	0.4948
Week 104				
Etanercept arm, met cont. criteria	7	0.88 (0.14)	+0.48 (0.12)	0.8947
Etanercept arm, did not meet cont. criteria	1	0.73 (N/A)	+0.64 (N/A)	0.4948

Source: Table 3, p C.19 of the submission. cont. = continuation; NA= not applicable; SD= standard deviation; SE= standard error

6.29 The table below further outlines how the health state utilities were derived in the submission:

Health state	Source of data in Study 1031	Base-case value	Values for sensitivity analyses
All subjects, baseline (starting utility)	Mean utility of all subjects at baseline.	0.495	None
Etanercept Group, 'Alive on treatment'	Mean utility of all subjects at baseline <u>plus</u> mean change in utility from baseline among subjects in the etanercept group who met continuation criteria.	Wk12: +0.400=0.895 Wks 40, 68, 92 and 104: same as Wk12.	Wk12: +0.400=0.895 Wk40: +0.453=0.947 Wk68: +0.451=0.946 Wk92: +0.359=0.854 Wk104: +0.480=0.975
Etanercept Group, 'Alive, not on treatment'	1. Same as baseline -or- 2. Mean utility of all subjects at baseline <u>plus</u> mean change in utility from baseline among subjects in the etanercept group who did not meet continuation criteria at Wk12.	Same as baseline across all weeks: 0.495	Wk12: +0.072=0.567 Wks 40, 68, 92 and 104: same as Wk12.
Placebo Group, 'Alive'	1. Same as baseline -or- 2. Mean utility of all subjects at baseline <u>plus</u> mean change in utility from baseline among subjects in the placebo group at Wk12.	Same as baseline across all weeks: 0.495	Wk12: +0.108=0.603 Wks 40, 68, 92 and 104: same as Wk12.

Source: March 2015 Submission, Section D, p.D23

6.30 While the use of trial-based utility values has many advantages, particularly in a disease such as nr-axSpA where there are unlikely to be published values available, the use of the EQ-5D values from Trial 1031 raised some concerns:

- Relying on the utility estimates for 12 weeks to form the basis of an economic model for over two years is problematic in that health-related quality of life is likely to vary greatly, over a two year time horizon, and even more over a more appropriate life-time horizon.
- The modelled increment of utilities between patients receiving etanercept and placebo (approximately 0.4) appeared large. The increment of 0.4 equated to a 40% difference in quality of life, almost the half-way point on a spectrum between full health and death.
- Considering that the model was highly dependent on these utility estimates, and that they did not reflect quality of life of patients over any consequential period of time, this modelling parameter was unreliable and most likely favoured etanercept.
- The model assumed that there was no improvement in health related quality of life (HRQoL) between weeks 0 and 12 in the placebo group (and subsequently in the extrapolation to 2 years). The submission only used average baseline utility values for patients in the placebo group or those who discontinued etanercept. This overestimated the incremental effect of etanercept in the model. The model was relatively sensitive to assumptions in changes in EQ-5D values in the placebo and off treatment groups.
- The ESC questioned the validity of taking an average of the utility values for all participants at baseline (0.4948) and using it across placebo and discontinued etanercept groups over the various time points.
- The ESC considered that the low proportion of participants that were reporting

utility inputs in the open label period may have given rise to reporting bias in favour of etanercept.

- The PBAC noted that although utilities were claimed to be trial based, patients on etanercept treatment were assigned a utility value based on the sum of the average baseline value for all patients and the improvement in utility of patients in the etanercept group from baseline to week 12 (0.4948 + 0.3999=0.8947). This modelling approach produced substantial discrepancy between the modelled and trial based utilities.

6.31 Overall, the clinical evidence did not support a cost-utility analysis. The model had an unreliable short time horizon of 2 years. Since treatment with etanercept for nr-axSpA could be expected to last decades, the model, as specified, was of limited validity.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Drug cost/patient/year: \$ [REDACTED].

6.32 The drug cost per patient per year was \$ [REDACTED], based on an effective DPMQ of \$ [REDACTED], and 13 packs used per year. The estimate of 13 packs per year was based on 4 packs prescribed in the initiation period (16 weeks) 6 packs prescribed in the first continuation period (24 weeks), and 3 packs prescribed in the second continuation period (12 weeks).

Estimated PBS usage & financial implications

6.33 This submission was considered by DUSC. The submission took an epidemiological approach to estimating PBS usage based on AS prevalence rates estimated by Dean (2014) and expert opinion. The table below displays the submission’s estimates of use and financial implications over the first 5 years of listing.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Assuming [REDACTED] initial prescriptions for the period up to 16 weeks, and [REDACTED] additional injections for every subsequent 24 week period where patients meet continuation criteria.

Source: Tables 9 and 17 pp E.19 and E.26 of the submission

The redacted table above shows that in Year 5, the estimated number of scripts dispensed would be 10,000-50,000 and the net cost to the PBS/RPBS/MBS would be between \$10-\$20 million per year.

6.34 The DUSC considered that the financial estimates provided by the submission were not likely to be accurate, given:

- The lack of reliable prevalence rates for nr-axSpA and the likely underestimation of prevalence by the submission,

- There is a high risk of over-diagnosis and use outside of the restriction in patients with back pain unrelated to spondyloarthritis.
- The estimates should not have included referral or diagnosis rates. Therefore, the number of eligible patients was underestimated by a factor of three.
- The continuation rate should have been based on the continuation rate of AS patients, rather than expert opinion, and it is likely underestimated.
- The estimate of an eligible population was based on a small sample from one rheumatology practice, which is not likely to be a reliable estimate.
- Underestimation of uptake rates.

6.35 In the pre-PBAC response the sponsor indicated that the continuation rate is based on the pivotal clinical study in nr-axSpA patients and not on expert opinion. Furthermore, the sponsor noted that the DUSC did not provide any reason for the opinion that the uptake rates are underestimated. However, the DUSC considered that it is likely that awareness of the disease would be promoted to clinicians and to the public.

For more detail on PBAC's view, see section 7 "PBAC outcome".

Quality Use of Medicines

6.36 The submission identified barriers to the appropriate, effective and safe use of etanercept and identified methods to address these issues, including use of educational materials for health professionals, development of relationships with stakeholders and provision of a patient support program.

Financial Management – Risk Sharing Arrangements

6.37 The submission noted that if etanercept received a positive recommendation for PBS listing, a risk sharing arrangement may be required, but did not provide specific details of such an arrangement.

7 PBAC Outcome

7.1 The PBAC rejected the submission on the basis that although the trial data suggested short term efficacy, the available evidence did not enable PBAC to characterise the likely magnitude of benefit with respect to patient relevant outcomes additional to the ASAS 40 (such as disease progression) in patients with non-radiographic axial spondyloarthritis (nr-axSpA). Even if the natural history of this condition was well characterised, the short term data and economic analysis did not allow PBAC to define a population in whom treatment could be expected to be cost effective.

7.2 The PBAC accepted the submission's nomination of placebo plus background NSAID treatment as the appropriate comparator, noting that etanercept and adalimumab are not TGA indicated for nr-axSpA.

7.3 In consideration of the clinical trial evidence, the PBAC noted that 32.4% (34 out of 105) of patients receiving etanercept in Trial 1031 achieved an ASAS 40 outcome at

week 12 while 15.7% (17 out of 108) of patients receiving placebo achieved an ASAS 40 outcome at week 12. Whilst these results indicated that the number of patients meeting the primary outcome measure in the study approximately doubled as a result of etanercept, in absolute number terms, the PBAC's view was that these results indicated that a large percentage of etanercept treated patients did not achieve an ASAS 40 outcome and that the clinical benefits of etanercept in nr-axSpA were modest.

- 7.4 The PBAC noted that the measures of etanercept's efficacy in the evidence (ASAS 40) focused on the signs and symptoms of the disease. It was unclear to the PBAC what the minimum clinically important difference in terms of changes in ASAS is. The PBAC accepted that whilst symptomatic improvement would be important to patients, etanercept's efficacy in terms of avoiding or reducing disease progression from nr-axSpA to ankylosing spondylitis had yet to be established.
- 7.5 Additionally, Trial 1031's outcome measurement for the randomised period of the trial was at 12 weeks. Given that the condition is likely to require long term treatment, the PBAC was not confident that any clinical benefit with etanercept would be maintained over the long term. Although the submission presented efficacy data up to 92 weeks in an extension study, the PBAC noted that the extension period was open-label in design and all patients received etanercept. As a result, the incremental benefit of etanercept over placebo during this longer treatment period was unknown.
- 7.6 In terms of the indirect comparisons of etanercept to adalimumab and certolizumab, the PBAC noted that whilst no statistically significant differences were reported in the indirect analyses, adalimumab and certolizumab had superior efficacy in terms of point estimates. The PBAC viewed these results as supportive of an emerging trend suggesting that etanercept's comparative efficacy, across various indications, may be less than other bDMARD therapies.
- 7.7 The PBAC noted that etanercept has 11 years of Australian safety data and 16 years of global safety data, and the safety profile of etanercept observed in Trial 1031 was similar to the safety profile in other populations. The submission's provision of a summary of the 21st periodic safety update report for etanercept, covered the reporting interval of February 3, 2013 to February 2, 2014. The PBAC agreed that no significant safety information was identified that would change what is currently known about the benefit risk profile of etanercept. Therefore, the PBAC considered that the submission's claim of inferior safety compared to placebo was reasonable.
- 7.8 With regards to the submission's economic modelling, the PBAC noted the overall ESC advice that the clinical evidence did not support a cost-utility analysis. The PBAC agreed that the economic model had an unreliable short time horizon of 2 years in view that treatment with etanercept for nr-axSpA could be expected to last decades. The PBAC noted that although utilities were claimed to be trial based, patients on etanercept treatment were assigned a utility value based on the sum of the average baseline value for all patients and the improvement in utility of patients in the etanercept group from baseline to week 12. This modelling approach produced substantial discrepancy between the modelled and trial based utilities. Doubt's over the magnitude of etanercept's incremental benefit over the long term and the absence of critical components for modelling the disease in the long term (as required for a chronic condition), such as the probabilities and consequences of

progressing to ankylosing spondylitis, or entering a remission state, all contributed to the view that the model, as specified, had limited interpretability.

- 7.9 DUSC advised that the patient numbers and financial estimates provided by the submission were not likely to be accurate. Amongst several reasons provided by DUSC, the PBAC particularly agreed that there is a lack of reliable prevalence rates for nr-axSpA and there was likely an underestimation of prevalence by the submission. The PBAC also agreed that there is a high risk of over-diagnosis and use outside of the restriction in patients with back pain unrelated to spondyloarthritis.
- 7.10 Given that some patients achieve an improvement in the signs and symptoms of disease with etanercept treatment, the PBAC identified that in any future re-submission, consideration could be given to limiting treatment to populations in which a higher treatment response is evident and cost-effective using a reliable economic model. Whether objective criteria of an increased CRP and/or MRI evidence of inflammation is sufficient to define a population of patients most likely to achieve a clinically acceptable response was also not immediately clear to the PBAC. The PBAC agreed that further elucidation on how the proposed PBS population would be identified in clinical practice so that inappropriate patients are not exposed to the risks of treatment, would aid in the targeting of treatment to patient population more likely to respond. The PBAC considered that any future re-submission would need to be major submission.
- 7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Pfizer Australia (the Sponsor) is disappointed that the PBAC did not recommend listing of etanercept for non-radiographic axial spondyloarthritis. With regard to the indirect comparison of etanercept vs adalimumab and certolizumab, as noted in the submission, the numerical differences arose due to the known differences in trial populations of the included studies. The Sponsor is considering the potential for a successful resubmission. The Sponsor notes with concern that the PBAC commented on the efficacy of etanercept across various indications, other than non-radiographic axial spondyloarthritis, without providing evidence to support the statements made.