

**7.03 ETANERCEPT,
25 mg injection [4 x 25 mg vials] (&) inert substance diluent [4
x 1 mL syringes], 1 pack;
50 mg in 1 mL single use pre-filled syringes, 4;
50 mg in 1 mL single use auto-injector, 4
Enbrel®,
Pfizer Pty Ltd.**

1 Purpose of Application

1.1 Authority required listing for etanercept for treatment of non-radiographic axial spondyloarthritis (nr-axSpA).

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the abbreviated version of the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ETANERCEPT				Enbrel® FZ
Initial treatment:				
4 vials powder for injection (25mg), 4 prefilled syringes solvent (1mL), pack size of 3	2	2	\$ [REDACTED] (effective: \$ [REDACTED])	
Injection, (50mg), in prefilled syringes solvent (1mL), 4	1	3	\$ [REDACTED] (effective: \$ [REDACTED])	
Injection, 50mg in auto-injector (1mL), 4	1	3	\$ [REDACTED] (effective: \$ [REDACTED])	
Continuing treatment				
4 vials powder for injection (25mg), 4 prefilled syringes solvent (1mL), pack size of 3	2	2	\$ [REDACTED] (effective: \$ [REDACTED])	
Injection, (50mg), in prefilled syringes solvent (1mL), 4	1	5	\$ [REDACTED] (effective: \$ [REDACTED])	
Injection, 50mg in auto-injector (1mL), 4	1	5	\$ [REDACTED] (effective: \$ [REDACTED])	

Category / Program	General Schedule (Code GE)
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
Condition:	Active <i>nr</i> Nonradiographic axial spondyloarthritis
PBS Indication:	Active <i>nr</i> Nonradiographic axial spondyloarthritis
Treatment phase:	Initial treatment – initial 1 (new patients or patients recommencing after a break of more than 24 months)
Clinical criteria:	Patient The condition must be nonradiographic axial spondyloarthritis, as defined by

Public Summary Document – March 2016 PBAC Meeting

	<p>Assessment of Spondyloarthritis International Society (ASAS) criteria. AND Patient must have chronic back pain for 3 months or more, AND Age of onset of chronic back pain must have been less than 45 years, AND Patient must not have failed treatment on PBS subsidised etanercept within the last 24 months, AND Patient must have: The condition must be sacroiliitis that is not visible on a plain X-ray but is visible on MRI; and The patient must have experienced one or more of the following: Inflammatory back pain; (a) Arthritis; (b) Enthesitis (heel); (c) Uveitis; (d) Dactylitis; (e) Psoriasis; (f) Inflammatory bowel disease; Good response to NSAIDs; (g) Family history of SpA spondyloarthritis; (h) HLA-B27; or (i) Elevated CRP OR The condition must have a positive test result for human leukocyte antigen B27 elevated (HLA-B27); and The condition must have an elevated C-reactive protein (CRP) level of greater than the upper limit of normal; and Patient must have experienced one or more of the following: Inflammatory back pain; (a) Arthritis; (b) Enthesitis (heel); (c) Uveitis; (d) Dactylitis; (e) Psoriasis; (f) Inflammatory bowel disease; Good response to NSAIDs; (g) Family history of SpA spondyloarthritis AND Patient must have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of \geq at least 4 AND Patient must have chronic back pain for 3 months or more AND Patient must have failed to achieve an adequate response following treatment with at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs), at the optimal dose, for a total period of 3 months. AND Patient must not receive more than 16 weeks of therapy under this restriction</p>
Treatment phase:	Initial treatment – initial 2 (re-commencement of treatment after break of less than 24 months)
Clinical criteria:	<p>Patient must have a documented history of nonradiographic axial spondyloarthritis, AND Patient must have previously received prior treatment PBS-subsidised therapy with this drug for this condition and is eligible to receive further therapy AND Patient must have previously demonstrated an adequate response to PBS-subsidised therapy with this drug for this condition AND Patient must not receive more than 16 weeks of therapy under this restriction</p>
Treatment phase:	Continuing treatment
Clinical criteria:	<p>Patient must have a documented history of nonradiographic axial spondyloarthritis, AND Patient must have demonstrated an adequate response to treatment with this drug, Patient must have previously received prior treatment PBS-subsidised therapy with this drug for this condition under Initial 1 or Initial 2 restriction and is eligible to receive further therapy OR Patient must have demonstrated an adequate response to PBS-subsidised therapy with</p>

	<i>this drug AND Patient must not receive more than 24 weeks of therapy under this restriction</i>
--	--

- 2.2 The re-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.
- 2.3 The re-submission proposed a Special Pricing Arrangement (SPA) with an effective price of \$ [REDACTED] for all doses and presentations of etanercept in the requested nr-axSpA listing. This effective price is a [REDACTED]% rebate from the public price (compared with a [REDACTED]% rebate in the previous submission). This price offer did not include the additional price reductions of [REDACTED]% for F.2 products and [REDACTED]% for the introduction of biosimilars included in the economic evaluation in the submission.
- 2.4 The ESC noted that the primary outcome measure in the trial was the ASAS 40 response rate; and other outcome measures were ASAS 20 response rates, ASAS 5/6, ASAS partial remission, ASDAS, BASDAI, BASMI, BASFI and SPARCC. However, BASDAI (i.e. Bath Ankylosing Spondylitis Disease Activity Index) was the only deciding factor used to assess patient’s eligibility to continue therapy under the proposed continuing criteria.
- 2.5 The submission proposed to limit etanercept to the subgroup of patients with sacroiliitis that is visible on MRI (MRI+) **and/or** an elevated C-reactive protein level of greater than the upper limit of normal (CPR+). The Pre-Sub-Committee Response (PSCR) (p1) offered to restrict etanercept to a better performing subgroup, MRI+ **and** CPR+. The ESC noted that appropriate changes would be required to the originally proposed restriction wording should etanercept be recommended for listing for the MRI+ and CPR+ subgroup.

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

3 Background

- 3.1 Etanercept was registered by the TGA for nr-axSpA in April 2015 for treatment of adults with active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or 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 .
- 3.2 The table below presents a summary of differences between the previous submission and current re-submission

Public Summary Document – March 2016 PBAC Meeting

Table 1: Summary of the previous submission and current re-submission

	Etanercept March 2015	Current re-submission
Requested PBS listing	Non radiographic axial spondyloarthritis PBAC Comment: none	•Same as March 2015
Requested price	•Public DPMQ of \$ [redacted] and \$ [redacted] (effective DPMQ of \$ [redacted] for all doses and presentations of etanercept in the nr-axSpA listing as a result of a [redacted] % rebate from the public price)	•Public DPMQ of \$ [redacted] (effective DPMQ: \$ [redacted] as a result of a [redacted] % rebate)
Main comparator	•Placebo •Secondary indirect comparisons against adalimumab and certolizumab PBAC Comment: "...the most relevant comparison would be between etanercept and NSAID background treatment versus placebo with NSAID background treatment. These were the treatment combinations that were included in the economic evaluation." (Public Summary Document (PSD), paragraph 5.1)	•Same as March 2015 •No secondary comparators were nominated.
Clinical evidence	•Trial 1031 consisting of 12 week randomised double blind phase and 92 week open label extension comparing etanercept with placebo. PBAC Comment: "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." (PSD, paragraph 7.5)	• Updated results of open label maintenance phase of Trial 1031. Includes sub-group analyses by MRI and CRP status.
Key effectiveness data	•Statistically significant improvement in ASAS 40 outcome PBAC Comment: "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." (PSD, paragraph 7.3)	•Same as March 2015 with additional subgroup analyses based on MRI and CRP status
Key safety data	•Summary of PSUR, trial AEs PBAC Comment: "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" (PSD, paragraph 7.7)	•Same as March 2015, with updated PSUR and data from the open label phase of Trial 1031
Clinical claim	•The submission claimed that etanercept was superior in terms of efficacy and inferior in terms of safety in comparison to placebo. PBAC Comment: "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	•Same as March 2015

	Etanercept March 2015	Current re-submission
	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." (PSD, paragraph 6.17)	
Economic evaluation	<ul style="list-style-type: none"> •Cost-utility model with cost/QALY \$45,000 - \$75,000 •Time horizon of 2 years •Trial based EQ-5D scores <p>PBAC Comment: "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." (PSD, paragraph 6.31)</p>	<ul style="list-style-type: none"> •Cost-utility model with cost/QALY \$45,000 - \$75,000 •Time horizon adjusted to 10 years from 2 years
Number of patients	<ul style="list-style-type: none"> •Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5. <p>PBAC Comment: none</p>	<ul style="list-style-type: none"> •Less than 10,000 in Year 1 decreasing to less than 10,000 in Year 5.
Estimated cost to PBS	<ul style="list-style-type: none"> •Less than \$10 million in Year 1 increasing to \$10 - \$20 million in Year 5 for a total of \$60 - \$100 million over the first 5 years of listing. <p>PBAC Comment: "The DUSC considered that the financial estimates provided by the submission were not likely to be accurate..." (PSD, paragraph 6.34)</p>	<ul style="list-style-type: none"> •\$20-\$30 million in Year 1 decreasing to \$10-\$20 million in Year 5 for a total of \$60-\$100 million over the first 5 years of listing.
PBAC decision	<ul style="list-style-type: none"> •Reject: <p>PBAC Comment: "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 the 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." (PSD, paragraph 7.1)</p>	-

Source: Compiled during the evaluation

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 ESC noted that nr-axSpA can progress to AS. The PSCR (p5) argued that both conditions are equally debilitating and control of nr-axSpA should be just as important as control of AS.
- 4.2 Etanercept is not likely to replace any pharmaceutical therapies. The ESC considered that etanercept is likely to be used in addition to NSAIDs, which are first line treatment, after failure to achieve a response after at least two NSAIDs for at least three months. Etanercept is the only anti-TNF approved by the TGA for active nr-axSpA.

5 Comparator

- 5.1 The submission nominated placebo as the main comparator. In March 2015, the PBAC noted that as most patients would be expected to be on treatment with background NSAIDs, the most relevant comparison would be between etanercept with NSAID background treatment versus placebo with NSAID background treatment (March 2015 PSD, paragraph 5.1).
- 5.2 Secondary comparisons of adalimumab and certolizumab pegol were not included in the re-submission. The evaluation considered this was appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

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

Clinical trials

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

Table 2: Trials and associated reports presented in the re-submission

Trial ID	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
	Interim analysis at Week 48. of open-label extension: 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.	February 2014
	Final 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	August 2015

<p>Brown MA, Bird PA, Robinson PC, Mease P, van den Bosch F, Surian C, Jones H, Szumski A, Marshall L and Wild Z. Baseline MRI and CRP as predictors of response to etanercept in the management of patients with non-radiographic axial spondyloarthritis.</p> <p>Brown M. Baseline MRI/CRP as predictors of response to etanercept in the management of patients with non-radiographic axial spondyloarthritis.</p> <p>Dougados M, van der Heijde D, Sieper J et al. 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.</p> <p>Dougados M, Tsai WC, Saaibi DL, Bonin R, et al. Evaluation of health outcomes with etanercept treatment in patients with early nonradiographic axial spondyloarthritis.</p> <p>Maksymowych WP, Dougados M, van der Heijde D, Sieper J, Braun J, Citera G, Van den Bosch F et al. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis. 48-week results from the EMBARK study.</p>	<p>56th Meeting of the Australian Rheumatology Association; 23-26 May 2015; Adelaide Australia.</p> <p><i>Int Med J</i> 2015; 45(suppl 2)39</p> <p><i>Arthritis Rheum</i> 2014; 66(8):2091–2102.</p> <p><i>The Journal of Rheumatology</i> 2015, 42(10)</p> <p><i>Ann Rheum Dis</i> 2015; 0:1-8</p>
--	--

Source: Table B.2.3, p. 33 of the re-submission

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

Table 3: 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

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

Source: compiled during the evaluation

Comparative effectiveness

6.5 A summary of the efficacy results of Trial 1031 is presented in the table below.

Table 4: 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

Source: Table B.6.1 p58 of the re-submission. ASAS=Assessment in Ankylosing Spondylitis;

- 6.6 In March 2015, the PBAC noted that “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 a large percentage of etanercept treated patients did not have an ASAS 40 outcome and that the clinical benefits of etanercept in nr-axSpA were modest.” (March 2015 PSD, paragraph 7.3)
- 6.7 The re-submission also included subgroup analyses by MRI and CRP status. A summary of these results is presented in the tables below.

Table 5: ASAS 40 response rates by subgroups at Week 12 mITT population

Subgroup	Etanercept n/N (%)	Placebo n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)
Overall population	35/105 (33.3)	16/107 (15.0)	0.18 (0.07, 0.30)	2.23 (1.32, 3.77)
CRP- /MRI-	2/11 (18.2)	0/14	0.18 (-0.07, 0.43)	6.25 (0.33, 118.22)
CRP-/MRI+	10/46 (21.7)	8/50 (16.0)	0.06 (-0.1, 0.21)	1.36 (0.59, 3.14)
CRP+/ MRI-	4/7 (57.1)	0/7	0.57 (0.19, 0.95)	9.00 (0.57, 141.13)
CRP+/ MRI+	19/41 (46.3)	8/36 (22.2)	0.24 (0.04, 0.45)	2.09 (1.03, 4.18)
CRP+ and/or MRI+	33/94 (35.1)	16/93 (17.2)	0.18 (0.06, 0.30)	2.04 (1.21, 3.45)

Table 6: ASAS 20 response rates by subgroups at Week 12 mITT population

Overall population	55/105 (52.4)	39/107 (36.5)	0.16 (0.03, 0.29)	1.44 (1.05, 1.96)
CRP- /MRI -	6/11 (54.6)	2/14 (14.3)	0.40 (0.06, 0.75)	3.82 (0.95, 15.36)
CRP-/MRI+	17/46 (37.0)	20/50 (40.0)	-0.03 (-0.23, 0.16)	0.93 (0.56, 1.53)
CRP+/ MRI-	5/7 (71.4)	1/7 (14.3)	0.57 (0.15, 0.99)	5.00 (0.77, 32.57)
CRP+/ MRI+	27/41 (65.9)	16/36 (44.4)	0.21 (-0.00, 0.43)	1.48 (0.97, 2.27)
CRP+ and/or MRI+	49/94 (52.1)	37/93 (39.8)	0.12 (-0.02, 0.27)	1.31 (0.95, 1.80)

Source: Table B.6.1, p59 and Table B.6.4, p61 of the re-submission. ASAS = Assessment in Ankylosing spondylitis. CI = confidence interval; CRP = C-reactive protein; MRI = magnetic resonance imaging

- 6.8 The ESC considered that the subgroup analyses presented in the re-submission did not appear to strongly indicate that etanercept is significantly more effective in MRI+ and/or CRP+ than in the overall trial population. The sub-group analyses showed that the greatest efficacy in terms of risk difference in ASAS 40 was achieved in MRI- and

CRP+ subgroup; however this was only based on seven patients. The next best performing subgroup was in MRI+ and CPR+.

- 6.9 More importantly, MRI+ and/or CRP+ patients are not a new patient population compared with the requested restriction in the March 2015 submission. In other words, the restriction, as well as the economic evaluation in the March 2015 submission had already been based on this subgroup. Consequently, this subgroup did not provide improvement in efficacy or cost-effectiveness, as requested by the PBAC in March 2015.

Comparative harms

- 6.10 The comparative safety data was unchanged in the re-submission. Statistical comparisons between etanercept and placebo in Trial 1031 were calculated during the previous 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 etanercept periodic safety update report.

Benefits/harms

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

Table 7: 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

- 6.12 On the basis of Trial 1031 presented by the submission, for every 100 patients treated with etanercept plus NSAIDs in comparison to placebo plus NSAIDs:
- Approximately 17 additional patients would have experienced a significant improvement in symptoms, measured with the ASAS 40, over 12 weeks.

- Between 0 and 9 additional patients would have experienced an eye disorder over 12 weeks.
- Between 2 and 11 additional patients would have experienced an injection site reaction over 12 weeks.

6.13 The ESC considered that Trial 1031 was not able to detect the increased risk of infection and malignancy reported with etanercept due to its exclusion criteria and the short duration of the study.

Clinical claim

6.14 As in the previous submission, the re-submission claimed that etanercept was superior in terms of efficacy and inferior in terms of safety in comparison to placebo.

6.15 In March 2015, the PBAC considered that “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 conclusion on efficacy” (March 2015 PSD, paragraph 6.17). The ESC noted that the resubmission presented results by subgroup in terms of CRP and MRI positivity but considered that no new evidence was provided that fundamentally challenges the PBAC’s previous consideration.

6.16 The PBAC considered that there were no new data for the PBAC to change its previous consideration on the claim of superior comparative effectiveness.

6.17 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.18 The submission included a cost-utility analysis (CUA) of etanercept versus usual care. The following tables present a summary of the structure, rationale of the model and key drivers of the model.

Table 8: Summary of model structure and rationale

Time horizon	10 years based on 12 weeks of randomised data from Trial 1031
Outcomes	QALYs derived from Trial 1031 EQ-5D scores
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.
Transition probabilities	Transition to death based on AIHW mortality tables; etanercept treatment discontinuation based on Trial 1031 data and assumptions.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: compiled during the evaluation

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10 years; assumed from 2 years of trial data and 12 weeks of utility data	High, favours etanercept
Extrapolation	Assumed 12 week utility increment is maintained for 10 years	High, favours etanercept

Source: compiled during the evaluation

- 6.19 The model was based on significant assumptions, particularly about sustained treatment effect and utility benefit in the long term. Given the lack of available evidence on nr-axSpA natural history and progression over time, it would be difficult to create an accurate or useful model in this context. Nevertheless, the evaluation considered that the re-submission’s measures of effect, which drive the model, were likely overestimated.
- 6.20 As requested by the PBAC, the re-submission increased the time horizon to 10 years. The model was organised into two phases: the first phase was structurally identical to the two-year model of the original submission; and the second phase extrapolated costs and effects to 10 years. Because treatment with etanercept and nr-axSpA could be expected to last decades, the 10-year time horizon is still short in the context of the indication. However, the absence of long-term clinical evidence poses challenges of extrapolation to a 10-year time horizon. One major issue of the re-submission’s extrapolation is that treatment effect is assumed to be maintained for the entire duration of the model.
- The PSCR (p2) acknowledged the concerns regarding the 10-year time horizon, but considered that the assumptions made “were both conservative and shielded the ICER from the uncertainty”.
 - The ESC considered that the 10 year time horizon was not conservative as it assumed a non-changing utility increment over 10 years, and was based on a utility increment that is likely unreliable (see paragraph 6.20).
 - Considering that the issue is lack of actual evidence on natural history or long-term effect to populate a model, the ESC considered it was unclear how any strategy employed by the re-submission could address uncertainty. In this regard, the ESC recalled that in March 2015, it considered that even if a longer time horizon was modelled, the economic model would still have remained unreliable.
- 6.21 The model extrapolated non-statistically significant increases in utilities between baseline and 12 weeks in Trial 1031 (although a difference was observed at week 8 for the ITT population) over a 10 year period, assuming that etanercept treatment effect would remain constant. The ESC considered that these estimates were unreliable and that it was highly unlikely that these trial EQ-5D scores from 12 weeks of treatment could be used to accurately model health related quality of life over 10 years.
- The PSCR (p2) considered that treatment effect was sustained among patients who continued treatment until 2 years, and on this basis, it was reasonable to assume a sustained treatment effect for 10 years.
 - The ESC considered that as nr-axSpA is expected to be a progressing disease, and no prevention or slowing of disease progression has been demonstrated with etanercept treatment, it was unreasonable to assume effect would be sustained for 10 years. Furthermore, the two-year data are based on non-comparative maintenance phase evidence, and so the QALY increment that drives the model is

actually only based on 12 weeks of data. Accordingly, the ESC considered that the re-submission’s assumption that treatment effect is maintained over 10 years was unrealistic and significantly underestimated the ICER.

- 6.22 As requested by the PBAC, the re-submission included transitions to AS. As there was no evidence that etanercept affects disease progression, these additions to the model have no impact on the ICER as they were assumed to be equal in the two arms of the model. The ESC noted that the resubmission assumed 10% of subjects had progressed to AS, and by 10 years the proportion increased to 50%. However, the re-submission did not account for transition probabilities from remission back to the nr-axSpA health state.
- 6.23 The results of the re-submission’s economic evaluation are presented in the table below.

Table 10: Results of the economic evaluation

Component	Etanercept	Placebo	Increment
Costs	\$ [REDACTED]	\$21,213	\$ [REDACTED]
QALYs	5.435	5.055	0.380
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Table D.5.1, p155 of the re-submission.

The redacted table shows an ICER in the range of \$45,000/QALY – \$75,000/QALY.

- 6.24 The submission included a sensitivity analysis where the utilities of etanercept and placebo converge linearly from 2 to 10 years. In this scenario, the ICER increased to \$45,000 – \$75,000 per QALY saved (the incremental costs are the same and the incremental QALYs decrease to 0.323). While this estimate is more reasonable, and more complex ways of extrapolating the data would ultimately not be supported with the available data, this extrapolation is basic and there is still significant potential for overestimating the incremental effect. However, the ESC recommended that this scenario was more appropriate for PBAC consideration than the base case in the submission.
- 6.25 The submission also included a sensitivity analysis that included the convergence in utilities discussed above and increased the time horizon to 15 years which resulted in an ICER of \$45,000/QALY – \$75,000/QALY.
- 6.26 In addition, the evaluation conducted a sensitivity analysis which removed the reductions in the price of etanercept in 2016 and 2017 assumed in the submission which resulted in an ICER of \$45,000/QALY – \$75,000/QALY.
- 6.27 The ESC noted the trial collected EQ-5D and SF-36; however, only EQ-5D was used in the model. The ESC considered that it would have been informative had the re-submission used SF-6D for conversion of SF-36 scores into utility measures as an alternative set of trial-sourced utility values in a sensitivity analysis.

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

- 6.28 The drug cost per patient per year was based on the effective price of a \$ [REDACTED] and 13 four-week treatment periods in a year.

Estimated PBS usage & financial implications

6.29 This re-submission was not considered by DUSC. DUSC advice was provided for the March 2015 submission. The re-submission included the same prevalence rates as the previous submission, but only applied them to the initial population prior to the first year of listing. The re-submission applied incidence rates subsequently. The evaluation considered the incidence rates appeared inappropriate as they are from over 15 years ago and from a Finnish population, and are actually converted prevalence rates. Furthermore, the application of an incidence method was unnecessary, as the DUSC had considered a prevalence approach to calculating patient population was reasonable. As in the March 2015 submission, the prevalence rate was underestimated. In addition, the re-submission included referral rates, which DUSC considered should not be included and no uptake rates were included in the re-submission, essentially assuming that all eligible patients would be treated with etanercept.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
March 2015 estimates					
Scripts					
March 2015 estimates					12,737
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
March 2015 estimates	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
March 2015 estimates	\$	\$	\$	\$	\$
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$
March 2015 estimates	\$	\$	\$	\$	\$

Source: Compiled during the evaluation

The redacted table shows that at year 5, the estimated number of patients in the re-submission was less than 10,000, and the net cost to the PBS would be \$10 – \$20 million.

6.30 The estimates follow a decreasing trend of patient numbers, scripts and costs from year 1 to 5, which is inconsistent with the previous submission and DUSC advice. This is driven primarily by the modified approach of using incidence rates to calculate the patient population. This approach has led to a financial model that is highly sensitive to several inputs and is unlikely to accurately estimate costs to the Government.

6.31 The PSCR (p3) provided revised financial estimates using a prevalence method of calculating the eligible population, removing referral and diagnosis and included uptake rates from the original re-submission. The PSCR also removed the percentage of patients without contraindications to TNF inhibitors from the financial estimates. While the estimated net cost to the PBS/RPBS in the revised estimates decreased in the first year of listing, the costs in years 2 to 5 are greater than those estimated in the re-submission, with particularly large increases in years 4 and 5

(year 4 increased by \$■■■■ and year 5 more than doubled, from \$10-\$20 million to \$30-\$60 million). These calculations were not verified, as a spreadsheet was not provided with the PSCR.

- 6.32 The ESC noted from the DUSC Utilisation Review (agenda item 10.3, March 2016 PBAC) increasing use of bDMARDs for AS, with no sign of stabilising. Despite the requirement for radiographically confirmed Grade II bilateral sacroiliitis or Grade III unilateral sacroiliitis, the ESC considered that there may be some use beyond the current AS restriction for nr-axSpA.
- 6.33 The ESC also noted concerns about the high risk of leakage beyond the proposed nr-axSpA restriction to chronic back pain.

Quality Use of Medicines

- 6.34 As in the March 2015 submission, the re-submission identified the same barriers to the appropriate, effective and safe use of etanercept and identified the same 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

- 6.35 As in the March 2015 submission, the re-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 request to list etanercept for nr-axSpA on the basis of an unacceptably high and uncertain incremental cost effectiveness ratio. In addition, the PBAC considered that the patient population remained poorly defined and justified. The PBAC considered there is a clinical need for effective subsidised therapy for this condition but noted that the clinical benefits of etanercept in nr-axSpA were modest.
- 7.2 The PBAC recalled that it had previously accepted that placebo plus background NSAID treatment was the appropriate comparator.
- 7.3 The PBAC noted that the resubmission presented the updated results of the open label maintenance phase of Trial 1031, subgroup analyses by MRI and CRP status, an updated periodic safety update report, a revised model (with the time horizon extended to 10 years) and revised utilisation and financial estimates. The PBAC recalled that in March 2015, it advised that a resubmission could give consideration to limiting treatment to populations in which a higher treatment response would be evident and cost-effective using a reliable economic model.
- 7.4 Based on the MRI and CRP status subgroup analyses, the resubmission requested listing for the MRI+ and/or CRP+ subgroup. The PBAC noted that the subgroups included in the analyses were not new patient populations but were previously included in the March 2015 submission. Accordingly, the PBAC considered that the

submission did not identify a patient population with a higher treatment response, as requested in March 2015.

- 7.5 The PBAC noted that the PSCR and pre-PBAC response indicated a willingness to limit the restriction to patients who are both MRI+ and CRP+ at baseline, as the sponsor considered the treatment benefits compared with placebo were greater in this subgroup than the MRI+ and/or CRP+ subgroup, in terms of ASAS 40 and ASAS 20 response rates. The PBAC considered that the subgroup analyses did not indicate that etanercept was significantly more effective for the primary outcome ASAS 40 in the MRI+ and CPR+ subgroup (RD: 0.24, 95% CI 0.04, 0.45) than in the overall trial population (RD: 0.18, 95% CI 0.07, 0.30). The PBAC acknowledged that the small incremental benefit of etanercept compared with placebo in this subgroup could be due to the higher placebo response rates, as argued by the pre-PBAC response. However, the PBAC considered that it could also signal that the identified subgroup may not be the group that would benefit the most from treatment with etanercept for the condition. In addition, the PBAC noted a recent paper (Weber et al., *Arthritis & Rheumatology*, Vol.67, No 4, April 2015) which questioned the value of using MRI as a diagnostic tool for nr-axSpA.
- 7.6 Overall, the PBAC considered that the clinical benefits of etanercept in nr-axSpA were modest and the submission did not provide any new evidence to change the PBAC's previous conclusion that the available evidence did not enable the 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 nr-axSpA or to define a patient population with a higher treatment response.
- 7.7 The PBAC recalled that in March 2015, it considered that the economic model for etanercept had an unreliable short time horizon of two years in view that treatment with etanercept for nr-axSpA could be expected to last decades. The re-submission increased the time horizon to 10 years; the PBAC agreed with the ESC that due to the lack of available evidence on the natural history and progression of nr-axSpA over time, this extrapolation was not well supported. At the same time, however the PBAC considered that a 10 year time horizon was still considered too short for the condition. The PBAC noted that the ICER had increased compared with the previous submission.
- 7.8 The PBAC agreed with the ESC that the extrapolation of a constant utility benefit associated with treatment with etanercept over 10 years was unrealistic and inappropriate, particularly in the context of a progressive disease, and given only 12 weeks of trial based data. The PBAC considered that the scenario in which the utilities of etanercept and placebo converge linearly from two to 10 years under a 15 year time horizon was more appropriate than the base case presented in the submission.
- 7.9 The PBAC noted that the re-submission included transitions to AS in the model. As there was no evidence that treatment with etanercept has an impact on disease progression, these additions to the model had no impact on the cost-effectiveness of etanercept.
- 7.10 The PBAC noted that a ■■■% price reduction was offered in the re-submission, but considered that the ICER remained unacceptably high and the cost-effectiveness of

etanercept for nr-axSpA was highly uncertain. In addition, it was not appropriate for the economic model to include a future price reduction associated with the assumed listing of a biosimilar of etanercept.

- 7.11 The PBAC noted that the re-submission did not incorporate the previous DUSC advice in the utilisation estimated in the re-submission. The PBAC noted that this resulted in calculations that were overly complicated, difficult to interpret, and even more underestimated than the March 2015 submission.
- The re-submission's financial estimates switched to an incidence approach, when DUSC considered the prevalence approach to be reasonable.
 - The incidence rates are applied to an initial prevalent population, prior to the first year of listing. This prevalent population is likely underestimated.
 - The re-submission included referral rates, which DUSC considered should not be included.
 - No uptake rates were included in the re-submission, essentially assuming that all eligible patients would be treated with etanercept.

The PBAC noted that the PSCR provided updated financial estimates which were not able to be verified. The pre-PBAC response argued that clinicians believe that concerns with regard to the financial burden of treating nr-axSpA with etanercept are unfounded and that, in reality, the nr-axSpA population that will be treated with etanercept is extremely small. In addition, the pre-PBAC response reiterated that the Sponsor is prepared to enter into a risk-share agreement with the Government.

- 7.12 Overall, the PBAC considered that there was no new key evidence submitted in this resubmission that fundamentally changed the PBAC's previous conclusion. The PBAC therefore rejected the resubmission and would welcome a major resubmission due to a clinical need for a specific group of patients with the condition. The PBAC considered that a future resubmission should present a revised model addressing the ESC and PBACs concerns with the utilities, time horizon and future assumed changes in the price.

- 7.13 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 is pleased that the PBAC recognised the clinical need for subsidised treatment for nr-axSpA. However, as we lodged a re-submission aimed at resolving the issues raised previously, we are disappointed that the PBAC did not recommend listing of

etanercept for nr-axSpA. This outcome means that patients with this disabling condition are still unable to access effective reimbursed treatment for their condition. As a consequence of the outcome, we are considering our options at this time.