



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Etanercept

Proprietary Product Name: Enbrel

Sponsor: Pfizer Australia Pty Ltd

September 2015

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AS	Ankylosing Spondylitis
ASAS	Assessment in Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASspiMRI-a	Ankylosing Spondylitis spine MRI score for activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI	Ankylosing Spondylitis spine Magnetic Resonance Imaging
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity
AS-WIS	Ankylosing Spondylitis Work Instability Index
AST	Aspartate Aminotransferase
AxSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BAS-G	Bath Ankylosing Spondylitis Patient Global Assessment Score
BL	Baseline
BP	Blood Pressure
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DMARDs	Disease-Modifying Anti-rheumatic Drugs
DNA	Deoxyribonucleic acid

Abbreviation	Meaning
DVU	Discovertebral units
EIU	Exposure In Utero
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EQ-5D	EuroQol EQ-5D Health State Profile
FDA	Food and Drug Administration
F/U	Follow-up
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen B27
hsCRP	High Sensitivity C-Reactive Protein
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
MASES	Maastricht Ankylosing Spondylitis Entheses Score
MCII	Minimum Clinically Important Improvement
MCS	Mental Component Score
MFI	Multidimensional Fatigue Inventory
mITT	Modified Intent-to-Treat

Abbreviation	Meaning
MOS	Medical Outcomes Study (MOS) Sleep Scale
MRI	Magnetic Resonance Imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spine Score
NA	Not Assessed
nr-AxSpA	Non-radiographic Axial Spondyloarthritis
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NY	New York
PASS	Patient Acceptable Symptom State
PBO	Placebo
PCS	Physical Component Score
PGA	Physician Global Assessment
PPD	Purified protein derivative
RA	Rheumatoid Arthritis
RASSS	Radiographic Ankylosing Spondylitis Spine Score
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard Deviation
SE	Standard Error
SF-36	36-Item Short-Form Health Survey
SI	Sacroiliac
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	Tuberculosis
TNF α	Tumor Necrosis Factor alpha

Abbreviation	Meaning
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WPAI	Work Productivity and Activity Impairment Questionnaire
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	17 April 2015
<i>Active ingredient:</i>	Etanercept
<i>Product name:</i>	Enbrel
<i>Sponsor's name and address:</i>	Pfizer Australia Pty Ltd 38-42Wharf Rd, West Ryde NSW 2114
<i>Dose forms and strengths:</i>	25 mg and 50 mg: Powder for injection and Water for injections 25 mg and 50 mg: Solution for injection in pre-filled syringe 50 mg: Solution for injection in Auto-injectors
<i>Containers/Pack sizes:</i>	<ul style="list-style-type: none">• 4 clear glass vials or• 4 single dose pre filled glass syringes with 4 pre-filled syringes containing water for injections or• 2, 4 or 12 Auto-injectors
<i>Approved therapeutic use:</i>	<i>Non-radiographic Axial Spondyloarthritis</i> <i>Treatment of adults with active* non-radiographic axial spondyloarthritis 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.</i> <i>*Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.</i>
<i>Route of administration:</i>	Subcutaneous (SC) injection
<i>Dosage:</i>	The recommended dose of Enbrel is 50 mg per week, given as a subcutaneous injection, EITHER once weekly as a single 50 mg injection OR twice weekly as two separate 25 mg injections given 3-4 days apart. Available data in non-radiographic axial spondyloarthritis suggest a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.
<i>ARTG numbers:</i>	107361, 124421, 157622, 90456 and 124422

Product background

This AusPAR describes the application by the sponsor to extend the indications for Enbrel (etanercept) to include

Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy.

Etanercept is a recombinant human tumour necrosis factor alpha (TNF α) inhibitor which binds to TNF α and blocks its interaction with the cell surface TNF α receptor. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary (CHO) mammalian expression system¹ and is currently approved for the treatment of rheumatoid arthritis, plaque psoriasis, psoriatic arthritis and ankylosing spondylitis (AS).² Etanercept is now manufactured using a serum-free process.

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition where the predominant symptom is back pain. The Assessment of Spondylo Arthritis international Society (ASAS) classification criteria for axSpA requires patients to have ≥ 3 months of back pain and an age at onset of <45 years. Additional requirements are *either* sacroiliitis on imaging plus 1 or more spondyloarthritis (SpA) features *or* Human Leukocyte Antigen B27 (HLA-B27) positivity plus 2 or more SpA features. The SpA features include: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's disease or colitis, a good response to NSAIDs, a family history of SpA, HLA-B27 positivity and elevated C-reactive protein (CRP) (Figure 1). axSpA includes both ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).

¹ Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand-binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the FC domain of human immunoglobulin subtype G1 (IgG1). This FC component contains the hinge, CH2 and CH3 regions but not the CHI region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilo daltons.

² Adults

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). ENBREX can be used in combination with methotrexate.

Severe, active, adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see CLINICAL TRIALS).

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. ENBREX has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (see CLINICAL TRIALS).

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Children and Adolescents

Juvenile Idiopathic Arthritis

Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who had an inadequate response to one or more DMARDs.

Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.

Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.

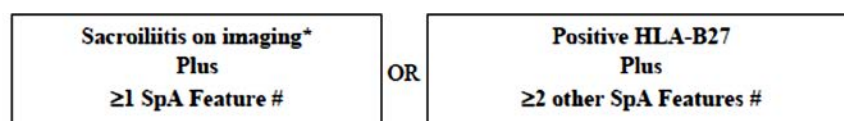
Active psoriatic arthritis in adolescents aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

ENBREX has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

Figure 1: ASA Classification Criteria for axial spondyloarthritis (SpA) in patients with ≥ 3 months of back pain and age of onset < 45 years.



# SpA Features	*Sacroiliitis on Imaging
Inflammatory back pain	Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA
Arthritis	Defined radiographic sacroiliitis according to the Modified New York criteria
Enthesitis (heel)	
Uveitis	
Dactylitis	
Psoriasis	
Crohn's or Colitis	
Good response to NSAIDs	
Family history of SpA	
HLA-B27	
Elevated CRP	

Reference: Sieper J, Rudwaleit M, Baraliakos X, et al. Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68(Suppl 2):ii1-44.

Abbreviations: AxSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; SpA=spondyloarthritis.

Patients with AS have the features of axSpA and meet the modified New York (NY) criteria for diagnosis.³ The diagnostic criteria include radiographic sacroiliitis of at least Grade 2 bilaterally or at least Grade 3 unilaterally⁴ but the radiological evidence of sacroiliac joint damage can take years to appear.

³ Modified New York criteria for diagnosis of ankylosing spondylitis

A definite diagnosis of AS can be made if any of the radiological criterion is associated with at least 1 clinical criterion.

Radiological criterion:

- Sacroiliitis grade ≥ 2 bilaterally or Grade 3 to 4 unilaterally
- Clinical criteria:
- Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in both the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

⁴ Modified New York grades for radiographic sacroiliitis

- Grade 0: normal.
- Grade 1: suspicious changes.
- Grade 2: minimal abnormality - small localised areas with erosion or sclerosis, without alteration in the joint width.
- Grade 3: unequivocal abnormality - moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis.
- Grade 4: severe abnormality - total ankylosis.

Patients with nr-axSpA have features of axSpA but do not meet the radiographic criteria for AS. The natural history of these patients is not well characterised, although some will progress to AS.

The initial management of nr-axSpA is with non-steroidal anti-inflammatory drugs (NSAIDs). Other agents that have been used include local corticosteroid injections and disease-modifying antirheumatic drugs (DMARDs), although the latter have not been shown to be effective for patients with purely axial disease and there is a lack of evidence for glucocorticoids in nr-axSpA.⁵

In Australia there are no currently approved treatments specifically for nr-axSpA.

The following European Union (EU) guidelines adopted by the TGA are relevant to this submission, in addition to the general guidelines:

- CPMP/EWP/4891/03 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis' (effective 23 February 2010)
- CPMP/EWP/2330/99 'Points to Consider on Application with 1. Meta-Analyses; and 2. One Pivotal Study' (effective 27 March 2002)

It was noted in the sponsor's submission that a Category 1 application for the changes identified below was under evaluation by TGA:

- extend the indication to include additional subtypes of Juvenile Idiopathic Arthritis (JIA)
- add once weekly dosing as an alternative dose regimen for JIA patients
- lower the approved age limit for polyarticular-course JIA.

At the time of this dossier, compilation the outcome of this other application was not known and therefore the draft Enbrel PI provided with this application did not include the changes proposed in the application to extend the JIA indication. The application to extend the indication in juvenile idiopathic arthritis was approved by the TGA in February this year [2015]. The sponsor was invited to submit an updated PI incorporating this change and any new safety-related changes as part of its response to the Consolidated List of Questions.

The clinical trial submitted in the dossier was designed in accordance with European Union (EU) guidelines on the clinical investigation of medicinal product for the treatment of ankylosing spondylitis.⁶

Regulatory status

Etanercept was first approved in Australia in September 2000.

In August 2014, the EU approved the following indication, based on a similar submission:

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs)

⁵ Robinson PC, Bird P, Lim I Saad et al *Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA)* Int J Rheum Dis 2014;17:548 - 556

⁶ EMA (2005). European Medicines Agency (EMA) Committee For Medicinal Products For Human Use (CHMP). Draft guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. CPMP/EWP/4891/03. and

EMA (2009). European Medicines Agency (EMA) Committee For Medicinal Products For Human Use (CHMP). Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. CPMP/EWP/4891/03.

The sponsor of Enbrel in the US and Canada is Amgen. The Australian sponsor understands that Amgen has not decided whether to submit an application for nr-axSpA in these countries. The following table summarises the international regulatory status of Enbrel.

Table 1: International regulatory status of Enbrel indicated for nr- axSpA

Country	Submission date	Approval date	Indication
EU (CP)	5 November 2013	28 July 2014	Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).
Israel	29 October 2014	23 December 2014	Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs)
Korea	11 July 2014	25 November 2014	Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).
Russia	27 August 2014	23 December 2014	Enbrel is indicated for the treatment of adults with severe non radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to, or are intolerant to, conventional therapy.
Turkey	11 June 2014	22 July 2014	For non-radiographic axial spondyloarthritis; it is indicated in adults with severe axial spondyloarthritis with objective signs of inflammation by magnetic resonance imaging (MRI) (along with or without elevated C reactive protein (CRP)) but without radiographic evidence of AS; who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs
Switzerland	2 July 2014	Pending	Etanercept is indicated for the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to, or are intolerant to, conventional therapy.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Etanercept (Enbrel) is a recombinant human tumour necrosis factor alpha (TNF α) antagonist which binds to TNF α and blocks its interaction with the cell surface TNF α receptor. It is currently approved for the treatment of ankylosing spondylitis (AS) as well as several other conditions (see *Product background* above). The sponsor stated the following rationale for the proposed extended indication in their covering letter:

Spondyloarthritis (SpA) encompasses closely related but clinically heterogeneous inflammatory diseases including ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease-related arthritis, reactive arthritis, and other 'undifferentiated' SpA. In general, patients are classified by whether they have predominantly axial involvement (axial SpA [axSpA]) or predominantly peripheral involvement (peripheral SpA). The severity of axSpA can span from self-limited inflammation to bony destruction of the spine whose most devastating clinical manifestation is the loss of mobility.

While AS is a well-characterised chronic and progressive form of axSpA, the natural history of nr-axSpA is not well known. Available evidence suggests that the majority of patients with newly diagnosed axSpA can be expected to be nr-axSpA patients and if left untreated, nr-axSpA may progress to AS. It should be noted however that while a subset of patients with nr-axSpA may have early AS, it is currently unknown what proportion of patients with nr-axSpA will progress to AS. It may take years from the onset of inflammatory back pain symptoms until the appearance of radiographic sacroiliitis and there are no established criteria to identify patients who are likely to progress. Nevertheless, the burden of disease on patients can be equally severe in the presence or absence of radiographic sacroiliitis and early therapeutic intervention may potentially impact the natural history of the disease progression.

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently recommended for patients with axSpA, including those with nr-axSpA. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine are sometimes used but have demonstrated minimal efficacy in treating axSpA. Thus, there is an unmet medical need for patients with nr-axSpA whose disease is not responsive to NSAIDs.

Guidance

See *Product background* above.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- One phase III study (B1801031)
- Literature references.

Paediatric data

The submission did not include paediatric data and the extended indication is not sought for paediatric patients.

Good clinical practice

The clinical study report for B1801031 included a statement that the study was conducted in accordance with Good Clinical Practice (GCP) guidelines as well as local ethical and regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no submitted pharmacokinetic studies.

Evaluator's conclusions on pharmacokinetics

There was no new clinical pharmacology data submitted. There is no reason to believe that the PK of etanercept would be altered in the proposed new patient population compared to those adult populations already studied.

The formulation of etanercept used in Study B1801031 is the same as the 50 mg/mL pre-filled syringe that is currently approved in the EU. The dosage regimen used in Study B1801031 (50 mg SC once weekly) is the same as that approved for the treatment of adults with rheumatoid arthritis (RA), Ankylosing Spondylitis (AS), psoriatic arthritis or psoriasis.

Comment: As the data were not available to the evaluator, the sponsor needs to confirm that the formulation of etanercept registered in Australia is the same as that used in Study B1801031.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no submitted pharmacodynamic studies.

Evaluator's conclusions on pharmacodynamics

There was no new clinical pharmacology data submitted. Anti-etanercept antibodies were not assessed in the Study B1801031.

Dosage selection for the pivotal studies

There is no proposed change to the approved dosage as the dosage regimen used in Study B1801031 was the approved regimen of 50 mg SC once weekly.

Efficacy

Studies providing efficacy data

One pivotal efficacy study (Study B1801031) was submitted. No other supporting studies were included.

Evaluator's conclusions on clinical efficacy for Non-radiographic Axial Spondyloarthritis (nr-AxSpA)

There was one pivotal efficacy study submitted in the dossier and no other supporting studies. Study B1801031 was a Phase III, randomised, placebo controlled, double-blind study of 12 weeks etanercept treatment in 215 adult patients with active axial spondyloarthritis despite optimal Non-steroidal anti-inflammatory drugs (NSAID) therapy but without meeting criteria for AS. At baseline, the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)⁷ was 6.0 indicating high disease activity and 81% of subjects had sacroiliitis on magnetic resonance imaging (MRI). The study had a second open label period of 92 weeks from which data to total treatment duration of 24 weeks were submitted.

Etanercept 50 mg SC weekly was compared to placebo on a background of stable, optimal dose NSAID treatment. Subjects were required to have active symptoms and inadequate response to at least 2 NSAIDs. X-rays at study entry were read centrally to confirm the patients did not have findings of AS and MRIs, also read centrally, confirmed the presence or absence of sacroiliitis.

The study met its primary endpoint as the proportion of subjects with AS Disease Activity Score (ASDAS) 40 response at Week 12 was significantly greater with etanercept plus NSAID compared to placebo plus NSAID (32% versus 16%). This treatment difference was less however, than the anticipated 25%. The positive responses were found on the individual components of the ASAS (subject assessment of disease activity, nocturnal back pain, total back pain, BASFI⁸, morning stiffness and lateral side flexion). The result was supported by sensitivity analyses and positive results across secondary endpoints of ASAS 20⁹, ASAS 5/6¹⁰, ASAS partial remission, BASDAI total score and BASDAI 50.

⁷ The BASDAI consisted of a 0 through 100 mm scale (zero being no problem and 100 being very severe) which was used to answer 6 questions pertaining to the 5 major symptoms of AS: fatigue; spinal pain; joint swelling and pain; morning stiffness duration; morning stiffness severity.

⁸ The BASFI was a set of 10 questions designed to determine the degree of functional limitation in those with AS. It used a VAS and assessed level of ability.

⁹ ASAS 20 responders were defined as subjects who satisfied the following criteria:

- An improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 cm scale (converted from 0 to 100 mm) in at least 3 of the following 4 domains:
 - Subject Assessment of Disease Activity,
 - Mean of subject assessment of total back pain,
 - Function represented by the BASFI score,
 - Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.
- Absence of deterioration (of at least 20% and absolute change of at least 1 unit) in the potential remaining domain.

¹⁰ The ASAS 5/6 required a 20% improvement in 5 of 6 criteria - the 4 domains of the ASAS response, a measure of spinal mobility (lateral spinal flexion), and hsCRP.

There was no significant effect on BASDAI 20, dactylitis or mobility endpoints (BASMI)¹¹ (except lateral flexion). The sponsor claimed the lack of effect on mobility was related to the study population having little mobility restriction at baseline. Etanercept was seen to result in a positive response on imaging of the sacroiliac (SI) joints and spine. The reading was central and blinded to treatment which is important due to variability in reading of radiological images. The response on health outcomes showed a positive effect on measures of physical function (36-Item Short-Form Health Survey (SF-36 PCS)) but little positive impact on quality of life (Ankylosing Spondylitis Quality of Life (ASQoL)) or well-being (BAS-G¹²).

There was persistence and maintenance of effect with treatment to Week 24, however longer term efficacy data to two years from the open label study are not yet available. Withdrawal of treatment and possible rebound in disease were not assessed.

A major issue with the submitted data was that there was no adjustment for multiple comparisons undertaken on the numerous secondary endpoints. A question on this has been raised. While subgroup analyses were hampered by small sample size, the main finding on post hoc analyses was that there was a notably greater treatment effect (in terms of ASAS 40¹³) in those with higher baseline high sensitivity CRP (hsCRP) level ($\geq 3\text{mg/L}$) (48% versus 21%). There was also a greater response in those with a higher baseline Spondyloarthritis Research Consortium of Canada (SPARCC) score (≥ 2) (42% versus 18%). The sponsor has been asked to discuss these findings further.

The efficacy data submitted indicated that the treatment is symptomatic and there is no evidence that there is any impact on disease progression. Due to the age cut-off of 50 years there are no efficacy data in the elderly population.

The study design was in accordance with EU guidelines for AS. The study's primary endpoint (ASAS response criteria) was in line with 2005 EMA draft guidelines on clinical investigation of medicinal products for the treatment of ankylosing spondylitis.¹⁴ With the introduction of the 2009 guideline, the primary endpoint was also analysed according to its criteria which differed on the pain assessment domain (total *or* nocturnal pain scores rather than total *and* nocturnal pain). Results for analysis using both criteria were concordant.

¹⁰ Assessment in Ankylosing Spondylitis (ASDAS) scores were calculated from the following:

1. Total back pain (BASDAI question 2),
2. Subject Assessment of Disease Activity,
3. Peripheral pain/swelling (BASDAI question 3),
4. Duration of morning stiffness (BASDAI question 6),
5. hsCRP in mg/L (or ESR)

¹¹ The BASMI consists of 5 clinical measurements to reflect axial status: intermalleolar distance, cervical rotation, modified Schober's test, lateral flexion and tragus to wall distance.

¹² The BAS-G was a 2 question assessment evaluating the effect of AS on the subject's wellbeing over the last week and last 6 months.

¹³ ASAS 40 responders were defined as subjects who satisfied the following criteria:

1. An improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 cm scale (converted from 0 to 100 mm) or an improvement of 100% for those domains that had a baseline score <2 in at least 3 of the following four domains:
 - Subject Assessment of Disease Activity,
 - Mean of subject assessment of nocturnal pain and total back pain,
 - Function represented by the BASFI score,
 - Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.

No worsening at all in any of the domains.

¹⁴ EMA (2005). European Medicines Agency (EMA) Committee For Medicinal Products For Human Use (CHMP). Draft guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. CPMP/EWP/4891/03.

Overall, the pattern of results in patients with nr-AxSpA are consistent with data from etanercept studies in AS patients although the degree of response is less and the positive response appears confined to those with evidence of inflammation on MRI or with elevated CRP.

Safety

Studies providing safety data

No safety studies were submitted.

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) and serious AEs (SAEs), AEs of particular interest, including investigator identified infection (a treated infection and/or serious infection), malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression, autoimmune disorders, Inflammatory bowel disease (IBD) and liver function abnormalities;
- Laboratory tests, including blood chemistry, fasting glucose and lipids, haematology, urinalysis;
- Physical examination and vital signs;
- IBD, psoriasis and uveitis evaluations.

Patient exposure

In Study B1801031, there were 225 randomised subjects and 224 received study drug, 111 etanercept and 113 placebo. The median exposure was 85 days in both groups with a total exposure of 24.1 and 25.3 subject-years in the etanercept and placebo groups, respectively in the double-blind period. In the open label period of Weeks 12 to 24, the median exposure was 78.0 days in both the etanercept (ETN)/ETN group (n=102) and the placebo/ETN group (n=106). The total exposure to etanercept from baseline to Week 24 was 47.4 subject years in the ETN/ETN group and 24.1 subject-years in the placebo/ETN group.

Safety issues with the potential for major regulatory impact

Liver toxicity

See Attachment 2 *Laboratory tests*.

Unwanted immunological events

Anti-etanercept antibody concentrations were not assessed in Study B1801031.

Comment: It would be expected that the immunological risks in the nr-AxSpA population would be the same as in other populations already studied.

Postmarketing data

Etanercept has been on the market since 1998 and patient exposure to February 2013 was estimated at 3.6 million patient-years. Most treatment is for rheumatoid arthritis. The most frequent serious events reported are pneumonia, sepsis, myocardial infarction and worsening of the condition for which the etanercept was used. The most frequent causes of death are infections, neoplasms and cardiac disorders. The sponsor conducted a review of the safety database for cases with axial spondyloarthritis as the indication for

etanercept. There were 125 cases of spondylitis with 4 cases of AxSpA (the other 121 were reported to be non-specific SpA, peripheral AxSpA or AS). The events reported were lack of effect, uveitis, herpes zoster, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hepatic steatosis and Sjögren's syndrome.

Evaluator's conclusions on safety

The safety database for the nr-AxSpA population was derived from the one Phase III clinical trial in which there were 111 patients exposed to double blind etanercept. The median duration of exposure in the double blind phase was 85 days with a total of 24.1 subject-years. The median exposure duration in the open label phase was 78 days. The total exposure to etanercept from baseline to Week 24 was 47.4 subject years in the ETN/ETN group and 24.1 subject-years in the placebo/ETN group.

There were no deaths in the study to Week 24. SAEs were infrequent (2 [1.8%] in each group during double-blind treatment). In the etanercept group, the SAEs were spondyloarthropathy and cholelithiasis. There were three discontinuations due to AEs in subjects treated with etanercept (hepatitis, worsening spondyloarthropathy and asthenia) during double blind treatment with a higher rate than placebo (2.7% versus 0.9%). There was one AE related discontinuation (acute bronchitis) during open label treatment.

During double blind treatment, treatment emergent AEs (TEAEs) were more frequent with etanercept than placebo (56.8% and 45.1%). The notable increased risk was injection site reactions. The overall rate of infections was similar between groups (23% versus 22%) while treated or serious infections were slightly higher in the etanercept group (9.9% versus 8.8%).

Up to Week 24 of the study, there were no reported cases of malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression or IBD. After Week 24 data cut-off, the sponsor reported one opportunistic infection (herpes zoster) and one demyelinating disorder (multiple sclerosis). In the open label period there were two subjects with acute anterior uveitis and in neither case was study drug ceased.

Grade 3 or 4 laboratory test results were higher with etanercept (2.7% versus 1.8%) and in particular a higher rate of raised ALT and AST. There was one etanercept treated subject with hepatitis (which led to discontinuation) but no cases meeting the Hy's Law criteria. Transient neutropaenia (Grade 3) was also reported in 2 (1%) patients during open label treatment. There was some lack of detail on laboratory assessments and question on this has been raised.

There were no reported pregnancies. Anti-etanercept antibodies were not assessed and safety in relation to treatment withdrawal was not examined.

Overall the safety risks appeared in line with current knowledge for etanercept. However the database was small and the maximum treatment duration was only 24 weeks which is shorter than the recommended minimum of 12 months.

First round benefit risk assessment

First round assessment of benefits

The benefits of etanercept in the proposed usage are:

- Efficacy compared to placebo on ASAS 40 of 32% versus 16% after 12 weeks treatment. The efficacy appeared largely confined to those with elevated hsCRP and possibly also those with evidence of inflammation on MRI.

- Efficacy is supported by positive results across secondary endpoints of disease activity and function. There was, however, little effect on mobility or quality of life.
- Efficacy was maintained to Week 24.
- No new safety signals.
- Safety data which is supported by a large existing safety database.

First round assessment of risks

The risks of etanercept in the proposed usage are:

- Injection site reactions.
- Infections and sepsis.
- Elevated liver enzymes and hepatitis.
- Central nervous disorder (CNS) disorders including demyelinating disorders.
- Other serious risks as outlined in the product information such as: opportunistic infections and tuberculosis; haematological reactions including pancytopenia; reactivation of hepatitis B, worsening of hepatitis C, allergic reactions, worsening of congestive heart failure; malignancy and lymphoproliferative disorders, autoimmune antibody formation; new onset psoriasis; interstitial lung disease; risk in patients with alcoholic hepatitis; hypoglycaemia in diabetic patients; risks during pregnancy and lactation; and drug interactions with anakinra and abatacept.
- A small safety database in the nr-AxSpA population.
- Lack of efficacy and safety data beyond 24 weeks.
- No data on effects on disease progression.
- No efficacy data in patients aged ≥ 50 years (exclusion criteria in the pivotal study).

First round assessment of benefit-risk balance

SpA, formerly termed spondyloarthropathy, refers to a group of diseases that share certain clinical features, including axial inflammation (spinal and/or sacroiliac), enthesitis (inflammation of ligament/tendon attachment to bone), dactylitis, oligoarthritis, inflammatory eye disease, inflammatory bowel disease, an association with prior or ongoing infection, mucocutaneous lesions typically affecting the genital regions, and, importantly, the human leukocyte antigen HLA-B27.

Subsets of SpA include ankylosing spondylitis; undifferentiated spondyloarthritis (USpA), which includes non-radiographic axial SpA (nr-axSpA); reactive arthritis (formerly called Reiter syndrome); psoriatic arthritis; inflammatory bowel related disease; and SpA in children.

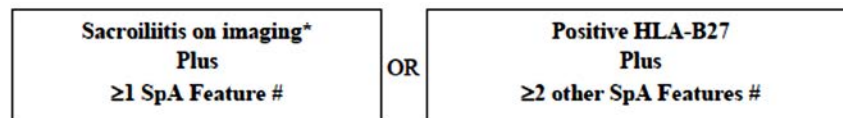
An alternate scheme classifies SpA according to whether the joint involvement is predominantly axial or peripheral: axial SpA which is SpA with predominantly axial involvement; and peripheral SpA where the SpA has predominantly peripheral involvement. Axial SpA patients who do not show defined radiographic changes of sacroiliitis are classified as having non-radiographic axial SpA (nr-axSpA). Patients with nr-axSpA were formerly classified among patients who have undifferentiated SpA (USpA).

The clinical manifestations of SpA include: musculoskeletal findings; eye involvement; skin, genital and mucosal lesions; and bowel mucosal inflammation. A family history of SpA and related conditions may also be present. A good response to NSAIDs is common and is supportive of the diagnosis.

Acute phase reactants may be increased. Plain radiographs are used to assess sacroiliitis but patients with axial involvement may have normal radiographs in early disease. Plain radiographs of the sacroiliac joints are normal in patients with USpA and nr-axSpA, in contrast to AS patients, whose sacroiliac joints would invariably show sclerosis, joint space widening, or erosion. Magnetic resonance imaging of the sacroiliac joint is indicated in patients with clinically suspected axial SpA who have negative or indeterminate plain radiographic findings at the sacroiliac joints.

The Assessment of Spondyloarthritis International Society (ASAS) criteria for the classification of AxSpA require patients to have back pain for at least three months and age of onset less than 45 years with sacroiliitis on imaging (MRI or X-ray) along with at least one SpA feature or be HLA-B27 positive and have at least two other SpA features. SpA features include inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA and elevated CRP (Figure 1).

Figure 1: ASAS Classification Criteria for AS in patients with ≥ 3 months of back pain and age onset at <45 years.



# SpA Features	*Sacroiliitis on Imaging
Inflammatory back pain	Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA
Arthritis	Defined radiographic sacroiliitis according to the Modified New York criteria
Enthesitis (heel)	
Uveitis	
Dactylitis	
Psoriasis	
Crohn's or Colitis	
Good response to NSAIDs	
Family history of SpA	
HLA-B27	
Elevated CRP	

Reference: Sieper J, Rudwaleit M, Baraliakos X, et al. Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68(Suppl 2):ii1-44.
 Abbreviations: AxSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; SpA=spondyloarthritis.

The sensitivity and specificity of these criteria were 83% and 84%, respectively in study of 649 patients.¹⁵ With these criteria 'sacroiliitis on imaging' is defined as active (acute) inflammation on magnetic resonance imaging that is highly suggestive of sacroiliitis associated with SpA or as definite radiographic sacroiliitis according to the modified New

¹⁵ Rudwaleit M, van der Heijde D, Landewé R, et al (2009). The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 68(6):777-83.

York Criteria. While it can be deduced that non-radiographic axSpA is a diagnosis of exclusion (axSpA patients who do not have ankylosing spondylitis on X-ray according to the modified New York (NY) criteria) it is not clear to the evaluator if this is a widely and consistently utilised classification and the ASAS Handbook¹⁶ does not clearly set out a specific definition for the non-radiographic subgroup of axial spondyloarthritis.

The management of nr-axSpA is similar to the management of patients with ankylosing spondylitis. Initial therapy is with NSAIDs. Secondary options include local glucocorticoid injections and DMARDs, although the latter have not been shown to be effective for patients with only pure axial disease. For those with inadequate response to NSAIDs and continuing pain and evidence of inflammation (for example, elevated CRP or inflammation on MRI) TNF inhibitors have been suggested. Adalimumab has been approved in the EU for severe axial SpA in patient without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI and who have inadequate response to or are intolerant of NSAIDs. The evaluator has noted that the application in Australia for this usage of adalimumab was withdrawn in 2013.

The design of the submitted study was in accordance with European guidelines and the endpoints are validated and have been accepted by the European regulators (ASAS 40 response being the primary endpoint for the submission for adalimumab). The use of centralised, blinded radiologists was important for ensuring reliable radiological assessments. It is noted that there has been discussion on whether the selected population of nr-AxSpA is a separately identified disease with established diagnostic criteria. In the submitted clinical trial there were 10 out of 225 (4.4%) of subjects who were randomised yet did not meet the ASAS criteria. Thus, even with specific training, specialist physicians may not accurately apply the ASAS criteria. While it appears that this classification system is being accepted by rheumatologists, a question has been raised for the sponsor to address in this issue and the diagnosis of nr-AxSpA within the Australian clinical practice context.

The efficacy of etanercept was demonstrated in one clinical trial with statistically significant results to 12 weeks, maintenance of effect to 24 weeks and support from secondary endpoints. There were however several issues with the efficacy of etanercept in the proposed population. For a chronic condition, the data to 24 weeks are felt to be insufficient for establishing long term efficacy. Secondly, the evaluator believes the degree of response in the total population (16% placebo corrected difference on the ASAS 40) may be of limited clinical benefit particularly given the treatment risks. Post hoc analyses pointed towards increase benefit in those with higher CRP (placebo corrected difference for those with hsCRP \geq 3 mg/L was 27%) and more SI joint inflammation on MRI (SPARCC score of at least 2). It would therefore appear that the use in such subgroups would have an improved benefit-risk balance and a question on this has been raised. Thirdly, efficacy was only assessed in adults younger than 50 years of age and therefore an indication for all adults is not appropriate. Lastly, the efficacy data presented are only for signs and symptoms of disease and there were no data presented on the effect of etanercept on disease progression or structural damage.

The safety data presented were consistent with other approved populations and there were no new safety signals. The safety database was, however, of limited size with the maximum exposure duration of 24 weeks. Therefore data to at least one year should be presented. For undertaking the benefit-risk assessment the evaluator believes that the risks of etanercept in the nr-AxSpA population would be of a similar significant nature to that already established in other adult populations such as those with AS.

¹⁶ Sieper J, Rudwaleit M, Baraliakos X, et al.(2009). The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis*. 68(Suppl 2):ii1–44.

Given the issues discussed above, the evaluator believes the benefits in the proposed broad indication are insufficient to outweigh the significant treatment risks that are already established for etanercept. It is recommended that, due to the lack of data on disease progression, the indication should be limited to treatment of signs and symptoms which would be in line with the wording used for AS. Patients included in the study had active disease with a BASDAI ≥ 4 and a mean of 6.0 and therefore treatment should be limited to patients with this high level of disease severity. The clinical benefit of treatment in the broad population was marginal therefore tailoring treatment to higher responding subgroups would appear logical.

In summary, the evaluator believes that the efficacy in the broad proposed population, whilst statistically significant, is of marginal clinical benefit and would be outweighed by the significant and serious risks of the treatment. Overall, the benefit-risk balance of Enbrel, given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

The evaluator does not recommend that etanercept be authorised for the indication of:

Axial spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy (see CLINICAL TRIALS).

The reasons for this are:

- 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 younger than 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.

Clinical questions

Pharmacokinetics

1. Can the sponsor confirm that the formulation of etanercept registered in Australia is the same as that used in Study B1801031?

Pharmacodynamics

None.

Efficacy

1. From the inclusion and exclusion criteria for Study B1801031 it can be deduced that the criteria for 'non-radiographic' sacroiliitis would be sacroiliitis on screening X-ray of either Grades 0, 1 or 2 unilaterally or Grades 0 or 1 bilaterally. However if historical

X-rays were used, the grading requirement was lower at 0 to 1 unilaterally or Grade 0 bilaterally. Are these assumptions correct?

2. In B180131 there were 80 to 82% of subjects who met the inclusion criteria for ASAS based on imaging rather than clinical criteria. It was stated that this was due to the finding of sacroiliitis on MRI. Given that the X-ray findings were as follows for the 225 randomised subjects (Grade 2 unilateral=80; Grade 1 bilateral=53; Grade 0 bilateral=47; Grade 1 unilateral=45), could the sponsor confirm the criteria used in the trial for 'non-radiographic' axial SpA? Does the sponsor agree that non-radiographic axSpA in the trial could be defined as patients fulfilling the ASAS criteria for axSpA but without X-ray changes consistent with AS?
3. Discuss how non-radiographic axial spondyloarthritis is diagnosed in Australia. Are the ASAS criteria used routinely? Is there an accepted and utilised definition for the subgroup with 'non-radiographic' axSpA? What would be the likelihood of disease misclassification and would there be a risk of treating patients who do not meet the ASAS criteria?
4. There were numerous secondary endpoints discussed in the study report. Why was there no adjustment for multiplicity on analysis of these endpoints? Discuss the implications for not having done this on the reported findings.
5. In B180131 in the open label period, the response in the placebo group who switched to etanercept (placebo/ETN) is higher than in the ETN/ETN group (52% versus 44%). In addition, a rapid response occurred during the first 4 weeks of etanercept treatment that was more than seen in the etanercept group during the first 4 weeks of double-blind treatment. Could the sponsor comment on whether these findings are due to chance or if there may be other explanations?
6. In the evaluator's opinion, the efficacy of etanercept appears limited to patients with elevated hsCRP level and possibly also those with greater degree of inflammatory change on MRI of the SI joints. Discuss efficacy in these groups in further detail and whether the sponsor believes it would be preferable to target the indication to subgroups with a higher treatment response rate.
7. For sites in Russia and the Czech Republic only certain questionnaires were translated (BASDAI, BASFI, Subject Assessment of Disease, total pain and nocturnal back pain assessments) resulting in lower numbers in some analyses on health outcomes. Could the sponsor clarify this issue? How many patients did this involve? Can the sponsor provide assurances that there were no other outcomes which many have been affected by such issues to do with translation or language differences?

Safety

1. Grade 3 and 4 laboratory test results and liver function tests were reported in the study report for B1801031. Other laboratory parameters were not reported. Discuss whether there are any other findings of note on clinical chemistry, renal function and haematology in both the double blind and open label periods of this study.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the *Clinical questions* and the evaluator's comments on these responses please see Attachment 2 Extract from the CER.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of etanercept in the proposed usage are unchanged from those identified in the First round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of etanercept in the proposed usage are unchanged from those identified in First round evaluation.

Second round assessment of benefit-risk balance

After the first round evaluation there were a number of issues which led the evaluator to conclude the benefit-risk balance for etanercept was not favourable. The sponsor's response has addressed a number of the concerns which were discussed in First round benefit-risk assessment.

All subjects were required to have screening X-rays of the SI joints. Historical X-rays of the SI joints could be used instead but needed to be obtained within 4 months of the screening visit. All X-rays, including historical ones, were sent for central reading. In Germany only, historical X-rays could be obtained within 12 months of screening. If screening X-rays were not evaluable, they were repeated. All MRIs were conducted locally but read by a central reader.

As the sponsor explained in the response (Q1 Efficacy, Attachment 2), there were 18 (8%) of the 225 subjects who were included on historical X-rays with a range of up to 96 days prior to screening. From this, it is assumed that 207 patients had their X-rays for inclusion taken during the screening period. As these data could not be located in the clinical study report, the sponsor has been asked to verify if these are correct assumptions. It is noted that the inclusion criteria were more stringent in terms of sacroiliitis changes for these historical X-rays to ensure progression to AS had not occurred in the intervening period.

The study included axial SpA patients (by the ASAS criteria) who were not severe enough to be diagnosed with AS on X-ray (as per the modified New York (NY) criteria for AS: sacroiliitis Grade 3 to 4 unilaterally or Grade ≥ 2 bilaterally¹⁷). Of the 369 SI joint X-rays read centrally, 71 were found to have AS by the modified NY criteria³ and excluded (Grade 2 bilateral=25; Grade 3 bilateral=12; Grade 4 bilateral=1; Grade 3 unilateral=29; Grade 4 unilateral=4). There were a further 73 subjects excluded from the trial for other reasons. This resulted in 225 subjects randomised (224 treated) with 111 and 113 in the etanercept and placebo groups respectively. There were a further 10 (4.4%) subjects excluded as they were found not to meet the ASAS criteria, leaving the modified Intent-to-Treat (mITT) population with 106 and 109 etanercept and placebo treated subjects, respectively. The trial population was also noted to have more males than females (60:40) which is what would be expected in an early AS population.

The evaluator finds that classification of patients in this trial has been thorough and the X-rays were read centrally to ensure consistency. Given these facts, there is no evidence to suggest that the trial has inadvertently included patients with AS or that the results could have been driven by inclusion of the more severe AS population.

¹⁷ Grade 0: Normal. Grade 1: Suspicious changes. Grade 2: Minimal abnormality – small localised areas with erosions or sclerosis, without alteration in the joint width. Grade 3: Unequivocal abnormality – moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis. Grade 4: Severe abnormality – total ankyloses.

The terminology 'non-radiographic' for the subgroup of axial spondyloarthritis is perhaps confusing as it implies there should be no changes on radiology whereas the trial population could have sacroiliitis on screening X-ray of either Grades 0, 1 or 2 unilaterally or Grades 0 or 1 bilaterally (or if historical X-rays were used, the grading requirement was lower at 0 to 1 unilaterally or Grade 0 bilaterally). This is presumably because only Grade 2 or higher bilaterally, or Grade 3 or higher unilaterally, is regarded as positive evidence of radiographic sacroiliitis. In addition, the ASAS criteria allow for subjects to be classified by 'imaging criteria' of at least one SpA feature and sacroiliitis on MRI. In the submitted study, 80% of subjects met the criteria of MRI changes of sacroiliitis. Another way of thinking of the included trial population is patients fulfilling the ASAS criteria for axial SpA but without X-ray changes consistent with AS.

There are no data available on the effects of etanercept on disease progression or structural damage in nr-AxSpA. The evaluator agrees that there is some evidence of anti-inflammatory effects so agrees that the indication may remain '*treatment of nr-axSpA*'. Nevertheless, it is recommended that a statement be included in the Clinical Trial section of the PI which makes the lack of data on disease progression clear.

Clinical data are only available for adults aged ≤ 50 years while the indication covers all adults. The evaluator accepts that data are available in the older age group for other indications and that a majorly different safety profile in the older nr-axSpA population would not be expected. As such, the evaluator agrees that the indication may remain for treatment of 'adults'. Nevertheless, an appropriate precaution stating this lack of data should be added to the Precautions Use in the Elderly section of the PI. The sponsor has agreed to alter the indication to a subpopulation with elevated CRP or MRI change. The subgroup of patients in the study with elevated hsCRP or ASAS MRI sacroiliitis included 94 and 95 patients in the etanercept and placebo groups, respectively, and excluded 26 (12%) of patients from the mITT population. The response on the primary efficacy endpoint of ASAS 40 in the mITT population was 32.4 versus 15.7%, that is, a difference of 16.4%, which increased to 18.3% in the subgroup with high baseline hsCRP (≥ 3 mg/mL) or positive MRI. The highest response was those with elevated hsCRP (treatment difference of 29.7%) although this subgroup was notably smaller (n=92). The evaluator contends that this modest change in response rate difference is particularly important in improving the benefit-risk balance of the product as it makes it clear that the product is not to be used in a patient population without these objective inflammatory changes. The proposed indication does, however, need rewording to be more specific in delineating that the patient population need 'objective signs of inflammation'. This change would be in line with the approved EU indication.

One of the main issues with etanercept use in the nr-AxSpA population is the lack of efficacy and safety data beyond 24 weeks of treatment duration. At this stage, due to these data limitations and the fact that the treatment may carry considerable risks, it is recommended not to continue therapy beyond 12 weeks in patients who are not responding to treatment. A statement needs to be included in the product information under Dosage and Administration to cover this issue. The wording in the EU label is:

Available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

The evaluator recommends that a more definitive stand is taken and that the wording state that therapy should not be continued beyond 12 weeks in a patient not responding to treatment.

It is acknowledged that the pivotal Study B1801031 is still ongoing with its 92 week open label extension period. A final report is due in June 2015. These data will further define the long term (104 weeks) efficacy and safety of etanercept in the nr-AxSpA population. A

further planned Study B1801381 is listed in the Risk Management Plan (RMP). This study has a primary objective to measure the proportion of subjects with nr-AxSpA who flare following withdrawal of etanercept once ASAS 40 has been achieved. Secondary objectives include measuring the mean time to flare after withdrawal of etanercept and assessing the efficacy of retreatment in subjects who experience a flare after withdrawal of etanercept. These data will be important in assessing the relapse profile after treatment discontinuation and the safety and efficacy effects of retreatment. The sponsor states the final report for this study will be available in 2019. Data from both these studies will need to be submitted for evaluation when available.

As previously discussed, the appropriate selection of patients with the correct diagnosis in line with the proposed indication may not be straightforward and should be done by specialist rheumatologists versed in the ASAS criteria. This should be taken into account in the RMP.

In summary, there were a number of issues after the first round evaluation and these have been addressed in the second round evaluation. These include:

- The marginal clinical benefit has been increased to a small extent by limiting to patients with MRI changes and elevated CRP. This change makes it clear that the product must be targeted at patients with inflammatory changes and not used in a broader population. The indication has been altered to reflect this. The product information now makes it clear that there is no evidence on disease progression.
- The safety of the product would be improved by advising that treatment needs to be ceased after 12 weeks if there has been no clinical response.
- The need for long term safety can be addressed by the submission of the data from the open label period of the pivotal trial (data to 104 weeks).
- A proposed study on treatment withdrawal and retreatment should address concerns from lack of data in this area.
- The lack of data in adults over 50 years can be addressed by appropriate precautions and is filled to some extent by safety data from other indications.
- Revisions to the PI have largely been addressed and remaining issues have been outlined. The details of the PI revisions are beyond the scope of this AusPAR.
- It is recommended, due to the complexity in identifying the indicated population in clinical practice, that treatment be initiated by trained rheumatologists and this be specified in the RMP.

It is accepted that the increase in clinical benefit is small with limiting the indicated population to those with the appropriate inflammatory changes. Nonetheless, when this is taken into account together with the other actions listed above which will address the safety concerns, the evaluator finds that the benefit-risk balance of etanercept becomes favourable. This finding is subject to alteration of the indication and other aspects of the PI in addition to the provision of long term data when available.

Second round recommendation regarding authorisation

The evaluator recommends that etanercept be authorised subject to the following:

- Alteration of the indication. A proposed indication is:

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

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

- Acceptance of the changes to the PI.
- Ensuring the Consumer Medicine Information (CMI) matches the changes proposed in the PI, in particular the revised indication and the fact that it is not recommended to continue treatment beyond 12 weeks in those who have had no response.
- Submission of long term safety and efficacy data from Study B1801031 for evaluation.
- Conduct of Study B1801381 which will assess effects on efficacy and safety of treatment withdrawal and retreatment. Data will need to be submitted for evaluation as soon as available.
- Clarification of the following relating to inclusion of patients from historical X-rays. It is assumed from the data submitted that 18 out of 225 patients were included on the basis of historical X-rays and that these historical X-rays were taken no more than 96 days before trial entry at screening. The remainder of subjects (n=207) would therefore have had X-rays taken during the screening period. As these data could not be located in the clinical study report, could the sponsor clarify if this is correct?
- In order to ensure that patients are correctly identified for treatment according to the specific indication, it is recommended that treatment should only be initiated by appropriately trained rheumatologists.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 5.0 (dated 12 April 2013) with an Australian Specific Annex (ASA) dated 3 February 2014 which were reviewed by the TGA's Pharmacovigilance and Special Access Branch (PSAB).

Safety specification

The sponsor provided a summary of Ongoing safety concerns which are shown at Table 2.

Table 2: Sponsor's summary of Ongoing safety concerns

Important identified risks - all indications	Malignancy (including lymphoma and leukemia) Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection) Lupus-like reactions Sarcoidosis and/or granulomas Injection site reactions Allergic reactions Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome) Systemic vasculitis (including ANCA positive vasculitis) Macrophage activation syndrome Central demyelinating disorders Peripheral demyelinating events (CIDP and GBS) Aplastic anemia and pancytopenia Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis Liver events in patients with history of hepatitis (including hepatitis B virus reactivation)
Important identified risks - specific indications	Change in morphology and/or severity of psoriasis in adult and pediatric populations Worsening of CHF in adult subjects Inflammatory bowel disease in JIA subjects
Important potential risks – all indications	Autoimmune renal disease Pemphigus/pemphigoid Amyotrophic lateral sclerosis Myasthenia gravis Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Liver failure Hepatic cirrhosis and fibrosis Severe hypertensive reactions Adverse pregnancy outcomes Potential for medication error (pre-filled pen) Potential for male infertility Weight Gain
Important potential risks - specific indications	Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects
Important missing information – all indications	Use in hepatic and renal impaired subjects Use in different ethnic origins Use in pregnant women

Abbreviations: ANCA= antineutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barre Syndrome; JIA=juvenile idiopathic arthritis; TB=tuberculosis.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified Ongoing safety concerns. Additional pharmacovigilance activities have also been proposed to further characterise all the specified Ongoing safety concerns except for the important potential risk: 'Potential for medication error (pre-filled pen)' and the important missing information: 'Use in hepatic and renal impaired patients'.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified Ongoing safety concerns are sufficient. The exceptions appear to be all the specified important potential risks [bar 'Adverse pregnancy outcomes', 'Potential for medication errors (pre-filled pen)' and 'Acute ischemic CV events in adult subjects'] and the important missing information 'Use in different ethnic origins' for which no risk minimisation activities are proposed. Furthermore, additional risk minimisation activities have been proposed for the important identified risks: 'Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection) and 'Worsening of congestive heart failure in adult subjects; and the important potential risk: 'Potential for medication error (pre-filled pen)'.

Reconciliation of issues outlined in the RMP report

Table 3 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 3: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>1. The ASA has not been compiled in accordance with the current <i>Risk Management Plan (RMP) Questions & Answers</i>, as found on the TGA website. Specifically the approved indications in Section 1.1.1 of the ASA are imprecise and the differences in indication between the EU and Australia have not been identified or explained. Furthermore to be consistent references to the 'global RMP' in Section 3.8.1 of the ASA should be amended to refer to the EU-RMP. Consequently the sponsor should revise the ASA accordingly and provide an updated version to the TGA for review.</p>	<p>The sponsor acknowledged this recommendation and revised the ASA accordingly.</p>	<p>This is acceptable. Nevertheless the ASA will require further revision, preferably before this application is approved (see Recommendations 2, 4 and 5 below)</p>
<p>2. Safety considerations may be raised by the clinical evaluator and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p>The sponsor acknowledged this recommendation.</p>	<p>The clinical evaluator has suggested wording for the indication which differs from that stated in the updated ASA. Consequently the sponsor should revise the ASA accordingly if required, preferably before this application is approved.</p>
<p>3. Even though uveitis and scleritis are no longer classified as important potential risks, the sponsor should amend the ASA to state that routine pharmacovigilance and routine risk minimisation are nevertheless applied to these safety concerns.</p>	<p>The sponsor acknowledged this recommendation and has added the following sentence to Section 2.1 of the ASA: <i>'Routine pharmacovigilance is conducted for all adverse reactions in addition to the risks identified in the RMP.'</i></p>	<p>This proposal is only acceptable if the sponsor provides an assurance that future Periodic Safety Update Reports (PSURs) will specifically report on the safety concerns: uveitis and scleritis.</p>
<p>4. The studies referenced in the pharmacovigilance plan will generate safety data</p>	<p>The sponsor acknowledged this recommendation and revised the ASA accordingly.</p>	<p><i>Attachment 1 – Additional pharmacovigilance activities and estimated</i></p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. It is acknowledged that the sponsor's correspondence dated August 2013 states that all paediatric study reports and updates that are submitted to the EU will also be submitted to Australia with the same timelines. Nevertheless to this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.</p>		<p><i>Australian submission dates</i> of the updated ASA does not appear to be consistent with or as comprehensive as Table 85: '<i>Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan</i>' of the updated EU-RMP. Consequently the sponsor should correct this oversight and revise the ASA preferably before this application is approved.</p>
<p>5. The sponsor should be justify and/or correct the observed inconsistencies between Part 5.3: '<i>Summary Of Risk Minimisation Measures</i>' of the EU-RMP and Section 3.4: '<i>Safety concerns addressed in Australian PI</i>, latest version submitted to TGA on 8 January 2014 of the ASA.</p>	<p>The sponsor acknowledged this recommendation and revised the ASA accordingly.</p>	<p>Table 2: '<i>Review of Safety Concern Alignment for Australian PI (19 August 2014) and EU SmPC (28 July 2014)</i>' of the updated ASA does not appear to include any information about the important identified risk: '<i>Systemic Vasculitis (Including ANCA Positive Vasculitis)</i>'. Consequently the sponsor should correct this oversight and revise the ASA preferably before this application is approved.</p>
<p>6. At this time the sponsor's handling of the potential for medication errors using routine pharmacovigilance and routine and additional risk minimisation activities continues to remain acceptable.</p>	<p>The sponsor acknowledged this recommendation.</p>	<p>Not applicable.</p>
<p>7. The proposed Australian risk minimisation activities are similar to what were previously accepted for Enbrel. At this time they</p>	<p>The sponsor acknowledged this recommendation.</p>	<p>Not applicable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
continue to be acceptable.		
<p>8. It is acknowledged that the sponsor's correspondence dated October 2013 provided copies of the package leaflet: 'Patient Instruction Leaflet', the 'More about Juvenile Idiopathic Arthritis (JIA)' brochure, the 'How to use your Enbrel vials for dilution' brochure and the 'Joint Defenders' App Instruction Sheet. Nevertheless the sponsor should provide copies of these current printed educational materials as attachments to a revised ASA. Furthermore an aspect of a specific condition of registration associated with the sponsor other submission was the provision of an amended version of the 'How to use your Enbrel vials for dilution' brochure to the TGA for review within a certain timeframe. The sponsor should clarify whether this specific condition of registration was fulfilled.</p>	<p>The sponsor states: <i>'The sponsor submitted the package leaflet 'Patient Instruction Leaflet', the brochures 'More about Juvenile Idiopathic Arthritis (JIA)' and 'How to use your Enbrel vials for dilution', and the 'Joint Defenders' App Instruction Sheet to the TGA on 28 August 2013 in the JIA extension of indications application. The updated 'Patient Instruction Leaflet' version submitted on 28 August 2013 referred to the 50 mg powder (instead of the 25 mg powder) as it was the sponsor's intention to replace the currently marketed 25 mg powder with the 50 mg powder presentation. However, there is insufficient global demand to manufacture the 50 mg powder, and Pfizer Australia is unable to proceed with launching it. As a result, the 'Patient Instruction Leaflet' has now been amended back to refer to the 25 mg powder. The revised version is provided in Appendix 1 to this Response [not in this AusPAR] and is also attached to the revised ASA.'</i></p> <p>'The 'How to use your Enbrel vials for dilution' brochure was updated to include the JIA dosing volume information to address the condition of registration. Subsequent to this revision, the 'How to use your Enbrel vials for dilution' brochure was retired from distribution and this information was incorporated into the 'Enbrel Booklet'. The updated 'Enbrel Booklet' is provided in Appendix 2 [not with tis AusPAR] and is also attached to the revised ASA. Paediatric dosing information was also added to the 'Patient Instruction Leaflet' which is supplied as a package insert. The sponsor recently reviewed the patient education materials for Enbrel and determined that all printed disease state brochures for Enbrel indications, including 'More about Juvenile Idiopathic Arthritis (JIA)', would be retired from distribution. As this material is no longer in use, the 'More about Juvenile Idiopathic Arthritis (JIA)' brochure is not attached to the revised ASA. For completeness, the sponsor notes the disease state brochure 'More</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	about Paediatric Plaque Psoriasis', which fulfilled a condition of registration for the extension of indications for Paediatric Plaque Psoriasis, has also been retired from use. However, information about the use of Enbrel, <i>including dosing information specific to Paediatric Plaque Psoriasis, is now available to patients in the 'Enbrel Booklet'. The printed patient education materials currently available for Enbrel and attached to the revised ASA are the 'Patient Instruction Leaflet', the 'Enbrel Booklet', the 'Patient/Carer Diary' and the 'Joint Defenders' App Instruction Sheet.'</i>	
9. In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.	The sponsor acknowledged this recommendation.	Not applicable.
10. In regard to the proposed routine risk minimisation activities, the draft consumer medicine information document is considered satisfactory.	The sponsor acknowledged this recommendation.	Not applicable.

Summary of recommendations

It is considered that the sponsor's response to the TGA has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The sponsor was asked to respond to safety considerations raised by the clinical evaluator and/or the clinical evaluation report, in the context of relevance to the RMP. The sponsor acknowledged this recommendation. Nevertheless the clinical evaluator has suggested wording for the indication which differs from that stated in the updated ASA. Consequently the sponsor should revise the ASA accordingly if required, preferably before this application is approved.

It was noted that even though uveitis and scleritis are no longer classified as important potential risks, the sponsor should amend the ASA to state that routine pharmacovigilance and routine risk minimisation are nevertheless applied to these safety concerns. The sponsor acknowledged this recommendation and has added the following sentence to Section 2.1 of the ASA: *'Routine pharmacovigilance is conducted for all adverse reactions in addition to the risks identified in the RMP.'* However, this is only acceptable if the sponsor provides an assurance that future PSURs will specifically report on the safety concerns: uveitis and scleritis.

It was acknowledged that the sponsor's correspondence dated August 2013 states that all paediatric study reports and updates that are submitted to the EU will also be submitted

to Australia with the same timelines. Nevertheless it was suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies in the pharmacovigilance plan and the anticipated dates for their submission in Australia. The sponsor acknowledged this recommendation and revised the ASA accordingly. However *Attachment I – Additional pharmacovigilance activities and estimated Australian submission dates* of the updated ASA does not appear to be consistent with or as comprehensive as Table 85: *‘Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan’* of the updated EU-RMP. Consequently the sponsor should correct this oversight and revise the ASA preferably before this application is approved.

The sponsor was asked to justify and/or correct the observed inconsistencies between Part 5.3: *‘Summary of risk minimisation measures’* of the EU-RMP and Section 3.4: *‘Safety concerns addressed in Australian PI, latest version submitted to TGA on 8 January 2014’* of the ASA. The sponsor acknowledged this recommendation and revised the ASA accordingly. However, Table 2: *‘Review of Safety Concern Alignment for Australian PI (19 August 2014) and EU SmPC (28 July 2014)’* of the updated ASA does not appear to include any information about the important identified risk: *‘Systemic Vasculitis (including ANCA Positive Vasculitis)’*. Consequently the sponsor should correct this oversight and revise the ASA preferably before this application is approved.

The sponsor has voluntarily deleted the tabular summaries previously found in Section 3.3: *‘Safety concerns and overview of planned pharmacovigilance actions’* of the initial ASA. Consequently it is recommended that sponsor provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in a revised ASA, preferably before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

The European Risk Management Plan (Version 5.3, dated 15 September 2014), with an Australian Specific Annex (Version 3, dated 17 September 2014) to be revised as agreed with the TGA, must be implemented.

Key changes to the updated RMP

In their response to the TGA requests the sponsor provided an updated EU-RMP (Version 5.3, dated 15 September 2014) with an updated ASA (Version 3, dated 17 September 2014). Key changes from the versions evaluated at First round evaluation are summarised below.

Table 5: Key changes to the EU-RMP and ASA

Document	Key changes
EU-RMP	<p>EMA nr-AxSpA indication – updates resulting from evaluation and approval of the EU application:</p> <p>Ongoing Study B1801031 and planned Study B1801381 in subjects with nr-AxSpA were added as post authorisation efficacy studies.</p> <p>EMA nr-AxSpA indication – other updates carried out during the evaluation of the EU application:</p> <p>Study 0881A1-3338 (B1801014) was removed as an ongoing</p>

Document	Key changes
	<p>pharmacovigilance activity and post-authorisation efficacy study because the final study report was submitted to EMA July 2013, and it was added to as a completed activity.</p> <p>The date of the final report for the STORK study was modified to February 2015.</p> <p>Study B1801130 (088Y1-4689), listed with a projected completion of study November 2013, has been completed. The RMP has been updated to reflect that the due date of the final report is November 2014.</p> <p>More specific dates for the following studies were included as follows: BSRBR - December 2014; ARTIS - November 2014; German JIA – May 2016; OTIS (Amgen) - December 2014.</p> <p>Part IV Table 87 has been renamed to 'Ongoing efficacy/effectiveness studies' and Study 0881A1-3338-WW (B1801014) has been deleted from this Table as this has been completed.</p> <p>Elements for a Public Summary was revised to be within the maximum word limits noted in the 'Guidance on format of the risk management plan (RMP) in the EU – in integrated format' (25 July 2013), and the text was revised to be more understandable to the majority of the general public.</p> <p>In Annex 5 the due date of BADBIR was corrected to align with the date included in the main body of the RMP.</p>
ASA	<p>This document has now been compiled in accordance with the current <i>Risk Management Plan (RMP) Questions & Answers</i> as found on the TGA website, including Section 1.3: 'Differences in Indication'. Nevertheless the clinical evaluator has suggested wording for the indication which differs from that stated in the updated ASA.</p> <p>The tabular summaries previously found in Section 3.3: 'Safety concerns and overview of planned pharmacovigilance actions' of the previous ASA have been deleted.</p> <p>Table 2: 'Review of Safety Concern Alignment for Australian PI (19 August 2014) and EU SmPC (28 July 2014)' has been included.</p> <p>Attachment I – <i>Additional pharmacovigilance activities and estimated Australian submission dates</i> has been included.</p> <p>Attachment III – <i>Patient Education Materials</i> has been included.</p>

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval for etanercept with a revised indication of

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation, as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to NSAIDs. *Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 .*

The clinical evaluator initially recommended rejection of the submission because the efficacy data supported symptomatic relief rather than prevention of disease progression; the proposed indication included adults of all ages when data were only available for patients < 50 years; the indication was too broad for a positive benefit- risk balance to be achieved; there was no efficacy and safety data beyond 24 weeks of treatment; and there was a 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.

After evaluation of the sponsor's responses to the concerns the clinical evaluator concluded that although the clinical benefit was marginal, the benefit-risk balance was favourable based on the following:

- The sponsor revised the initial indication to add a statement about CRP and MRI with the proposed wording as follows:

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/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to NSAIDs'. The sponsor has also proposed reformatting of the indications and the removal of the instruction to refer to Clinical Trials where this text is included in an indication.

- Uncertainty about the number of patients affected by the use of historical X-rays was resolved to the satisfaction of the evaluator. Use of historical X-rays caused concern about the classification of patients but the evaluator was satisfied that measures were taken to ensure patients without AS were included and those with AS were excluded. The evaluator noted that 80% of patients had MRI findings of sacroiliitis.
- The PI should contain instructions that treatment should be ceased after the first 12 weeks of therapy in patients not responding, although the sponsor had not yet agreed to this statement.
- The long term safety can be addressed by the submission of data from the open label period of the study.
- There is a proposed study about treatment withdrawal and retreatment (Study 1081381).
- The lack of data in patients more than 50 years of age can be addressed through the PI and the extrapolation of safety data from other indications.

Pharmacology

No new pharmacology data were submitted.

Efficacy

Study B1801031

This was a Phase III, multicentre, 12 week randomised, double blind (DB), placebo-controlled, two-arm study with a 92 week open label extension period (total 104 weeks) in patients ≥ 18 years and < 50 years with active axial spondyloarthritis despite optimal NSAID therapy, to evaluate the efficacy of etanercept 50 mg SC, weekly taken together with a stable background NSAID at optimal dose. All patients who completed the 12 week DB period then entered a 92 week open label period of etanercept + NSAID therapy. The open label portion of the study is ongoing. An interim clinical study report encompassing the 12 week DB period and the first 12 weeks of the open label period was provided for evaluation.

Patients had a diagnosis of axial spondyloarthritis of more than three months but less than 5 years duration, a BASDAI¹⁸ of ≥ 4 , axial symptoms of back pain with a less than favourable response to at least 2 NSAIDs, taken separately, at optimal doses for a total combined duration of > 4 weeks. X-ray results from a central reader determined eligibility (to exclude AS). In all countries historical X-rays taken within 4 months of screening may have been utilised but the subjects with historical X-rays had to exhibit radiological sacroiliitis Grade 0 to 1 unilaterally or Grade 0 bilaterally. In Germany, for patients who were not eligible to have new spine and/or pelvic X-rays due to local regulations could have had X-rays accepted if they had been obtained within 12 months of screening.

Exclusion criteria were extensive including with patients that met the radiological criteria for AS, other inflammatory arthritis or orthopaedic or medical causes of chronic back pain, active infection, use of DMARDs (other than sulfasalazine, hydroxychloroquine or methotrexate) within 4 weeks of baseline, prednisolone >10 mg /day, recent parenteral steroid or previous biological response modifiers. Randomisation included stratification by MRI results (positive or negative for sacroiliitis).

The patients were 60.47% male and 73.49% White, with a mean \pm standard deviation (SD) age of 32.0 ± 7.8 years and a mean body mass index (BMI) of 25 kg/m^2 . Most met the inclusion criteria based on ASAS imaging rather than clinical criteria (82% of the etanercept group and 80% of the placebo group and the mean disease duration was 2.4 years. There groups were similar for other baseline characteristics, including prior use of DMARDs (26.13% of the etanercept group and 23.01% of the placebo group) although baseline use of corticosteroid was 10% (n=11) in the placebo group and 5% (n=5) in the etanercept group. Baseline NSAIDs were of similar potency. One NSAID at a time with a stable dose was permitted during the DB period. It could be ceased or the dose lowered during the open label treatment period. DMARDs (sulfasalazine, hydroxychloroquine or methotrexate) were allowed at a stable dose and oral corticosteroids needed to be ≤ 10 mg of oral prednisolone. Baseline BASDAI was 5.96 (SD 1.8) and 81% had sacroiliitis on MRI. The study had a 90% power to detect, at a 0.05 significance level, a difference of 25%

¹⁸ Bath Ankylosing Spondylitis Disease Activity Index: Garrett et al J Rheumatol 1994; 21:2286-2291
The Bath Ankylosing Spondylitis Disease Activity Index consists of a 1 to 10 scale (1 being no problem and 10 being the worst problem) which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

- Fatigue
- Spinal pain
- Joint pain/swelling
- Enthesitis
- Duration of morning stiffness
- Severity of morning stiffness

Each symptom is given a score of 0 – 10, the mean of the two scores relating to morning stiffness is taken and the resulting score (0 – 50) is divided by 5 to give the BASDAI. Scores of ≥ 4 suggest suboptimal disease treatment.

between the etanercept + NSAIDs groups (herein referred to as the etanercept group) and the placebo + NSAID group (herein referred to as the placebo group).

Two hundred and twenty five patients were randomised and 224 received at least one dose of study drug (111 in the etanercept group and 113 in the placebo group). Eighteen patients had historical X-rays up to 96 days prior to screening. SI joint findings were Grade 2 unilaterally in 80 patients, Grade 1 unilaterally in 45 patients, Grade 1 bilaterally in 53 patients and Grade 0 bilaterally in 47 patients. Ten patients (4.4%) did not meet the ASAS criteria. Fifteen patients discontinued in the DB period. Two hundred and nine completed the DB period, 208 entered the open label phase. At Week 24 there were 200 subjects (98 and 102 from the etanercept and placebo groups respectively), with 4 subjects from each group discontinuing. The reasons for discontinuation included not meeting the inclusion criteria (3 patients each group in the DB period and 1 in the open label period in the placebo group) and AEs (3 in the etanercept group in the DB period and 1 in the placebo group in the DB period and 1 in the open label period). Compliance with study medication was $\geq 80\%$ in all but one patient during the DB period and 98% in the open label period.

For the radiographic study endpoints, there was central reading of X-rays and MRIs with MRI scores provided by two independent readers and adjudication by a third if the results were discordant.

The primary efficacy endpoint of proportion of subjects with an ASAS 40 response¹⁹ at Week 12 compared with baseline (mITT population, Last observation carried forward (LOCF)):

- 15.7% placebo (+ NSAID)
- 32.4% etanercept (+ NSAID)
- Difference 16.6% (95%CI: 5.4%, 27.9%, p=0.0062)

At Week 24 (after 12 weeks open label therapy) the ASAS 40 response was observed in 44.0% of patients in the etanercept/etanercept group and 51.9% in the placebo/etanercept group.

In subgroup analyses, no baseline demographic or disease characteristics had a significant interaction on logistic regression of the primary endpoint. Patients with taking etanercept a higher baseline hsCRP had a greater ASAS 40 response at 12 weeks compared with those with a normal CRP (ASAS 40 at Week 12: 47.9% versus 20.7% for elevated versus normal hsCRP, respectively p = 0.0033 for the interaction on a post hoc fitted logistic regression of ASAS 40 on baseline hsCRP). There were trends for greater response if they had a higher Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint (SIJ) scores (ASAS 40 response at Week 12: 41.8% for score ≥ 2 versus 17.9% for a score < 2), HLA-B27 type (ASAS 40 response at Week 12: 39.4% for positive versus 21.2% for negative), age < 40 years (ASAS 40 response at Week 12: 36.8% < 40 years versus 15.8% ≥ 0 years) and with a history of uveitis (ASAS 40 response at Week 12: 62.5% with a history versus

¹⁹ Definition of ASAS 40 in Study B1081031

ASAS 40 responders were defined as subjects who satisfied the following criteria:

1. An improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 cm scale (converted from 0 to 100 mm) or an improvement of 100% for those domains that had a baseline score < 2 in at least 3 of the following four domains:

- Subject Assessment of Disease Activity,
- Mean of subject assessment of nocturnal pain and total back pain,
- Function represented by the BASFI score,
- Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.
- No worsening at all in any of the domains.

These definitions represent the 2005 EMA guideline on clinical investigation of medicinal products for the treatment of AS.

30.6% without a history). There was a similar response to etanercept based on baseline MRI sacroiliitis [ASAS 40 response: positive at baseline 33.3% (29/87) versus negative at baseline 31.6% (6/19)]. All subgroups had small numbers.

There were multiple other efficacy outcomes and analyses were undertaken without adjustment for multiplicity. Table 6 contains a tabulated summary of the key secondary endpoints. At Week 12, ASAS 20 responses were in 52.4% and 36.1% in etanercept and placebo groups, respectively. ASAS partial remission (a score of 2 or less [scale of 0 to 10 cm] for each of the 4 domains in the score) occurred in 24.76% of the etanercept group and 11.93% of the placebo group. Significant differences between the etanercept and placebo groups at 12 weeks were noted for subject assessment of disease activity, nocturnal and total back pain, lateral side flexion score, proportion of patients with ASDAS hsCRP 'inactive disease', BASDAI 50 and BASFI. The BASMI score between baseline and Week 12 was not statistically significant between the two groups. No statistically significant differences between etanercept and placebo groups were seen in quality of life and anxiety/depression scales.

Table 6: Summary of Selected Secondary Efficacy Endpoints Study B1801031

Variable	Week 12			Week 24	
	ETN N=106	Placebo N=109	p-Value	ETN/ETN N=100	Placebo/ ETN N=105
Clinical Outcomes - mITT					
ASAS 20, % of subjects	52.38	36.11	0.0195	65.00	71.15
ASAS Partial Remission, % of subjects	24.76	11.93	0.0209	32.00	42.86
ASAS 5/6, % of subjects	33.01	10.38	<0.0001	40.21	41.75
Subject Assessment Disease Activity, mean change (% improvement)	-2.06 (35.4)	-1.26 (21.9)	0.0102	-2.92 (50.6)	-3.21 (55.5)
Nocturnal back pain, mean change (% improvement)	-1.96 (35.3)	-1.03 (19.2)	0.0091	-2.79 (50.4)	-3.25 (60.4)
Total back pain, mean change (% improvement)	-1.99 (35.9)	-1.12 (20.5)	0.0064	-2.76 (50.0)	-2.92 (53.7)
BASDAI morning stiffness (2 items), mean change (% improvement)	-2.26 (34.6)	-1.43 (22.2)	0.0134	-3.71 (57.1)	-4.00 (61.9)
BASMI Lateral Side Flexion, mean change (% improvement)	1.63 (10.3)	0.45 (2.7)	0.0450	1.97 (12.4)	0.92 (5.5)
hsCRP, mean change (% improvement)	-2.98 (43.7)	0.14 (2.2)	0.0038	-4.62 (64.9)	-4.56 (72.0)
ASDAS hsCRP Inactive Disease, % of subjects	40.00	17.43	0.0004	42.86	58.10
ASDAS hsCRP, mean change (% improvement)	-1.10 (36.6)	-0.49 (16.6)	<0.0001	-1.48 (49.0)	-1.55 (52.7)
BASDAI 50, % of subjects	43.81	23.85	0.0029	50.00	62.86
BASDAI Total score, mean change (% improvement)	-1.96 (32.7)	-1.31 (22.0)	0.0186	-2.86 (48.0)	-3.26 (54.5)
BASFI Total score, mean change (% improvement)	-1.41 (33.4)	-0.84 (21.6)	0.0164	-1.89 (44.5)	-1.85 (48.3)
PGA, mean change (% improvement)	-2.74 (48.5)	-2.04 (40.0)	0.0156	-3.66 (63.9)	-3.26 (63.0)
BASMI, mean change (% improvement)	-0.31 (22.7)	-0.25 (21.3)	0.6871	-0.48 (35.7)	-0.32 (27.1)
Imaging endpoints - mITT					
SPARCC Sacroiliac Joint Score, mean change (% improvement)	-3.77 (46.9)	-0.84 (10.9)	<0.001	NA	NA
SPARCC-Spine 6 Discovertebral Units (DVU) Total Score, mean change (% improvement)	-2.12 (45.4)	-1.16 (33.4)	0.0414	NA	NA
ASSpMRI-a Total Score, mean change (% improvement)	-0.73 (40.9)	-0.33 (25.6)	0.0132	NA	NA

Abbreviations: ASAS=Assessment in Ankylosing Spondylitis; ASDAS=Ankylosing Spondylitis Disease Activity Score; ASSpMRIa=Ankylosing Spondylitis spine MRI score for activity; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; DVU=Discovertebral units; ETN=etanercept; hsCRP=highly sensitive C-reactive protein; mITT=modified intent-to-treat, N=the total number of subjects in the treatment group in the indicated population; NA=not assessed; PGA=physician global assessment; SPARCC=Spondyloarthritis Research Consortium of Canada.

Safety

In Study B1081031 a total of 217 patients were exposed to etanercept. The total exposure to etanercept in the etanercept/etanercept group from baseline to Week 24 of the open label phase was 47.4 patient years. In the DB period the rate of Treatment Emergent AEs (TEAEs) was 56.8% in the etanercept group and 45.1% in the placebo group. General disorders and administration site conditions (mostly injection site reactions) were higher with etanercept (18.0% versus 3.5%) as were Musculoskeletal and connective tissue

disorders (10.8% versus 5.3%) and Skin disorders (12.6% versus 4.4%). Infections/infestations were similar between groups (23.4% versus 22.1%). Of the events in that System Organ Class (SOC) the most common was infection (nasopharyngitis and sinusitis). In the open label period TEAEs were reported in 34.3% and 50.0% in the etanercept/etanercept and placebo/etanercept groups, respectively. The rate of treatment emergent infections was 12.0% compared with 9.9% and 8.8% in the DB period for the etanercept and placebo groups respectively, with the most frequently reported events were bronchitis and urinary tract infection (UTI) (1.4% each). At 24 weeks there was one opportunistic infection (herpes zoster in a 50 year old woman diagnosed about 6 months post commencement of etanercept that resolved with etanercept treatment interruption and valaciclovir) and one demyelinating disorder (multiple sclerosis (MS) in a 41 year old woman diagnosed with MS on Day 357). No deaths were reported to Week 24 of the study. Four patients (2 in each group) in the DB period and one in the open label period had serious AEs (SAEs). In the DB period there were 3 discontinuations due to AE in the etanercept group from hepatitis, worsening spondyloarthritis and asthenia. There was one AE related discontinuation in the placebo group from an anal abscess. One discontinuation in the open label period occurred due to acute bronchitis.

Grade 3 or 4 elevations of laboratory tests were more frequent with etanercept than placebo (2.7% versus 1.8%) in the DB period and 4.3% in the open label period. There were 5 cases of elevated liver enzymes; 2 in the DB period and 2 in the open label period in patients taking etanercept. There was one event of hepatitis (AST > 2 times upper limit of normal (ULN), ALT > 10 times ULN). Two patients had an ALT and/or AST <5 x ULN and had etanercept temporarily discontinued. None met Hy's Law criteria. Transient Grade 3 neutropenia occurred in 1% of patients in the open label phase. Immunogenicity was not specifically assessed in this study.

Etanercept was first marketed in 1998 and patients' exposure as of February 2013 was estimated at 3.6 million patient-years. The most common reason for treatment was rheumatoid arthritis and the most frequently reported serious events were pneumonia, sepsis, myocardial infarction and disease progression. The most frequent causes of death were infections, neoplasm and cardiac disorders. Spondylitis was the diagnosis among 125 cases with 4 cases of axSpA. The AEs reported were drug ineffective, uveitis, herpes zoster, increased ALT, hepatic steatosis and Sjögren's syndrome.

Clinical evaluator's recommendation

The evaluator recommends that etanercept be authorised subject to a series of conditions (see *Second round recommendation regarding authorisation* above).

Risk management plan

PSAB has accepted the EU Risk Management Plan for etanercept (Enbrel), version 5.3, dated 15 September 2014) with the Australian Specific Annex (ASA), Version 3 dated 17 September 2014.

The following were outstanding matters and should be followed up with PSAB in the sponsor's Pre Advisory Committee for Prescription Medicines (ACPM) Response:

- Revision of the ASA in accordance with the requirements of the RMP evaluator as outlined in the RMP evaluation report.

Risk-benefit analysis

Delegate's considerations

Efficacy

The study population comprised patients fulfilling the ASAS criteria for axial spondyloarthritis but without the radiological changes consistent with AS at the time the films were taken. This is a disorder for which the natural history is not well defined. It is not clear if some patients relapse and remit or what proportion of patients are likely to respond to NSAIDs alone.

The potential challenges with classification or misclassification in the relatively newly recognised clinical entity of nr-axSpA have been raised by the clinical evaluator, who has recommended that the use of etanercept for the proposed indication should be limited only to rheumatologists. However, the sponsor has proposed to provide Dosing and Administration advice that treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of a list of disorders that includes non-radiographic axial spondyloarthritis. In the Australian context this is most likely to be rheumatologists.

The study met its primary endpoint in that there was a statistically significant difference between the etanercept and placebo treatment groups at 12 weeks and the overall response was sustained at 24 weeks. Patients initially randomised to the placebo group in the DB period achieved an ASAS 40 response after 12 weeks of etanercept therapy in the open label period. Patients with an elevated hsCRP had a higher response rate and there were trends for a greater response in younger patients, HLA-B27 positivity and with a history of uveitis. There was no apparent difference between those patients who were positive or negative for sacroiliitis on baseline MRI, although the numbers were very small in the negative group. There were multiple additional endpoints, with most parameters measured showing a difference between etanercept and placebo, although spinal mobility as measured by the BASMI score and quality of life measures showed no improvement. It should be noted there was no adjustment for multiplicity in the analysis of these numerous endpoints.

The sponsor has relied on a single study with only 12 weeks of DB controlled data and a further 12 weeks of open label data, so for approximately half the participants in the study the exposure was only 12 weeks. The differentiation of the patients with nr-axSpA and AS relied heavily on the results of X-rays. In all countries these could have been 4 months out of date and in Germany could have been taken within 12 months. A higher threshold for eligibility was applied with radiological sacroiliitis Grade 0 to 1 unilaterally or Grade 0 bilaterally. There was no exclusion criterion based on MRI findings. There is the possibility of misclassification of the disease. In the trial 5 patients from the etanercept group and 4 patients from the placebo group failed to meet the ASAS classification. One additional patient ineligible patient was randomised but did not receive study medication. The patients that did not meet the ASAS criteria were excluded from the intention to treat analyses.

There were only 225 patients randomised to the study and of those 111 patients were randomised to etanercept arm of the DB period. By the end of the 12 week open label period only 200 patients remained in the study. Less than 100 patients were treated for 24 weeks with the etanercept and NSAID combination. Around 16% of patients had an ASAS 40 response on NSAIDs alone after meeting the eligibility criteria for the study (previous inadequate response to NSAIDs). The contribution from the ongoing NSAIDs to the response observed in the first 12 weeks of the open label phase of the study is uncertain.

The short duration of the study data presented in the submission is a major concern because patients with this nr-axSpA diagnosis are likely to require long term therapy and

long term efficacy data was not included in this submission. The postmarketing experience internationally is not of sufficient duration to provide an understanding of the long-term effectiveness of etanercept in patients with nr-axSpA. It is uncertain whether treatment with etanercept has disease modifying effects for those patients likely to progress to AS if untreated as is implied in the wording of the proposed indication. There was a greater reduction in SPARCC score at 12 weeks¹⁹ in the etanercept/NSAID group compared with the placebo/NSAID group and it is noted that there are imaging endpoints at 48 weeks and 104 weeks in the study protocol but the interim analysis of the study only included data to 24 weeks. The ACPM is requested to comment about the adequacy and sufficiency of the efficacy data in support of the proposed indication and the sponsor has been requested to provide any available updates to these data.

Safety and RMP

A relatively small number of patients have been exposed to etanercept for this proposed indication and there are insufficient numbers to detect uncommon or rare events in this specific population. The previously characterised safety profile is supported by the clinical data so far. No new safety concerns have been identified for this population but the exposure is of a short duration and the numbers of patients exposed relatively small. The known risks are outlined in the current PI. Because of the limited clinical trial exposure to date, it is uncertain whether the nr-axSpA population has the same risks as other populations with spondyloarthropathies, and as this is a heterogeneous population whether there are subgroups within the population that are more (or less) vulnerable to the known risks of etanercept. The sponsor has proposed to narrow the indication to include only those patients with objective evidence of active disease. The ACPM is asked to provide advice about whether the narrowing of the indication better defines the population of patients with nr-axSpA for which the benefit-risk is more likely to be favourable or if further refinement of the indication is required. It is unclear if there are sufficient efficacy gains among non-responders after 12 weeks of etanercept had sufficient efficacy gains to outweigh the potential risks of ongoing therapy. The sponsor will be requested to comment on this matter in the pre-ACPM response. ACPM is also requested to comment.

Dose

The dose of 50 mg SC weekly is consistent with the dosage regimen for the other spondyloarthropathies. The sponsor has included a twice weekly dosage regimen for nr-axSpA but clinical trial used a dosage regimen on 50 mg weekly. The sponsor will be requested to comment.

Indication

The sponsor has revised the initial indication to the following:

Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation, as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to NSAIDs.

This better reflects the subgroup of patients in the pivotal study in which the efficacy outcomes were most favourable. The ACPM is asked to provide comment about whether there are other parameters that should be included in the indication that better defines the population that is most likely to have a favourable benefit risk profile.

Data deficiencies

A single clinical study was provided in support of the new indication with only 111 patients taking etanercept in the 12 week DB arm. This DB period was for 12 weeks but only an additional 12 weeks of data from the open label phase of the study has been provided. A relatively small number of patients with nr-axSpA have been exposed to

etanercept and the interpretation of any subgroup analysis is limited by the small numbers.

Conditions of registration

The following are proposed as conditions of registration:

1. The implementation in Australia of the EU Risk Management Plan for etanercept (Enbrel), version 5.3, dated 15 September 2014 with the Australian Specific Annex (ASA), Version 3 dated 17 September 2014 and any subsequent revisions, as agreed with the TGA.
2. The following studies/reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
 - a. The final clinical study report for Study B1801031.
 - b. Study 1801381

Summary of issues

The primary issues with this submission are as follows:

1. Whether the duration of clinical trial experience, that is 12 weeks DB trial and 12 weeks extension is sufficient to support the extension of indication for a condition requiring long-term treatment.
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 a positive benefit-risk profile.

Questions for the sponsor

The sponsor is requested to address the following issues in their Pre-ACPM Response:

1. It is noted that 18 patients had historical X-rays for screening with a range of up to 96 days prior to screening. Did all the remaining patients have X-rays used for eligibility for study entry within the 4 week screening period?
2. Please indicate if any patients were recruited or screened prior to Protocol Amendment 2 to change the primary endpoint being implemented.
3. The date of the Clinical Study Report for Study B1081031 is 18 September 2013. Please indicate if there are any other interim analyses of Study B108301 planned prior to the completion of the final clinical study report at the conclusion of the 92 week open label period. If any updates are available please provide these in the Pre-ACPM response.
4. What proportion of the non-responders in the etanercept group in the double-blind period (at 12 weeks) achieved an ASAS 40 in the open label period?
5. For the psoriasis indications the sponsor has included specific advice in the Dosage and Administration section of the PI that treatment should be discontinued in patients that do not show a significant response at 12 weeks. For the nr-axSpA population, is there a similar treatment period beyond which non-responders should not be treated?
6. Please justify a twice weekly 25 mg dosage regimen for nr-axSpA, given the study was conducted with weekly 50 mg doses.
7. Please provide additional details about the diagnosis of hepatitis in the patient with elevated liver function tests. Please include the patient's medical history and results of serology and imaging.

Proposed action

The Delegate was not in a position to say, at this time, that the application for etanercept (Enbrel) should be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Is the nr-axSpA population adequately defined?
2. Is there a subgroup of patients with a diagnosis of nr-axSpA where spontaneous remission can be expected?
3. Is the 12 weeks of DB, controlled data plus the 12 weeks of open label efficacy data sufficient to support the proposed extension of indication?
4. Does the committee consider that the sponsor's proposed narrowing of the indication to include patients with active disease and objective evidence of inflammation is sufficient to identify patients for whom the benefits outweigh the risks? Are there other refinements of the indication that could further define this group of patients such as a BASDAI score of ≥ 4.0 ?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Pfizer Australia submitted an application to extend the indications for Enbrel (etanercept) to include treatment of patients with nr-AxSpA. The clinical evaluator noted a favourable benefit/risk balance in the indicated population when limited to those with appropriate inflammatory changes, and recommended approval subject to the revised indication.

In this pre-ACPM response, Pfizer would like to provide comments on issues raised in the TGA Delegate's Overview. The matters being addressed are identified by *italic* type.

The revised, proposed indication follows:

Treatment of adults with active non-radiographic axial spondyloarthritis 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 .*

The results from Study B1801031 presented in this application demonstrate significant clinical benefit of etanercept in subjects with nr-AxSpA. Pfizer strongly believes the benefit/risk balance of etanercept for the treatment of nr-AxSpA is positive in a well-defined patient population with active disease indicated by objective evidence of inflammation, that is, those with elevated CRP or MRI changes, despite treatment with NSAIDs.

Enbrel was first approved in Australia in September 2000 and with more than 15 years postmarketing experience internationally the safety profile of etanercept is well established. The postmarketing experience continues to grow with recent approvals for treatment of Enbrel in nr-AxSpA in the EU, Korea and Russia in addition to 9 smaller markets. Overall, the safety profile of etanercept in nr-AxSpA was found to be similar to the profile which has emerged from both clinical trials and postmarketing data of etanercept use for the treatment of current approved indications for AS and RA.

Summary of issues

1. *Whether the duration of clinical trial experience, that is 12 weeks DB trial and 12 weeks extension is sufficient to support the extension of indication for a condition requiring long-term treatment.*

Study B1801031 was designed and conducted in accordance with the 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis' CPMP/EWP/4891/03 which states under Section 3.2 Therapeutic Confirmatory Studies:

For products other than NSAIDs (e.g. TNF-inhibitors), percentage of patients with an ASAS 20 or preferably ASAS 40 at 12 or 24 weeks is also an acceptable endpoint' And 'AS is a chronic disease and, therefore, symptomatic treatment is expected to be maintained in the long term. Therefore, although efficacy may be demonstrated in 12- 24 weeks in controlled clinical trials, maintenance of the effect in longer extensions (e.g. 1 year) should be assessed...

It was also considered important to avoid a prolonged exposure of subjects to treatment with placebo thus 12 weeks of DB treatment was used.

In response to the Delegate's request to submit any other interim analyses of Study B1801031, a 48 week interim Clinical Study Report (CSR) is now available and is provided with this response. This report provides clinical, health and work outcomes and safety data to Week 48 and details the effect of etanercept on SIJ and spinal MRI inflammation at 48 weeks compared to baseline and 12 weeks. Additionally, this report presents results of a post hoc analysis evaluating the relationship between MRI and clinical outcomes. A summary of the results is presented below.

A total of 92% (208/225) of patients entered the open label phase at Week 12 (etanercept, n=102; placebo, n=106). The percentage of patients achieving ASAS 40 increased from 33% to 52% between Weeks 12 and 48 for etanercept/etanercept (ETN/ETN) and from 15% to 53% for placebo/etanercept (PBO/ETN) patients, within-group p-value <0.001 for both.

In a post hoc analysis of clinical outcomes, within-group improvement in response between Weeks 12 and 48 in the ETN/ETN group was significant at p<0.001 for ASDAS, BASDAI and BASFI; total back pain was significant at p<0.01; BASMI and CRP were not significant. Between Weeks 24 and 48, within-group improvement was significant at p<0.01 for BASFI; p<0.05 for ASDAS, BASDAI and total back pain; BASMI and CRP were not significant. This post hoc analysis indicates in the open label period that patients experienced greatest clinical improvement between Weeks 12 and 48.

For the dichotomous efficacy outcomes, the improvement in response between Weeks 12 and 48 was significant for all measurements except ASDAS inactive disease: p<0.001 for ASAS 40 and ASAS 5/6; p<0.01 for ASAS 20 and BASDAI 50; p<0.05 for ASAS partial remission.

Between Weeks 24 and 48, the within-group improvement in response was significant only for BASDAI 50 (p<0.05). So, for dichotomous as well as continuous efficacy outcomes, subjects in the ETN/ETN treatment group demonstrated continued clinical improvement between Weeks 12 and 48 that was greatest between Weeks 12 and 24.

Between Weeks 12 and 48, the health related quality of life and productivity outcome measurements of EuroQol EQ-5D Health State Profile (EQ-5D) utility score, SF-36 Physical Component Score (PCS) and Mental Component Score (MCS), and Work Productivity and Activity Impairment Questionnaire (WPAI) overall continued to improve. At 48 weeks, 64% (48/75) of subjects experienced a minimal clinically important difference (MCID) EQ-5D total index score improvement ≥ 0.05 , compared to 60% at 12 weeks. Between Weeks 12 and 48, the percentage of subjects with a ≥ 5 point improvement in the SF-36 physical component score increased from 52% (44/85) to 62% (48/77). The percentage of

subjects with a ≥ 5 point improvement in the SF-36 mental component score was maintained between Weeks 12 and 48 (40% for both time points).

Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ and spinal MRI scores continued to improve to Week 48. Between baseline and Week 48, mean (SD) improvement in SPARCC SIJ was -5.8 (10.3). The improvement between Weeks 12 and 48 was -1.1 (2.9).

Between baseline and Week 48, mean (SD) improvement in SPARCC spinal was -4.8 (11.3). The improvement between Weeks 12 and 48 was -1.9 (4.7). The within-group p-value for change from baseline to Week 48 and for Week 12 to Week 48 was <0.001 for all.

Overall, there was continued improvement in most clinical, quality of life, and laboratory measures from the start of the open label period at the 12 week time point to the 48 week time point. The overall efficacy patterns observed in the study were consistent with those found in previous etanercept studies in subjects with AS and there were no new or unexpected safety findings. The overall benefit/risk of etanercept treatment in this well-defined patient population was positive.

The duration of clinical trial experience of 12 weeks DB trial and 48 weeks open label extension is consistent with the EU guidance and is considered sufficient to support the extension of indication as requested.

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 a positive benefit-risk profile.*

The initial application sought approval for the nr-AxSpA indication:

Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy.

This indication was modified to include objective criteria of elevated CRP and/or MRI change as requested by the clinical evaluator and supported by the Delegate.

Further refinements are now proposed for the indication wording in this Pre-ACPM Response to include '*objective signs of inflammation*' and the definition of '*active*' (BASDAI score ≥ 4). These amendments further clarify and strictly define the nr-AxSpA patient population proposed for treatment with Enbrel. Pfizer proposes the following indication for consideration by the ACPM:

Treatment of adults with active non-radiographic axial spondyloarthritis 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. Advice sought from ACPM

- a. *Is the non-radiographic axial spondyloarthropathy (nr-axSpA) population adequately defined?*

To be certain of the diagnosis of nr-AxSpA and ensure that patients with AS were not included in the study, subject selection for Study B1801031 was based on strict adherence to the ASAS classification criteria for nr-AxSpA and the requirement that no subject was to meet the 1984 modified NY criteria for AS³.

The study utilised central reading of pelvic X-rays to determine whether a subject met the ASAS criteria for sacroiliitis, to ensure AS patients were excluded from the study. Subjects with axial spondyloarthritis as defined by the ASAS classification criteria but with

radiographic sacroiliitis of Grade 3 to 4 unilaterally or Grade 2 bilaterally as defined in the modified NY criteria for AS³, were excluded from the study.

The proposed indication wording above well defines the nr-AxSpA population studied for which a positive/benefit risk profile has been demonstrated.

- b. Is there a subgroup of patients with a diagnosis of nr-axSpA where spontaneous remission can be expected?*

A subgroup of patients with a diagnosis of nr-AxSpA where spontaneous remission can be expected has not been identified to date. There is no universally accepted measure of remission in nr-AxSpA but a widely used measure is ASAS partial remission. In Study B1801031, 13 out of 109 (12%) of placebo subjects achieved this milestone after 12 weeks, as compared to 25 out of 105 (24%) in the etanercept treatment group. This number of placebo subjects is too small to conduct a meaningful subgroup analysis.

- c. Is the 12 weeks of DB, controlled data plus the 12 weeks of open label efficacy data sufficient to support the proposed extension of indication?*

The sponsor acknowledges the Delegate comment on duration of study data and the evaluator assessment of a small clinical benefit considering the 24 week data available. Study 1801031 was designed with consideration to the EU 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis CPMP/EWP/4891/03', which states '*the percentage of patients with an ASAS 20 or preferably ASAS 40 at 12 or 24 weeks is also an acceptable endpoint*'.

Study 1801031 achieved its primary endpoint and was supported by a wide range of secondary endpoints that also showed improvement in clinical signs and symptoms, disease activity, imaging assessments of inflammation of the SI joints and spine, and subject reported outcomes. As requested by the Delegate, further interim analysis data is now available and a 48 week interim CSR is provided with this response. The 48 week CSR reports the percentage of patients achieving ASAS 40 increased from 33% to 52% between Weeks 12 and 48 for ETN/ETN and from 15% to 53% for placebo (PBO)/ETN patients, within-group p value <0.001 for both. This clearly demonstrates the clinical benefit of Enbrel treatment in nr-AxSpA is significant and robust, with continued efficacy in the longer-term. Please see response to Summary of Issues Question 1.

- d. Does the committee consider that the sponsor's proposed narrowing of the indication to include patients with active disease and objective evidence of inflammation is sufficient to identify patients for whom the benefits outweigh the risks? Are there other refinements of the indication that could further define this group of patients such as a BASDAI score of ≥ 4 ?*

The sponsor amended the indication and refined the patient population to include 'objective signs of inflammation' and define 'active' as a BASDAI score of ≥ 4 , as requested in the second round clinical assessment and supported by the Delegate.

The clinical evaluator noted a favourable benefit-risk balance in the indicated population when limited to those with appropriate inflammatory changes, and recommended approval subject to the revised indication. Please also see response to Summary of Issues Question 2.

RMP evaluation

The Delegate notes:

Indication

The indication in the ASA has been updated to reflect the recommendations of the Request for ACPM Advice and is identical to the indication proposed in this Pre-ACPM Response.

Uveitis and scleritis

Pfizer provides an assurance that future Enbrel PSURs will specifically report on the safety concerns: uveitis and scleritis when such cases occur.

Submission of paediatric study reports

Attachment 1 of the updated ASA has been amended to include all paediatric study reports and updates in the RMP pharmacovigilance plan that will be submitted to Australia.

Systemic Vasculitis (Including ANCA Positive Vasculitis)

Table 2 of the updated ASA has been amended to include the important identified risk 'Systemic Vasculitis (Including ANCA Positive Vasculitis)'.

Pharmacovigilance plan and risk minimisation plan summary table

The sponsor removed the tabular summary previously located in Section 3.3 of the ASA as it duplicated content in the EU RMP and was not Australian specific. A summary of the proposed pharmacovigilance plan is provided in the EU RMP and is now referenced in the ASA. A tabular summary of the risk minimisation activities for Australia has been provided in Section 4 of the ASA.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Enbrel Powder and solution both containing 25 mg and 50 mg of etanercept to have an overall positive benefit-risk profile for the amended indication;

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 (see CLINICAL TRIALS).*

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

In making this recommendation the ACPM acknowledged that the aim of treatment is to cover both those with inflammatory back symptoms prior to X-ray changes and those already with visible changes. Earlier treatment appears to improve disease course and overall prognosis. One of the reasons for delayed diagnosis is the requirement for X-ray changes. It was noted that ASAS criteria have been validated.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI); with the modification of the indication as proposed above.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Is the non-radiographic axial spondyloarthritis (nr-axSpA) population adequately defined?*

The ASAS criteria appear to be reasonably sensitive and specific. However, they have not been validated outside specialist clinics. Restriction to align with the pivotal study inclusion criteria appears appropriate as the Sponsor has agreed.

2. *Is there a subgroup of patients with a diagnosis of nr-axSpA where spontaneous remission can be expected?*

The ACPM advised that spontaneous remission is possible in most inflammatory rheumatic diseases. However, the rate of spontaneous remission is unknown. Another uncertainty is the rate of relapse once TNF inhibitors are ceased in nr-axSpA patients (approximately 80% in AS patients).

3. *Is the 12 weeks of double-blind, controlled data plus the 12 weeks of open label efficacy data sufficient to support the proposed extension of indication?*

The evidence just meets the EMA guideline standards. However, there are many uncertainties. Given that treatment may be lengthy, registration should be conditional on provision of longer term data as well as a randomised study of whether patients are able to cease drug. In addition, further information on what is an appropriate course of therapy prior to declaring a lack of response and ceasing treatment (i.e. 12 weeks, 16 weeks or longer).

The ACPM advised that the trial cut-off of 12 weeks for treatment failure should be applied unless the sponsor can provide data in support of suitable response over a longer duration.

Further long term data is required to determine if etanercept has an effect on imaging outcomes and long term disability in nr-axSpA. In AS, NSAIDs (but not TNF inhibitors), have been shown to retard radiographic progression.

4. *Does the committee consider that the sponsor's proposed narrowing of the indication to include patients with active disease and objective evidence of inflammation is sufficient to identify patients for whom the benefits outweigh the risks? Are there other refinements of the indication that could further define this group of patients such as a BASDAI score of ≥ 4.0 ?*

The ACPM advised that requiring both CRP plus MRI changes at this point of time would be suitable. Including the BASDAI, as has been agreed by the sponsor, is endorsed.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Enbrel containing etanercept (rch) for the new indication:

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/or MRI change who have had on moderate response to NSAIDs.*

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

Specific conditions of registration applying to these goods

1. The etanercept EU Risk Management Plan (IEU RMP), version 5.3, dated 15 September 2014 with an Australian Specific Annex (version 4, dated 19 January 2015), included with submission PM-2013-04552-I-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The provision, as evaluable data as part of category 1 submissions to the TGA, of each of the following studies being conducted by you:
 - a. The final study report for the open label extension of Study B1801031
 - b. Study 180381 to investigate the withdrawal and retreatment of adult subjects with non-radiographic axial spondyloarthritis.

Attachment 1. Product Information

The Product Information approved for Enbrel at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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