Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Etanercept (rch)

Proprietary Product Name: Brenzys

Sponsor: Samsung Bioepis AU Pty Ltd[1]

June 2017

Updated July 2017

TGA Health Safety Regulation

[1] ERA Consulting Pty Ltd was the sponsor of this submission but after the inclusion of the product on the ARTG the sponsor was changed to Samsung Bioepis AU Pty Ltd.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
AE	Adverse Event
ANOVA	Analysis of Variance
AS	Ankylosing Spondylitis
AUC_{inf}	Area Under Concentration-Time curve from time zero to infinity
AUC_{last}	AUC-Time curve from time zero to last detectable drug concentration
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body Mass Index
CI	Confidence interval
CL/F	Apparent Drug Clearance
C_{max}	Maximum serum concentration
CRP	C-Reactive Protein
CS	Corticosteroids
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-Rheumatic Drug
ESR	Erythrocyte Sedimentation Ratio
ETN	Etanercept
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
GCP	Good Clinical Practice

Abbreviation	Meaning
HAQ-DI	Health Assessment Questionnaire – Disability Index
ITT	Intention-to-Treat
JSN	Joint Space Narrowing
LEF	Leflunomide
mTSS	modified Total Sharp Score
MTX	Methotrexate
Nab	Neutralising Antibodies
NSAID	Non-Steroidal Anti-Inflammatory Drug
NRI	Non-Responder Imputation
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per Protocol Set
PsA	Psoriatic Arthritis
PSOR	Plaque Psoriasis
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to C_{max}
TNF	Tumour Necrosis Factor
TNFR	Tumour Necrosis Factor Receptor
ULN	Upper Limit of Normal

Abbreviation	Meaning
US	United States (of America)
VAS	Visual Analogue Scale

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	15 July 2016
Date of entry onto ARTG	22 July 2017
Active ingredient:	Etanercept (rch)
Product name:	Brenzys
Sponsor's name and address:	Samsung Bioepis AU Pty Ltd, 201 Elizabeth Street, Sydney NSW 2000[2]
Dose form:	Solution for Injection
Strengths:	50 mg and 50 mg
Containers:	Prefilled syringe Auto-injector
Pack size:	4s
Approved therapeutic use:	***Adults(~ 18 years)***

Rheumatoid arthritis

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

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

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. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque psoriasis

Adult patients with moderate to severe chronic Plaque psoriasis,

[2] ERA Consulting (88 Jephson St Toowong QLD 4066) was the sponsor of this submission however after the inclusion on the ARTG of Brenzys prefilled syringe and auto-injector, the sponsor changed to Samsung Bioepis AU Pty Ltd.

	who are candidates/phototherapy or systemic therapy ***Ankylosing spondylitis*** *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 an inadequate response to NSA/Ds.* **Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAIJ score of ≥4*
Route(s) of administration:	Subcutaneous (SC)
Dosage:	50 mg once weekly[3] see PI (Attachment 1) for further details.
ARTG numbers:	245252 prefilled syringe and 245253 auto injector

Product background

This AusPAR describes the application by the sponsor, ERA Consulting (Australia) Pty Ltd, to register etanercept (Brenzys) as a biosimilar of the reference product etanercept (Enbrel) by Pfizer Australia Pty Ltd.

The sponsor is applying for the same indications as approved for Enbrel but only the adult indications and not the paediatric indications of juvenile idiopathic arthritis or paediatric plaque psoriasis as follows:

> *Brenzys is indicated for the treatment of:*
>
> ***Adults (≥ 18 years)***
>
> ***Rheumatoid arthritis***
>
> *Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Brenzys can be used in combination with methotrexate.*
>
> *Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.*
>
> ***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. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.*
>
> ***Plaque psoriasis***
>
> *Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.*

[3] ***Plaque psoriasis***: Higher responses may be achieved from initial treatment for up to 12 weeks with a dose of 50 mg given twice weekly, after which, the dose should be reduced to the standard dose of 50 mg per week. Treatment should be discontinued in patients who do not show a significant PASI response after 12 weeks. If re-treatment with Brenzys is indicated the dose used should be 50 mg per week.

Ankylosing spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

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 an inadequate response to NSAIDs.*

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

Brenzys, also known as SB4, is not indicated for use in children less than 18 years of age. Brenzys is only presented as a 50 mg pre-filled syringe and 50 mg pre-filled auto-injector, while the recommended dose of etanercept for paediatric patients is 0.8 mg/kg given once weekly.

This is the first biosimilar version of etanercept (Enbrel).

Etanercept is a soluble Tumour Necrosis Factor (TNF) receptor (TNFR) p75 fragment, crystallisable fusion protein that competitively inhibits human tumour necrosis (TNF) by binding to it, and thereby preventing the interaction between TNF and TNFR. As a consequence, TNF is rendered biologically inactive because TNF mediated signal transduction requires cell surfaces receptors to be cross-linked. Brenzys consists of a genetically produced dimer of a chimeric protein engineered by fusing the extracellular ligand binding domain of human TNFR-2 to the fragment crystallisable region domain of human IgG1. Brenzys is produced by DNA technology in a Chinese hamster ovary mammalian expression system.

In this submission, similarity to Enbrel (reference product) is claimed and the submission is clinically supported by a single pivotal Phase III study comparing the efficacy and safety of Brenzys with Enbrel in RA patients (with an open label extension) and a single Phase I study providing pharmacokinetic and safety data in healthy male volunteers. The development program for Brenzys was guided by the European Medicines Agency (EMA) and FDA requirements for biosimilar medicines.

The reference drug, Enbrel, used in the pivotal Phase III study was sourced from the European Union (EU) and a bridging comparability exercise was undertaken with the Australian registered Enbrel. The healthy volunteer study compared Brenzys with EU and US sourced Enbrel.

The TGA has produced a specific guideline in relation to biosimilar medicines, along with the adoption of numerous EU guidelines that explain the background to biosimilars and regulatory aspects. The TGA published guideline is called 'Evaluation of biosimilars' which was published on 30 July 2013 (https://www.tga.gov.au/publication/evaluation-biosimilars) and was recently updated in December 2015. This guideline notes that a biosimilar medicine is a version of an already registered biological medicine that:

- Has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies.
- Before a biosimilar medicine can be registered in Australia, a number of laboratory and clinical studies need to be performed to demonstrate the comparability (biosimilarity) of the new biosimilar to the reference biological medicine already registered in Australia.
- The TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on the assessment of comparability.

- For a biosimilar to be registered in Australia, the reference medicine must be a biological medicine that has been registered in Australia based on full quality, safety and efficacy data and the Australian reference medicine must have been marketed in Australia for a substantial period and have a volume of marketed use so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications. However it may be possible for the sponsor to compare the biosimilar in certain clinical studies and in in vivo non-clinical studies to a medicine not registered in Australia in which case the reference medicine must be approved for general marketing by a regulatory authority with similar scientific and regulatory standards as the TGA (such as EMA or US FDA) and a bridging study must be provided to demonstrate that the comparability studies are relevant to the Australian reference medicine.
- To justify extrapolated indications based on the adopted EU guideline[4].
- To have a clearly distinguishable tradename from all other products and the active ingredient is to use the same name as the reference's active ingredient without a specific biosimilar identifier suffix. The WHO is considering a naming convention for the active ingredients of all biological medicines, including biosimilars.
- The inclusion of comparative clinical trial information in the PI along with a clear distinction of the clinical trial information generated on the reference medicine.
- There may be post-registration requirements and all biosimilars must have an RMP.

There are a number of specific EU guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/556/95 Rev 1: Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001). Effective: 29 January 2007
- EMEA/CHMP/EWP/438/04: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. Effective: 5 February 2008
- CPMP/EWP/4891/03: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Effective: 23 February 2010
- CHMP/EWP/2454/02: Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis. Effective: 28 July 2005
- CHMP/437/04/Rev 1: Guideline on Similar Biological Medicinal Products. Effective: 25 May 2015
- EMEA/CHMP/BMWP/14327/2006: Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins. Effective: 22 June 2009
- EMEA/CHMP/BMWP/42832/2005/Rev 1: Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues. Effective: 1 July 2015

Regulatory status

This is an application for a new biological entity.

Brenzys has been approved in Europe (January 2016) under the name Benepali with only a 50 mg strength. It was also approved in Canada in August 2016. In Europe all five

[4] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues Section 6

indications were approved however in Canada the sponsor has only applied for two indications of RA and Ankylosing Spondylitis (AS). The approved indications in Europe are as follows:

Rheumatoid arthritis

Benepali in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate.

Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Benepali is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease modifying antirheumatic drug therapy has been inadequate. Etanercept has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Axial spondyloarthritis

Ankylosing spondylitis

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

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).

Plaque psoriasis

Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

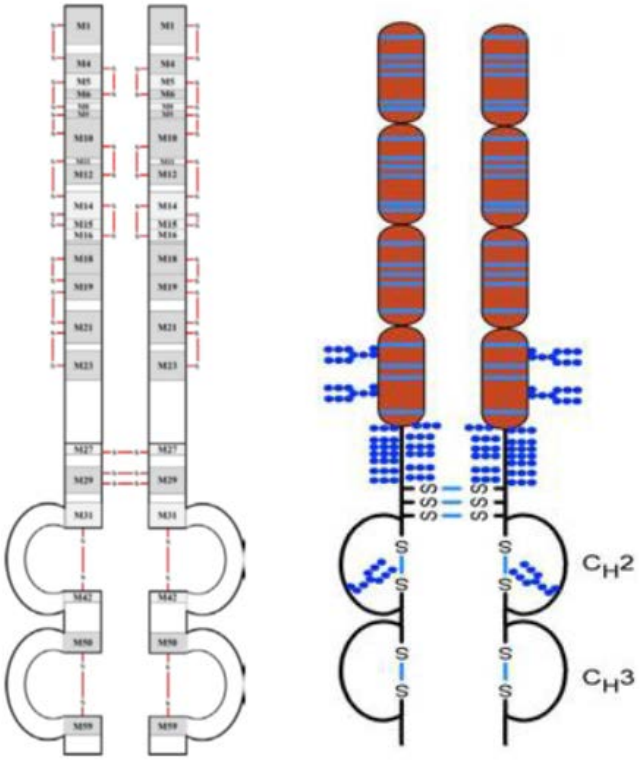
II. Quality findings

Drug substance (active ingredient) and Drug product

Structure

Brenzys is a homodimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human TNFR2/p75 to the Fc domain of human IgG1. SB4 is produced by Chinese hamster ovary (CHO) cell expression system as a dimeric, secreted, soluble protein. The Fc component comprises the hinge, CH2 and CH3 regions but the CH1 region is excluded. The Fc region is dimerised via 3 disulphide bonds. SB4 consists of 934 amino acids (467 for the single chain) and has a molecular weight (MW) of approximately 130 kDa. Below is a schematic structure of Brenzys.

Figure 1: Schematic structure



MW: 130 kD

The drug product contains etanercept (ETN), sucrose, sodium chloride, Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic heptahydrate and Water for Injection.

Biosimilarity

Enbrel etanercept (rch) 50 mg solution for injection pre-filled syringe (AUST R 124422) is the reference product in the studies. The studies used a non-Australian reference product (EU Enbrel); as the EU Enbrel is manufactured from a different site as the Australian registered product (AU Enbrel), the company also provided a bridging comparability study between AU Enbrel and EU Enbrel.

Analytical test methods were selected from the methods applied in the similarity assessment based on ICH Q6B[5]. Each category except[information redacted]included at least one representative method to demonstrate the comparability.

The structural, physicochemical and biophysical attributes of SB4 and EU Enbrel (AU Enbrel) were studied. Based on all the comparison studies, biosimilarity has been fully demonstrated with respect to quality aspects between SB4 and Enbrel.

It is noted that SB4 has:

- a lower level of high molecular weight product aggregates than that of EU Enbrel; *no new peaks are identified and the chromatograms of SB4 and EU Enbrel overlap almost completely*.
- a lower level of host cell protein impurities than the EU Enbrel. *There is an order of magnitude reduction in SB4 compared to Enbrel but these measurements were in ppm (microgram/mg protein). When this is related to the fact that the product contains only 50 mg of the active ingredient, the difference in the HCP content is in nanograms. This by any measure is very small. The lower contents of these proteins in SB4 could be seen as making it safer 'immunogenically' compared to Enbrel.*
- in terms of glycan profile
  - The N-linked glycosylation sites of SB4 and Enbrel are identical.
  - The relative quantity of N-glycan species by Hydrophilic Interaction Ultra-performance Liquid Chromatography (HILIC-UPLC) showed that SB4 has a higher the afucosylated glycan content than Enbrel and the charged glycan content in SB4 is lower than observed in Enbrel.
  - All O-linked glycosylated sites identified in SB4 are identical to those found in Enbrel.
  - The O-linked glycans were analysed by β-elimination .The results showed that SB4 and EU Enbrel are similar in terms of some of their content. The content of [information redacted] in SB4 is slightly higher compared to EU Enbrel.

The differences in glycan profile are very minor, similarity ranges are quite narrow and more importantly, there are no new glycan species detected. Implications of these differences can only be borne out in the clinical or nonclinical studies.

All manufacturing steps are validated.

The sponsor is required to provide valid GMP clearances for all manufacturing sites for product registration.

Specifications

All analytical procedures are validated.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data show that the drug product is light sensitive and degradation is significant in the naked syringe. However, in the commercial pack no significant changes are observed.

[5] ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. Note For Guidance On Specifications: Test Procedures And Acceptance Criteria For Biotechnological/Biological Products

The shelf life is three years when stored at 2-8°C.

The drug product may be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks. It should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

Stability studies have been conducted in accordance with relevant ICH guidelines.

Degradation pathways assessed include oxidation and freeze-thaw cycles.

Details of the potency assays

Competitive inhibition binding assay to TNF-α by FRET and TNF-α neutralisation assay by reporter gene for biological activities.

Biopharmaceutics

For bioavailability/bioequivalence, see *Clinical findings* below and Attachment 2.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Brenzys.

Issue that requires the attention of clinical delegate

The GMP clearances are still under review by the TGA GMP Clearance Unit. The sponsor is required to provide valid GMP clearances for all manufacturing sites for product registration.

Proposed conditions of registration for delegate

Batch release testing

1. It is a condition of registration that all batches of Brenzys imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Brenzys imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

   The sponsor must supply:

   a. Certificates of Analysis of all active ingredient (drug substance) and final product.

   b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

   c. Evidence of the maintenance of registered storage conditions during transport to Australia.

   d. One pack of 4 pre-filled syringes or one pack of auto-injector pens of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Compliance with Certified Product Details (CPD)

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

III. Nonclinical findings

Introduction

The submitted nonclinical dossier was in accordance with the relevant guideline[6], containing comparative in vivo pharmacology, pharmacokinetic and toxicity studies. Comparative in vitro pharmacology studies were submitted in Module 3 and evaluated by the quality evaluator.

The EU and US-sourced Enbrel were used as comparators in the nonclinical studies. The Australian-sourced Enbrel was not used, and no nonclinical data were provided to verify the comparability of the various sources of Enbrel. Provided adequate comparability of the EU/US-sourced and Australian sourced versions of Enbrel is demonstrated in Module 3, the submitted nonclinical dossier is considered adequate.

Pharmacology

Etanercept inhibits binding of tumour necrosis factors, TNF-α and TNF-β (LT-α), to its soluble and cell surface receptors. The pharmacological activity of the Brenzys and the EU Enbrel forms of etanercept were compared in a series of in vitro assays (evaluated by the quality evaluator). There was no significant difference between the two test items in terms of their binding of human TNF-α and LT-α3 and similar results were observed in a TNF-α neutralisation assay. There were no significant differences between the two test items in binding TNF-α from different species.

The presence of an Fc domain indicates a potential for etanercept to interact with Fc receptors and the immune system, but this is not important for the efficacy of the test item. There were no significant differences in the binding affinities for the two test items against FcγRI, FcγRIIa, FcγRIIb and FcRn. The Brenzys form of etanercept appeared to have a greater affinity for the FcγRIIIa (V-type and F158 allotype) and FcγRIIIb receptors, which may be associated with the slightly higher levels of afucosylated N-glycans on the Brenzys form of etanercept. However, the affinity was still considered to be low (in the micromolar, rather than nanomolar range), and there was no significant difference in the toxicity profile of the two test items in cynomolgus monkeys. Therefore, this difference is not expected to affect the safety profile of the drug. There were no significant differences between the test items in the C1q (complement) binding assay, CDC assay, ADCC assay and in an assay to assess apoptosis of cells with membrane-expressed TNF-α.

In a mouse model of collagen-induced arthritis, an acceptable and established animal rheumatoid arthritis model, Brenzys (intraperitoneally (IP)) was effective at slowing the progression of disease and improving tissue pathology (including preservation of cartilage). There was no significant difference in efficacy at doses of 1 to 10 mg/kg IP every

[6] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues: EMA/CHMP/BMWP/403543/2010

3 days (1 to 10 times the clinical dose on an mg/kg basis). When compared with Enbrel sourced from the EU and US, at equivalent doses there was no significant difference in the clinical response. However, in the more sensitive histopathology assessments, higher mean severity scores were observed with Brenzys than with either Enbrel batch (4.4 compared to 1.5-2.3 with a 1 mg/kg dose). This trend appeared to be fairly consistent when considering the data in different ways (such as different doses, different tissue sections and incidences in different severity ranges). This suggests that Brenzys was weaker in efficacy than Enbrel in this assay. It is unknown if this difference is clinically-relevant or will be evident in patients.

No animal studies were submitted to support the use of Brenzys in the remaining proposed indications. Therefore, no comment can be made from a nonclinical perspective to support the use of Brenzys for these indications.

Pharmacokinetics

Systemic exposures to etanercept were similar following SC dosing with Brenzys, EU Enbrel and US Enbrel at equivalent doses to rats or cynomolgus monkeys. Exposures following repeated dosing with 1 mg/kg SC (but not 15 mg/kg SC) of all test items were lower on Day 25 compared to Day 1, likely a result of anti-drug antibody formation. Overall, there were no significant or meaningful differences in pharmacokinetic parameters between Brenzys, EU Enbrel and US Enbrel in animals, suggesting that the differences in the glycosylation profiles observed in the physicochemical analyses did not significantly impact the pharmacokinetics of the test item.

Toxicology

One comparative Good Laboratory Practice (GLP) compliant repeat-dose toxicity study of 4 weeks duration was submitted. The toxicity profile of Brenzys in cynomolgus monkeys was compared with that of EU Enbrel and US Enbrel. The duration of the study and the choice of species are considered acceptable. The clinical route and more frequent clinical dosing regimen (twice weekly) were used. The doses chosen are acceptable, resulting in exposures (AUC) covering and exceeding (up to 20 times) the clinical exposure in patients receiving 50 mg SC/week Brenzys. While a comparative toxicity study in non-human primates is generally not recommended for this type of product[7], it is considered appropriate in this case given the glycosylation differences observed in the physicochemical comparisons between the Brenzys and Enbrel forms of etanercept and the differences observed in the in vitro Fc receptor binding assays. However, group sizes were small (3/sex) and only gross differences in the toxicity profiles would be evident in this study.

The only notable finding was evidence of an infection in isolated animals (with different test articles), likely an exacerbation of a pre-existing infection secondary to the immunosuppressive action of the test item. There were no significant differences in the toxicity profiles of the Brenzys and Enbrel forms of etanercept, suggesting the glycosylation differences and Fc receptor affinity differences have no obvious effect on the safety of the test item.

Anti-drug antibodies (ADAs) were detected in animals from all low dose groups and most high dose groups. The presence of ADAs appeared to be associated with a faster clearance of the test item in the low dose group.

[7] Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-clinical and Clinical Issues: EMA/CHMP/BMWP/403543/2010.

In monkeys, there was no significant difference in the immunogenicity of the test item from different sources; however, this endpoint in animals has a low predictive value for what may be seen in patients.

Injection site reactions were similar across the three test articles.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2[8]. At the time of submission, this matched the existing category for Enbrel. However, the Pregnancy Category for Enbrel has recently been changed to Category D[9] (as of 7 December 2015). Therefore, Pregnancy Category D is considered to be more appropriate for this product.

Paediatric use

Brenzys is not proposed for paediatric use, which is in contrast to the originator product, Enbrel.

Nonclinical summary and conclusions

- The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat-dose toxicity. The scope of the nonclinical program is adequate under the relevant EU guideline. These studies were conducted using EU and US-sourced Enbrel as the reference product. No nonclinical data were provided to verify the comparability of the EU/US sourced and Australian sourced Enbrel.
- No meaningful differences between Brenzys and Enbrel were observed in the comparative in vitro pharmacology studies. In an animal rheumatoid arthritis model, Brenzys had similar efficacy to Enbrel in terms of footpad volumes and clinical responses, but less tissue damage was evident with Enbrel compared to Brenzys. The clinical relevance of this difference is unknown.
- No animal studies were submitted to support the use of Brenzys for the remaining proposed indications.
- The pharmacokinetic profile of etanercept was similar between Brenzys and Enbrel.
- The toxicity profiles of Brenzys and Enbrel were similar in monkeys in a 4 week comparative repeat-dose toxicity study.
- Provided adequate comparability of the EU/US sourced and Australian sourced versions of Enbrel is demonstrated in Module 3, and the slight difference in efficacy observed in the animal model is not evident clinically, there are no objections on nonclinical grounds to the registration of Brenzys to treat patients with rheumatoid arthritis. No comment can be made from a nonclinical perspective to support the use of Brenzys for other indications.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

[8] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

[9] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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

TNF plays a central role in the molecular and cellular events occurring in the pathogenesis of several autoimmune inflammatory conditions. Elevated concentrations of TNF have been found in the synovium of those with active RA, Psoriatic Arthritis (PsA) and AS, as well as in the skin lesions of Plaque Psoriasis (PSOR). Anti-TNF medicines work by neutralising the activity of soluble TNF and preventing its binding to the 2 main TNF receptors. These receptors are expressed on the membrane of monocytes and T lymphocytes and circulate in the blood in soluble forms. Etanercept (ETN) is a recombinant human TNFR p75 fusion protein, which inhibits the binding of TNF to the surface of cells expressing TNFR such as T-lymphocytes in the synovium of patients with active RA. Enbrel is currently approved in Australia for use in 5 treatment indications. The central therapeutic effect of Enbrel in all these indications is mediated by TNF blockade. Reducing disease activity and slowing the progression of inflammatory disease are the key therapeutic goals in autoimmune disease with significant inflammatory characteristics. ETN is well established and widely used in adult rheumatology clinical practice for 15 years, with a well characterised benefit: risk profile.

Guidance

The sponsor states that this submission is consistent with the TGA pre-submission planning form. A pre-submission meeting between drug developer and the TGA was held on 6 November 2014, with discussion of the development program and planned registration package for SB4 in Australia. The objectives of the meeting were

a. to clarify the appropriate reference product for SB4 in the supporting clinical trials (that is, Australian or European sourced Enbrel),

b. to discuss with the sponsor about the proposed treatment indications and the rationale/requirements for extrapolation of treatment indications, and

c. to comment on the format of the Australian Risk Management Plan (RMP).

The following guidance documents are relevant to this submission:

- CPMP/EWP/556/95 Rev 1 (pdf,176kb)
  Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis
  Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001)
  Published: TGA Internet site
  Effective: 29 January 2007
- EMEA/CHMP/EWP/438/04 (pdf,125kb)
  Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis
  Published: TGA Internet site
  Effective: 5 February 2008
- CPMP/EWP/4891/03 (pdf,78kb)
  Guideline on Clinical Investigation of Medicinal Products for the Treatment of

Ankylosing Spondylitis
Published: TGA Internet site
Effective: 23 February 2010

- CHMP/EWP/2454/02 (pdf,276kb)
  Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis
  Published: TGA Internet site
  Effective: 28 July 2005
- CHMP/437/04/Rev 1 (pdf,120kb)
  Guideline on Similar Biological Medicinal Products
  Published: TGA Internet site
  Effective: 25 May 2015
- EMEA/CHMP/BMWP/14327/2006 (pdf,160kb)
  Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins
  Published: TGA Internet site
  Effective: 22 June 2009
- EMEA/CHMP/BMWP/42832/2005/Rev 1 (pdf,165kb) Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues
  Published: TGA Internet site
  Effective: 1 July 2015
- EMEA/CHMP/BMWP/403543/2010 (pdf,212kb)
  Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues
  Published: TGA Internet site (effective: 17 August 2015)
- CPMP/EWP/QWP/1401/98 Rev 1 (pdf,237kb)
  Guideline on the Investigation of Bioequivalence
  Published: TGA Internet site
  Effective: 16 June 2011

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier contains a single Phase I trial (Study SB4-G11-NHV) that aimed to compare the pharmacology, safety and tolerability of 3 different formulations of ETN (SB4, EU sourced Enbrel and US sourced Enbrel) and a single pivotal Phase III trial (Study SB4-G31-RA) in adult patients with active RA. The clinical program had the objective of achieving regulatory guidelines for the demonstration of biosimilarity between SB4 and the approved reference product, Enbrel.

The submission contained the following clinical information:

- 1 clinical pharmacology study (Study SB4-G11-NHV) in healthy male volunteers that provided pharmacokinetic (PK) data and supporting safety information.
- 1 pivotal efficacy/safety study (SB4-G31-RA) in adult patients with active RA, which included a PK sub-study reporting exploratory steady-state PK data.

There were no PK analyses, no dose-finding studies and no other efficacy/safety studies in the proposed treatment indication populations.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Both of the studies provided in this submission for SB4 were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

In accordance with the relevant TGA adopted EU guidelines (EMA/CHMP/42832/2005 Rev 1 and EMA/CHMP/BMWP/403543/2010), the clinical dossier presented 2 studies for demonstrating similarity in PK characteristics between SB4 and Enbrel. The clinical Phase I trial (Study SB4-G11-NHV) in young-middle aged, healthy male volunteers was considered the primary PK study for demonstrating similarity, and the steady-state PK sub-study of the pivotal Phase III clinical trial (Study SB4-G31-RA) provides supporting evidence for PK similarity in a patient population. Neither of the studies had significant deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The PK characteristics of SB4 and the approved reference product Enbrel (EU and US sourced) were investigated in 2 clinical trials. Study SB4-G11-NHV was specifically designed to evaluate the PK of SB4 in healthy male volunteers aged between 18 and 55 years, and to demonstrate the PK equivalence of SB4 with Enbrel (EU and US sourced) for the co-primary endpoints of AUC_{inf} and C_{max}. These co-primary PK endpoints are appropriate for demonstrating PK similarity. It was agreed with the EMA and US FDA to determine PK equivalence using a single dose, crossover trial for which AUC_{inf} and C_{max} would lie within the pre-determined equivalence margin of 0.8 to 1.25. This was observed to be correct for Study SB4-G11-NHV, in which SB4 was demonstrated to have geometric LS means ratios compared to both EU and US sourced Enbrel close to 1 (and always within the 0.8-1.25 equivalence margin) for both primary PK endpoints. Study SB4-G11-NHV also demonstrated that SB4 was bioequivalent with the appropriate reference products of Enbrel in terms of the key secondary PK parameters including AUC_{last}, T_{max} and $T_{1/2}$.

Study SB4-G31-RA demonstrated that SB4 and EU sourced Enbrel achieve similar levels of drug exposure (AUC, C_{max} and C_{min}) between Weeks 2 and 24. However, both formulations of ETN exhibited high inter-patient variability in drug exposure with the CV% (for various key PK parameters) ranging from 36.6-53.9% for SB4 and 48.1-65.7% for EU sourced Enbrel.

Both studies showed mean serum concentration-time profile data consistent with the known PK characteristics of ETN. In particular, ETN is slowly absorbed from the site of SC injection (mean T_{max} was 70-75 hours in Study SB4-G11-NHV and 48 hours in Study SB4-G31-RA) and slowly cleared with the mean $T_{1/2}$ ranging from 96-106 hours. Both studies had a low incidence of subjects developing anti-drug antibodies so it is difficult to make any meaningful interpretation about the potential impact of immunogenicity on the PK characteristics of SB4.

The clinical dossier for SB4 contained PK assessments collected in healthy male volunteers and a subset of 79 adult patients with active RA (that is, 1 approved treatment indication of the use of Enbrel). Hence, it is unknown whether or not there any significant PK

differences between Enbrel and SB4 exist for the other claimed treatment indications in adults (such as AS, PsA and PSOR), although it would seem unlikely. The sponsor has not provided evidence from a literature review that there is no clear difference in the PK of ETN across its various treatment indications. Furthermore, no data has been obtained in children, but the sponsor is not requesting consideration of the approved paediatric treatment indications for ETN.

All enrolled patients in Study SB4-G31-RA were taking concomitant weekly low oral Methotrexate (MTX) with ETN, while none of the subjects in Study SB4-G11-NHV were taking concomitant immunosuppression. However, there has been no clinical study with SB4 in diseased individuals (for example, adult subjects with PSOR or AS) where the concurrent use of MTX is typically not part of the treatment strategy with ETN. It is unknown whether the PK and immunogenicity profile (anti-drug antibody status) of SB4 in those other adult treatment patients may be significantly altered without the concurrent use of MTX.

Overall, the PK assessments provided in this submission for the registration of SB4 as a biosimilar product of Enbrel are appropriate and the data largely meets the minimum criteria of supporting evidence for PK bioequivalence.

Pharmacodynamics

Studies providing pharmacodynamic data

This submission did not contain any specific pharmacodynamic (PD) data for SB4 collected in the 2 clinical studies. The sponsor states that the PD effects of ETN have been well characterised in the published Enbrel trials and registration process. Furthermore, the sponsor asserts that in vitro and in vivo non-clinical studies provided in this submission demonstrate similarity between SB4 and Enbrel in anti-TNF mediated PD effects. As a proposed biosimilar of Enbrel, the sponsor states that no further PD studies of SB4 are required by the relevant guidelines[10] and that clinical evidence for comparability can be demonstrated by PD surrogate endpoints or clinical evidence. In the case of SB4, clinical evidence for similarity was aimed to be demonstrated by clinical rather than PD endpoints. In patients with active RA, acute phase reactants of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be useful PD markers. Both CRP and ESR are sensitive indicators of the inflammatory activity of RA, and their measurement is included among the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for improvement in RA.

Evaluator's conclusions on pharmacodynamics

In summary, the sponsor has not submitted any clinically derived PD data in this submission apart from the change in serum inflammatory markers (ESR and CRP) over time in the pivotal clinical Phase III study (SB4-G31-RA). This data will be presented in the clinical efficacy section of this report and in general shows there was similarity of PD effect (for serum inflammatory markers) between the 2 formulations of ETN in an adult RA treatment population. The sponsor has also provided in vitro studies examining binding and cell based assays, as well as an in vivo efficacy study in mouse model of collagen antibody-induced arthritis to support similarity in the PD activity of SB4 compared to Enbrel.

[10] EMEA/CHMP/BMWP/ 42832/2005 and EMA/CHMP/BMWP/403543/2010

Dosage selection for the pivotal studies

The dose and regimen of ETN selected for the pivotal and supporting study was based on the doses used in the Enbrel registration trials. This is an appropriate rationale for a biosimilarity submission.

In the pivotal study involving adult patients with active RA (Study SB4-G31-RA), ETN 50 mg injections were given once weekly by SC injection. ETN therapy was co-administered with oral MTX 10-25 mg/week and folic acid (at least 5 mg/week). In addition, more than half of the enrolled subjects were taking concurrent Non-Steroidal Anti-Inflammatory Drug (NSAID) and/or low dose oral corticosteroid therapy during the study. The dose of ETN examined in the single pivotal clinical trial, as well as the background doses and rates of therapy are consistent with clinical practice in Australia. In Study SB4-G31-RA, no loading dose of ETN was utilised, which is consistent with clinical practice and the current approved posology for Enbrel.

In the supporting Phase I clinical study (SB4-G11-NHV) which evaluated healthy male volunteers aged between 18 and 55 years, the investigated dose of ETN was 50 mg by SC injection on 2 occasions, separated by at least 28 days. No concomitant background therapy was allowed, which is appropriate for this type of study.

Efficacy

Studies providing efficacy data

One pivotal efficacy/safety study (SB4-G31-RA) in adult patients with active RA, which included a PK sub-study reporting exploratory steady-state PK data was submitted (see Attachment 2 for details).

Evaluator's conclusions on clinical efficacy for Rheumatoid Arthritis

This submission contained a single pivotal Phase III trial (Study SB4-G31-RA) in adult patients with active RA that recruited a total of 596 patients (299 received SB4 therapy and 297 received Enbrel treatment) and provided efficacy data for up to 52 weeks of therapy. The pivotal study was well designed, had an appropriate primary efficacy endpoint (ACR20[11] response rate at Week 24), was appropriately powered for the stated equivalence margin and used appropriate statistical analyses (both full analysis set [FAS] and per population set [PPS] analyses). Although the pre-defined equivalence margin of ±15% is at the upper limit of acceptability, the sponsor has adequately justified that range. Furthermore, the equivalence margin was discussed prior to submission with the TGA and EMA.

Although Study SB4-G31-RA recruited patients with RA of appropriate demographic and disease activity characteristics at baseline, the majority of subjects (70.8%; 422/596) were Disease Modifying Anti-Rheumatic Drug (DMARD) naïve, excluding MTX, prior to involvement in the trial. The current approved treatment indication for Enbrel in patients with RA states 'Active, adult rheumatoid arthritis (RA) in patients who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).' The prior RA therapy features of the cohort recruited into Study SB4-G31-RA does not adequately reflect the patient characteristics of the current approved treatment indication

[11] ACR 20 is viewed as a threshold to show that a drug is better than a placebo or not treating at all. ACR 20 literally stands for American College of Rheumatology and twenty percent improvement.

for the reference product, which is a major deficiency of the current supporting dataset for SB4.[12]

In Study SB4-G31-RA, SB4 and Enbrel demonstrated similar outcomes for the primary efficacy endpoint of the rate of ACR20 response at 24 weeks. This outcome was shown in both the per protocol set 1 (PPS1) (78.1% [193/247] for SB4 versus 80.5% [190/236] for Enbrel) as well as in the FAS population (73.6% [220/299] for SB4 versus 71.7% [213/297] for Enbrel). The 95% CI for the treatment difference was within the predefined equivalence margin of -15% to +15, thereby supporting the therapeutic equivalence of SB4 to the reference product, Enbrel.

Various subgroup analyses of the primary efficacy endpoint by patient factors of interest were also performed. The rate of ACR20 responses at Week24 (using the PPS1 cohort) was equivalent between the 2 treatment groups for the following variables: baseline CRP reading (≥ 10 mg/L versus < 10 mg/L), region (EU versus non-EU), age (<65 years versus ≥ 65 years), gender, race/ethnicity and presence of anti-drug antibodies (yes/no).

Similar efficacy between the 2 treatment groups in Study SB4-G31-RA could also be shown for all secondary efficacy endpoints including the ACR20 response rate at Week 52, rate of ACR50 and ACR70 response at Weeks 24 and 52, as well as the DAS28 and EULAR response criteria. Study SB4-G31-RA also assessed structural X-ray outcomes at Week 52. The mean changes from baseline to Week 52 in the mTSS and its component scores demonstrate that SB4 and Enbrel are equivalent for radiographic outcomes (that is, retarding the structural progression of joint damage) in adult patients with active RA.

The comparison of the primary endpoint result (that is, ACR20 response rate at Week24) of Study SB4-G31-RA with the published data for ETN (60% overall; Table 10 Attachment 2) shows a moderately higher proportion of patients in the SB4 (73.6%) and Enbrel groups (71.7%) achieving clinical response in Study SB4-G31-RA. Likewise, when comparing the results of Study SB4-G31-RA with the results of other prospective trials in adult patients with active RA, the rates of ACR20 response are somewhat higher than the range (60-65% typically) reported with other anti-TNF medicines. The higher response rates observed in Study SB4-G31-RA probably reflect a relatively under-treated cohort of patients prior to inclusion as 70.8% of subjects were DMARD naïve excluding MTX at screening.

Overall, the efficacy data from a single pivotal trial (Study SB4-G31-RA) is sufficient to establish therapeutic equivalence between SB4 and Enbrel for the treatment indication of adult patients with active RA. The trial complied with most aspects of the TGA adopted guideline[13] for the assessment of RA. In particular, the study design, efficacy outcomes (clinical and radiological), overall number of evaluated subjects and the duration of drug exposure meet the minimum standards outlined in the guidance document. However, the prior RA treatment characteristics of the cohort enrolled into the single pivotal study is not sufficiently reflective of the approved treatment indication for the reference product (Enbrel) which states that patients must have an inadequate response to at least 1 DMARD prior to the initiation of ETN.

Justification for extension to all adult approved indications for Enbrel

The sponsor has provided several references relating to the efficacy and safety of Enbrel in various other treatment indications in adult patients. However, the submission did not include any specific evaluation of that material with respect to justifying the attainment of all 5 approved Enbrel treatment indications by extrapolation. This is a major deficiency of

[12] Adult patients with active RA who were MTX inadequate responders for at least 6 months prior to involvement in this trial were studied (see page 33 below).
[13] CPMP/EWP/556/95 Rev 1

the current submission. Regarding an application for a biosimilar medicine that includes extrapolation of indications, the relevant regulatory guideline[14] states '*Applicants should support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism of action(s)*.' Furthermore, the sponsor has not included any report justifying that a single clinical study in patients with RA is a sensitive clinical test model for the other requested treatment indications.

Psoriatic arthritis

There is no efficacy study for SB4 in PsA. The sponsor's justification for approval is extrapolated from the collected PK data, mechanism of action and a single non-inferiority study performed in patients with RA.

Plaque psoriasis

There is no efficacy study for SB4 in PSOR. The sponsor's justification for approval is extrapolated from the collected PK data, mechanism of action and a single non-inferiority study performed in patients with RA.

Ankylosing spondylitis

There is no efficacy study for SB4 in AS. The sponsor's justification for approval is extrapolated from the collected PK data, mechanism of action and a single non-inferiority study performed in patients with RA.

Non-radiographic axial spondyloarthritis

There is no efficacy study for SB4 in non-radiographic axial spondyloarthritis. The sponsor's justification for approval is extrapolated from the collected PK data, mechanism of action and a single non-inferiority study performed in patients with RA.

Evaluator's conclusion on extrapolation of treatment indications

The sponsor has provided evidence from non-clinical studies (not assessed as part of this report) that show similarity in structure for SB4 and Enbrel, as well as comparable inhibition of TNF activity in vitro and reduction in several animal models of inflammation, including murine collagen-induced arthritis. ETN is a dimeric soluble form of the p75 TNF receptor that can bind to 2 TNF molecules.

The efficacy data obtained in adult patients with active RA (Study SB4-G31-RA) provides evidence to suggest similar responses for SB4 and Enbrel in that patient cohort (powered as an equivalence trial). The sponsor has not provided sufficient justification, based on the non-clinical findings of SB4 structure and function, in conjunction with bioequivalence data from PK studies and a single Phase III efficacy study in RA (Study SB4-G31-RA) that SB4 and Enbrel are therapeutically equivalent across the treatment indications. Extrapolation of the PK and efficacy data generated in the 2 trials in this submission which examined adult patients with RA and healthy male volunteers aged 18-55 years to other approved indications for Enbrel such as active PsA, PSOR and inflammatory spondylitis is not justifiable on the basis of the results of the pre-clinical studies supported by the current limited evidence in RA. Although many of these conditions share similar and overlapping pathophysiological immunological mechanisms, their clinical features are varied and RA may not be a clinical test model of sufficient sensitivity to extrapolate efficacy and safety data. The extent and type of information provided in this submission does not justify the approval of SB4 in accordance with the guideline on similar biological medicinal products containing monoclonal antibodies[15]. Therefore, the evaluator does not

[14] EMA/CHMP/BMWP/403543/2010
[15] EMA/CHMP/BMWP/403543/2010

recommend approval of the sponsor's request to register SB4 for all adult treatment indications that Enbrel is currently approved for in Australia.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In this submission, there was only 1 pivotal efficacy trial (Study SB4-G31-RA), which collected the following safety data:

- Adverse events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed at Weeks 2 and 4, every 4 weeks between Weeks 4 and 16, and every 8 weeks between Weeks 24 and 52, with an additional post-treatment follow-up visit at Week 56.
- AEs of particular interest, including serious infection, Tuberculosis (TB) and injection site reactions were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, clinical chemistry and urinalysis, were performed at baseline, Weeks 2 and 4 weeks, every 4 weeks between Weeks 4 and 16 and then every 8 weeks up until Week 52.
- Screening tests for tuberculosis (Chest X-ray and QuantiFERON Gold testing) were taken at baseline, but not routinely collected thereafter.
- Vital signs such as blood pressure, heart rate and temperature were performed at each scheduled study visit. Subject weight was recorded at baseline and thereafter at the discretion of the site investigator.
- Electrocardiogram (ECG) for central reading was taken at baseline and thereafter as required by clinical indication up to Week 52.
- Urine pregnancy testing was performed at baseline and every 4 weeks thereafter in women of reproductive age.
- Serum for Anti-drug antibodies (ADA) to ETN, anti-nuclear antibodies and anti-dsDNA antibodies was collected at baseline, as well as Weeks 0, 2, 4, 8, 12, 16, 24 and 52.

Other studies evaluable for safety only

There were no dose-response and non-pivotal efficacy studies provided in this submission.

The submission also contained a single clinical pharmacology study (Study SB4-G11-NHV), which enrolled a total of 138 healthy male subjects aged 18-55 years in 3 study parts (46 subjects per study part) (see Attachment 2).

Patient exposure

Study SB4-G31-RA

In this trial, all 596 subjects were randomised and received at least one 50 mg weekly dose of ETN (either SB4 or Enbrel). The duration of exposure to ETN in Study SB4-G31-RA was comparable for the 2 treatment groups. The mean duration of exposure was 338.9 days (range: 34 to 371 days) in the SB4 group and 323.5 days (range: 14 to 371 days) in the Enbrel arm. The majority of continuing subjects (85 to 90%) in both treatment groups

received all doses of study treatment up to day 281 (that is, > 9 months in Study SB4-G31-RA) resulting in a similar cumulative exposure to ETN for both treatment arms.

Study SB4-G11-NHV

Among the 138 subjects who enrolled in Study SB4-G11-NHV, 132 subjects completed both Period 1 and Period 2 of the trial and received at least 2 x 50 mg doses of ETN via different formulations (SB4, EU sourced Enbrel or US sourced Enbrel).

In Part A, 46 subjects received 1 dose of SB4 therapy and 45 subjects received 1 dose of EU sourced Enbrel. In Part B of the study, 45 subjects received 1 dose of SB4 and 46 subjects received 1 dose of US sourced Enbrel. In Part C, 45 subjects received 1 dose of EU sourced Enbrel and 43 subjects received 1 dose of US sourced Enbrel.

Safety issues with the potential for major regulatory impact

Serious and/or opportunistic infection

In Study SB4-G31-RA, a higher number of infection related serious adverse events (SAEs) were recorded with EU sourced Enbrel (5 events in 5 subjects; 1.7% of 297) compared with those who received SB4 (1 event in 1 subject; 0.3% of 299). In this trial, the types of serious infection observed were similar to that reported with the known safety profile of ETN. There were no reports of active TB or serious opportunistic infection in Study SB4-G31-RA but subjects were carefully screened at baseline for reactivation of TB.

Malignancy potential

Malignancy is an important potential safety concern with ETN therapy in all treatment indications. Study SB4-G31-RA reported 4 cases of malignancy in SB4 treated patients (breast cancer, lung cancer with cerebral metastases, basal cell skin carcinoma and gastric adenocarcinoma). One subject who received Enbrel in the same trial developed invasive ductal breast cancer. The relative imbalance of identified malignancy cases between the 2 treatment groups is probably within the expectations given the small overall patient numbers involved and relatively short duration of treatment follow-up (56 weeks). No lymphoproliferative disorders were reported in the SB4 study program, but this remains an important risk with long-term ETN therapy in all treatment indications.

Neurological events

No reports of demyelinating disorders such as multiple sclerosis or Guillain-Barré Syndrome were recorded in either of the 2 studies in this submission but this remains an important identified risk with ETN therapy that requires ongoing surveillance.

Unwanted immunological events

Injection site reactions were an AE of special interest in the SB4 clinical development program and were reported in both clinical studies (all treatment groups). In Study SB4-G31-RA, a higher number of injection site reactions (almost all were considered to be treatment related) were reported in Enbrel versus SB4 treated subjects (22 injection site reactions were recorded in 11 (3.7% of 299) subjects in the SB4 treatment group and 157 reactions were observed in 52 (17.5% of 297) subjects in the Enbrel arm). The most commonly reported type of injection site reaction was injection site erythema. No patient discontinued ETN in Study SB4-G31-RA because of injection site reaction. It remains unclear as to whether or not the increased incidence of injection site reactions with Enbrel versus SB4 reflects a true and significant safety difference, and what is the potential mechanism. In all 3 Parts of Study SB4-G11-NHV, injection site reactions were reported at a similar frequency (4.3 to 6.5%) in subjects receiving the 3 different formulations of ETN (SB4, EU and US sourced Enbrel). No severe immediate or delayed type hypersensitivity reactions were observed in either trial. No lupus-like or allergic reactions were observed in either clinical trial in this submission.

Both studies revealed a comparatively low rate of testing positive for ADA with SB4 therapy with no clear clinical significance to their development determined thus far. However, all enrolled patients in Study SB4-G31-RA were taking concomitant weekly low oral MTX with ETN, while none of the subjects in Study SB4-G11-NHV were taking concomitant immunosuppression. The submission does not include any clinical study with SB4 in diseased individuals (for example, adult subjects with PSOR or AS) where the concurrent use of MTX is typically not part of the treatment strategy with ETN. As such, the immunogenicity profile (ADA status) of SB4 in those other adult treatment patients may be significantly different without the concurrent use of MTX.

Postmarketing data

To date, SB4 has not yet been approved or marketed in any country. However, there is a large volume of long-term clinical experience with Enbrel in the requested treatment indications to indicate that if SB4 meets the criteria for biosimilarity with Enbrel (reference product), then a predictable positive benefit: risk assessment can be concluded.

Evaluator's conclusions on safety

The safety profile of anti-TNF drugs, including ETN, is well characterised in the published literature. In this submission for the registration of SB4 (biosimilar medicine of ETN), the safety population consisted of 596 adult patients with active RA who were treated with at least 1 dose of either SB4 or Enbrel during the Phase III clinical trial (SB4-G31-RA). Of these patients, 299 received treatment with SB4 for a mean duration of 339 days (11 months) and 297 subjects were given Enbrel for a mean duration of 323.5 days (10.5 months). In addition, 138 healthy male subjects aged between 18 and 55 years were evaluated in the Phase I Study SB4-G11-NHV (46 subjects received cross-over therapy with either SB4 or EU or US sourced Enbrel). The size of the safety population and the duration of exposure to SB4 are consistent with the regulatory guidelines[16] for presenting a safety population of sufficient size and follow-up duration to assess for possible registration. However, there are other issues identified in this evaluation which indicate that further safety data or clarification by the sponsor is required before meeting the minimum safety requirements of the biosimilar regulatory guideline.

The most frequently reported drug-related AEs (experienced by ≥ 4% of patients) in Study SB4-G31-RA were in the SOCs of general disorders and administration site conditions (mainly, injection site reactions), infection related AEs and (abnormal) investigations (for example, raised liver enzymes and various haematological abnormalities). The frequency and severity of drug-related AEs in Study SB4-G31-RA was comparable between the SB4 and Enbrel treatment groups apart from a higher incidence of injection site reactions with EU sourced Enbrel (18.5%) versus SB4 (4.0%). In Study SB4-G11-NHV, a similar pattern of the most commonly reported treatment emergent AEs was observed in all treatment groups (SB4 therapy, EU sourced Enbrel and US sourced Enbrel). The 2 most common drug-related AEs in healthy male volunteers were headache and injection site reactions.

Given the mechanism of action of ETN, infection is an AE of special interest. The overall number of subjects experiencing infection related AEs (25.6-28.4%) was comparable between the 2 treatment groups in Study SB4-G31-RA. However, there was higher number of infection related SAEs with EU sourced Enbrel (5 events in 5 subjects; 1.7% of 297) compared with those who received SB4 (1 event in 1 subject; 0.3% of 299) in Study SB4-G31-RA. There were no reports of active TB in Study SB4-G31-RA but subjects were carefully screened at baseline for reactivation of TB. In Study SB4-G11-NHV, infection related AEs affected < 10% of all subjects with no clear discernible differences in the

[16] CPMP/EWP/556/95rev1/FINAL

pattern and type of infection observed in healthy volunteers treated with either formulation of ETN. The most common type of infectious AE by PT in both adults with active RA and healthy male volunteers was nasopharyngitis.

Two patients died in Study SB4-G31-RA (cardiopulmonary failure and gastric adenocarcinoma), but neither fatality was considered by the site investigators to be related to SB4 (both subjects received SB4 therapy). The evaluator opined a view that causality may be related to SB4; ETN has a potential association with malignancy, and worsening of cardiac failure is a potential risk in those at risk of major adverse cardiovascular events. Malignancies were reported in 4 patients (1.3%) treated with SB4 therapy and 1 subject (0.3%) who received Enbrel in Study SB4-G31-RA. The observed rate of drug-related, treatment-emergent SAEs was similar for both treatment groups (5.1-6.0%) in Study SB4-G31-RA. However, the pattern of drug-related SAEs in Study SB4-G31-RA was somewhat different for patients treated with SB4 versus Enbrel. In particular, 4 subjects treated with SB4 recorded 6 hepatobiliary SAEs versus no such events in the Enbrel group. However, in the Enbrel arm there were 2 individual reports of chorioretinopathy and significant neutropenia.

In both clinical studies, the frequency of patients who were discontinued due to drug-related AEs was low and similar between treatment groups (5.4-6.7% in Study SB4-G31-RA). The 2 most frequent AEs leading to permanent study treatment discontinuation in Study SB4-G31-RA were injection site reactions and exacerbation of RA. However, other reasons for discontinuation from ETN in Study SB4-G31-RA included infection (2 patients in the SB4 group and 1 in the Enbrel arm); skin complaints (1 patient in the SB4 group and 2 subjects in the Enbrel arm), haematological abnormalities (1 patient in each group) and 2 gallstone-related AEs in SB4 treated individuals.

Injection site reactions were reported in both clinical studies (all treatment groups). In Study SB4-G31-RA, 22 injection site reactions were recorded in 11 (3.7% of 299) subjects in the SB4 treatment group and 157 reactions were observed in 52 (17.5% of 297) subjects in the Enbrel arm. The most commonly reported injection site reactions at the PT level were injection site erythema. It remains unclear as to whether or not the increased incidence of injection site reactions with Enbrel versus SB4 reflects a true and significant safety difference, and if so, what is the potential explanation. In all 3 Parts of Study SB4-G11-NHV, injection site reactions were reported at a similar frequency (4.3-6.5%) in subjects receiving 3 different formulations of ETN (SB4, EU and US sourced Enbrel). No severe immediate or delayed type hypersensitivity reactions were observed in either trial.

In Study SB4-G31-RA, 3.4-5.4% of subjects developed ≥ 2-fold increases in serum transaminases and there were a few cases of serious hepatobiliary AEs reported in SB4 treated subjects. Even though there was a slightly higher incidence of raised serum transaminases and hepatobiliary AEs with SB4 therapy versus Enbrel, the majority of these AEs were not treatment related and probably do not reflect a true safety difference between the 2 formulations of ETN. In addition, there were a few significant cases of neutropenia and thrombocytopenia recorded in both ETN treatment groups of Study SB4-G31-RA. These cases are consistent with the Australian PI for Enbrel and published literature.

The incidence of subjects developing anti-ADA antibodies was relatively low with SB4 and their clinical relevance is yet to be defined with no discernible link to the risk of infection, injection site related reactions or any other significant safety concern (such as hepatobiliary AEs). By Week 52 in Study SB4-G31-RA, there was a statistically higher rate of positive ADA results in the Enbrel group (13.2%; 39/297) compared to SB4 therapy (1.0%; 3/299; $p<0.001$). Only 1 subject in the Enbrel treatment group tested positive for neutralising antibodies to ETN during the entire study. The majority of patients (in both treatment groups) who tested positive for ADA did so at Week 8 of therapy, and ADA positivity persisted throughout the trial. By Day 29 in Study SB4-G11-NHV, no subject

treated with SB4 tested positive for ADA, 7 subjects after receiving EU sourced Enbrel were positive for ADA (including 1 subject with NAb) and 10 subjects after receiving US sourced Enbrel tested positive for ADA. It is unclear why there is a clear imbalance between SB4 and Enbrel therapy for the detection of ADA to ETN in both submitted studies and the sponsor has made no comment about this observation.

In Study SB4-G31-RA, 4 cases of malignancy were reported in SB4 treated patients (breast cancer, lung cancer with cerebral metastases, basal cell skin carcinoma and gastric adenocarcinoma) and 1 subject who received Enbrel developed invasive ductal breast cancer. No lymphoproliferative disorders were reported in either clinical study in this submission although this is a potential identified risk for anti-TNF therapy that is outlined in the RMP and the proposed Australian PI. Other previously identified safety concerns with ETN such as systemic lupus erythematosus or lupus-like syndromes and demyelinating disorders were not reported in any of the studies in the SB4 trial program.

The analysis of AEs reported during treatment with SB4 and the reference product Enbrel in Studies SB4-G31-RA and SB4-G11-NHV have not revealed any significant differences in the incidence and type of AEs. Moreover, no new safety signals have emerged from the submitted dataset to indicate the known risk profile of ETN has altered. The current safety dataset for SB4 is limited to 56 weeks of treatment follow-up and it would be important to continue collecting data beyond this time frame as part of post-marketing pharmacovigilance if approval was granted. Nonetheless, the safety data for Enbrel exceeds 15 years of treatment follow-up and it is likely that SB4 will demonstrate a similar safety profile over longer term follow-up based on the similar short term safety experience between the 2 formulations of ETN. However, as Study SB4-G31-RA recruited subjects who were predominately naïve to conventional DMARD therapy (excluding MTX), it is unclear if both formulations of ETN will demonstrate a similar safety profile in all of the patient populations for which Enbrel is currently approved.

First round benefit-risk assessment

First round assessment of benefits

The benefits of SB4 in the proposed usage are:

- Comparable efficacy response rates to Enbrel in improving the symptoms and signs of active RA in adult patients who were predominantly treatment naïve excluding MTX, including equivalent rates of ACR20 response at Week 24 (78.1 to 80.5% in the PPS1 cohort) as well as many secondary clinical efficacy variables (such as other levels of clinical response at 24 and 52 weeks) reporting similar rates of treatment response.
- Comparable efficacy response rates to Enbrel in slowing progression of disease associated structural progression (similar mean changes in mTSS and its component scores at Week 52).
- Demonstration of similar pharmacokinetic properties to Enbrel in healthy male volunteers (single dose, crossover design) and adult subjects with active RA (multiple dose therapy at steady state).
- Provision of an alternative formulation of ETN to treat various autoimmune inflammatory conditions in adults such as inflammatory spondylitis, psoriatic arthritis and skin psoriasis.
- Lower observed incidence of injection site reactions and development of anti-drug antibodies (of unclear clinical significance) with SB4 therapy compared to EU sourced Enbrel.

First round assessment of risks

The risks of SB4 in the proposed usage are:

- Increased risk of infection (overall and serious) which is comparable to alternative ETN therapy (EU sourced Enbrel).
- Increased risk of injection site reactions, which occurred at a lower frequency in those who received SB4 versus Enbrel in the 2 clinical trials.
- Safety not established in those with a high risk of infection as these patients were excluded from the trial populations (that is, some limitations to external validity).
- Rare reports of significant adverse events such as neutropenia, hepatobiliary disorders and malignancy of unclear relationship to SB4 or Enbrel therapy.
- Safety data in patients with inflammatory arthritis (RA) limited to < 54 weeks of treatment follow-up at present.
- No information regarding the safety of switching therapy (single 1–way changes or multiple switching) between the 2 formulations of ETN.
- Risk of off label use in children and adolescents where Enbrel has an approved treatment indication (paediatric PSOR and Juvenile Idiopathic Arthritis).
- Risk of potential for prescribing and dispensing errors given that the sponsor is specifically not requesting registration of the 2 approved paediatric treatment indications for Enbrel, and not providing a 25 mg vial presentation with an alternative posology (25 mg twice weekly) as per Enbrel.

First round assessment of benefit-risk balance

The submission indicates that the benefit-risk balance of SB4 is favourable for the treatment of active RA in adult patients, who are predominately treatment naïve to conventional DMARDs (Study SB4-G31-RA). However, the evaluator considered that the clinical data provided with SB4 therapy did not match the approved target population of the reference product (Enbrel). This is a major deficiency of the current submission. [17]It is unclear if the inclusion of predominately DMARD naïve subjects with active RA makes the detection of potential efficacy differences between the 2 formulations of ETN more or less sensitive. Treatment naïve subjects with active RA will demonstrate higher placebo adjusted clinical response rates than DMARD experienced patients. In developing and justifying the equivalence margin and sample size calculations for the single pivotal study (SB4-G31-RA) in this submission, the sponsor has used data from 3 trials which enrolled DMARD experienced subjects with active RA (Table 7 Attachment 2).

Furthermore, the currently available dataset on the benefit-risk balance of SB4 in adult patients with RA is limited to 52 weeks of treatment follow-up. This submission also contains a sufficient volume of data to support the claim that SB4 is pharmacokinetically equivalent to the reference product, Enbrel, in adult patients with active RA (Study SB4-G31-RA) and healthy young-middle aged males (Study SB4-G11-NHV).

The sponsor has not provided a review of the literature on the role of TNF in the disorders covered by the therapeutic indications of Enbrel and the potential mechanisms of action of the various anti-TNF medications. The mechanism of action of ETN is complex but the primary mode of action results from direct blocking of TNF receptor-mediated biological activities. ETN is a soluble TNFR fusion protein that competitively inhibits TNF by binding

[17] The evaluator was initially concerned at the high proportion of patients who were DMARD naïve however this was subsequently clarified in the round two assessment that all patients had received at least 6 months of methotrexate prior to randomisation at a mean weekly dose of 15.5 mg and that this was an appropriate level of prior MTX use before considering anti-TNF treatment. See page 53 below.

to it, thereby blocking the interaction between TNF and TNF receptors. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to AS and PSOR. However, the sponsor has not provided any justification for the extrapolation of indications for SB4 to include that which are approved for Enbrel on the basis of biosimilarity. Extrapolation of the PK, efficacy and safety data generated in the 2 trials in this submission which examined adult patients with RA and normal healthy volunteers is not justifiable on the basis of the results of the pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the ETN molecule). Despite sharing similar and overlapping pathophysiological immunological mechanisms, RA is considered a clinical disease model of limited sensitivity for assessing the efficacy and safety of SB4 in inflammatory spondylitis, PsA and PSOR.[18]

On the safety aspect, there is an increased risk of infection (overall and serious) with SB4 which appears to be comparable to Enbrel. The 2 submitted studies show a risk of injection site reactions with SB4, which is numerically lower than that observed with Enbrel therapy. There are limitations to the current dataset which will require ongoing pharmacovigilance. The efficacy and safety of SB4 in patients at a high risk of infection is not established. In addition, there is no information about the safety and efficacy of switching to SB4 from Enbrel, or vice versa. Furthermore, the current dataset has evaluated SB4 use in healthy volunteers and adult subjects with active RA (of limited characteristics to the approved patient population for Enbrel) and the submission did not include any information (clinical or pharmacokinetic) on the use of SB4 in other adult treatment indications or in children and adolescents with inflammatory conditions where Enbrel is also approved for use.

First round recommendation regarding authorisation

The evaluator does not recommend acceptance of the sponsor's proposed registration of SB4 to include RA or any of the current approved treatment indications for Enbrel in adult patients. The current submission provides evidence that SB4 is therapeutically equivalent to Enbrel in improving the signs and symptoms, as well radiographic outcomes in adult patients with active RA that are predominately treatment naive. However, this target treatment population is not consistent with the approved RA treatment population for Enbrel (that is, for use in patients who have an inadequate response to 1 or more DMARD drugs prior to anti-TNF therapy).[19] In addition, the sponsor has not provided any clinical data or literature review assessment in any of the other requested treatment indications to justify that SB4 can obtain any of the other approved treatment indications for Enbrel in adults by extrapolation of information. Moreover, the sponsor is specifically not requesting registration of the 2 approved paediatric treatment indications for Enbrel and not providing a 25 mg vial presentation, which raises concern for potential prescribing and dispensing errors occurring with the registration of 2 ETN formulations in Australia.

The following are recommended conditions prior to further consideration of the proposed registration of SB4:

- Satisfactory response to the questions outlined in Attachment 2,
- Provision of study report for the open-label, extension phase of Study SB4-G31-RA, and

[18] Lee H. Is Extrapolation of the Safety and Efficacy Data in One Indication to Another Appropriate for Biosimilars? Amer Ass Pharm Sci 2014; 16: 22-6.
[19] The majority of patients were not naïve to conventional DMARDs therapy but had received MTX. See also page 53 below.

- Literature review of the non-RA proposed treatment indications in adult subjects with satisfactory justification as to why SB4 should be able to claim those same indications by extrapolation of Enbrel data.

The evaluator would recommend that a registry study be a condition of registration if the application for SB4 is approved.

Second round clinical evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the potential benefits of SB4 in the proposed usage are better than expected after the first round evaluation. In particular, the sponsor has clarified details about the population recruited into the single pivotal clinical efficacy trial (Study SB4-G31-RA) to indicate that adult patients with active RA who were MTX inadequate responders for at least 6 months prior to involvement in this trial were studied. This is representative of the RA population approved to receive treatment with Enbrel. Study SB4-G31-RA demonstrated that SB4 exhibited comparable efficacy response rates to Enbrel in improving the symptoms and signs of active RA in adult patients (for example, ACR20 response rates of 78.1-80.8% for SB4 and 80.5-81.5% for Enbrel at 24 and 52 weeks) as well as for many secondary clinical efficacy variables and slowing the structural disease progression. In addition, the preliminary data available in the open-label, extension phase of Study SB4-G31-RA indicates that there is maintenance of treatment effect with SB4 for up to 100 weeks of continuous therapy, and that for patients who switch from Enbrel to SB4 at Week 52 there is a high rate of clinical response at Week100 (that is, 48 weeks after treatment switch).

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of SB4 in the proposed usage are unchanged from those identified the first round. The sponsor has provided preliminary data with a longer duration of treatment follow-up (up to 100 weeks) in a subset of patients involved in the single pivotal trial (Study SB4-G31-RA), which does not appear to indicate any new safety concerns (incidence or type) with SB4. Furthermore, a limited number of patients (n=119) who have switched from EU sourced Enbrel to SB4 after 1 year of therapy appear to have no additional safety concerns for up to 48 weeks after switching ETN formulations.

Second round assessment of benefit-risk balance

The updated submission indicates that the benefit-risk balance of SB4 is favourable for the treatment of active RA in adult patients, who are inadequate responders to MTX (Study SB4-G31-RA). In the response, the sponsor has provided data with SB4 therapy which matches the approved target population of the reference product, Enbrel.

Furthermore, the preliminary data from the open-label, extension phase of Study SB4-G31-RA supports the favourable benefit-risk balance of SB4 in adult patients with RA to 100 weeks of treatment follow-up. This submission also contains a sufficient volume of

data to support the claim that SB4 is pharmacokinetically equivalent to the reference product, Enbrel, in adult patients with active RA (Study SB4-G31-RA) and healthy, young-middle aged males (Study SB4-G11-NHV).

In the response, the sponsor has provided a review of the literature on the role of TNF in the disorders covered by the therapeutic indications of Enbrel and its potential mechanism of action. The mechanism of action of ETN is complex but the primary mode of action results from direct blocking of TNF receptor-mediated biological activities. ETN is a soluble TNFR fusion protein that competitively inhibits TNF by binding to it, thereby blocking the interaction between TNF and TNF receptors. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to AS and PSOR. Moreover, the sponsor has provided sufficient justification for the extrapolation of indications for SB4 to include that which are approved for Enbrel on the basis of biosimilarity. Extrapolation of the PK, efficacy and safety data generated in the 2 trials in this submission which examined adult patients with RA and normal healthy volunteers is adequate on the basis of the results of the pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the ETN molecule).

On the safety aspect, there is an increased risk of infection (overall and serious) with SB4 which appears to be comparable to Enbrel. The 2 submitted studies show a risk of injection site reactions with SB4, which is numerically lower (for local events) than that observed with Enbrel therapy. There are limitations to the current dataset which will require ongoing pharmacovigilance. The efficacy and safety of SB4 in patients at a high risk of infection is not established. The updated submission contains limited information about the safety and efficacy of switching to SB4 from Enbrel, or vice versa.

Second round recommendation regarding authorisation

The evaluator recommends acceptance of the sponsor's proposed registration of SB4 to include all of the 5 approved adult treatment indications for Enbrel. The submission provides robust evidence that SB4 is therapeutically equivalent to Enbrel in improving the signs and symptoms of active RA in adult patients. In terms of safety, the 2 formulations of ETN appear to be clinically equivalent for the incidence and type of clinically significant safety concerns. The SB4 clinical study program appears to show a lower incidence of local injection site reactions and immunogenicity in RA patients treated with SB4 compared to Enbrel, which remains of unclear explanation. Moreover, the safety profile (incidence and type) of SB4 is within historical expectations for ETN in the target population.

In the response, the sponsor has provided a review of the literature on the role of TNF in the disorders covered by the therapeutic indications of Enbrel and the potential mechanisms of action. The mechanism of action of ETN is complex but the primary mode of action results from direct blocking of TNF receptor-mediated biological activities. ETN is a soluble TNFR fusion protein that competitively inhibits TNF by binding to it, thereby blocking the interaction between TNF and TNF receptors. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to AS and PSOR. The sponsor has now provided sufficient justification for the extrapolation of indications for SB4 to include that which are approved for Enbrel on the basis of biosimilarity. Extrapolation of the PK, efficacy and safety data generated in the 2 trials in this submission which examined adult patients with RA and normal healthy volunteers is justifiable on the basis of the results of the pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the ETN molecule). Overall, the results observed in Study SB4-G31-RA can be considered a clinical disease model of adequate sensitivity for assessing the efficacy and safety of SB4 in inflammatory spondylitis, PsA and PSOR.

After the sponsor's response, there is residual concern that the sponsor is specifically not requesting registration of the 2 approved paediatric treatment indications for Enbrel and not providing a 25 mg vial presentation, which has the potential for prescribing and dispensing errors occurring with the registration of 2 ETN formulations in Australia.

The evaluator would recommend that approval of the sponsor's proposed registration be subject to regular periodic safety update reports and the provision by the sponsor to the TGA of the final clinical study report for the open-label, extension phase of Study SB4-G31-RA.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP (Version: 2.0, dated 4 May 2015) with an Australian Specific Annex (ASA) Version: 1.0, dated 11 June 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 1.

Table 1: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Malignancy (including lymphoma and leukaemia) 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 anaemia and pancytopenia Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis Liver events in patients with history of viral

Summary of safety concerns	
	hepatitis (including hepatitis B virus reactivation)
Important identified risks – specific indications	Change in morphology and/or severity of psoriasis Worsening of CHF[20] in adult 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 errors (pre-filled pen) Potential for male infertility Weight gain
Important potential risks-specific indications	Acute ischemic CV events in adult subjects Potential for paediatric off-label use
Missing information	Use in hepatic and renal impaired subjects Use in different ethnic origins Use in pregnant women

Abbreviations: ANCA= anti-neutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barré Syndrome; TB=tuberculosis.

Pharmacovigilance plan

The ASA proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information, including the use of specific adverse event (AE) follow-up (FU) forms for the important identified risks: 'Malignancy (including lymphoma and leukaemia), 'Central demyelinating disorders' and 'Peripheral demyelinating events (chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS))'; and the important potential risks: 'Amyotrophic lateral sclerosis', 'Progressive multifocal leukoencephalopathy' and 'Adverse pregnancy outcomes'. Additional pharmacovigilance activities in the form of a long term clinical study and registries are also proposed to further characterise all the specified safety concerns and missing information, except for the important potential risk: 'Potential for medication

[20] CHF=congestive heart failure

errors (pre-filled pen)' and 'Potential for paediatric off-label use' and the missing information: 'Use in hepatic and renal impaired subjects' and 'Use in different ethnic origins'.

Risk minimisation activities

The ASA proposes the application of routine risk minimisation activities for all the important identified risks, the important potential risks: 'Adverse pregnancy outcomes', 'Potential for medication errors (pre-filled pen)' and 'Potential for paediatric off-label use' and the missing information: 'Use in hepatic and renal impaired subjects' and 'Use in pregnant women'. Therefore no risk minimisation activities are proposed for the majority of important potential risks or for the missing information: 'Use in different ethnic origins'. Additional risk minimisation activities in the form of a patient card and an educational program for Health care Professionals (HCPs) and patients are also proposed for the important identified risks: 'Serious and opportunistic infections (including TB, Legionella, Listeria, parasitic infection)' and 'Worsening of CHF in adult subjects'; and the important potential risks: 'Potential for medication errors (pre-filled pen)' and 'Potential for paediatric off-label use'.

Reconciliation of issues outlined in the RMP report

Table 2 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
TGA recommendation 1: Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. The issues identified by the sponsor as relevant to the RMP were: Section 1) Any association between opioid use / Body Mass Index (BMI) and the incidence of TEAEs (Q8) Section 2) Any explanation for the lower incidence of injection site reactions Section 3) Any comment for the lower incidence of anti-drug antibodies Section 4) Data from the open label extension study and discussion for any safety concerns, including	All of the questions have been answered separately in the sponsor's response to the clinical questions. The following is a brief summary, and the actions required regarding the RMP are discussed. Section 1) No significant difference in the incidence of TEAEs was observed between opioid users / non-users and across categories of BMI values. There are no pre-existing safety concerns proposed in the RMP for SB4 related to this question. As no safety concerns were raised in this section, the Applicant believes that there is no need for further discussion to address these issues in the RMP. Section 2) Injection site reactions (ISRs) are	The sponsor's response is acceptable and no modification to the RMP is required at this point in time. This may change when the final CSR for Study SB4-G31-RA which includes the 100 week data is provided.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
results post-switching.	designated as an important identified risk in the RMP for SB4. However, as a decreased risk compared with the originator Enbrel was reported, the sponsor does not consider this finding a safety concern. Besides this, the study SB4-G31-RA is already described in the RMP section SVII.3.1.5 Injection site reactions. Therefore the Applicant concludes there is no need for further discussion. Section 3) Similar to question 2, the sponsor does not consider lower immunogenicity to be a safety concern. Also, immunogenicity is not listed as a safety concern in the RMP for SB4. As described in the 52-week CSR, the overall safety is comparable between SB4 and Enbrel treatment groups. Consequently, lower immunogenicity with a comparable safety profile was not considered to be a safety concern and thus was not discussed further. Section 4) Briefly, for the summary of adverse events, the incidence of all TEAEs, SAEs, AESIs, TEAE leading to IP discontinuation and deaths were comparable between the SB4/SB4 treatment group and the switched Enbrel/SB4 treatment group in both the entire 100-week period and the extension period alone. When investigating the TEAEs that occurred during the extension phase on the SOC level, the incidence of	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	TEAEs that occurred during the extension phase was comparable between the SB4/SB4 and Enbrel/SB4 treatment groups. For the incidence of ADAs, the 100-week overall incidence of ADA for SB4/SB4 was 3.2%, lower than that of the Enbrel/SB4 treatment group (15.1%). Since the full CSR has not yet been published, it may be premature to make a definite conclusion; however, the major summary results obtained up to this date do not suggest a significant harm after switching from Enbrel to SB4. In conclusion, the proposed safety questions for the Consolidated report have been adequately addressed and do not warrant any further consideration for applicability in the RMP for SB4.	
TGA recommendation 2: The following statement in the ASA should be amended as highlighted: 'For additional risk minimisation, a format similar to the EU-RMP (such as the patient alert card [PAC] and educational programs) will be provided, with separate review and approval by the TGA'.	The sponsor has revised the implementation plan of additional risk minimisation in Australia according to the TGA recommendation.	The sponsor's response is acceptable.
TGA recommendation 3: The ASA states: 'In order to inform regarding the safe and proper use of the auto-injector, the sponsor will develop and implement an	The sponsor has revised the plan to provide the needle-free demonstration device to clinicians for patient education purposes. The needle-free demonstration	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
additional risk minimisation plan in the form of a training and educational program for patients, HCPs, and company staff, specifically for the safe use of the auto-injector'. However, as previously noted the ASA also states: 'Availability of a needle free demonstration device: This device allows patients to practice injections prior to using the actual pre-filled auto-injector. These devices have been made available to clinicians for training purposes in the clinician's office'. Given the existing presence in the Australian market of the innovator administered presumably via a different auto-injector device, it is agreed that a range of HCPs, not just the prescriber, will require an educational program to be able to inform patients on the safe and proper use of the auto-injector. This would include making the needle-free demonstration device available to all relevant HCPs, not just clinicians. Consequently the sponsor should amend the ASA accordingly	devices will now be made available to all relevant healthcare professionals at their practice sites, not only to clinicians. In addition, the sponsor has replaced the term 'use' with 'administer' for clarity. The revised statement is (changes underlined): '3.2.1 Potential for medication errors – pre-filled pen Additional risk minimisation activities: Training program will be launched to avoid medication errors that can occur from auto-injectors and help HCPs and patients to administer SB4 properly. Availability of a needle free demonstration device: This device allows patients to practice injections prior to using the actual pre-filled auto-injector. These devices have been made available to all relevant HCPs for training purposes in their practice sites.'	
TGA recommendation 4: In regard to the important potential risk: 'Potential for medication errors (pre-filled pen)', the sponsor should provide at least copies of the draft Australian educational materials in print format for HCPs and patients as an attachment to a revised ASA.	The drafts for the educational materials for the PFP (as intended to be part of the additional risk minimisation activities) are now attached on the revised ASA as an Appendix in PDF format. The contents are: a. Auto-injector Instructions for Use (AI IFU) – These are the instructions for using	The draft educational materials are acceptable. Final version should be provided to the TGA when available.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	the auto-injector to deliver a dose of SB4. The IFU was developed based on multiple rounds of human factors testing with patients, caregivers and healthcare providers. The IFU is booklet-format, with information on the device components, storage and disposal, steps for use, and common questions (derived from user testing). Each package of SB4 auto-injectors contains a copy of the IFU. b. Auto-injector Injection Training Video – This instructional video is being developed to support patients, caregivers and healthcare providers in the administration of SB4 by auto-injector. It is based on the printed IFU booklet available in every package of SB4 auto-injectors. It offers a live-action demonstration of the delivery of a full dose, and emphasizes information on storage, disposal, and common use errors. It also includes contact information (telephone, website) to connect users to additional support should they need it. (Note: the video is presented as in drawboard format for now).	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	c. Demonstration Auto-Injector (aka Training Device) – This training tool allows users patients, caregivers, healthcare providers), to simulate injection with the SB4 auto-injector without delivering actual medication. It does not contain a needle or active product, but mimics the form, function and feel of the SB4 auto-injector. This training tool is reusable, tested to withstand at least 100 activations before a replacement is needed. d. Injection Demonstration Kit for Healthcare Providers – This kit co-packages the demonstration auto-injector and demonstration pre-filled syringe for SB4. It also provides a set of dual demonstration instructions for use (single sheet, with the auto-injector IFU on one side, pre-filled syringe IFU on the other side), and contact information to access additional patient support. The kit is designed to be used by healthcare providers, to assist with injection training for patients and caregivers using SB4. e. Patient Welcome Kit with Travel-Sized Instructions for Use (IFU) – This kit includes a carrying case designed	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	to fit two SB4 auto-injectors or two SB4 pre-filled syringes. It also provides contact information for additional patient support, and travel-sized instructions for use. The travel-sized IFUs mirror the versions provided in each box of SB4 auto-injectors or pre-filled syringes. However, the format is single sheet, accordion fold, with steps for injection on one side, and storage, disposal and travel information on the other side. The materials are in draft stage and may be subject to change until finalisation. However, the general structure as proposed will be maintained. It is also to be noted that the distributor for SB4 in Australia is Merck (MSD) Australia, which is separate from the MAH and thus the Merck logo is apparent in the materials.	

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 (see *Outstanding issues* below).

There are additional recommendations.

Outstanding issues

Issues in relation to the RMP

The key outstanding issue is the proposed approach to risk minimisation for off-label paediatric use in Australia. It is recommended that the sponsor implement the same risk minimisation activities in Australia as proposed in the EU RMP. Specifically, *the contraindication for use in paediatric populations should be re-instated in the Patient Alert Card and educational programs.*

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

ACSOM advice identified a number of concerns with the proposed pharmacovigilance and risk minimisation strategies. The key issues were:

- *Off-label use in the paediatric population*
  ACSOM considered that off-label use in the paediatric population was likely. It is noted that in the dose form Brenzys is provided it is only suitable for adolescents weighing ≥ 62.5 kg.
- *The lack of Australian patient registries*
  Australian patients will not be included in the overseas registries. The sponsor's justification for this was '*there is no evidence to show regional or racial differences in the safety profile of etanercept, it is considered that the proposed EU pharmacovigilance activities are applicable to the Australian population*.' ACSOM proposed that the Sponsor consider explore the possibility of using the Australian Rheumatology Association Database (ARAD)
- *Non-melanoma skin cancer (NMSC)*
  The incidence of NMSC is likely to differ in Australia compared to the EU. ACSOM recommended the wording of the PI be altered to recommend skin examinations be performed 'at least annually' instead of 'periodically'. In addition, the lack of an Australian patient registry means than region-specific variations in the incidence of NMSC would not be captured. This could in part be overcome by other measures, such as the use of a specific adverse event follow-up form for NMSC, rather than relying on the general malignancy FU form. The sponsor should consider strategies that would enable effects of etanercept on NMSC in the Australian population to be identified.
- *Immunogenicity*
  The committee noted the limited safety data in patients (submitted data only in patients with RA) with the lack of data regarding immunogenicity identified as a concern.

The concerns regarding off-label use in the paediatric population are an outstanding issue in the RMP, as indicated in Section 1. The other issues raised by the committee have been considered. Potential effects of Brenzys on NMSC and immunogenicity are expected to be detected through the proposed routine pharmacovigilance measures.

The item was discussed at ACSOM Meeting 31 (19 February 2016)

Key changes to the updated RMP

EU-RMP (Version: 2.0, dated 4 May 2015) with an Australian Specific Annex (ASA) Version: 1.0, dated 11 June 2015, has been superseded by:

EU-RMP Version 3.1 (dated 1 October 2015; DLP 21 April 2015) and Australian Specific Annex Version 1.1 (dated 18 February 2016[21])

The key difference between version 1.0 and 1.1 of the ASA is the removal of risk minimisation activities for potential paediatric off-label use (patient alert card and education program for HCPs and patients). These risk minimisation measures are retained in version 3.1 of the EU-RMP. Briefly, the sponsor has stated that routine risk minimisation activities (PI and CMI) are sufficient in Australia due to prescription of etanercept being restricted to relevant specialists, and only being available under the Pharmaceutical benefit Scheme (PBS) under strict prescribing criteria.

The evaluator does not support the removal of the paediatric contraindication from the Patient Alert Card and the Education Programs for Brenzys. It is acknowledged that the

[21] Note: The Sponsor has not updated the date on page 1 of the ASA, but has updated the date in the footer.

prescribing practices in Australia help to minimise off-label paediatric use. However, the lack of a paediatric indication is an important point of difference between Enbrel and Brenzys. As off-label use in the paediatric population is an Important Potential Risk for Brenzys it is appropriate to use the PAC and Education Programs as tools to minimise these risks.

Sponsor's justification for removing paediatric off-label use from risk minimisation activities

The sponsor proposes to remove the Patient Alert Card (PAC) and Education Program from the additional risk minimization activities. The reasoning is as follows:

Routine activities are the same for Australia as those proposed in the EU-RMP, and there is precautionary warning in the CMI and PI. In Australia, access to anti-TNFs is very restricted. It is heavily regulated through an authority prescription with strict clinical criteria requirements, and under such a regulated a process where an off-label prescription would not get approval to be filled. With this restricted access, there is very low potential for off-label paediatric use. Hence it is considered that standard RMP activities, including the precautionary warnings in the PI and CMI as well as routine pharmacovigilance activities with follow up on any off-label use, will be sufficient in the Australian environment.

Therefore, in summary, the ASA will differ from the EU-RMP in that there will be no additional risk minimisation activities for off-label paediatric use since there is:

- Adequate precautionary warning is included in the CMI and PI, which the company considers to be sufficiently appropriate.
- Off label use warnings in the Patient alert card (PAC) are not appropriate as the PAC is intended to alert patients to possible symptoms and alert HCPs to any safety concerns arising from the use of the product that would require medical intervention.
- Routine pharmacovigilance activities will include follow up of any off- label use in paediatrics.

Off-label paediatric use in the Australian setting is also unlikely to occur for the following reasons:

- Strict clinical criteria applied by the PBS, including the requirement for authority prescription, means that off-label prescriptions for SB4 will not be approved for paediatric patients.
- SB4 is unlikely to be accessed on the private market for paediatric use as the originator is available for paediatric use via the PBS.

Further, the PAC is intended to provide treatment guidelines in case of emergency (for example, persistent infections and congestive heart failure), and it would still apply to persistent infections and congestive heart failure to be consistent with the Enbrel PAC as mentioned in the Enbrel AusPAR. The PAC is provided to Brenzys prescribing physicians for distribution to patients receiving Brenzys. Given that Brenzys is only indicated for adult patients and there are significant distribution controls on Australian medicines, it is unlikely that Brenzys would be prescribed and supplied to a paediatric patient.

Suggested wording for the conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

The European Risk Management Plan (version 3.1, 1 October 2015, data lock point 21 April 2015), with Australian Specific Annex (version 1.1, 18 February 2016), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality evaluator has recommended approval on quality grounds, pending outstanding GMP clearances, and has recommended batch release testing as a condition of registration. The excipients in Brenzys are similar to the reference product Enbrel, with the exception of containing no L-arginine hydrochloride in Brenzys and adjustments in the concentrations of sodium chloride and sodium phosphate. The sponsor used the EU sourced Enbrel as the reference product in the clinical study, therefore a bridging comparability study was undertaken to compare EU and Australian sourced Enbrel. The structural, physicochemical and biophysical attributes of Brenzys and EU Enbrel were studied. Based on all the comparison studies, biosimilarity has been demonstrated with respect to quality aspects between Brenzys and EU Enbrel (and a bridging comparability study between EU Enbrel and Australian Enbrel showed high comparability in terms of structural, physicochemical, biophysical and biological attributes), including Fc related biological assays, however some differences were noted as follows:

a. A lower level of high molecular weight product aggregates in Brenzys compared to EU Enbrel however no new peaks are identified and the chromatograms of Brenzys and EU Enbrel overlap almost completely.

b. A lower level of host cell protein impurities in Brenzys compared with EU Enbrel. The lower level of host cell proteins in Brenzys might make it safer immunogenically however when the amount of active (50 mg) is considered, this difference relates to only nanograms in difference and is thus very small.

c. A higher amount of afucosylated glycan content in Brenzys compared to Enbrel and a lower amount of charged glycan content in Brenzys compared to Enbrel. As the afucosylated glycan level in therapeutic proteins is not considered to be related to the action of etanercept and the charged glycan is not significant, these differences were not considered to be meaningful.

d. The O-linked glycans showed a slightly higher peak in Brenzys compared to EU Enbrel for one of the peaks but not the other two. In relation to these glycan differences the quality evaluator commented that the differences in glycan profile are very minor, similarity ranges are quite narrow and more importantly, there are no new glycan species detected. Implications of these differences can only be borne out in the clinical or non-clinical studies.

Sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents (virus, prions and mycoplasma) in the manufacturing of Brenzys have been controlled to an acceptable level.

Container safety was deemed acceptable and there were no objections from a microbiological perspective or bacterial endotoxin testing.

A shelf life of 24 months when stored at 2 to 8°C was supported by the data. The drug product may be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks.

The PI, CMI and labels from a quality perspective were accepted by the evaluator.

Nonclinical

The nonclinical evaluator had no objections to the registration of etanercept for patients with rheumatoid arthritis providing the EU/US sourced and Australian sourced Enbrel were demonstrated to be comparable by the quality evaluator and a slight difference in efficacy observed in the animal model is not evident clinically. The evaluator did not provide comment on the other indications requested by the sponsor but clarified that all indications were supported on nonclinical grounds as in vitro investigations did not indicate inferior affinities or efficacies of Brenzys compared to EU and US-Enbrel and is therefore not expected to differ in its pharmacological activity for other indications. The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat-dose toxicity. The scope of the nonclinical program was adequate under the relevant EU guideline. The studies were conducted using EU and US-sourced Enbrel as the reference product and no nonclinical data were provided to verify the comparability of the EU/US sourced and Australian sourced Enbrel. No meaningful differences between Brenzys and Enbrel were observed in the comparative in vitro pharmacology studies and the pharmacokinetic profile of etanercept was similar for both Brenzys and Enbrel suggesting that the differences in the glycosylation profiles observed in the physicochemical analyses did not significantly impact the pharmacokinetics of Brenzys.

The toxicity profiles of Brenzys and Enbrel were similar in monkeys in a 4 week comparative repeat-dose toxicity study suggesting the glycosylation differences and Fc receptor affinity differences have no obvious effect on the safety of Brenzys. In an animal rheumatoid arthritis model, Brenzys had similar efficacy to Enbrel in terms of footpad volumes and clinical responses but less tissue damage was evident with Enbrel compared to Brenzys.

There were no significant differences in the binding affinities for the two test items against FcγRI, FcγRIIa, FcγRIIb and FcRn. The Brenzys form of etanercept appeared to have a greater affinity for the FcγRIIIa (V-type and F158 allotype) and FcγRIIIb receptors, which may be associated with the slightly higher levels of afucosylated N-glycans on the Brenzys form of etanercept. However, the affinity was still considered to be low (in the micromolar, rather than nanomolar range), and there was no significant difference in the toxicity profile of the two test items in cynomolgus monkeys. Therefore, this difference was not expected to affect the safety profile of the drug. There were no significant differences between the test items in the C1q (complement) binding assay, CDC assay, ADCC assay and in an assay to assess apoptosis of cells with membrane-expressed TNF-α.

In the mouse model of rheumatoid arthritis, Brenzys was effective at slowing the progression of disease and improving tissue pathology and there was no significant difference in efficacy compared to Enbrel. However the more sensitive histopathology assessments suggested Brenzys may be weaker in efficacy than Enbrel therefore further analysis of this potential difference was requested. The response indicated that the effect of Brenzys appeared to be weaker than Enbrel (difference in inflammation and pannus) and the prevalence of animals with histopathological score 0 (normal) was statistically different between the groups. The evaluator concluded that the biological significance of this difference is unclear and that all references to histopathological changes should be removed from the PI and only clinical scores in animals retained.

Clinical

The clinical evaluator has recommended approval for all five of the approved adult indications for Enbrel. The evaluator provided the following recommendation regarding authorisation:

> *The evaluator recommends acceptance of the sponsor's proposed registration of SB4 to include all of the 5 approved adult treatment indications for Enbrel. The submission provides robust evidence that SB4 is therapeutically equivalent to Enbrel in improving the signs and symptoms of active RA in adult patients. In terms of safety, the 2 formulations of ETN appear to be clinically equivalent for the incidence and type of clinically significant safety concerns. The SB4 clinical study program appears to show a lower incidence of local injection site reactions and immunogenicity in RA patients treated with SB4 compared to Enbrel, which remains of unclear explanation. Moreover, the safety profile (incidence and type) of SB4 is within historical expectations for ETN in the target population.*
>
> *In the response, the sponsor has provided a review of the literature on the role of TNF in the disorders covered by the therapeutic indications of Enbrel and the potential mechanisms of action. The mechanism of action of ETN is complex but the primary mode of action results from direct blocking of TNF receptor-mediated biological activities. ETN is a soluble TNFR fusion protein that competitively inhibits TNF by binding to it, thereby blocking the interaction between TNF and TNF receptors. This is thought to prevent various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to AS and PSOR. The sponsor has now provided sufficient justification for the extrapolation of indications for SB4 to include that which are approved for Enbrel on the basis of biosimilarity. Extrapolation of the PK, efficacy and safety data generated in the 2 trials in this submission which examined adult patients with RA and normal healthy volunteers is justifiable on the basis of the results of the pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the ETN molecule). Overall, the results observed in Study SB4-G31-RA can be considered a clinical disease model of adequate sensitivity for assessing the efficacy and safety of SB4 in inflammatory spondylitis, PsA and PSOR.*
>
> *After the response, there is residual concern that the sponsor is specifically not requesting registration of the 2 approved paediatric treatment indications for Enbrel and not providing a 25 mg vial presentation, which has the potential for prescribing and dispensing errors occurring with the registration of 2 ETN formulations in Australia.*
>
> *The evaluator would recommend that approval of the sponsor's proposed registration be subject to regular periodic safety update reports and the provision by the sponsor to the TGA of the final clinical study report for the open-label, extension phase of Study SB4-G31-RA.*

The clinical dossier included the following data:

- 1 clinical pharmacology study (Study SB4-G11-NHV) in healthy male volunteers that provided pharmacokinetic (PK) data and safety information.
- 1 pivotal clinical study (SB4-G31-RA) in adult patients with active RA for 52 weeks, including a PK sub-study.
- 1 open label extension study of SB4-G31-RA for 52 weeks with switching data.

Pharmacokinetics

In accordance with the relevant TGA adopted EU guideline[22], the clinical dossier presented 2 studies for demonstrating similarity in PK characteristics between Brenzys and Enbrel. The clinical Phase 1 trial (Study SB4-G11-NHV) in young-middle aged, healthy male volunteers was considered the primary PK study for demonstrating similarity, and the steady-state PK sub-study of the pivotal Phase 3 clinical trial (Study SB4-G31-RA) provided supporting evidence for PK similarity in a patient population.

The first study was in 138 healthy male volunteers, aged 18 to 55 years, with a single dose crossover design that compared 50 mg SC Brenzys with EU and US sourced etanercept for PK variables (primarily AUC_{inf} and C_{max} using 0.8-1.25 confidence limits) and also compared EU and US sourced etanercept as supportive evidence. Results demonstrated that:

a. Brenzys and EU Enbrel were comparable for AUC_{inf} (90%CI 0.947 to 1.036) and C_{max} (90%CI 0.985 to 1.092) with T_{max} and $t_{1/2}$ also similar.

b. Brenzys and US Enbrel were comparable for AUC_{inf} (90%CI 0.958 to 1.067) and C_{max} (90%CI 0.977 to 1.114).

c. EU Enbrel and US Enbrel were comparable for AUC_{inf} (90%CI 0.915 to 1.104) and C_{max} (90%CI 0.947 to 1.127).

The second study was a sub-study of the Phase III clinical study in rheumatoid arthritis. This substudy was conducted in 79 patients (41 Brenzys and 38 EU Enbrel) who provided baseline and trough levels at 2, 4, 8, 12, 16 and 24 weeks. At each time point of evaluation, the mean serum trough concentrations of etanercept between Brenzys (ranging from 2.419 µg/mL at week 2 to 2.886 µg/mL at Week 24) and EU Enbrel arm (ranging from 2.066 µg/mL at week 2 to 2.635 µg/mL at Week 24) were similar but slightly higher following Brenzys injections at all the time points apart from Week 2. Overall, steady state concentrations for Brenzys and Enbrel were achieved by Weeks 2 to 4 of therapy. Both formulations of etanercept exhibited moderately high inter-patient variability with the CV% ranging from 36.6-53.9% for Brenzys and 48.1-65.7% for EU sourced Enbrel. At Week 8, AUC, C_{max} and C_{min} were moderately higher (30% for AUC, 26% for C_{max} and 42% for C_{min}) following Brenzys therapy versus EU Enbrel injections. Apparent drug clearance (CL/F) was 26% lower in the Brenzys arm versus the Enbrel group. The median T_{max} was comparable between the 2 formulations at just under 48 hours. Anti-drug antibody formation was examined to assess potential impact on PK but the number of results was too low to provide meaningful interpretation.

Pharmacodynamics

This submission did not contain any specific PD data for Brenzys collected in the 2 clinical studies. The sponsor states that the PD effects of etanercept have been well characterised in the published Enbrel trials and registration process. Furthermore, the sponsor asserts that in vitro and in vivo non-clinical studies provided in this submission demonstrate similarity between Brenzys and Enbrel in anti-TNF mediated PD effects. As a proposed biosimilar of Enbrel, the applicant states that no further PD studies of Brenzys are required by the relevant guidelines[23] and that clinical evidence for comparability can be demonstrated by PD surrogate endpoints or clinical evidence. In the case of Brenzys, clinical evidence for similarity was aimed to be demonstrated by clinical rather than PD endpoints. In patients with active RA, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be useful PD markers. Both CRP and ESR are sensitive

[22] EMA/CHMP/42832/2005 Rev 1
[23] EMEA/CHMP/BMWP/ 42832/2005 and EMA/CHMP/BMWP/403543/2010

indicators of the inflammatory activity of RA and their measurement is included in the efficacy assessment.

Efficacy

The dose selected for the pivotal study was based on the approved dose used in the Enbrel registration studies which is acceptable.

Study SB4-G31-RA

This study was a 52 week, multinational, multicentre, randomised, double-blind, parallel-group, comparative equivalence trial of self-administered 50 mg SC Brenzys weekly versus 50 mg SC EU Enbrel weekly in addition to a background of 10-25 mg methotrexate (MTX) in 596 patients with active rheumatoid arthritis despite MTX treatment. There were 3 global and 3 country specific protocol amendments during the study but these did not result in major changes to the study design or adversely affect the integrity of the study's outcomes or statistical analysis. The study had 80% power and an equivalence margin of ±15% based on 50% of the observed difference in the response rate between Enbrel and placebo of about 35%. To declare equivalence between the 2 treatment groups, the 2-sided 95% CI of the difference of the two populations should be contained within ± 15%. Study completion to Week 52 was 83 to 87%. Protocol deviations occurred in 26% of subjects but were similarly matched across treatments. At baseline, both groups had comparable demographic and disease characteristics (mean 52 years, 84% female, 93% Caucasian, mean 6 years of RA, 71% DMARD naïve excluding MTX, 30% prior NSAIDs (53% during the study), 23% prior corticosteroids (57% during the study), 0% prior anti-TNF drug, mean 15.5 mg of MTX at baseline with a mean 47-48 months prior use, mean 24 tender joints, mean 15 swollen joints, mean 13.7mg/L CRP, mean 46.5mm/h ESR, 79% Rheumatoid factor positive, 31-35% hypertensive).

The primary efficacy outcome using the validated ACR20 response at Week 24, per-protocol analysis, demonstrated equivalence at 78.1% for Brenzys and 80.5% for Enbrel (treatment difference of –2.37%, 95% CI–9.54% to 4.80%); that is, within the pre-specified equivalence margins. The full analysis set cohort and available data demonstrated similar findings (76.7% for Brenzys and 78.3% for Enbrel, -1.52%, 95% CI –8.40%, 5.36%). The rate of ACR20 responses at Week 24 (using the PPS1 cohort) was equivalent between the two treatment groups for the following variables: baseline CRP reading (≥ 10 mg/L versus < 10 mg/L), region (EU versus non-EU), age (< 65 years versus ≥ 65 years), gender, race/ethnicity and presence of anti-drug antibodies (yes/no). Secondary efficacy endpoints comparing Brenzys to Enbrel with (treatment difference) were supportive:

- ACR20 at Week 52 (PPS2): 80.8% versus 81.5% (–0.74%, 95%CI -8.03%, 6.56%)
- ACR50 at Week 24 (PPS1): 46.2% versus 42.4% (4.36%, 95%CI -4.33%, 13.05%)
- ACR70 at Week 24 (PPS1): 25.5% versus 22.5% (3.29%, 95%CI -4.18%, 10.76%)
- ACR50 at Week 52 (PPS2): 58.5% versus 53.2% (4.50%, 95%CI -4.67%, 13.67%)
- ACR70 at Week 52 (PPS2): 37.5% versus 31.0% (7.02%, 95%CI -1.69%, 15.74%)
- DAS28 score at Week 24 (baseline mean 6.50): -2.57 versus -2.50
- DAS28 score at Week 52: -2.91 versus -2.80
- EULAR at Week 24: good was 32.1% versus 29.8%, moderate was 55.1% versus 58.5%
- EULAR at Week 52: good was 41.7% versus 34.6%, moderate was 51.0% versus 56.5%
- Major Clinical Response (ACR70 for 6 months) at Week 52: 20.8% versus 18.3%

- Change from baseline in the mTSS at Week 52: 0.45 units versus 0.74 units (-0.27, 95%CI -0.80, 0.26). The change from baseline in each component of the mTSS was also similar in the two treatment groups.

An open label extension phase of an additional 52 weeks was undertaken and an interim report was provided by the sponsor (full report to be a condition of registration). During the extension, 245 patients from Poland and Czech Republic were enrolled with 126 maintained on Brenzys and 119 who were previously on Enbrel and now switched to Brenzys. Methotrexate dosing was maintained at a mean 15.7 mg and about 95% completed 100 weeks of therapy. At Week 100, the rate of ACR20 response was 77.9% in the continuing Brenzys group (79.2% at Week 52 in this group) and 79.1% in the treatment switch arm (compared with 82.4% in this group). ACR50 and 70 showed a similar maintenance of response.

Safety

The mean exposure to Brenzys was 339 days with 212 patients exposed for ≥ 358 days. The overall number of treatment emergent AEs was comparable between Brenzys and Enbrel (58.5% versus 60.3%) as were most of the most frequent types (infections and infestations-28.4% versus 25.6%, general disorders and administration site conditions-9.4% versus 20.5%, (abnormal) investigations-13.7% versus 12.8%, musculoskeletal and connective tissue disorders-10% versus 9.8% and gastrointestinal disorders-7.4% versus 10.1%). Local injection site reactions were lower on Brenzys than Enbrel (3.7% versus 17.5%) which were mostly erythema. A total of 17 treatment emergent hepatobiliary AEs were reported in 11 subjects from the Brenzys group only however only two were considered treatment related (chronic cholecystitis and liver disorder). This included 4 AEs of cholelithiasis in 4 subjects, 3 AEs of liver disorder in 3 subjects, 3 AEs of chronic cholecystitis in 2 subjects, 2 AEs of bile duct stone in 1 subject and 1 AE each of biliary colic, cholangitis, cholecystitis and gall bladder perforation. Most of the hepatobiliary AEs were rated as mild or moderate in severity, but 1 event was regarded as severe. No patient who recorded a hepatobiliary AE tested positive for anti-drug antibodies. The evaluator considered these hepatobiliary findings as spurious given only two were considered treatment related. The most common AEs are listed below (Table 3). Anti-drug antibody status, age (< 65 years/≥ 65 years) and race/ethnicity were not associated with an increased risk of AEs. Subject weight at baseline or concurrent opioid therapy was not associated with a statistically increased incidence of overall or infection related AEs.

Table 3: Most Common Adverse Events (≥2% incidence) by Preferred Term in Study SB4-G31-RA

Treatment	SB4 50 mg N=299			Enbrel® 50 mg N=297			Total N=596		
Preferred term	n	(%)	E	n	(%)	E	n	(%)	E
Any TEAEs	175	(58.5)	533	179	(60.3)	646	354	(59.4)	1179
Upper respiratory tract infection	24	(8.0)	28	16	(5.4)	18	40	(6.7)	46
Alanine aminotransferase increased	18	(6.0)	25	17	(5.7)	26	35	(5.9)	51
Nasopharyngitis	15	(5.0)	17	16	(5.4)	17	31	(5.2)	34
Headache	13	(4.3)	15	8	(2.7)	16	21	(3.5)	31
Hypertension	11	(3.7)	16	11	(3.7)	12	22	(3.7)	28
Rheumatoid arthritis	9	(3.0)	10	10	(3.4)	11	19	(3.2)	21
Aspartate aminotransferase increased	8	(2.7)	13	9	(3.0)	10	17	(2.9)	23
Viral infection	7	(2.3)	7	5	(1.7)	5	12	(2.0)	12
Injection site erythema	6	(2.0)	16	33	(11.1)	85	39	(6.5)	101
Bronchitis	6	(2.0)	6	6	(2.0)	6	12	(2.0)	12
Rash	6	(2.0)	6	4	(1.3)	4	10	(1.7)	10
Rhinitis	6	(2.0)	6	4	(1.3)	5	10	(1.7)	11
Leukopenia	6	(2.0)	7	3	(1.0)	4	9	(1.5)	11
Pharyngitis	5	(1.7)	5	8	(2.7)	9	13	(2.2)	14
Diarrhoea	5	(1.7)	5	7	(2.4)	8	12	(2.0)	13
Urinary tract infection	5	(1.7)	5	7	(2.4)	9	12	(2.0)	14
Cough	4	(1.3)	4	10	(3.4)	11	14	(2.3)	15
Lymphocyte count decreased	4	(1.3)	4	6	(2.0)	8	10	(1.7)	12
Erythema	2	(0.7)	4	10	(3.4)	10	12	(2.0)	14
Dizziness	2	(0.7)	3	7	(2.4)	7	9	(1.5)	10
Injection site rash	2	(0.7)	2	6	(2.0)	11	8	(1.3)	13
Injection site reaction	1	(0.3)	1	8	(2.7)	13	9	(1.5)	14

PT = preferred term; TEAE = treatment-emergent adverse event.

Adverse drug reactions were slightly lower on Brenzys than Enbrel (29.4% versus 36.7%). Two deaths were reports in the Brenzys group (cardiopulmonary failure and gastric adenocarcinoma). Serious AEs occurred in 6% versus 5.1% with infection being most common (0.3% versus 1.7%). A total of 12 subjects (4.0%) in the Brenzys group and 15 subjects (5.1%) in the Enbrel arm had a positive QuantiFERON Gold test at baseline or during the trial up to Week 52. There were no reports of active TB or serious opportunistic infection but subjects were carefully screened at baseline for reactivation of TB. There were no reports of Hepatitis B virus reactivation. Four subjects in the Brenzys group developed 6 hepatobiliary SAEs, which consisted of various events related to gallstones (including 1 case of cholangitis), all considered unrelated. No patients in the Enbrel arm experienced hepatobiliary SAEs. Malignancies occurred in 4 patients on Brenzys versus one patient on Enbrel and no lymphoproliferative disorders were reported. There were no reports of demyelinating disorders. Discontinuations due to AEs were similar (5.4% versus 6.7%). Elevated alanine aminotransferase (ALT) occurred in 5.4% versus 3.4% and high GGT occurred in 2.3% versus 0.7%. There were no possible Hy's law cases. Changes in serum creatinine were similar (3.1% versus 4.1%). There were no notable differences in haematology. There was a statistically higher rate of positive ADA results in the Enbrel group (13.2%) compared to Brenzys (1.0%) and ADA positivity persisted throughout the study. Only one subject on Enbrel developed neutralising antibodies. Positive ANA was detected in 2.7% versus 1.6%. ECG and vital sign changes were mostly similar.

In the open label extension phase, AEs were reported in 47.6% of continuing Brenzys patients versus 48.7% in the switched patients. After switching from Enbrel to Brenzys at Week 52, the incidence and type of overall AEs, treatment related AEs, SAEs (including serious infection) and AEs leading to discontinuation were similar to those in the continuing Brenzys treatment group. Some notable AEs were recorded for patients continuing versus switching: thrombocytopenia (1 versus 1), cardiac failure (0 versus 2),

herpes zoster (0 versus 2) and oral candidiasis (0 versus 2). Only one patient became ADA positive after switching (non-neutralising).

The safety profile of Brenzys appeared to be similar to EU Enbrel in the pharmacokinetic study. Injection site reactions were also comparable at 4.3% versus 6.5% (EU Enbrel) and in the second part were 6.5% versus 6.5% (US Enbrel). Treatment related AEs were slightly higher on Brenzys (26.1% versus 21.7%). There were no deaths or serious AEs. Two subjects had significant LFT abnormalities (1 in each group). No subject treated with Brenzys tested positive for ADA versus 7 subjects on EU Enbrel and 10 subjects on US Enbrel. Among the ADA positive subjects, only 1 subject treated with EU Enbrel had neutralising antibodies.

Risk management plan

The TGA has accepted the EU Risk Management Plan for Brenzys (etanercept), version 3.1, dated 1 October 2015 (data lock point 21 April 2015), with the Australian Specific Annex, version 1.1, dated 18 February 2016.

The following were outstanding matters which should be followed up by the sponsor with the RMP evaluator in PSAB and in the Pre-ACPM Response:

The key outstanding issue is the proposed approach to risk minimisation for off-label paediatric use in Australia. It is recommended that the sponsor implement the same risk minimisation activities in Australia as proposed in the EU RMP. Specifically, the contraindication for use in paediatric populations should be re-instated in the Patient Alert Card and educational programs.

ACSOM identified a number of concerns as summarised under *Pharmacovigilance findings, Advice from the Advisory Committee on the Safety of Medicines (ACSOM)* above.

Excluding the potential for off-label use in paediatric populations, the RMP evaluator advised that the potential effects of Brenzys on NMSC and immunogenicity are expected to be detected through the proposed routine pharmacovigilance measures and the use of overseas registries was acceptable.

Risk-benefit analysis

Delegate's considerations

Pharmacokinetics

Brenzys demonstrated comparable pharmacokinetics to EU Enbrel in healthy male volunteers using AUC_{inf} and C_{max} in a study design that was agreed with the EMA and US FDA to determine PK equivalence using a single dose, crossover trial for which AUC_{inf} and C_{max} would lie within the pre-determined equivalence margin of 0.8 to 1.25. In the substudy of the Phase III study in RA, similar levels of drug exposure were seen but slightly higher following Brenzys injections with moderately high inter-patient variability. At Week 8, Brenzys PK parameters were more moderately higher than EU Enbrel. This data only provides PK information for one of the approved adult indications (RA). The sponsor provided literature to indicate that PK characteristics of Enbrel are similar across the approved adult treatment indications (RA, PSOR and AS) as well as between healthy and diseased adult subjects and although the literature review did not include PK data from all treatment indications (PsA and non-radiographic axial spondyloarthritis), the clinical evaluator considered there is a high likelihood of similar patient and disease characteristics between adult subjects with PSOR and/or PsA; and those with AS or non-radiographic axial spondyloarthritis. The sponsor also provided an integrated analysis of

the PK profiles of Enbrel (derived from population PK modelling) which indicated that health status (health versus disease) or inflammatory joint disease type (RA or AS) does not significantly impact upon the PK of Enbrel. Overall, the PK data and justification are acceptable.

No pharmacodynamic data was provided which is acceptable given the other available data submitted in a nonclinical and clinical setting.

Efficacy

The efficacy of Brenzys is supported by a single equivalence study comparing it with EU Enbrel in a rheumatoid arthritis population taking a stable dose of methotrexate. Brenzys demonstrated equivalence to Enbrel for the primary endpoint and was supported by several secondary endpoints, consistent with the EU guideline on rheumatoid arthritis. The equivalence margin chosen in this study allowed for up to a 15% difference in efficacy but is considered to be the maximal acceptable margin and was the same margin used in another anti-TNF biosimilar study. The selected efficacy endpoints are accepted validated measures that have been used in previous RA studies and are consistent with the EU guideline.

The evaluator was initially concerned at the high proportion of patients who were DMARD naïve however this was subsequently clarified in the round two assessment that all patients had received at least 6 months of methotrexate prior to randomisation at a mean weekly dose of 15.5 mg and that this was an appropriate level of prior MTX use before considering anti-TNF treatment. A higher rate of corticosteroid and NSAID use occurred during the study compared to prior use before but most concomitant medications were started prior to the first etanercept injection and therefore unlikely to have significantly affected the results. The pattern of prior MTX and other DMARD use in the study, as well as the measures of disease activity at baseline in this trial are consistent with the approved RA treatment indication for Enbrel which states '*patients who have had an inadequate response to one or more DMARDs*'. The ACR20 response rate at Week 24 (Brenzys 73.6% and Enbrel 71.7%) was moderately higher than seen in previously published Enbrel studies (60% overall) and somewhat higher than the range (60 to 65% typically) reported with other anti-TNF medicines which the evaluator considered probably reflected a relatively under-treated cohort of patients prior to inclusion.

Overall, Brenzys has satisfactorily demonstrated comparable efficacy to EU Enbrel for adult patients with active rheumatoid arthritis. Given that biosimilarity has been demonstrated with respect to quality aspects between Brenzys and EU Enbrel and a bridging comparability study between EU Enbrel and Australian Enbrel showed high comparability then it is reasonable to conclude that AU Enbrel and Brenzys should have similar efficacy. The quality evaluator noted some minor quality difference between EU Enbrel and Brenzys but these did not appear to effect efficacy and the concerns raised by the nonclinical evaluator of potentially reduced efficacy did not appear to be apparent clinically. In addition, preliminary data from the open-label, extension study indicated a maintained response in those who continued treatment with Brenzys for 100 weeks and those who switched to Brenzys at Week 52.

Paediatric indications, 25 mg strength and dosing

The sponsor has not applied for the two paediatric indications that are currently approved for Enbrel, has not applied for a 25 mg presentation that is currently registered for Enbrel and has deleted dosing instructions for the adult indications of 25 mg twice weekly. In Europe, Brenzys (Benepali) also does not contain a 25 mg twice weekly dose for the adult indications in the EU Summary of Product Characteristics (SmPC) and only has a 50 mg presentation with no paediatric indications. These differences between Brenzys and Enbrel raise a question about whether a product can be designated as a biosimilar when it does not contain all the same indications, strengths and dosages as approved for its

reference product. Taking each strength as a separate entity, as would be registered on the Australian Register of Therapeutic Goods, then for that strength, 50 mg, the product can be considered a biosimilar to Enbrel for the adult indications. A sponsor does not necessarily have to include all strengths and indications of the reference product and in some circumstances it may not be possible if two indications are sufficiently different that they require additional clinical data. Whilst it may be preferable for a biosimilar to be as similar to the reference to avoid confusion and errors in prescribing and dispensing, the Delegate considers that this is not mandatory in all aspects. However the absence of paediatric indications does raise the potential for off-label use which ACSOM considered was likely but that the dose form provided was only suitable for adolescents. The RMP evaluator recommended the sponsor implement the same risk minimisation activities in Australia as in the EU, including the contraindication for use in paediatric populations should be re-instated in the Patient Alert Card and educational programs. The Delegate supports this approach.

Deleting dosing instructions of 25 mg twice weekly from the PI may also be confusing and potentially misleading since this dose has been demonstrated to be safe and efficacious for etanercept. However it is a further extrapolation of the submitted evidence with a lack of PK data on this regimen. It is possible that a dose of 25 mg could be delivered from a pre-filled syringe although there would be wastage.

Safety

The safety profile of Brenzys was acceptable and mostly comparable to EU Enbrel from the pivotal study with an adequate sample size and duration of exposure that is consistent with the EU guideline on rheumatoid arthritis. Infection related AEs occurred with a similar frequency on both treatments but slightly higher serious infection AEs were reported on Enbrel. Local injection site reactions were noted to be less frequent on Brenzys in the pivotal study but similar in the PK study across the Brenzys, EU Enbrel and US Enbrel groups. The sponsor hypothesised that quality aspects of Brenzys may be an explanation, and it was noted in the quality comparability exercise that Brenzys had a lower level of host cell protein impurities but overall considered there was no clinically meaningful difference between the etanercept products for injection site reactions.

Positive ADA results were also lower on Brenzys in both studies and this was also hypothesised to be related to quality aspects however the clinical implications of this observation are unclear as the evaluator has noted that the development of ADA to any formulation of etanercept has not been shown to significantly influence clinical outcomes. The immunogenicity profile of Brenzys may also be different in studies where concomitant MTX is not used. Hepatobiliary AEs were higher on Brenzys (17 versus 0) with serious hepatobiliary events also higher at 6 versus 0 however only two were considered treatment related and the evaluator did not consider this to reflect a true safety difference. The explanation for this difference is unclear however liver function test (LFT) abnormalities were slightly higher on Brenzys. Two patients died on the Brenzys arm which the evaluator considered possibly related. Malignancies were slightly higher on Brenzys (4 versus 1) and this will need monitoring in the RMP through overseas registries. There were no reports of active TB, serious opportunistic infection, Hepatitis B virus reactivation, lymphoproliferative disorders, demyelinating disorders, systemic lupus erythematosus or lupus-like syndromes. The extension phase data did not appear to show any new safety concerns with continuing patients, however this data is preliminary.

Extrapolation of indications

The TGA has adopted EU guideline 'EMEA/CHMP/BMWP/42832/2005 Rev1 which discusses extrapolation of indications. The guideline notes:

> *The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of*

clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication. Additional data are required in certain situations, such as

1. *the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications*

2. *the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications*

3. *the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive for differences in all relevant aspects of efficacy and safety.*

Immunogenicity is related to multiple factors including the route of administration, dosing regimen, patient-related factors and disease-related factors (e.g. co-medication, type of disease, immune status). Thus, immunogenicity could differ among indications. Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.

Brenzys and Enbrel showed similarity in quality aspects as well as comparable inhibition of TNF activity in vitro, similar nonclinical pharmacokinetics, similar toxicity profile in monkeys, similar clinical pharmacokinetics in healthy male volunteers and similar efficacy and safety in rheumatoid arthritis patients. Published literature was provided to suggest the immunogenicity profile of Enbrel was similar across the approved adult indications and that the pharmacokinetics of Enbrel were similar across some of the adult indications. A common mechanism of action exists and there is a similar safety profile across the adult indications. Unlike the other anti-TNF drugs, etanercept also binds lymphotoxin (TNF-beta or LTα3), which has an important role in the inflammatory response however the efficacy of etanercept is mainly dependent on inhibiting soluble TNF. Whilst etanercept represents a very different class of molecule, it shows the same spectrum of activity as the monoclonal anti-TNF antibodies in RA, PsA, AS and PSOR. The sponsor also provided comparability data on LTα3 binding to Brenzys and Enbrel which showed the ranges for the binding activity for Brenzys and EU Enbrel were similar to US Enbrel (reference).

There is some controversy in the literature about whether or not RA is a sensitive clinical model for extrapolation of efficacy and safety data to other treatment indications, however, the clinical evaluator ultimately considered this to be less relevant with etanercept and the proposed indications requested in this submission. Although RA is associated with the smallest placebo adjusted response to etanercept (compared to the 4 other requested adult treatment indications) and the diseases have several pathophysiological mechanisms, antagonism of endogenous TNF by etanercept is a common pathway of producing response. Overall, the clinical evaluator considered RA to be an acceptably sensitive model to allow for extrapolation of indications. The Delegate considers the similarity between EU Enbrel and Brenzys demonstrated in the clinical data in one indication and the justification provided to extrapolate to other adult indications to be reasonable, consistent with the EU guideline. The clinical unit in TGA that handles psoriasis indications also supported the extrapolation to adult plaque psoriasis.

Methotrexate was used in the clinical study and it is not known if there would be differences in PK or immunogenicity without it in the other approved adult indications. There is published data indicating that concomitant methotrexate alters the

immunogenicity, and potentially the pharmacokinetic profile, of anti-TNF therapy and there are significantly lower rates of concurrent MTX use with anti-TNF therapy in inflammatory spondylitis, skin psoriasis and psoriatic arthritis. Therefore there is potential for a different immunogenicity response when methotrexate is not used. The sponsor indicated that the rate of anti-drug antibody development was similar across the pivotal trials for Enbrel regardless of concomitant MTX use and that a subgroup analysis from the pivotal study did not identify any correlation between concurrent MTX dose and the incidence of testing positive for ADA up to 52 weeks with either Brenzys therapy or EU sourced Enbrel. The clinical evaluator considered the immunogenicity profile for patients treated with Brenzys can therefore be reasonably extrapolated to other approved indications of Enbrel. The Delegate recommends the sponsor follow up this issue in the Periodic Safety Update Reports (PSURs) to discuss the potential difference in immunogenicity for patients treated with or without concomitant methotrexate.

RMP

An acceptable RMP with ASA has been provided however there is an outstanding issue with regards to paediatric off-label use which has been discussed above. The sponsor has plans for several European and 2 United Kingdom (UK) based registry studies, each of up to 10 years duration, across the range of proposed adult treatment indications but is not proposing any Australian based registries or studies given the similarities of populations. The RMP evaluator considered no further changes to the RMP were necessary at this time. ACSOM suggested the sponsor could explore the possibility of using the Australian Rheumatology Association Database (ARAD). Given this is the first biosimilar of etanercept and that there are some differences from the EU/UK population and Australia, including risk of skin cancer, the sponsor should consider this matter further.

Switching

The open label extension study suggest that for the 119 patients who switch from EU Enbrel to Brenzys at Week 52 there is a maintenance of clinical response at Week 100 (48 weeks after treatment switch) and there did not appear to be new safety concerns with a low rate of immunogenicity. However there were some notable reports of significant adverse events in the extension period that were only reported in the switching group (cardiac failure (2), herpes zoster (2) and oral candidiasis (2)). This data is nevertheless limited, preliminary and one way only with no data available on multiple switching and should be confirmed when the final report is available.

Overall

The quality, nonclinical and clinical evaluators have all recommended approval. The Delegate considers that sufficient data and justification have been provided, consistent with adopted EU guidelines, to support the similarity of Brenzys to Australian Enbrel to support the registration of Brenzys on quality, safety and efficacy grounds for all five adult indications that are approved for Enbrel. However the Delegate notes the potential risk of off-label use for paediatric indications and risk of prescribing and dispensing errors due to the lack of the 25 mg strength.

Data deficiencies

There is a lack of data in paediatric patients and data using the alternative adult dosing protocol of 25 mg twice weekly. There is no 25 mg strength proposed for registration. There is no direct evidence of similarity in four of the requested indications. Data provided on the effects of switching are limited and do not include switching from Brenzys to Enbrel or multiple switching. Data in patient populations not concomitantly exposed to methotrexate is lacking and there is no data in patients at high risk of infection due to an exclusion criterion.

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment in the Pre-ACPM response:

1. The implementation in Australia of the EU Risk Management Plan for Brenzys (etanercept), version 3.1, dated 1 October 2015 (data lock point 21 April 2015), with the Australian Specific Annex, version 1.1, dated 18 February 2016, included with submission PM-2015-01528-1-3, and the responses in the Pre-ACPM Response dated [date], and any subsequent revisions, as agreed with the TGA.
2. The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as Category 1 submission(s):
    a. Final study report for open-label, extension phase of Study SB4-G31-RA
3. Batch Release Testing
    a. It is a condition of registration that all batches of Brenzys imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
    b. It is a condition of registration that each batch of Brenzys imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Summary of issues

The primary issues with this submission are as follows with further information in the Discussion section:

1. The sponsor has applied for five adult indications that are approved for Enbrel and has submitted clinical data in patients with rheumatoid arthritis only. The rheumatoid arthritis indication is approved for DMARD inadequate responders consistent with the submitted trial design and is also approved with or without methotrexate use. The submitted study was mostly conducted with methotrexate use. The rheumatoid arthritis indications also have a claim for slowing the progression of structural damage in patients with high risk erosive disease.
2. The sponsor has submitted a justification to extrapolate the submitted evidence from rheumatoid arthritis patients along with healthy volunteer and RA patient pharmacokinetic data and other data to support the registration of the other four adult indications.
3. The rate of injection site reactions and immunogenicity appeared to be lower for Brenzys compared to Enbrel from the clinical trial submitted. However the number of hepatobiliary adverse events was higher on Brenzys and malignancies occurred in 4 patients on Brenzys compared to one patient on Enbrel.
4. The sponsor is only applying for the adult indications that are approved for Enbrel and not the paediatric indications of juvenile idiopathic arthritis and paediatric plaque psoriasis that are also approved for Enbrel. The sponsor is also only applying for a 50 mg presentation that is approved for Enbrel and not the 25 mg presentation that is also approved for Enbrel. Information from the Brenzys clinical trial has been included in the PI.
5. Enbrel is approved for adults at doses of 25 mg twice weekly or 50 mg once weekly for the adult indications. Since the sponsor of Brenzys is only applying for the 50 mg

strength presentation, then they are proposing to delete reference to the 25 mg twice weekly dosing instructions from the PI for the adult indications. There is a potential for confusion by having different dosing instructions across etanercept PIs or not stating that a lower dose of 25 mg twice weekly is efficacious and safe. The EU did not include this dose in the biosimilar SPC.

6. The open label extension study suggests there is clinical response maintained and there did not appear to be new safety concerns with a low rate of immunogenicity in patients switching from Enbrel to Brenzys but there is no data available for the reverse or multiple switching. However there were some significant adverse events reported.
7. The quality evaluator noted some minor differences between Brenzys and Enbrel in the comparability analysis.

Proposed action

The Delegate had no reason to say, at this time, that the applications for Brenzys should not be approved for registration, pending further advice from ACPM.

Request for ACPM advice

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

1. What are ACPM's views on the efficacy and to what extent is there sufficient clinical trial evidence of similarity to support the indications relating to rheumatoid arthritis for this biosimilar etanercept?
2. To what extent are there sufficient evidence and/or justification from the submitted data to support extrapolation of the data to the other four adult indications of psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and non-radiographic axial spondyloarthritis?
3. What are ACPMs views on the comparability of the safety profiles of Brenzys and Enbrel and the significance of the differences in rates of injection site reactions, immunogenicity, hepatobiliary adverse events and malignancies reported?
4. What are ACPM's views on the biosimilarity of Brenzys with Enbrel when it is only approved for the adult indications and only for a single strength presentation and is the information in the PI and CMI adequate?
5. Should the PI contain the 25 mg twice weekly dosing instructions for the adult indications and if so, should it also say that the 25 mg strength is not available for this brand and to use an alternative brand if a 25 mg dose is required?
6. What are ACPM's views in relation to the data available on switching from Enbrel to Brenzys and is this adequately covered in the PI?
7. What are ACPMs views on the significance of the differences noted in the quality comparability evaluation?

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.

Questions for the sponsor

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

1. Provide an updated on the outstanding GMP clearances.

2. Comment on the potential clinical implications of each of the differences noted in the comparability exercise between Brenzys and Enbrel, as discussed above in the quality evaluation.
3. What is the explanation for the differences observed between Brenzys and Enbrel for hepatobiliary adverse events, including serious events and LFT increases and could this be related to any minor differences in quality?
4. How does the sponsor intend to reduce the risk of off-label use for paediatric indications? In the response, address the advice of the RMP evaluator and ACSOM and provide updated RMP materials to the RMP section.
5. What further studies are planned in regards to the efficacy and safety of switching patients between Enbrel and Brenzys or multiple switching?
6. How might the binding of lymphotoxin differ across the five indications?
7. There is a potential for immunogenicity responses to be different in indications that do not normally use concomitant methotrexate, such as psoriasis. What ongoing monitoring of immunogenicity will be undertaken in patients where concomitant methotrexate is not routine, for example via appropriate RMP measures and / or inclusion in regular PSUR updates? Note ACSOMs comments on immunogenicity.
8. How does the sponsor intend to capture information on Australian patient outcomes given Australian patients will not be included in a registry, including for non-melanoma skin cancer? In the response please address the recommendations provided by ACSOM on registries and non-melanoma skin cancer, including the use of a specific adverse event follow up form.

Summarise how the sponsor is informing prescribers that Brenzys is a biosimilar product, that it is only approved for the adult indications, is only available in 50 mg strength and how this is being communicated in any educational materials

Response from sponsor

Response to Question 1

As noted, there are outstanding GMP Clearances that are currently under review and are expected to be resolved.

Response to Question 2

In accordance with the TGA's question, the sponsor provides comments on potential clinical implications of each of the differences noted in the results of the comparability exercise between Brenzys and EU Enbrel from the quality evaluation. Based on the discussion below, it is concluded that the slight differences (points a – d) between Brenzys and Enbrel would not have clinical impact.

Response to Question 2a - Level of high molecular weight species and aggregates

In biological medicines, the capacity of aggregates to cause increased immunogenicity and affect safety and efficacy is well known.[24] The size exclusion chromatography (SEC) analysis of SB4 showed a lower level of high molecular weight (HMW) product aggregates in SB4 compared to EU Enbrel, with no new peaks identified and chromatograms overlapping almost completely. The result indicates that the HMW species of SB4 are composed mainly of [information redacted], while those in EU Enbrel are composed of [information redacted]. Overall, based on the slightly lower level of HMW species in SB4 compared to EU Enbrel an immunogenic response is less likely to occur with SB4. Hence

[24] Rosenberg AS. Effects of protein aggregates: an immunologic perspective. AAPS J. 2006; 8(3): E501-7.

the observed differences will have minimal adverse clinical impact in terms of immunogenicity, safety and efficacy.

Response to Question 2b - Level of host cell protein impurities

Host cell proteins (HCPs) impurities derived from the host cell expression system may cause an immune response and side effects following the administration of drugs to patients. SB4 exhibited lower levels of residual HCP impurity than EU Enbrel when expressed either as [information redacted]or [information redacted]. Since the antibody used to determine HCP impurity levels was developed for SB4, it would be expected to be more sensitive in detecting HCP in SB4 compared to EU Enbrel. However, residual HCP impurity levels in SB4 were consistently lower than residual HCP levels in EU Enbrel. Therefore, the differences in HCP impurity levels would not support any expected negative clinical impact in terms of potential immunogenicity for SB4 compared to EU Enbrel.

Response to Question 2c N-linked glycan content

Impact of afucosylated glycans

It is known that higher afucosylated glycan content in monoclonal antibodies can cause higher FcγRIIIa binding activity, and in turn higher ADCC, since at the molecular level the interaction between afucosylated IgG1 and FcγRIIIa has increased affinity compared to the fucosylated form due to a lack of steric hindrance (by the absence of fucose).[25]

Analysis showed that the levels of afucosylated glycans in SB4 batches were higher than those for EU Enbrel; this difference was not considered to be significant, since the binding affinity of SB4 to FcγRIIIa was within the similarity range. Furthermore, ADCC is not considered as the principal mechanism of action of etanercept. Moreover, there are no known associations between afucosylated glycans and pharmacokinetics (PK). In addition, afucosylated forms of human immunoglobulin G (IgG) are observed as natural components in normal human serum. Therefore, afucosylated glycans would not have immunological impact.

Impact of charged glycans

It is known that sialic acids can have a significant impact on the PK since higher sialylation resulted in higher exposure (lower clearance).[26] However, as presented, the content of total sialic acid (TSA) was similar between SB4 and EU Enbrel, indicating that the difference in charged N-glycans will not affect the PK profiles. Moreover, the level of N-glycolylneuraminic acid (NGNA), known to induce immunogenic responses[27], was similar between SB4 and EU Enbrel. Therefore, it is concluded that the level of charged glycans would not induce immunogenicity.

Response to Question 2d - Level of O-linked glycans

The analysis result of O-linked glycans showed a slightly higher peak in SB4 compared to EU Enbrel for [information redacted]but not for [information redacted]. As mentioned above, sialic acids can have significant impact on the PK. However, the content of TSA was similar between SB4 and EU Enbrel, due to the O-glycan occupancy of SB4 being lower than that of EU Enbrel, which compensates for the high level of[information redacted], and thus resulting in a similar TSA content. Therefore, it is unlikely that the difference on O-glycan structures would have impact on clinical outcomes.

[25] Ferrara C, Stuart F, Sondermann P, Brunker P and Uman P. The Carbohydrate at FcRIIIa Asn-162 AN ELEMENT REQUIRED FOR HIGH AFFINITY BINDING TO NON-FUCOSYLATED IgG GLYCOFORMS* The Journal of Biological Chemistry Vol. 281, No. 8, pp. 5032–503

[26] Liu L. Antibody Glycosylation and Its Impact on the Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies and Fc-Fusion Proteins. Journal of Pharmaceutical Sciences 104:1866–1884, 2015

[27] Noguchi A et al. Immunogenicity of N -Glycolylneui·aminic Acid-Containing Carbohydrate Chains of Recombinant Human Erythropoietin Expressed in Chinese Hamster Ovary Cells. J. Biochem. 117, 59-62 (1995)

In addition, to assess the effect of glycans on the biological activity of etanercept, a glyco-SAR study was performed. The results showed that the N- and O-glycans do not have a significant effect on the biological activity of etanercept.

Response to Question 3

As requested by the TGA, an explanation for the differences observed in hepatobiliary adverse events (17 events in 11 subjects in the SB4 versus none in the Enbrel) including serious events and laboratory values has been provided as follows:

- After extensive analysis of AE profiles, medical, surgical, medication history and laboratory values of the clinical data of SB4-G31-RA, the AEs that were reported in the SB4 treatment group belonging to the System Order Class (SOC) Hepatobiliary disorders that caused the imbalance in in hepatobiliary adverse events were of biliary origin rather than pure hepatic events, leading to an imbalance of 8:0 rather than 11:0 subjects.
- When reviewing the liver enzyme laboratory values or other hepatobiliary-related AEs belonging to other SOCs, the balance was comparable between the two treatment groups, suggesting against drug- induced hepatotoxicity.
- After discussing with the Data Safety Management Board (DSMB), the DSMB expressed that the meaningful difference should be 6:0 (subjects), considering that the problem is bile stones and only 6 of the 8 mentioned above were actually symptomatic.
- Following an analysis of potential biliary risk factors, it was found that all of the subjects had at least 1 type of risk factor for bile stones, namely age, sex, obesity, past history of bile stones, cardio-metabolic conditions and certain medications which were reported to be associated with cholelithiasis.
- In particular, an imbalance in terms of cardio-metabolic risk factors (hypertension, diabetes, dyslipidemia, coronary heart disease and BMI (obesity)) was observed in the baseline medical history, such that these were higher in the SB4 treatment group as compared to Enbrel treatment group on the population level.

Therefore, the sponsor concludes that the apparent imbalance of hepatobiliary events in the SB4 treatment group is not due to any causal effects by SB4 treatment as such but could rather be explained by an unequal distribution of baseline biliary disease risks in the SB4 treatment group compared with the Enbrel treatment group.

The sponsor further assessed whether any quality attributes may have induced the imbalance in hepatobiliary adverse events. As discussed in detail in the response to Question 2, extensive analysis revealed that the minor differences in quality attributes would not lead to the higher incidence in hepatobiliary adverse events in the SB4 treatment group. Furthermore, there have been no reports which have identified a correlation between quality attributes and hepatobiliary events. The imbalance of hepatobiliary adverse events between SB4 and Enbrel is unlikely to be derived from minor differences in quality.

Response to Question 4

The sponsor proposes to reduce the risk of off-label use in paediatric indications by including the following statement in the Patient Alert Card (PAC).

> *Brenzys is used in adults for the following conditions:*
>
> *rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, non-radiographic axial spondyloarthritis. Brenzys is not indicated for use in children under 18.*

The sponsor proposes to include the following statement in the educational materials. The educational materials comprise instruction for use in the form of a video and booklet describing how to use SB4 properly in order to avoid medication errors.

Brenzys is used in adults for the following conditions:

rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, non-radiographic axial spondyloarthritis. Brenzys is not indicated for use in children under 18.

The revised ASA-RMP incorporating the changes with the updated PAC and the education materials will be submitted to TGA after the ACPM recommendation and prior to the Delegate's decision.

Response to Question 5

Switching studies have already been conducted through the 100 week extension study for SB4-G31-RA. Through the initial response the sponsor has provided preliminary results showing that no major issues have occurred after switching from Enbrel to SB4. As requested by TGA PM, the full results will be submitted after the approval. There are no additional switch studies planned post approval to specifically address the efficacy and safety in patients transitioning from Enbrel to Brenzys.

Response to Question 6

Lymphotoxin is a general term that refers to a family of trimeric molecules composed of various combinations of α and β monomers including LTα3, LTα1β2 and LTα2β1.[28] Lymphotoxin-α (LTα3) (formerly known as TNF- β) is structurally similar to sTNF-α in that it is a soluble homotrimer composed of 17 kDa monomers and it binds specifically to TNFR1 and TNFR2 to exert its biologic activities. The affinities of LTα3 for TNFR1 and TNFR2 are comparable to those of TNF-α; but, unlike TNF-α, LTα3 does not rapidly dissociate from TNFR2[28]. Etanercept, like soluble forms of TNF receptors also binds lymphotoxin, although the pharmacological significance of the binding remains unknown.[29]

A recent meta-analysis did not identify any relation between LTα polymorphisms and susceptibility to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[30] No studies could be identified that specifically investigated binding affinity of LTα3 affinity across indications.

The role of LTα3 in the inflammatory response has not been studied to the same extent as TNF-α but LTα3 has been reported to stimulate inflammation in several in vitro and in vivo studies.[31,32] Elevated levels of LTα3 have been identified in 21.9% of RA patients compared to 0% in controls.[33]

Another study reported that LTα3 is expressed in synovial tissue of RA patients, although it was detected at lower levels than TNF-α, and was decreased in response to etanercept

[28] Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008 Feb;117(2):244–79
[29] Marotte H and Cimaz R. Etanercept -- TNF receptor and IgG1 Fc fusion protein: is it different from other TNF blockers? Expert Opin. Biol. Ther. (2014) 14(5): 569-572
[30] Zhang C, Zhao MQ, Liu J, Huang Q, Li P, Ni J, Liang Y, Pan HF, Ye DQ. Association of lymphotoxin alpha polymorphism with systemic lupus erythematosus and rheumatoid arthritis: a meta-analysis. Int J Rheum Dis. 2015 May;18(4):398-407.
[31] Calmon-Hamaty F, Combe B, Hahne M, Morel J. Lymphotoxin alpha stimulates proliferation and pro-inflammatory cytokine secretion of rheumatoid arthritis synovial fibroblasts. Cytokine. 2011 Feb;53(2):207–14
[32] Buhrmann C, Shayan P, Aggarwal BB, Shakibaei M. Evidence that TNF-beta (lymphotoxin alpha) can activate the inflammatory environment in human chondrocytes. Arthritis Res Ther. 2013;15(6):R202
[33] Robak T, Gladalska A, Stepien H. The tumour necrosis factor family of receptors/ligands in the serum of patients with rheumatoid arthritis. Eur Cytokine Netw. 1998 Jun;9(2):145–54.

treatment.[34] However, a clinical trial investigating the efficacy of a monoclonal antibody targeting LTα3 in the treatment of RA failed to reach statistical significance.[35] Also, elevated levels of LTα3 were identified, in juvenile idiopathic arthritis (JIA) patients but these did not seem to correlate with disease activity.[36] No information regarding the clinical effects of LTα3 in ankylosing spondylitis (AS) could be identified, but a study investigating expression of LTα3 in the synovium of psoriatic arthritis (PsA) patients found that LTα3 serum level did not correlate with the clinical and laboratory parameters of the response.[37] Together, these data support the notion that sTNF-α and not LTα3 is the main determinant for etanercept efficacy across the five indications.

Regardless of the role of LTα3 across the various authorised indications, SB4 demonstrated similar LTα3 binding activity. LTα3 binding activity of SB4 ranged from 98 to 115%, whereas that from EU Enbrel ranged from 96 to 111%. The LTα3 binding activity of SB4 DS and DP was within the similarity range of 87 to 116% which supports the similarity in LTα3 binding activities of SB4 and EU Enbrel. Therefore, the sponsor concludes that no differences are expected in terms of LTα3 activities across the requested indications.

Response to Question 7

As noted by the TGA, there is the potential for immunogenicity responses to be different in indications that do not normally use concomitant methotrexate, such as psoriasis.

However, anti-drug antibodies (ADAs) against Enbrel did not show a particular impact on clinical outcomes (Enbrel SmPC). This has also been supported by the results of Study SB4-G31-RA, as ADA status did not particularly affect efficacy or safety profiles of SB4 and Enbrel (such as injection site reactions). However, the sponsor will monitor immunogenicity through the occurrence of injection site reactions and/or lack of efficacy in other indications than RA, where concomitant methotrexate is not customary, through routine pharmacovigilance.

Response to Question 8

The sponsor will amend the PI; to monitor skin cancer annually in patients with risk for non-melanoma skin cancer according to ACSOM's recommendations, given Australian patients will not be included in a registry.

Non-melanoma skin cancers will be monitored through routine pharmacovigilance. In addition, the sponsor will produce a specific AE form for non-melanoma skin cancer and send to the reporter if a skin cancer case is reported, as recommended by ACSOM. Data obtained from this form will be collected and reported to the TGA.

Response to Question 9

The sponsor proposes to inform prescribers that Brenzys, an etanercept biosimilar product, is only approved for adult indications and thus available in a 50 mg strength by the following means:

[34] Neregard P, Krishnamurthy A, Revu S, Engstrom M, af Klint E, Catrina AI. Etanercept decreases synovial expression of tumour necrosis factor-alpha and lymphotoxin-alpha in rheumatoid arthritis. Scand J Rheumatol. 2014;43(2):85–90.
[35] Kennedy WP, Simon JA, Offutt C, Horn P, Herman A, Townsend MJ, et al. Efficacy and safety of pateclizumab (anti-lymphotoxin-alpha) compared to adalimumab in rheumatoid arthritis: a head-to-head phase 2 randomized controlled study (The ALTARA Study). Arthritis Res Ther. 2014;16(5):467.
[36] Bjørnhart B, Svenningsen P, Gudbrandsdottir S, Zak M, Nielsen S, Bendtzen K, Müller K. Plasma TNF binding capacity in patients with juvenile idiopathic arthritis. Int Immunopharmacol. 2005 Jan;5(1):73-7.
[37] Murdaca G, Colombo BM, Contini P, Puppo F. Determination of lymphotoxin-alpha levels in patients with psoriatic arthritis undergoing etanercept treatment. J Interferon Cytokine Res. 2012 Jun;32(6):277–9.

- A Dear HCP letter
- Patient alert card and IFU education material

Promotional materials will include only the 50 mg/1 mL strength.

Advisory Committee Considerations

The ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Brenzys solution for injection in prefilled syringe and autoinjector containing 50 mg/1 mL of etanercept (rch) to have an overall positive benefit–risk profile for the proposed indication;

Brenzys is indicated for the treatment of:

Adults (≥ 18 years)

Rheumatoid arthritis

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

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

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. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque psoriasis

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

Ankylosing apondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

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 an inadequate response to NSAIDs.*

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

In making this recommendation the ACPM

- noted that no meaningful differences between Brenzys and Enbrel were observed in structural, physiochemical and biophysical attributes from the comparative studies, including biological assays.
- noted there were no significant differences in the nonclinical data or comparative clinical pharmacology data.
- was of the view that the efficacy and safety data from a single pivotal study (SB4-G31-RA) are sufficient to establish therapeutic equivalence between Brenzys and Enbrel for the treatment of adult patients with active RA.

- advised that clinical data can be extrapolated to the other four adult indications according to EU guidelines.
- expressed concern that there are insufficient data about the effect of multiple switching between Brenzys and Enbrel.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Australian patients should be included on the proposed registry. The ACPM noted that there is sufficient difference between the genetic mix in Australia compared to Europe. In addition, there is a high incidence of non-melanotic skin cancers as well as melanomas in the Australian population. The ACPM noted that use of bDMARDs is also different due to funding arrangements compared to the use of bDMARDs in the clinical study.

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), and specifically advised on the inclusion of the following:

- Include a statement under '*Comparative safety of Brenzys and Enbrel*' that there are limited data about switching between Enbrel and Brenzys, and that if switching occurs the patient should be closely supervised and monitored.
- Include a statement in the *Dosage and administration* section that Brenzys is not available in a 25 mg strength.
- Under *Adverse events* include the hepatobiliary adverse event data.
- Under *Precautions*: Melanoma and non-melanoma skin cancers: include similar wording as included in the Enbrel PI.

Specific advice

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

1. *What are ACPM's views on the efficacy and to what extent is there sufficient clinical trial evidence of similarity to support the indications relating to rheumatoid arthritis for this biosimilar etanercept*?

The ACPM noted that the quality data indicated that the two products, Enbrel and Brenzys, had slight differences which are not clincally significant. The ACPM advised, that there is sufficient clinical trial evidence of similarity in rheumatoid arthritis to support equivalence.

2. *To what extent is there sufficient evidence and/or justification from the submitted data to support extrapolation of the data to the other four adult indications of psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and non-radiographic axial spondyloarthritis*?

The ACPM advised that based on similar mechanism of disease, similar quality aspects and the biosimilarity demonstrated in the clinical study in rheumatoid arthritis, that it is appropriate to extrapolate the efficacy and safety data to the other four adult indications.

3. What are ACPMs views on the comparability of the safety profiles of Brenzys and Enbrel and the significance of the differences in rates of injection site reactions, immunogenicity, hepatobiliary adverse events and malignancies reported?

The ACPM noted that the safety profile was similar and acceptable. The ACPM agreed that the sponsor's pre-ACPM response had sufficiently explained the hepatobiliary adverse events but considered the hepatobiliary adverse event data should be included in the PI.

4. *What are ACPM's views on the biosimilarity of Brenzys with Enbrel when it is only approved for the adult indications and only for a single strength presentation and is the information in the PI and CMI adequate?*

The ACPM noted that biosimilarity is acceptable based on the adult indications only and that the information in the PI was acceptable however it should be clearer which studies in the Clinical Trials and Adverse Effects section were specifically from Enbrel.

5. *Should the PI contain the 25 mg twice weekly dosing instructions for the adult indications and if so, should it also say that a 25 mg strength is not available for this brand and to use an alternative brand if a 25 mg dose is required?*

The ACPM advised that the PI should not have the dosing instructions for the 25 mg twice weekly dosing but should include a statement under the *Dosage and administration* section that Brenzys is not available in a 25 mg strength.

6. *What are ACPM's views in relation to the data available on switching from Enbrel to Brenzys and is this adequately covered in the PI?*

The ACPM was of the view that switching was not adequately covered in the PI. The PI should state that there are limited data about switching between Enbrel and Brenzys, and that if switching occurs the patient should be closely supervised and monitored.

7. *What are ACPMs views on the significance of the differences noted in the quality comparability evaluation?*

The ACPM advised that there are no clinically significant differences in the quality comparability evaluation.

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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of [AUST R 245252 - Brenzys etanercept(rch) 50 mg solution for injection pre-filled syringe and AUST R 245253 - Brenzys etanercept(rch) 50 mg solution for injection auto-injector, indicated for:

Adults (~ 18 years)

Rheumatoid arthritis

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

Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

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. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Plaque psoriasis

Adult patients with moderate to severe chronic Plaque psoriasis, who are candidates/phototherapy or systemic therapy

Ankylosing spondylitis

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 an inadequate response to NSA/Ds.*

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

Specific conditions of registration applying to these goods

1. The Brenzys European Risk Management Plan (RMP), (version 3.1, 1 October 2015, data lock point 21 April 2015) with Australian Specific Annex (version 1.2, 14 July 2016), included with submission PM-2015-01528-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   Submission of the proposed Brenzys healthcare professional educational material and patient alert card for use in Australia for review and agreement by the TGA prior to supply of the product.

2. An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1),

3. The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ ASA, as soon as possible after completion, for evaluation as a Category 1 submission(s):

   a. Final study report for open-label, extension phase of Study SB4-G31-RA

4. Batch Release Testing

   It is a condition of registration that all batches of Brenzys imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   It is a condition of registration that each batch of Brenzys imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI for Brenzys approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, 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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