Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for etanercept (rch)

Proprietary Product Name: Enbrel

Sponsor: Pfizer Australia Pty Ltd

April 2014

TGA Health Safety Regulation

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 <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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 abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACR Pedi 30 Response	American College of Rheumatology Paediatric 30 Response
ADR	Adverse drug reaction
AE	Adverse Event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine transaminase
ANCA	Anti-neutrophil cytoplasmic antibody
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing Spondylitis
AST	Aspartate transaminase
BMI	Body mass index
BSA	Body surface area
CER	Clinical Evaluation Report
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CMI	Consumer Medicines Information
COSTART	Coding symbols for a thesaurus of adverse events terms
CRP	C-Reactive Protein
CS	Corticosteroid
DMARD	Disease modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
EMA	European medicines agency

Abbreviation	Meaning
eoJIA	Extended oligoarticular JIA
ERA	Enthesitis related arthritis
ETN	Etanercept
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG1	Immunoglobulin G1
ILAR	International League of Associations for Rheumatology
ISR	Injection Site Reaction
IV	Intravenous
JCA	Juvenile chronic arthritis
JIA	Juvenile Idiopathic Arthritis
JRA	Juvenile Rheumatoid arthritis
LFT	Liver function test
LOCF	Last observation carried forward
LOM	Limitation of movement
MAS	Macrophage activation syndrome
MG	Myasthenia gravis
MTX	Methotrexate
NRI	Non responder imputation
NSAID	Non-steroidal anti-inflammatory
PD	Pharmacodynamic
PGA	Physician Global Assessment
PI	Product Information

Abbreviation	Meaning
pJIA	Polyarticular course JIA
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PML	Progressive multifocal leukoencephalopathy
PPD	Tuberculosis skin test
PsJIA	Psoriatic arthritis
PSUR	Periodic Safety Update Report
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Mean duration
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent AE
TGA	Therapeutic Goods Administration
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
US	United States
VAS	Visual analogue scale
VFE	Valid for efficacy
WCC	White cell count

Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	12 February 2014
Active ingredient:	Etanercept (rch)
Product name:	Enbrel
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose forms:	Powder for injection vial and diluent syringe composite pack, solution for injection prefilled syringe and solution for auto injection.
Strengths:	25 mg powder for injection vial and diluent syringe composite pack. 50 mg powder for injection vial and diluent syringe composite pack. 25 mg solution for injection prefilled syringe. 50 mg solution for injection prefilled syringe. 50 mg solution for auto injection.
Containers:	Vial, Pre-filled syringe and Autoinjector
Pack size:	4
Approved therapeutic use:	Juvenile Idiopathic Arthritis • Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more disease modifying antirheumatic drug (DMARDs). • Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate. • Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy. • Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate

	Enbrel has not been studied in children aged less than 2 years.
Route of administration:	Injection
ARTG numbers:	90456, 107316, 124421, 124422, 157627

Product background

This AusPAR describes the application by the sponsor to register Enbrel for the following indication:

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more disease modifying antirheumatic drug (DMARDs).*
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*
- *Active enthesitis related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.*
- *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant* to, methotrexate

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

This application is an abridged submission requesting 3 significant changes to the current approved treatment indication for etanercept (ETN) in patients with Juvenile Idiopathic Arthritis (JIA). Firstly, the sponsor is requesting an extension of indication to include the treatment of additional sub-types of JIA, Enthesitis related arthritis (ERA), psoriatic arthritis (PsJIA) as well as extended oligoarticular JIA (eoJIA). The current JIA indication for ETN is active polyarticular course JIA (pJIA), which was approved in Australia on 2 October 2001.

Secondly, the sponsor is requesting to lower the age limit of treatment from the currently approved 4 years of age to 2 years of age for those patients with eoJIA and pJIA. The requested age limit for treatment in the other new JIA sub-types (ERA and PsJIA) is 12 to 17 years. =

Thirdly, the sponsor wishes to add a once weekly dosing regimen (0.8 mg/kg, up to a maximum of 50 mg) as an alternative treatment posology for patients with JIA. The current recommended dose for children 4 to 17 years of age is 0.4 mg/kg (up to a maximum of 25 mg), given twice weekly as a subcutaneous (SC) injection with an interval of 3 to 4 days between doses. The sponsor application letter is dated 6 February 2013.

Etanercept (ETN) is currently approved in Australia for the treatment of pJIA, Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and chronic plaque psoriasis under the registered trade name of Enbrel. The sponsor does not propose to use this submission for a different registered drug name for this indication and no change in the drug formulation or presentation is proposed.

Etanercept (ETN) is a human tumour necrosis factor (TNF) receptor fusion protein produced by recombinant Deoxyribonucleic acid (DNA) technology in a Chinese Hamster Ovary (CHO) mammalian expression system. It's produced by fusing the human tumour necrosis factor receptor 2 (TNFR2/p75) to the Fc domain of human Immunoglobulin G 1 (IgG1) to competitively inhibit the interaction between TNF and its receptors.

The current approved JIA treatment indication for ETN in Australia is

> *Active polyarticular course juvenile idiopathic arthritis in patients (4 to 17 years) who have had an inadequate response to one or more disease modifying anti-rheumatic drugs. Enbrel has not been studied in children less than 4 years of age.*

ETN also has several other approved treatment indications in Australia such as active RA, PsA, and AS in adult patients; as well plaque psoriasis in children, adolescents and adults.

Regulatory status

At the time the TGA considered this application ETN was registered for supply in Australia as a 25 mg powder for injection, and a 50 mg solution (in 1 mL) for injection in either a pre filled syringe or auto injector device.

No new dosage forms or strengths are proposed in this submission.

Etanercept has been considered by the Advisory Committee on Prescription Medicines (ACPM) or Peer Review previously as follows:

- April 2000 (209th meeting) recommended for approval for rheumatoid arthritis.
- August 2001 (217th meeting) recommended for approval for juvenile chronic arthritis.
- June 2003 (228th meeting) recommended for approval for psoriatic arthritis.
- February 2004 (232nd meeting) recommended for approval for ankylosing spondylitis and slowing progression of structural damage in rheumatoid arthritis.
- December 2004 (237th meeting) recommended for approval to change the rheumatoid arthritis indication and approve the 50mg once weekly dose in RA.
- February 2005 (238th meeting) recommended for approval for plaque psoriasis.
- December 2006 (Peer Review) recommended for approval for 50mg once weekly.
- May 2007 (Peer Review) recommended for approval to extend the psoriatic arthritis indication.

Etanercept for the JIA variations has been approved in the European Union (EU) (August 2011 (extension of age range), and July 2012 (new JIA subtypes and once weekly dosing regimen for JIA). The current US label includes pJIA for patients aged greater than or equal to 2 years, and once weekly dosing for all indications, including the JIA indication. The new JIA subtypes and once weekly dosing regimen dossier was submitted to Switzerland in February 2013 (extension of age range for JIA from "age 4 years and older" to "age 2 years and older" was approved March 2012). The approved EU indication is:

> ***Juvenile idiopathic arthritis***
>
> *Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.*
>
> *Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.*
>
> *Treatment of enthesitis related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.*
>
> *Enbrel has not been studied in children aged less than 2 years.*

Product Information

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

II. Quality findings

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

III. Nonclinical findings

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

IV. Clinical findings

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

Introduction

ETN is a recombinant, humanized tumour necrosis factor (TNF) receptor fusion protein, which has high affinity binding to TNF and blocks its interaction with cell surface TNF receptors.

Clinical rationale

JIA encompasses a diverse group of arthritic conditions of unknown aetiology that begin before the sixteenth birthday, and persist for at least 6 weeks. It is one of the most physically disabling conditions of childhood, with prevalence in Australia of 0.3% according to the Australian Institute of Health and Welfare 2012 report. JIA is a heterogeneous disorder, and the subtypes have varying clinical and laboratory features that may reflect distinct immunopathogenic processes. The pathogenesis of each subtype is multifactorial and likely to be triggered by environmental stimuli in genetically susceptible individuals. JIA is a WHO endorsed, internationally accepted umbrella term that has replaced all previously used nomenclatures such as juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA).

Further information is contained within the Clinical Evaluation Report (CER) at Attachment 2.

Guidance

The TGA has recommended review and consideration of one specific regulatory guideline pertaining to the requested extension of indication. The TGA has adopted the EU guideline CPMP/EWP/422/04 “Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis” (effective 26 June 2009).

The sponsor has recommended consideration of 2 related guidelines in reviewing this submission: Committee for Medicinal Products for Human Use (CHMP) guidelines on Clinical Trials in Small Populations (July 2006) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Choice of Control Group in Clinical Trials (January 2001).

Other relevant EU guidelines, adopted by the TGA are: CPMP/ICH/2711/99 "Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population" (effective 19 April 2001), EMEA/CHMP/PEG/194810/2005 "Reflection Paper: Formulations of Choice for the Paediatric Population" (effective 29 June 2009) and CHMP/EWP/147013/2004 "Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population" (effective 24 August 2009).

Contents of the clinical dossier

The submission contained the following clinical information:

- One pivotal efficacy/safety trial (Study 0881A1-3338) evaluating the efficacy and safety of ETN in patients with eoJIA, ERA and PsJIA.
- No specific dose finding studies.
- One supporting, open label trial of up to 10 years duration (Study 20021618) providing efficacy/safety data in patients with polyarticular JIA. This is a long term extension trial of the previously submitted pivotal ETN treatment study in patients with active polyarticular JIA (Study 16.0016).
- One Phase IV registry study of 36 months duration in patients with active polyarticular or systemic JIA (Study 20021626), which provided supporting safety and efficacy data, particularly in children 2 to 4 years of age at the commencement of ETN treatment.
- The sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.
- There was no new clinical pharmacology information.

Paediatric data

The submission included paediatric efficacy and safety data as the requested extension of treatment indication is for patients aged 2 to 17 years (depending on JIA subtype).

Good clinical practice

The pivotal clinical trial (Study 0881A1-3338) and the 2 supporting trials (Studies 20021618 and 20021626) evaluating the use of ETN in children and adolescents with active JIA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic (PK) data was provided in this submission.

Evaluator's conclusions on pharmacokinetics

The PK properties of ETN in patients aged 4 to 17 years with active polyarticular JIA have been previously assessed. No new PK data was provided in this submission and the sponsor is not proposing any changes to the PK section of the current Product Information (PI). For subjects aged 2 to less than 4 years of age, no PK data for ETN have ever been presented, or probably investigated.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic (PD) data was provided in this submission.

Evaluator's conclusions on pharmacodynamics

The PD properties of ETN when used in patients aged 4 to 17 years with active polyarticular JIA have been previously assessed. No new PD data were presented in this submission and the sponsor is not proposing any changes to the PD section of the current PI.

Dosage selection for the pivotal studies

Although no specific dose finding studies have been performed for patients with JIA, the dose and administration frequency of ETN used in the pivotal study (0881A1-3338), and proposed by the sponsor for licensing, have been reasonably justified.

The sponsor is proposing that ETN be administered by SC injection at a weekly dose of 0.8 mg/kg (up to a maximum weekly dose of 50 mg). The therapy can be given either twice weekly (3 to 4 days apart) at a dose of 0.4 mg/kg (as per the currently approved posology in children with JIA), or once weekly at a dose 0.8 mg/kg. In the pivotal trial (Study 0881A1-3338) patients received ETN at a dose of 0.8 mg/kg once weekly. The once weekly dosing regimen is also approved for children and adolescents with plaque psoriasis; and for adults with RA, psoriasis and AS. Based on PK modelling data, simulation results suggest that ETN 0.8 mg/kg/week given by once weekly injection versus twice weekly 0.4 mg/kg achieves a comparable drug exposure. The doses of background treatment with Methotrexate (MTX), corticosteroids and non-steroidal anti-inflammatory (NSAID) when used by patients in the pivotal study (0881A1-3338) were appropriate, and consistent with contemporary clinical practice in Australia.

Efficacy

Studies providing efficacy data

The pivotal efficacy study (0881A1-3338) was a Phase IIIb, single treatment, open label trial conducted in 2 parts to evaluate the efficacy and safety of ETN in children and adolescents with eoJIA, ERA or PsJIA.

Study 20021618 was a long term (up to 10 years), open label, extension study for paediatric subjects with active Disease modifying antirheumatic drug (DMARD) refractory JIA who previously participated in the initial ETN JIA treatment study (16.0016).

Study 20021626 was an open label, non-randomized, Phase IV registry study for children aged 2 to 18 years with a diagnosis of polyarticular or systemic JIA who were recently commenced upon or currently receiving ETN alone, or in combination with MTX, with or without other non-biological DMARDs.

Further information can be found in the CER.

Evaluator's conclusions on efficacy

For etanercept for the treatment of active juvenile idiopathic arthritis in patients aged 2 years and older.

Juvenile idiopathic arthritis affects approximately 1 in 1000 children in Australia, and the majority of cases are one of the 5 subtypes included in this submission. There is significant unmet need for additional effective therapies as response to current treatment options is variable.

In support of the extension of indication of ETN to include the treatment of active extended oligarticular juvenile idiopathic arthritis in patients 2 years of age and older; and active enthesitis related arthritis and psoriatic arthritis in patients 12 years of age and older, the sponsor has provided data from a single pivotal Phase III trial (Study 0881A1-3338) which had a 12 week, open label, active treatment period; followed by a long term extension phase which was not included in this submission. The study recruited 127 patients who had demonstrated an inadequate response to conventional DMARD treatment (typically MTX), or appropriate prior therapy for study participants with ERA.

Supportive evidence of efficacy was provided by a 10 year, open label study (Study 20021618) which enrolled 58 paediatric subjects with polyarticular JIA; and a 36 month registry trial (Study 20021626) whereby 397 paediatric patients received ETN, either alone or in combination with MTX. The registry study included 47 subjects aged between 2 to 4 years with polyarticular JIA.

The submission has gained approval in the European Union (EU) and is consistent with the sponsor recommended guidelines of interest (that is, CHMP guidelines on Clinical Trials in Small Populations (July 2006) ICH guidelines on Choice of Control Group in Clinical Trials (January 2001)). However, the submission is not entirely consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EU guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis" (effective 26 June 2009). In particular the lack of an active treatment then randomised treatment withdrawal design is not evident in the pivotal study. Otherwise, the 3 trials collectively provide a sufficient exposure for evaluation of efficacy that is appropriate for the claimed indications. Furthermore, a sufficient number of patients have been studied for an acceptable duration of therapy. For Study 0881A1-3338, the choice of efficacy endpoints and statistical analysis were appropriately performed. Because all the trials were open label, strategies to maintain blinding and randomisation procedures were not considered.

The baseline demographic and disease related characteristics of patients in the JIA ETN treatment studies are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were female, of Caucasian ethnicity with a broad age range between 2 and 17 years. However, there are some caveats to the generalizability of the treatment population. For example, Study 0881A1-3338 excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (for example, abnormal haematology or liver function tests).

The pivotal trial (Study 0881A1-3338) enrolled patients with moderately active JIA (of 3 different subtypes), and demonstrated that ETN is an effective treatment in those who have either failed to respond to conventional treatment options, such as Disease modifying antirheumatic drugs (DMARDs), (often MTX) and/or non-steroidal anti-inflammatory drugs (NSAIDs). The primary efficacy endpoint of Study 0881A1-3338 was the proportion of subjects who achieved an American College of Rheumatology Paediatric 30 Criteria (ACR Pedi 30) response at 12 weeks of open label ETN treatment. Overall, 88.6% of patients (109 out of 127; 95% Confidence Interval (CI) 81.6%, 93.6%) achieved this outcome. The rate of ACR Pedi 30 response for each of the 3 examined JIA subtypes was

89.7% (52 out of 58; 95% CI 78.8%, 96.1%) for eoJIA, 83.3% (30 out of 36; 95% CI 67.2%, 93.6%) for ERA and 93.1% (27 out of 29; 95% CI 77.2%, 99.2%) for PsJIA indicating a similar treatment response among the JIA subtypes.

The results of Study 0881A1-3338 (overall, and for each of the 3 JIA subtypes) compared favourably to historical placebo control data (meta-analysis of 6 studies[1]), as well as an active historical control (Study 16.0016;[2]). The odds ratios and 95% CIs for both comparisons (Study 0881A1-3338 versus placebo, and then active historical control data) showed a statistically significant difference in the rate of ACR Pedi 30 response at week 12 compared with historical placebo; and a comparable treatment effect with ETN therapy when Study 0881A1-3338 was compared to an historical control group. These results represent a clinically meaningful, treatment related outcome.

Results for the secondary efficacy endpoint analyses in Study 0881A1-3338 also showed a consistent and significant treatment with ETN. The rates of achieving an ACR Pedi 50 response at Week 12 were high at 81.1% (99 out of 122), and the majority of patients were observed to achieve an even higher level of clinical response (ACR Pedi 70 response was 61.5% (75 out of 122) at 12 weeks).

Response to ETN treatment was also seen using different efficacy measures such as each of the 6 core components comprising the ACR Pedi criteria, duration of morning stiffness and pain visual analogue scale (VAS) scores. Moreover, a proportion of patients (12.1% (15 out of 124)) achieved inactive disease status at Week 12. The pivotal study also did a subgroup analysis of treatment response to ETN in 3 different age brackets (2 to 4 years, 5 to 11 years, and 12 to 17 years) of patients with eoJIA. No difference in the rate of ACR Pedi 30 response was observed in patients according to age at enrolment.

Studies 20021618 (10 year, open label extension trial) and 20021626 (registry data) are supportive of the key efficacy findings of the pivotal trial by demonstrating:

- Persistence of efficacy response for up to 10 years with continued ETN therapy in Study 20021618. For example, the rate of ACR Pedi 30 response was consistently greater than 50% at all yearly intervals up until 7 years, which is the last year whereby the number of ongoing assessable patients was greater than 20.
- The mean improvements from baseline in all 6 of the JIA ACR core set variables showed a relatively stable and sustained pattern of improvement over time (94.7%) in Study 20021618, apart from some fluctuation in C Reactive Protein (CRP) values between years 7 to 10.
- At 3 years of follow up in Study 20021626, the mean percentage improvement in Physician Global Assessment (PGA) of disease activity, number of active joints, and paediatric quality of life was significant in those who received ETN, either alone or in combination with MTX.
- Study 20021626 also showed that in a subgroup analysis of patients aged 2 to less than 4 years; the treatment effect of ETN was comparable to older aged subjects.

Overall the efficacy data in this submission supports the efficacy of ETN in the treatment of 5 subtypes of juvenile idiopathic arthritis (as per the International League of Associations for Rheumatology (ILAR) criteria), with moderate to severe disease active at baseline, with or without concurrent DMARD (often MTX), in patients aged 2 years to 17 years. In addition to the current approved ETN dosing regimen of 0.4 mg/kg twice weekly, many patients in the trial program received 0.8 mg/kg once weekly with no significant

[1] Ruperto N, Pistorio A, Martini A, et al. A meta-analysis to estimate the "real" placebo effect in juvenile rheumatoid arthritis (JRA) trials (abstract). Arthritis Rheum 2003; 48 Suppl 9: S90.
[2] Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000; 342: 763-769.

variability in treatment response being observed. The program also included a significant number of patients 2 to 4 years of age at the commencement of ETN (that is, younger than the currently approved 4 years of age) and no difference in treatment response has been identified.

Safety

Studies providing safety data

There were no studies that assessed safety as the primary outcome.

No specific dose response studies have been conducted but additional safety data was provided by 2 non pivotal, efficacy trials. Study 20021618 is an open label, long term extension study for paediatric patients with active DMARD refractory JIA, who previously participated in the initial ETN JIA Study (16.0016). Throughout the first year of Study 20021618, all adverse events (AEs), both serious and non-serious, were collected. However, after 12 months, only AEs that met the serious criteria (SAEs) were collected along with predefined events of interest (hospitalizations, deaths, serious infections, malignancy, and new signs or symptoms of other connective tissue disease). In this trial, AEs were classified according to a modified version of the Coding Symbols for a Thesaurus of Adverse Events Terms (COSTART) dictionary. Anti ETN antibodies were a pre specified safety endpoint in the protocol, but the analysis was not conducted.

Supporting safety data collected as part of a single registry study (20021626) was also presented in this submission. Study 20021626 is an open label, multicentre registry study examining the long term safety of ETN compared to MTX in subjects with JIA.

Patient exposure

In the pivotal Study 0881A1-3338, 127 subjects received at least 1 dose of ETN in Part 1 (first 12 weeks). Sixty of these patients had eoJIA, 38 subjects with ERA, and 29 patients with PsJIA. The 60 subjects with eoJIA consisted of 15 subjects in the 2 to 4 year age group, 23 subjects in the 5 to 11 years age group, and 22 subjects in the 12 to 17 year age group. The mean duration (SD) of ETN treatment in Part 1 of Study 0881A1-3338 was 12.61 weeks (1.61 weeks), with a range of 1 to 15 weeks (median 13.0 weeks). Overall ETN exposure in the pivotal trial population was 29.16 subject years. The mean (SD) weekly ETN dose was 34.97 mg (13.12 mg), and ranged from 8.0 to 56.0 mg. Consistent with the lower mean baseline age and weight for the subjects with eoJIA, the mean weekly ETN dose was lower for this JIA subtype (26.5 mg) compared with the ERA (42.6 mg) and PsJIA (42.5 mg) subtypes.

Of the 69 paediatric subjects who participated in the double blind Study 16.0016, 58 subjects received at least 1 dose of ETN in the long term, open label, extension trial 20021618 (up to 10 years of follow up). Patients in this study received ETN as either 0.4 mg/kg twice weekly or 0.8 mg/kg once weekly, up to a maximum weekly dose of 50 mg. The overall ETN exposure for the 58 subjects in Study 20021618 was 341.98 subject years. The mean exposure to ETN was 614 doses administered over a mean period of 2153 days.

In the registry trial (Study 20021626), a total of 594 subjects were included in the safety analysis: 197 received MTX alone, 103 received ETN monotherapy, and 294 were given ETN with MTX. Drug administration information was not collected in the study and therefore exposure of ETN and MTX were estimated from the reported drug start date and end date, assuming the subject took the drug as prescribed. The mean (and SD) years of exposure for each arm in the registry program was as follows: 1.97 years (1.09) for the MTX only arm, 2.17 years (1.04) for the ETN alone group, and 2.16 years (1.02) for the

ETN + MTX arm. The median (and range) number of years exposed was 2.18 years (0.1 to 3.7) for the MTX only arm, 2.84 years (0.2 to 3.8 years) for the ETN alone group, and 2.79 years (0.1 to 3.5) for the ETN with MTX arm. The overall patient exposure in Study 20021626 to MTX was estimated to be 387.8 patient years and 859.3 patient years for ETN (alone, and in combination with MTX).

Safety issues with the potential for major regulatory impact

Liver toxicity

This has been addressed in the CER.

Malignancy potential

This has been addressed in the CER.

Injection site reactions

This has already been addressed in this report.

Risk of opportunistic infection

In Part 1 of Study 0881A1-3338, no patient who had a history of appropriate vaccination developed a preventable infection. However, 2 subjects with no history of vaccination experienced varicella zoster infection and met the pre specified study protocol criteria for opportunistic infection. A 13 year old female with ERA developed herpes zoster infection affecting 2 dermatomes on Day 16. No specific treatment was given and ETN was continued. The adverse event (AE) resolved after 12 days without complications. A 6 year old female with eoJIA experienced varicella infection 1 day prior to being hospitalized with bronchopneumonia (Study Day 38). Both infections resolved with treatment, and it is unclear whether the 2 infectious episodes were linked.

A total of 4 subjects experienced varicella zoster infection in Study 20021618. Two of the 4 cases were recorded as SAEs, and 2 of the cases occurred during the first year of the trial. At least 3 of the 4 affected subjects had not been vaccinated against varicella.

Screening for tuberculosis was a requirement of screening at baseline in both studies. No patients experienced tuberculosis during either study.

Post marketing data

Overall experience in those under 18 years of age

Among patients under the age of 18 years treated with ETN for any indication, a total of 23 deaths and 11 malignancies have been recorded. The malignancies included Hodgkin's disease (4 cases), Acute Lymphocytic Leukaemia (2 cases), Acute Myeloid Leukaemia (1 patient), Leukaemia – not otherwise specified (1 subject), Lymphoma (1 case), renal cancer (1 patient), and colon cancer (1 case). Malignancies were reported in 7 patients with JIA. These included cases of Hodgkin's disease (4), Acute Lymphocytic Leukaemia (2) and Leukaemia – not otherwise categorized (1). In June 2008, the Food and Drug Administration (FDA) issued an early communication regarding a possible association between use of TNF inhibitors in children and young adults, and the subsequent development of malignancies. Further analysis of the background rates of malignancy in paediatric/juvenile patients with inflammatory arthritis suggested that there is a potential increased risk of malignancy in paediatric patients with JIA. The sponsor regards the issue of paediatric malignancy as an identified safety concern for ETN, and has added information to the warnings and precautions section of the PI to include a specific precaution.

The types and reporting proportion of infections in JIA patients were generally similar to those reported for all ETN users. Many of the viral infections that were reported in juvenile patients treated with ETN are common in children in the general population. The comparison of the distribution of adult RA and juvenile JIA infections revealed no unexpected findings.

There have been reports of inflammatory bowel disease occurring in JIA patients and other paediatric patients who received ETN. The PI contains a precaution regarding reports of inflammatory bowel disease occurring in JIA patients being treated with ETN. The PI also states that ETN is not an effective treatment for inflammatory bowel disease, and that a causal relationship with ETN is unclear because clinical manifestations of bowel inflammation have been observed in untreated JIA patients.

To identify the potential effects of TNF inhibition upon the vaccination response in juveniles, the sponsor's pharmacovigilance database was searched for any reports up until 2 February 2011 in patients less than 17 years of age for reports of vaccination failure, vaccine complication, vaccine breakthrough infection (using the standardized MedDRA query (SMQ) terms for lack of efficacy or effect). Two reports with a vaccine as a co-suspect medication were identified; but neither case involved a lack of efficacy or reduced efficacy of the vaccine. The current ETN PI addresses the issue of paediatric immunization in the "Precautions" section, stating, '*if possible, bring paediatric patients up to date with immunisations according to current local guidelines before beginning etanercept therapy*.'

Other safety concerns identified in the post marketing period which have resulted in modifications to the current PI include:

- Enhancement of special warnings and/or precautions regarding infections including fatal infections, tuberculosis (with recommendations for testing, prophylaxis and monitoring), sepsis and opportunistic infections (including invasive fungal infections, and the possibility of unrecognized fungal infection resulting in death).
- Information regarding hepatitis B reactivation and worsening of hepatitis C.
- Additional warnings and precautions regarding several haematologic reactions (including sometimes fatal aplastic anaemia and pancytopenia), neurologic events (central demyelination disorders and peripheral demyelinating polyneuropathies (including Guillain Barre syndrome), autoantibody formation, cardiac disorders (worsening congestive heart failure), and the possibility of hypoglycaemia in diabetic etanercept users.
- Additional adverse reactions have been added: autoimmune events (such as development of autoantibodies, lupus like syndrome, autoimmune hepatitis, systemic vasculitis including anti neutrophil cytoplasmic antibody (ANCA) positive vasculitis, cutaneous vasculitis (including leucocytoclastic vasculitis)), elevated liver enzymes, interstitial lung disease (including pulmonary fibrosis and pneumonitis), macrophage activation syndrome (MAS), erythema multiforme, psoriasis (all types; new onset, and exacerbations including all subtypes) and psoriasiform rash, pruritus, rash, seizures, Stevens Johnson syndrome, toxic epidermal necrolysis, and uveitis.

Literature reports of ETN use in patients aged 17 years or below

Literature database publications were searched and support the good tolerability, as well as effective control and remission of JIA with ETN. There have been reports of improved growth in patients with JIA treated with ETN. Other safety information has included a 6 year study in which 127 patients (mean age 13.7 years) with JIA received ETN for a mean duration of 24.1 months. Several types of AEs rarely described previously were noted. Neuropsychiatric AEs (30 cases in total) which includes non-specific signs (headaches, vertigo, fatigue, hyperactivity, nervousness, and anxiety), behavioural alterations (aggressiveness), neuropsychiatric syndromes (pain amplification, panic attacks,

depression, anorexia nervosa) and rare organic signs (hypoglossal paralysis). In many cases, the patients were non responders and the dose had been increased. All of the AEs resolved with dose reduction, and less frequently with discontinuation of ETN or neuropharmacological therapy. Five cases of inflammatory bowel disease were observed in the above trial including 2 cases diagnosed as Crohn's disease. All cases resolved with discontinuation of ETN. Thrombocytopenia and/or leucopenia (2 patients) resulted in 1 patient discontinuing ETN treatment, although both cases were considered to be drug related. Relapses of chronic iridocyclitis (4 cases) were also observed in this study and 1 patient discontinued ETN because of this AE.

Other AEs reported in the literature include the development of extra capillary glomerulonephritis in a 15 year old girl. The AE resolved after discontinuation of ETN and treatment with prednisone. Other case reports in the literature include:

- Crohn's disease developing in an 11 year old female. This resolved after discontinuation of ETN,
- Urachal cyst requiring surgery in a 17 year old male, and
- Macrophage Activation Syndrome developing in a 10 year old male. This resolved after discontinuation of ETN and treatment with prednisone and cyclosporine A.

Spontaneous reports in JIA patients

Up until 2 February 2011, a total of 1937 spontaneous, medically confirmed events (occurring in 671 cases) were reported in patients under the age of 18 who received ETN for the treatment of JIA. The patients varied in age from less than 1 year to 17 years (mean 10.66 years, median 11.0 years). The type of AEs reported in JIA subjects were similar to those received for the overall ETN treated paediatric population. The most frequently reported AEs were aggravation of arthritis, injection site reactions, and pyrexia. The most frequently reported SAEs were aggravation of underlying medical condition and pyrexia (20 events each); and uveitis and injection site reactions (16 events each). The cases of uveitis would frequently resolve with discontinuation of ETN, however, uveitis is often associated with JIA itself, and therefore these events probably represent a form of treatment failure rather than a drug related AE. Similarly, fever often accompanies common childhood illnesses, including active JIA, and as such these reports are confounded by alternative aetiological explanations versus drug related.

Experience in patients aged less than 4 years

ETN was not approved anywhere in the world for children younger than 4 years of age until 2008 in US. Up until 2 February 2009, a total of 121 AEs have been identified from 38 reports in children below 4 years of age who had received ETN. The type of AEs recorded was similar to that seen in juvenile patients, apart from accidental overdose in 4 patients (including 2 errors in dosing by healthcare professionals). As the recommended dosing of ETN in children is weight based, there is the potential for incorrect dose calculations. The sponsor proposes a communication plan to healthcare professionals about dosing.

Two deaths have been reported in children under the age of 4 years with JIA. One fatality occurred in a 2 year old female with interstitial lung disease who died of sepsis 3 months after receiving their last treatment with ETN. The other death occurred in a 3 year old female. The patient died of a subarachnoid haemorrhage in the setting of seizures and respiratory tract infection. In addition, there is 1 report of malignancy in the less than 4 year old age category. A 3.5 year old male developed Acute Lymphocytic Leukaemia after receiving less than 12 doses of ETN (exact duration of therapy unclear). The outcome of the malignancy is unknown.

The German JIA registry has recorded data on 25 JIA patients below the age of 4 years, 10 of whom had non systemic subtypes of JIA. This cohort has received ETN for a mean

duration of 19 months. Two AEs (varicella zoster infection and fever) have been reported. No SAEs or treatment discontinuations due to medication intolerance have been recorded.

Evaluator's conclusions on safety

In this submission, the total clinical safety dataset for the use of ETN in patients aged 2 to 18 years with active JIA consists of 582 patients in 3 studies, all of whom received ETN 0.8 mg/kg/week (either once weekly by SC injection, or 0.4 mg/kg twice weekly). Most of the patients in the dataset received concurrent MTX and/or NSAID, and just over 10% were taking concurrent low dose oral corticosteroid (CS). A total of 62 patients aged between 2 and 4 years of age at the commencement of ETN therapy are included within to the total JIA paediatric exposure population.

In the pivotal Study 0881A1-3338, the overall exposure to ETN was 29.16 patient years, and the total exposure to ETN in the long term, open label extension trial (Study 20021618) was 342 patient years. In the supporting registry trial (Study 20021626) the total exposure to ETN cannot be accurately determined because drug administration information was not collected. Nonetheless, there is sufficient data to make a meaningful assessment of safety at least for up to 3 years of treatment in the paediatric population with polyarticular JIA.

Infection was the most common AE recognised in the ETN JIA studies with 45.7% of patients (58 out of 127) in the pivotal study experiencing an infection related AE. The majority of infections were mild in severity, self-limiting, and predominately involved either the upper respiratory tract or gastrointestinal system. However, 3 infectious SAEs at a rate of 0.103 per 100 patient years in Study 0881A1-3338 were reported. Four patients in the pivotal study developed varicella zoster infections. It is unclear if the use of concurrent MTX and/or CS increases the risk of infection associated with ETN. Subject age did not appear to be a determinant of the risk of infection (as evidenced by the subgroup analysis of younger patients (2 to 4 years of age) in Study 20021626. The rate of serious infection appears to be highest in the first 2 years of ETN treatment, and becomes less frequent in extended periods of treatment (as observed in the 10 year Study 20021618).

Injection site reactions were common type of AE occurring in patients given ETN. In Study 0881A1-3338, 10 subjects (7.9% of 127) experienced an Injection Site Reaction (ISR), and 11 patients (19.0% of 58) reported this type of AE in Study 20021618. The majority of injection site reactions were mild, resolved without specific intervention and did not result in discontinuation from ETN treatment.

No deaths were reported in the pivotal or supporting studies. However, a few paediatric deaths were identified in the post marketing surveillance, of which infection was contributory in at least 2 of these cases.

Elevations in hepatic transaminases (Aspartate transaminase (AST) and Alanine transaminase (ALT)) were recorded in up to 9.5% of patients treated with ETN in the pivotal study (0881A1-3338). The majority of these changes in liver function tests were mild and without associated clinical implications.

The incidence of JIA subjects developing anti ETN antibodies is low (4.8% using the combined incidence observed in Studies 0881A1-3338 and 16.0016) and their clinical relevance is yet to be defined with no discernible link to the risk of infection, infusion related reactions or loss of efficacy.

In summary, the safety data indicates that ETN has an acceptable overall short term safety profile in the treatment of 5 subtypes of JIA in patients aged 2 to 18 years with moderately to severely active disease. In polyarticular JIA (Rheumatoid Factor (RF) positive or negative) there is sufficient long term safety data in the current submission but for the newly requested JIA subtypes (eoJIA, ERA and PsJIA) there is limited longitudinal safety

follow up. There are some significant safety concerns including the risk of serious infection, opportunistic infection, injection site reactions, and abnormal liver function tests. Significant pharmacovigilance would be required if approval is granted for extension of indication in JIA. This would include vigilance for opportunistic infections and malignancy.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ETN in the proposed usage are:

- Significant rates of clinically meaningful JIA ACR responses (ACR Pedi 30, 50, 70 and 90) were seen in the first 12 weeks of treatment with ETN in Study 0881A1-3338, as well as for extended periods of treatment in Studies 20021618 (up to 10 years) and 20021626 (up to 36 months).
- Pivotal study (0881A1-3338) showed a responder rate of 88.6% (109 out of 127) at 12 weeks in the ACR Pedi 30 response (primary efficacy endpoint) which was a statistically significant and clinically meaningful higher rate of ACR Pedi 30 response compared to historical placebo control data, and an equivalent efficacy response to an active historical control dataset.
- An alternative SC dosing strategy of 0.8 mg/kg once weekly versus 0.4 mg/kg twice weekly is clinically comparable and offers flexibility in posology for patients receiving ETN.
- Younger patients (2 to 4 years of age) who are not within the current approved treatment indication appear to have ETN treatment responses comparable to older paediatric patients affected by JIA.
- ETN offers an alternative treatment strategy for patients with moderately severely active JIA (5 of the 8 subtypes), which currently have limited treatment options and a significant unmet therapeutic need.

First round assessment of risks

The risks of ETN in the proposed usage are:

- ETN treatment carries an increased risk of infection, and serious infection. While most infections are mild and self-limiting, it is likely that ETN therapy will lead to cases of serious infection and potentially death. No deaths were reported in the clinical studies, however post marketing experience has identified deaths with infection as a contributing factor.
- Increased risk of opportunistic infections, in particular varicella zoster infection, was observed in the pivotal study (0881A1-3338).
- ETN carries a risk of injection site reactions (7.9% of 127 patients in Study 0881A1-3338).
- Changes in laboratory parameters, in particular abnormal liver function tests, were seen in the studies involving JIA patients. These were of no clinical significance to the majority of subjects in the studies, but some individual patients develop clinically significant laboratory abnormalities.
- Limited numbers of paediatric patients with certain subtypes of JIA (eoJIA, ERA and PsJIA) have received long term (multiyear) treatment with ETN. This may be

important for safety issues such as development of malignancy and autoimmune disorders.

First round assessment of benefit-risk balance

The short term, benefit risk balance of ETN in the target population of subjects aged 2 to 17 years with active JIA (covering 5 of the 8 subtypes) is favourable. ETN is administered by subcutaneous injection, either weekly or every 3 to 4 days, and the sponsor has proposed a weekly dose of 0.8 mg/kg (up to maximum weekly dose of 50 mg). This dosing regimen has been justified in this submission, based primarily on the results of the single pivotal trial (Study 0881A1-3338). In addition, the sponsor request to extend the use of ETN as a therapy option in younger children (aged 2 to 4 years) has been justified in this submission by non-randomized data collection in this subgroup of patients.

First round recommendation regarding authorisation

This evaluator recommends acceptance of the sponsor's proposed areas of extension of indication for ETN to include the treatment of additional subtypes of JIA (in accordance with the contemporary ILAR classification of JIA), lowering the age limit of treatment from the currently approved 4 years of age to 2 years of age for those patients with extended oligoarticular and polyarticular JIA, and the addition of a once weekly dosing regimen (0.8 mg/kg, up to a maximum of 50 mg) as an alternative treatment posology for patients with JIA, subject to:

- Satisfactory response to the questions in this report,
- Regular periodic safety update reports, and
- The sponsor providing the TGA with an interim clinical study report of the safety data for Part 2 of Study 0881A1-3338.

Clinical questions

Pharmacokinetics

- The sponsor is requested to provide any PK data available in younger subjects (aged 2 to 4 years of age) to support the hypotheses for ETN dosing in this younger subgroup of patients?

Pharmacodynamics

Nil.

Efficacy

- The sponsor is requested to provide an update (if available) on the efficacy data collected in Part 2 of Study 0881A1-3338?

Safety

- The submission did not present any safety data (including any interim data) collected in Part 2 of Study 0881A1-3338, which is the pivotal trial supporting the extension of JIA indication to 3 additional subtypes. The sponsor is requested to provide an update on the availability of the safety data in Part 2, and if this data is unavailable then

provide comment as to why provision of the information should not be a specific condition of approval of this submission?

- The sponsor is requested to present the safety data for Parts 1 and 2 of Study 0881A1-3338 in a tabular format, which identifies those adverse events that were considered to be related to study treatment?
- In Part 1 of Study 0881A1-3338, 2 subjects (a 6 year old female with eoJIA experiencing bronchopneumonia, and a 17 year old female with PsJIA suffering pyelocystitis) developed serious infections requiring hospitalization, treatment with intravenous (IV) antibiotics, and discontinuation from study medication. Both events were considered by the site investigators to be mild in severity, and unrelated to study drug. The sponsor is requested to provide comment on the justification for the severity grading, and the assessment of causal relationship to study medication?
- In Study 20021618, 2 paediatric patients with systemic JIA developed macrophage activation syndrome. The sponsor is requested to provide comment on whether etanercept was continued or not in these patients, and were the adverse events considered to be drug related?

Second round evaluation of clinical data submitted in response to questions

The sponsor's response dated 28 August 2013 addresses 6 questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Please provide any PK data available in younger subjects (aged 2 to 4 years of age) to support the hypotheses for ETN dosing in this younger subgroup of patients?

The sponsor concurs that no direct PK data has been obtained in children aged 2 to 4 years. In the initial pivotal licensing study (16.0016), PK data was collected from 69 children with JIA aged between 4 and 17 years. The sponsor states that a modest extrapolation of the PK data (that is the relationship between age or body weight, and ETN clearance) would seem to be a reasonable assumption for children aged 2 to 4 years. THE EVALUATOR does not concur with this assumption as the PK of drugs in this younger age cohort (2 to 4 years) is highly variable and can be significantly different to older children. This opinion is expressed in the EMA guideline CHMP/EWP/147013/2004 "Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population" (effective 24 August 2009).

In addition, the sponsor asserts that the PK reasoning supporting posology appears to be supported by the efficacy and safety observations in these younger children. Polyarticular JIA subjects aged 2 to less than 4 years, were observed to have a similar incidence and type of AEs as older children, and demonstrated similar mean improvements in various efficacy outcomes as older subjects. This observation is valid to some degree but the overall extent of ETN exposure in the youngest age group (2 to 4 years) is limited in experience thus far.

Please provide an update (if available) on the efficacy data collected in Part 2 of Study 0881A1-3338?

Study design, endpoints and disposition

Study 0881A1-3338 was a Phase III, single treatment, open label trial conducted in 2 parts in children and adolescents with eoJIA, ERA or PsJIA. Part 1 was primarily designed to assess the efficacy of ETN over 12 weeks. At Week 12, patients who completed treatment with ETN were eligible to enter into Part 2 (another 84 weeks of follow up). In Part 2 of the study, patients continued to receive SC ETN 0.8 mg/kg (to a maximum dose of 50 mg) once weekly. The inclusion/exclusion criteria and study centres involved in Part 2 were

identical to those of Part 1. Once patients completed 96 weeks of treatment and follow up (that is Parts 1 and 2), they could participate in an 8 year extension trial (Study B1801023).

Efficacy endpoints were a secondary outcome in Part 2 of the trial with assessments of clinical benefit being performed every 12 weeks between weeks 12 and 96. The efficacy endpoints included rates of ACR Pedi response (30/50/70/90/100), each of the individual components comprising the ACR Pedi criteria, inactive disease status, pain assessment, duration of morning stiffness, and variables relating specifically to the ERA (tender entheseal score, overall back pain, nocturnal back pain, and modified Schober's test) and PsJIA subtypes (percentage of Body Surface Area (BSA) affected by psoriasis, and PGA of psoriasis).

The baseline demographic and disease related characteristics of the population who continued into Part 2 of the study were identical to those reported at entry into Part 1 of the trial.

The final clinical study report (dated 28 June 2013) for Parts 1 and 2 of Study 0881A1-3338 was included in the sponsor response. The last patient observation was completed on 30 January 2013. All 127 patients who received at least 1 dose of ETN during the trial were included in the mITT population for the primary efficacy analysis. A total of 18 of 127 (14.2%) subjects discontinued from ETN before Week 96 of the trial – 5 in Part 1 (4 because of AEs and 1 due to protocol violation), and 13 in Part 2. Of the 13 patients who discontinued in Part 2, 5 did so because of insufficient efficacy (2 subjects in each in the eoJIA and ERA subgroups, and 1 subject with PsJIA). In addition, 2 patients (1 in the ERA subgroup, and the other in the PsJIA cohort) experienced significant protocol violations and were excluded from the efficacy analysis of Part 2.

Statistical considerations

For the combined population as well as each of the 3 JIA subtypes, the efficacy analyses in Part 2 were based on the observed data recorded in the mITT cohort. Descriptive summary statistics were provided for each efficacy endpoint analysed at all time-points in the study (that is every 12 weeks between Weeks 12 and 96). For the ACR Pedi responses, sensitivity analyses were also performed using alternative methods for handling missing data such as a Last Observation Carried Forward (LOCF) approach as well as a Non Responder Imputation (NRI) strategy. No sample size calculation was undertaken.

Efficacy results

The primary efficacy endpoint in Part 1 was the ACR Pedi 30 response at Week 12 in the overall cohort. At weeks 24, 48 and 96, the rate of ACR Pedi 30 responses were at least maintained or slightly better in the continuing treatment cohort (94.3% (115 out of 122) at Week 24, 94.1% (112 out of 119) at Week 48, and 99.1% (107 out of 108) at Week 96) than that observed at Week 12 (88.6%; 109 out of 123. Moreover, ACR Pedi 30 response rates were similar in each of the 3 JIA subtypes.

For the higher levels of ACR Pedi response (50, 70, 90 and 100), the proportion of subjects in the overall population who achieved these endpoints was consistently higher with each visit between weeks 12 and 96. For example, approximately twice as many subjects achieved an ACR Pedi 90 response at Week 96 (65.4%; 70 out of 107) compared to Week 12 (29.8%; 36 out of 121). When considering only the subjects with eoJIA, the percentages of subjects in each age group (n = 15 for 2 to 4 years, n = 23 for 5 to 11 years, and n = 22 for 12 to 17 years) who achieved ACR Pedi 30 response at weeks 12, 24, 48 and 96 were similar. In addition, each of the individual components comprising the ACR Pedi variable showed sustained mean improvements from baseline in all JIA subtypes up to Week 96. For example, the mean Childhood Health Assessment Questionnaire (CHAQ) score at Week

96 reduced by 74.2% (absolute reduction of 0.61 from a mean baseline score of 0.80; n = 109 subjects).

At Week 12, 15 subjects (12.1% of 124) fulfilled the criteria for inactive disease. This outcome improved to 24.8% (30 out of 121) at Week 24, 29.7% (35 out of 118) at Week 48, and 34.0% (36 out of 106) at Week 96. The mean pain assessment scores and duration of early morning stiffness also improved from baseline in all JIA subtypes at sequential visits up to Week 96. The mean pain VAS score at baseline was 5.06 (range: 0 to 10), and for patients in each of the 3 JIA subgroups, pain reduced significantly by Week 96 (-3.80 for subjects in the eoJIA group (n = 53), -4.72 for patients in the ERA arm (n = 30), and -3.58 for subjects in the PsJIA subtype (n = 25)). The mean percentage decrease in morning stiffness from baseline to Week 96 in eoJIA (n = 54) was 64.15% (baseline 72.8 minutes), in patients with ERA (n = 30) was 86.9% (baseline 89.3 minutes), and in subjects with PsJIA (n = 25) was 45.0% (baseline 54.3 minutes).

The secondary efficacy variables relating specifically to the ERA (tender entheseal score, overall back pain, nocturnal back pain, and modified Schober's test[3]) and PsJIA subtypes (percentage of BSA affected by psoriasis, and PGA of psoriasis) improved from baseline at all time-points up to Week 96.

In subjects with ERA, the mean change from baseline to Week 96 in 4 additional secondary efficacy endpoints was assessed in 30 of 38 potential subjects. After 96 weeks of ETN treatment, the mean reduction in the tender entheseal score was 5.03 (baseline mean 5.87), overall back pain reduced by 14.1 mm (baseline mean of 25.9 mm), nocturnal back pain reduced by 6.74 mm (baseline mean 16.4 mm), and the modified Schober's test improved by 0.27 cm (baseline mean 15.0 cm). In subjects with PsJIA, the mean change from baseline to Week 96 in 2 additional secondary efficacy endpoints was assessed in 25 subjects. After 96 weeks of ETN treatment, the mean percentage of BSA affected by psoriasis reduced by 7.88% (baseline mean 10.41%), and the PGA of psoriasis improved by 1.28 (baseline mean 1.83).

Evaluator assessment

The Part 2 efficacy results of Study 0881A1-3338 indicate that ETN can produce sustained responses (up to 96 weeks of follow up) in the majority of subjects, which are clinically significant. All 3 JIA subtypes demonstrated response to ETN, which was also similar across a broad age range in the eoJIA subset. The inclusion of the Part 2 efficacy data supports the sponsor application for extension of indication for ETN in JIA by providing data on the maintenance of response over 96 weeks of follow up.

Please provide an update on the safety data collected in Part 2 of Study 0881A1-3338, and if not available, comment as to why provision of the information should not be a specific condition of approval of this submission?

Dataset and exposure

The sponsor has submitted the final clinical study report for Parts 1 and 2 of Study 0881A1-3338 which includes the safety data for patients who continued to receive ETN for up to 96 weeks. The mean duration of ETN treatment in Parts 1 and 2 of Study 0881A1-3338 was 89.1 weeks, with a range of 1 to 100 weeks (median 96.0 weeks). Overall ETN exposure in the pivotal trial population was 215.1 patient years – 103.6 in the eoJIA group, 61.3 in the ERA subtype, and 50.2 in the PsJIA cohort. The mean weekly dose of ETN was 37.85 mg, with a range of 10.0 to 50.0 mg (median 44.0 mg). Consistent with the Part 1 data, subjects with eoJIA had a lower mean baseline age and weight, and

[3] Schober's test is a test used in rheumatology to measure the ability of a patient to flex his/her lower back.

therefore received a lower mean weekly dose of ETN (29.5 mg) compared to the other 2 JIA subtypes (46.5 mg for the ERA group, and 46.0 mg for the PsJIA arm).

Overview of adverse events (including Common AEs)

Overall, 300 AEs (excluding infections and ISRs) were experienced by 73.2% (93 out of 127) of subjects at an event rate of 1.395 AEs per patient year (total exposure of 215.1 patient years). The most common types of AE were headache (0.107 per patient year), followed by pyrexia (0.056 per patient year), and diarrhoea (0.046 per patient year). No significant differences for the incidence and type of AEs were observed across the JIA subtypes. In the eoJIA population which included children across a broad age range (2 to 17 years), AEs occurred at a higher frequency in the 2 younger cohorts (1.54 per patient year for 2 to 4 year old subjects, and 1.45 per patient year for 5 to 11 year old children) compared to older patients (1.01 per patient year for 12 to 17 year old subjects).

Infections

Overall, 355 treatment emergent infections were recorded in 73.2% (93 out of 127) of subjects at an event rate of 1.65 infections per patient year during the 96 week study. The most common types of infection were upper respiratory tract infection (0.386 per patient year), followed by pharyngitis (0.232 per patient year), and gastroenteritis (0.102 per patient year). No significant differences for the incidence and type of AEs were observed across the JIA subtypes. In the eoJIA population which included children across a broad age range, infections occurred at a higher frequency in the 2 youngest cohorts (3.31 per patient year for 2 to 4 year old subjects, and 2.25 per patient year for 5 to 11 year old children) compared to older patients (1.14 per patient year for 12 to 17 year old subjects).

Injection site reactions

In total, 63 ISRs were recorded in 16 (12.6% of 127) subjects at an event rate of 0.293 ISRs per patient year during Parts 1 and 2 of the study. The incidence and severity of ISRs was similar between the 3 JIA subtypes. Most ISRs were rated as mild or moderate in severity, and none resulted in a subject withdrawing from ETN.

Discontinuations due to adverse events

Three subjects (2.4% of 127) withdrew due to AEs in the 96 week trial, 2 of which were due to significant infections (bronchopneumonia and pyelocystitis). Both of the infection related withdrawals occurred in Part 1 of the study. The third subject who permanently discontinued ETN on Day 29 was a 13 year old male who developed fever, asthenia and weight loss on Day 16. A diagnosis of Crohn's disease was confirmed by endoscopy on Day 66.

Serious adverse events (including serious and opportunistic infections)

A total of 15 subjects (11.8% of 127) reported 16 SAEs (excluding infections) during the study. All were single types of SAEs except for 2 cases of JIA flare. In addition, 11 subjects (8.7% of 127) experienced 11 serious infections. All were single types of serious infection apart from 3 cases of gastrointestinal infection. In addition, 8 subjects suffered infections considered preventable by vaccination, 7 of whom were not vaccinated. These preventable infections included 4 cases of varicella (all in young subjects with eoJIA), 2 cases of herpes zoster (1 each in the ERA and PsJIA groups), and single reports of influenza and rubella (both in the eoJIA cohort). One of herpes zoster cases affected 2 dermatomes. One patient with ERA developed latent tuberculosis during the trial, which was detected by a routine follow up tuberculosis skin test (PPD test) becoming positive (negative at baseline).

Death and malignancy

No fatalities or cancers were observed in Parts 1 and 2 of Study 0881A1-3338.

Autoimmune disorders

Four patients (3.1% of 127) developed autoimmune disorders 2 cases of uveitis, and single cases of iridocyclitis and Crohn's disease. All of these events are likely to represent disease associated manifestations rather than drug related AEs.

In addition, 3 subjects were recorded as developing Crohn's disease during the trial (including 1 case which was diagnosed 3 months after ceasing ETN). The relationship between ETN and the development of Crohn's disease is unclear as adolescent patients with JIA are at risk of developing the condition as part of the associated disease spectrum.

Laboratory abnormalities

Overall, 10 subjects (7.9% of 127) recorded Grade 3 or 4 abnormalities of laboratory tests during the trial. This included 4 subjects with leucopenia (3 eoJIA, and 1 PsJIA patient), and 6 subjects had abnormalities of liver function tests (3 eoJIA, 2 ERA and 1 PsJIA patients). However, over the course of the 96 week study, a total of 26 subjects (20.6% of 127) developed liver function test abnormalities – 14 patients had increases of serum transaminases and/or bilirubin between 2 and 3 times Upper Limit of Normal (ULN), and 12 subjects had abnormalities of liver function greater than 3 times ULN. All 26 subjects with abnormalities of liver function tests were taking concurrent DMARD therapy – 21 were taking MTX and 5 were receiving sulfasalazine. In addition, 13 of the 26 patients were taking concurrent NSAID. The frequency of abnormal function tests was higher in the eoJIA group (27.1%; 16 out of 59) compared to the 2 other JIA subtypes (15.8% (6 out of 38) for ERA, and 13.8% (4 out of 29) for PsJIA).

Immunogenicity

Serum for anti to ETN antibodies was collected at baseline; weeks 12, 48 and 96; or upon early withdrawal in Study 881A1-3338. In total, 26 subjects (20.5% of 127) tested positive for anti to ETN antibodies on at least 1 occasion during the trial, of which 10 subjects (7.9% of 127) tested positive on at least 2 occasions. None of the subjects with positive anti to ETN antibody results tested positive for neutralizing antibodies. Fourteen of the patients developed positive anti to ETN antibodies for the first time at Week 48, and 6 did so at Week 12. There was no clear correlation between the occurrence of anti to ETN antibodies and the development of AEs.

Vital signs and growth parameters

Overall, 12 subjects (9.5%) developed changes in blood pressure readings over the course of the study. This included 3 cases of reduced blood pressure (systolic or diastolic) and 9 reports of increased blood pressure, most of which were transient in nature. There was no evidence of a decline in expected growth as measured by changes in height, weight or Body Mass Index (BMI) from baseline to Week 96.

Evaluator assessment

The safety of ETN in children and adolescents over 96 weeks of treatment follow to up in Study 0881A1-3338 demonstrates an acceptable profile with no new safety signals becoming evident. In addition, the incidence of expected AEs (for example risk of infection and injection site reactions) did not differ from the known frequency and pattern. The submission of the Part 2 safety data supports the sponsor application for extension of indication for ETN in JIA, and exceeds the recommendations of the relevant regulatory guidelines in terms of providing sufficient patient experience in a juvenile treatment population.

Please present the safety data for Parts 1 and 2 of Study 0881A1-3338 in a tabular format, which identified those adverse events that were considered to be related to study treatment?

The sponsor response has referred to 2 tables in the final clinical study report for Study 0881A1-3338, which present the incidence and System Organ Class (SOC) type of treatment emergent AEs by severity and relationship to ETN for the all exposure safety population (n = 127), as well as each of the 3 JIA subtypes involved in Study 0881A1-3338. The site investigator assessed the determination of relationship between ETN and AE.

In Parts 1 and 2 (combined) of Study 0881A1-3338, 96 subjects (75.6% of 127) recorded infections, of which 16.5% (21 out of 127) were considered to be treatment related. Most of the treatment related infections were mild (13 subjects, 10.2%) or moderate in severity (7 subjects, 5.5%). Similar to the Part 1 data, the most common sites of treatment related infections involved the upper respiratory tract (n = 11), ear (n = 5), gastrointestinal system (n = 3) and skin and soft tissues (n = 2). No significant differences in the incidence or severity of infection were observed across the 3 JIA subtypes.

Excluding infections, the combined safety data in Parts 1 and 2 of Study 0881A1-3338, observed 93 subjects (73.2% of 127) experiencing treatment emergent AEs, of which 14.2% (18 out of 127) were considered to be treatment related. Most of the treatment related non to infectious AEs were mild (12 subjects, 9.4%) or moderate in severity (6 subjects, 4.7%). The incidence and type of treatment related AEs showed a similar pattern to that observed in the overall AE assessment (irrespective of relationship to study medication). The most common individual types of AEs that were assessed as being treatment related included investigation abnormalities (n = 5; mainly abnormal liver function tests), nervous system disorders (n = 5; headache and dizziness), general disorders (n = 3; fatigue and asthenia), and ear complaints (n = 3; vertigo and tinnitus). No significant differences in incidence or severity of infection were observed across the 3 JIA subtypes.

In Part 1 of Study 0881A1-3338, 2 subjects (a 6 year old female with eoJIA experiencing bronchopneumonia, and a 17 year old female with PsJIA suffering pyelocystitis) developed serious infections requiring hospitalization, treatment with IV antibiotics, and discontinuation from study medication. Both events were considered by the site investigators to be mild in severity, and unrelated to study drug. The sponsor is requested to provide comment on the justification for the severity grading, and the assessment of causal relationship to study medication?

The sponsor concurs that the site investigators rated both of these serious infections as being mild in severity, and unrelated to study medication. However, the sponsor states that it assessed the bronchopneumonia SAE as being medication related. The sponsor has made no specific comment about its assessment of a causal relationship between ETN therapy and the SAE of pyelocystitis. The sponsor also states that it does not assess the severity of AEs, and infections represent a known risk associated with ETN, which is included in the current PI. In my opinion, both infectious SAEs have an association with ETN, and this is a known risk with anti TNF therapy.

In Study 20021618, 2 paediatric subjects with systemic JIA developed macrophage activation syndrome. Please provide comment on whether etanercept was continued or not in these patients, and were the adverse events considered to be drug related?

The sponsor has provided additional case details for both cases (8 year old female, and 11 year old male) that experienced macrophage activation syndrome in Study 20021618. Neither event was considered to be drug related by the investigator. ETN was temporarily

ceased in both subjects, and the AE resolved after 6 to 17 days following hospitalization and additional supportive treatment. Macrophage activation syndrome may occur as a disease related complication of systemic JIA, and is included in the PI for ETN. The evaluator concurs with the sponsor response on this question, in that macrophage activation syndrome is most likely to be a disease related manifestation of JIA than be drug related.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ETN in the proposed usage are unchanged from those identified.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of ETN in the proposed usage are unchanged from those identified.

Second round assessment of benefit-risk balance

The benefit-risk balance of ETN, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The submitted data indicates a favourable, short and medium term benefit risk assessment for ETN in the proposed usage, and this evaluator would recommend acceptance of the sponsor's proposed extension of indication for ETN to include the treatment of additional subtypes of JIA. In addition, this evaluator would recommend accepting the proposal to lower the age limit of treatment from the currently approved 4 years of age to 2 years of age for those patients with extended oligoarticular and polyarticular JIA, as well as the addition of a once weekly dosing regimen (0.8 mg/kg, up to a maximum of 50 mg) as an alternative treatment regimen.

The current ETN product information (PI) does not classify JIA according to the ILAR criteria as the pivotal JIA licensing study (16.0016) commenced in 1997, that is prior to the development of the ILAR classification. However, the evaluator concurs with the sponsor's proposal to amend the current PI to incorporate the internationally accepted contemporary classification of JIA by the ILAR criteria. The submitted data in this application is consistent with adopting this proposal.

If this submission is approved, a recommended condition of registration is the provision of regular periodic safety update reports by the sponsor.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Global RMP Version 5.0, dated 12 April 2013 which was reviewed by the TGA.

Table 1. Summary of Risk Management Plan

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Malignancy (including lymphoma and leukemia)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS, BSPAR, German JIA Registry, B1801023 **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210, BADBIR **Pediatric Psoriasis:** 20050111, PURPOSE	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS, BSPAR, German JIA Registry, 0881A1-3338-WW, B1801023, B1801130 **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210, BADBIR **Pediatric Psoriasis:** 20050111, PURPOSE	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Allergic reactions		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Systemic vasculitis (including ANCA positive vasculitis)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** ARTIS **JIA:** ARTIS, 0881A1-3338-WW, B1801023 **AS:** ARTIS **PsA:** ARTIS **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Lupus-like Reactions		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Sarcoidosis and/or granulomas		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Injection site reactions		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Macrophage activation syndrome		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Central demyelinating disorders		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS, BSPAR, German JIA Registry, 0881A1-3338-WW, B1801023 **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210, BADBIR **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Peripheral demyelinating events (CIDP and GBS)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** RABBIT **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.

Peripheral demyelinating events (CIDP and GBS)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Investigation of risk factors	Same as above.	Same as above.

Aplastic anemia and pancytopenia		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS, 0881A1-3338-WW, B1801023 **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210, BADBIR **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Interstitial lung disease (including pulmonary fibrosis and pneumonitis)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** ARTIS **JIA:** 0881A1-3338-WW, B1801023 **AS:** ARTIS **PsA:** ARTIS **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Autoimmune hepatitis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** ARTIS **JIA:** ARTIS, 0881A1-3338-WW, B1801023 **AS:** ARTIS **PsA:** ARTIS **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Liver events in patients with history of hepatitis (including hepatitis B virus reactivation)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

3.1.2. Important Identified Risks – Specific Indications

Change in morphology and/or severity of psoriasis in adult and pediatric populations		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Worsening of congestive heart failure in adult subjects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Inflammatory bowel disease in JIA subjects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023	To collect additional post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

3.1.3. Important Potential Risks – All Indications

Autoimmune renal disease		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Pemphigus/pemphigoid		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Amyotrophic lateral sclerosis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Myasthenia gravis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** ARTIS **JIA:** ARTIS, 0881A1-3338-WW, B1801023 **AS:** ARTIS **PsA:** ARTIS **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept
Investigation of risk factors	Same as above.	Same as above.

Encephalitis/ leukoencephalomyelitis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Progressive multifocal leukoencephalopathy		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Liver failure		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Hepatic cirrhosis and fibrosis		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Severe hypertensive reactions		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Adverse pregnancy outcomes		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** OTIS, STORK **JIA:** OTIS, 0881A1-3338-WW, B1801023, STORK **AS:** OTIS, STORK **PsA:** OTIS, STORK **Adult Psoriasis:** OTIS, BADBIR, 20040210, STORK **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Potential for medication errors (pre-filled pen)		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: none	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Potential for male infertility		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Weight gain		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Use in different ethnic origins		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Investigation of risk factors	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **Adult Psoriasis:** 20040210 **Pediatric Psoriasis:** 20050111 (Note: these long-term extension studies will follow the small number of subjects of different ethnic origins from the original study)	To collect additional post-marketing data that may identify a change in the safety profile for etanercept.

Use in pregnant women		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence of maternal complications and congenital anomalies	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** OTIS, BSRBR, RABBIT, STORK **JIA:** OTIS, 0881A1-3338-WW, B1801023, STORK **AS:** OTIS, BSBR, STORK **PsA:** OTIS, STORK **Adult Psoriasis:** OTIS, BADBIR, 20040210, STORK **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors which could lead to congenital anomalies	Same as above.	Same as above.

Impaired growth and development in juvenile subjects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **JIA:** 0881A1-3338-WW, B1801023 **Pediatric Psoriasis:** 20050111	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

Acute ischemic cardiovascular events in adult subjects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data. Additional pharmacovigilance: **RA:** BSRBR, RABBIT, ARTIS **JIA:** ARTIS **AS:** BSRBR, ARTIS **PsA:** BSRBR, ARTIS **Adult Psoriasis:** 20040210	To collect additional clinical trial and post-marketing data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

3.1.5. Important Missing Information – All Indications

Use in hepatic and renal impaired subjects		
Areas Requiring Confirmation or Further Investigation	**Proposed Routine and Additional PhV Activities**	**Objectives**
Incidence of adverse events in patients with hepatic or renal impairment	Routine pharmacovigilance includes: reporting of individual adverse event reports (spontaneous, clinical trials) and aggregate review of adverse event reports and safety data.	To collect additional post-marketing adverse event data that may identify a change in the safety profile for etanercept.
Investigation of risk factors	Same as above.	Same as above.

6.1.4. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks – All Indications		
Malignancy (including lymphoma and leukemia)	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.	None proposed
Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)	SmPC section 4.3 Contraindications SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: The possibility exists for TNF-antagonists to affect host defenses against infection.	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Lupus-like reactions	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Biological-derived proteins can induce an unwanted immune response that is triggered by more than one single factor.	None proposed
Sarcoidosis and/or granulomas	SmPC section 4.8 Undesirable effects; if indicated additional changes to SmPC will be undertaken. Justification: Sarcoidosis events in placebo-controlled, active-controlled, and open-label trials of etanercept have been reported. Assessment of potential risk is ongoing.	None proposed
Injection site reactions	SmPC section 4.8 Undesirable effects Justification: Injection site reactions have been reported in patients treated with etanercept.	None proposed
Allergic reactions	SmPC section 4.3 Contraindications SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Allergic reactions have been associated with etanercept usage.	None proposed
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)	SmPC section 4.8 Undesirable effects Justification: Cases of severe cutaneous adverse reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.	None proposed
Systemic vasculitis (including ANCA positive vasculitis)	SmPC section 4.8 Undesirable effects Justification: Uncommonly, cases of systemic vasculitis including ANCA positive vasculitis have been reported.	None proposed
Macrophage activation syndrome	SmPC section 4.8 Undesirable effects Justification: Cases of macrophage activation syndrome have been reported.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Central demyelinating disorders	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Demyelinating events have occurred in patients treated with etanercept.	None proposed
Peripheral demyelinating events (CIDP and GBS)	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects; if indicated additional changes to SmPC will be undertaken. Justification: Very rare reports of peripheral demyelinating polyneuropathies (including GBS) have been occurred in patients treated with etanercept.	None proposed
Aplastic anemia and pancytopenia	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Rare cases of pancytopenia and very rare cases of aplastic anemia, with some fatal outcomes, have been reported.	None proposed
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	SmPC section 4.8 Undesirable effects Justification: Uncommonly, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported.	None proposed
Autoimmune hepatitis	SmPC section 4.8 Undesirable effects Justification: Rarely, autoimmune hepatitis has been reported.	None proposed
Liver events in patients with history of hepatitis (including hepatitis B virus reactivation)	SmPC section 4.4 Special warnings and precautions; if indicated, additional changes to SmPC will be undertaken. Justification: Reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus who are receiving TNF-antagonists including etanercept has been reported. There have been reports of worsening of hepatitis C in patients receiving etanercept. Assessment of potential risk is ongoing	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks – Specific Indications		
Change in morphology and/or severity of psoriasis in adult and pediatric populations	SmPC section 4.8 Undesirable effects Justification: Uncommonly, psoriasis including new onset and pustular, primarily involving palms and soles has been reported.	None proposed
Worsening of congestive heart failure in adult subjects	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects; if indicated; additional changes to SmPC will be undertaken. Justification: There have been post-marketing reports of worsening of CHF with and without identifiable precipitating factors in patients taking etanercept. Assessment of potential risk is ongoing.	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to congestive heart failure.
Inflammatory bowel disease in JIA subjects	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects. Justification: Assessment of potential risk is ongoing.	None proposed
Important Potential Risks – All Indications		
Autoimmune renal disease	MAH reviewed topic, available evidence did not support inclusion of this safety concern as an adverse drug reaction. Justification: Assessment of potential risk is ongoing.	None proposed
Pemphigus/ pemphigoid	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Amyotrophic lateral sclerosis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Myasthenia gravis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Encephalitis/ leukoencephalo-myelitis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Progressive multifocal leukoencephalopathy	MAH reviewed topic, available evidence insufficient at this time to support inclusion of this safety concern as an adverse drug reaction. Justification: Assessment of potential risk is ongoing.	None proposed
Liver failure	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Hepatic cirrhosis and fibrosis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Severe hypertensive reactions	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Adverse pregnancy outcomes	SmPC section 4.6 Pregnancy; if indicated, additional changes to SmPC will be undertaken. Justification: Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available. Assessment of potential risk is ongoing.	None proposed
Potential for medication errors (pre-filled pen)	Clear Package Leaflet Instructions for use of the pre-filled pen. Justification: There have been reports of medication errors in patients treated with the etanercept pre-filled pen.	Educational materials Training is given to patients, care givers and healthcare professionals (HCPs) in the appropriate use of the PFP. The experiences from providing training to patients in the US, where a similar Enbrel PFP was introduced for more than two years prior to launch of the PFP in the EU, have been utilised. Based on experience from the US, EU post launch experience and market

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		research studies, numerous enhancements have been made to the HCP and patient training materials and resources including: • Market research in the form of a "use study" was conducted with European rheumatology and dermatology patients in order to identify improvements in the instructions for use. Furthermore, readability testing of the PFP Package Leaflet was satisfactorily completed in 2007 and further readability testing is currently being conducted. The outcome of this latest round of testing will be used to determine the need for updates to the instructions for use section of the leaflet. In addition, a highly visual teaching guide was developed to facilitate HCP training of patients in the clinician's office. This teaching guide has been made available to support clinicians in their training of patients. • Availability of a needle free demonstration device. This device allows patients to practice injections prior to using the actual PFP. These devices have been made available to clinicians for training purposes in the clinician's office. • Availability of instructional materials in both print and DVD formats. HCPs have been provided with print and DVD instructional materials to share with patients to demonstrate the proper use of the PFP. At the discretion of the local affiliate, a toll-free telephone number and website for assistance may also be made available.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Potential Risks –Specific Indications		
Impaired growth and development in juvenile subjects	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Acute ischemic CV events in adult subjects	SmPC section 4.8: Undesirable effect; if indicated, additional changes to SmPC will be undertaken. Justification: Serious adverse events of acute ischemic CV events have been reported in clinical trials. Assessment of potential risk is ongoing.	None proposed
Important Missing Information – All Indications		
Use in hepatic and renal impaired subjects	SmPC section 4.2 Posology and administration SmPC section 4.4 Special warnings and precautions; if indicated, additional changes to SmPC will be undertaken. Justification: Clinical experience in these populations is limited. Assessment of potential risk is ongoing.	None proposed
Use in different ethnic origins	If indicated, changes to SmPC will be undertaken. Justification: There is limited experience in some ethnic origins. Assessment of potential risk is ongoing.	None proposed
Use in pregnant women	SmPC section 4.6 Pregnancy and lactation; if indicated, additional changes to SmPC will be undertaken. Justification: There are no studies with etanercept in pregnant women. Assessment of potential risk is ongoing.	None proposed

Reconciliation of issues outlined in the RMP report

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

Table 2. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
The following two important areas of missing information specific for the JIA indication should be added to the list of ongoing safety concerns. Assessment of spinal mobility (paediatric patients with ERA). Clinically inactive disease and remission rates and the effectiveness of re-treatment upon disease relapse (paediatric patients with	The 2 noted efficacy assessments specific to JIA (that is, assessment of spinal mobility in paediatric patients with ERA, and clinically inactive disease and remission rates and the effectiveness of re-treatment upon disease relapse in paediatric patients with eoJIA, PsA, or ERA) have been removed from the list of safety concerns and included in Part IV (Plan for Post authorisation Efficacy Studies) of the RMP as they relate to efficacy rather than safety. Per the European Medicine Agency's (EMA's) Guideline on good pharmacovigilance practices, Module V – Risk management	This is acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
eoJIA, PsA, or ERA).	systems (EMA/838713/2011, dated 22 June 2012), post authorisation efficacy studies that address efficacy uncertainties are to be presented in Part IV of the RMP. Therefore, the sponsor feels that these 2 efficacy uncertainties that need to be addressed in relation to etanercept therapy in patients with JIA should remain within the RMP section for post authorisation efficacy studies (Part IV) and not within the RMP section on safety specification (Part II). Per the guideline, the safety concerns falling under 'important missing information' in Part II, Module SVIII (Summary of the safety concerns) should relate to the populations not studied in clinical trials that are presented in Part II, Module SIV (Populations not studied in clinical trials), and do not relate to efficacy uncertainties that need to be addressed. In Version 4.3 of the etanercept RMP (dated 16 August 2012), the sponsor added these 2 efficacy uncertainties as 'important missing information' in the list of ongoing safety concerns because the EMA had requested that they be included in the etanercept RMP; however, the new template for the RMP, which contained the new efficacy section, had not yet been released by EMA. With the next update of the RMP (Version 5.0 dated 12 April 2013), the sponsor converted the etanercept RMP to the new RMP template released by EMA in November 2012 and therefore moved these 2 efficacy uncertainties from the safety specification section to the new efficacy section.	
It is noted that the potential risk of uveitis was removed from the RMP Version 2.0. This is a pertinent risk to children treated with etanercept, especially in light of the current application to extend indication to children 2 years of age. The sponsor should provide justification for the removal of this risk from the listed ongoing safety concerns.	A comprehensive assessment of reports of uveitis in association with etanercept treatment was conducted by Pfizer. Largely as a result of information from post marketing reports uveitis was included as an adverse drug reaction (ADR) in the Product Information for etanercept and is considered an uncommon event. An analysis of the clinical trial incidence of uveitis associated with the use of etanercept across all indications undertaken at the time of the assessment revealed that the exposure adjusted event rate for uveitis in etanercept treated subjects was lower compared with the exposure adjusted rate in placebo treated subjects. The literature review identified some articles which indicated a causal association of uveitis to etanercept therapy, while others indicated that while etanercept was not causal, it was not an effective therapy for uveitis. Uveitis was removed as a risk from the March 2010 etanercept RMP (Version 2.0) because the level of risk was felt to be adequately communicated by the update to the Product Information and because no	The evaluator acknowledges the sponsor's comments regarding the risk of uveitis. However, due to the highly serious nature of this condition, together with the current application to extend treatment to children from 2 years of age, this remains an important potential risk that should be included in the list of ongoing safety concerns and specifically reported on within PSURs. Furthermore, the clinical evaluator appears to support the inclusion of this risk in the list of

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	additional information was expected to be acquired that would alter the risk/benefit profile of etanercept due to this event. Routine pharmacovigilance is conducted by Pfizer, including individual case review, literature review, and statistical and non-statistical signal detection approaches. Should any new information about this event be identified that would change the benefit risk profile, regulatory authorities would be notified and appropriate changes would be made to the Product Information and the RMP.	ongoing safety concerns (see second round clinical evaluation report).
Scleritis is a known adverse event associated with etanercept therapy. This was included in the latest PSUR (dated 27th March 2013) and has been included in the proposed Australian PI. It is recommended that this be added to the list of ongoing safety concerns for consistency.	Scleritis was also added as an ADR to the Product Information for etanercept following a comprehensive assessment largely on the basis of post marketing and literature reports. The incidence of scleritis in double blind clinical trials was comparable between etanercept and placebo treated subjects. Furthermore, there was no evidence that the exposure adjusted rate of scleritis increased with long term use of etanercept in clinical trials. Therefore, scleritis was not included as a risk in the RMP because the level of risk was felt to be adequately communicated by the update to the Product Information and because no additional information was expected to be acquired that would alter the risk/benefit profile of etanercept due to this event. As stated for uveitis, routine pharmacovigilance activities are utilized to monitor all events including scleritis for changes in reporting patterns.	The evaluator acknowledges the sponsor's comments regarding the risk of scleritis. However, due to the highly serious nature of this condition, together with the current application to extend treatment to children from 2 years of age, this remains an important potential risk that should be included in the list of ongoing safety concerns and specifically reported on within PSURs. Furthermore, the clinical evaluator appears to support the inclusion of this risk in the list of ongoing safety concerns (see second round clinical evaluation report).
Table 6.1.4 of the global RMP Version 5.0 does not include the important potential risks of male infertility and weight gain have not been listed. This should be amended.	During the conversion of the etanercept RMP to the new RMP format, the potential risks of male infertility and weight gain were inadvertently excluded from Summary of Risk Minimisation Measures. Pfizer agrees to add these 2 potential risks at the time of the next update of the etanercept all indication RMP (April 2014). In addition, the identical copy of this table will also be revised to include these 2 potential risks.	This is acceptable.
It is recommended that the sponsor consider an Australian paediatric JIA registry study to further investigate and elucidate the ongoing safety concerns associated with etanercept and the extension of	Pfizer has given consideration for an Australian biologics registry for patients with JIA, however, does not consider this a practical initiative. Due to the very small number of Australian patients with JIA who are treated with Enbrel, a registry would not be able to generate sufficient data to demonstrate clinically meaningful safety data.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
indication/new dose regime. A study protocol should be submitted to the TGA for review. This recommendation is in light of the small sample size of Study B1801023, restricted investigation to only eoJIA, ERA and PsA, and the reduction to only one ongoing study into etanercept after 2013.	There are, however, several international registries in operation that collect safety data on JIA patients using Enbrel. In Europe, where Enbrel is approved for once weekly dosing, these include registries in Germany (the children etanercept registry, JuMBO; BIKER), England (BSPARBNDR), The Netherlands (ABCRegister) and Spain, Switzerland and Italy (IPERN).	
It is unclear if the event specific questionnaires have already been distributed and are currently in use. It is requested that the sponsor clarify the release date of these questionnaires.	The questionnaires are currently in use in Australia. Effective dates for the current versions are provided below. • Amyotrophic Lateral Sclerosis (ALS) Questionnaire Oct 2003 • Demyelination Questionnaire 19 Nov 2003 • Guillain Barre Syndrome Questionnaire: 04 Feb 2005 • Lymphoma 09 Sep 2005 • Mycosis Fungoides / Cutaneous Cell Lymphoma 30 Nov 2007 • Progressive Multifocal Leukoencephalopathy (PML) 23 Dec 2009 • Patients less than or equal to 30 years old with Malignancy 15 Feb 2012 • JIA Subtype 19 Mar 2013	This is acceptable.
The following forms appear to be a generic adverse event forms and should be amended to adequately capture etanercept dose and duration of therapy. It is noted that forms such as the "Mycosis Fungoides Questionnaire" do contain Enbrel specific questions and capture dosages used and duration of therapy. This information should be consistently gathered across all questionnaires. Amendments should be made to: "Progressive Multifocal Leukoencephalopathy (PML) Questionnaire" "Guillain Barre Syndrome Questionnaire" "Amyotrophic Lateral Sclerosis (ALS)"	Pfizer agrees to amend these questionnaires in the next annual update of the etanercept all indication RMP (April 2014). The questionnaires are used in addition to our normal request for information (via Pfizer AE Report form). For cases that require a special events questionnaire, Pfizer asks for: • Identifiable patient • Identifiable reporter • Suspect product • Daily dose and regimen • Route of administration • Indication • Start date • Stop date or duration of therapy • Concomitant medications • Daily dose and regimen • Stop date (and if relevant, stop time) and duration of treatment • Medical History • Adverse event • Full description including body site and severity • Seriousness criteria • Onset date (or time to onset) if not available, best available date or treatment duration. • Time lag from stop date, if event occurred after cessation of treatment	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	• Outcome • Specific tests and/or treatment required and their results • Causal relationship assessment	
In regards to the malignancy specific questionnaire, the current version is restricted to patients less than 30years old. This age limit should be increased, or ultimately removed as a large number of potential adverse events will not be adequately recorded.	In November 2011, the US Food and Drug Administration (FDA) required that all marketing authorization holders for TNF inhibitors participate in an enhanced pharmacovigilance program to assess the risk of malignancy in paediatric, adolescent and young adult (less than 30 years of age) patients. The FDA requirement included active query of reporters to obtain additional clinical information related to malignancy diagnosis. The malignancy questionnaire was specifically designed to gather information for this program and, therefore, Pfizer must retain the questionnaire in its present form to comply with the FDA requirement. Other pharmacovigilance activities related to malignancies are outlined in Part III Pharmacovigilance Plan in the RMP and include, for example, numerous registries. Where deemed necessary, questionnaires have been designed to gather data (for example, lymphoma and mycosis fungoides) for specific malignancies.	This is acceptable.
It is recommended that the sponsor utilise the additional questionnaires of: "Pregnancy and exposure in utero": In light of the most recent interim analysis of the OTIS study (global RMP Version 5.0, part 3), the inclusion of a "pregnancy and exposure in utero" questionnaire should be re considered to further elucidate this ongoing safety concern. The OTIS data suggests that a higher proportion of major birth defects in etanercept exposed pregnancies compared to disease matched controls. The final analysis of this data should be submitted to the TGA as soon as it is available. "Paediatric Event": See section regarding the specific follow up for JIA below.	The final report for the OTIS registry will be submitted to TGA when available (currently anticipated in November 2014). Pfizer does not have a specific "pregnancy and exposure in utero" questionnaire for Enbrel. Rather, Pfizer has a special events questionnaire for exposure in utero that is used for all products (see Appendix 1). With respect to the evaluator's recommendations regarding specific JIA subtype questionnaire revision, and designing an additional targeted questionnaire for paediatric adverse event: The JIA subtype questionnaire is added to our standard AE reporting form which would capture patient's age, etanercept dose, duration of therapy, and details of the adverse event. Each case is assessed for follow up requirements. The necessary (targeted event) questionnaires are then collated with the standard AE reporting form, each containing the case number (to allow cross referencing).	This is acceptable
The specific JIA subtype questionnaire submitted in Annex 7 should be revised as follows: The "Specific JIA Subtype" questionnaire should be removed and the details captured in this questionnaire	Paediatric Adverse Event Questionnaire Pfizer agrees to develop a paediatric adverse event questionnaire similar to the one previously in use at legacy Wyeth and will include it in the next annual update of the etanercept all indication RMP (April 2014). Specific JIA Subtype Questionnaire The specific JIA subtype questionnaire is a	This is acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
subsequently incorporated into each of the targeted questionnaires listed above. This would improve consistency and quality of adverse event data. An additional targeted questionnaire should be designed for a "Paediatric Adverse Event". This general form should include the JIA subtype questions, in addition to fields designed to capture the patient's age, etanercept dose, duration of therapy and details of the adverse event. This would significantly improve the reporting quality of paediatric adverse events.	commitment with the European Medicines Agency (EMA) and therefore cannot be removed and should remain as a standalone questionnaire.	
It is recommended that all study reports and updates that are submitted to the EU, also be submitted simultaneously to Australia with the same timelines.	Pfizer agrees that all paediatric study reports and updates that are submitted to the EU will also be submitted to Australia with the same timelines. There will be annual update reports for JIA Study B1801023 included in the annual updates of the etanercept all indication RMP.	This is acceptable, however the sponsor should clarify if the "etanercept all indication RMP" referred to here is actually the "Global RMP" submitted with this application.
The sponsor should clarify the pharmacovigilance activities assigned to the two areas of important missing information specific to the JIA indication: Assessment of spinal mobility – paediatric patients with ERA Clinically inactive disease and remission rates and the effectiveness of re treatment upon disease relapse – paediatric patients with eoJIA, PsA, or ERA	The following 2 pharmacovigilance activities that address the 2 efficacy uncertainties (that is, assessment of spinal mobility in paediatric patients with ERA, and clinically inactive disease and remission rates and the effectiveness of re treatment upon disease relapse in paediatric patients with eoJIA, PsA, or ERA) are discussed in Part IV of the etanercept RMP: Study 0881A1-3338 (that is, B1801014) and Study B1801023.	This is acceptable
The current package leaflet should be submitted to TGA for review. It is recommended that the package leaflet contain clear instructions on storage, preparation and administration of etanercept. This should also include pictures describing correct administration technique, in addition to a dosing table with weight, ratios of diluents and dose. This will enhance safety regarding prescribing, administration and dose escalation.	Pfizer intends [information redacted]. In order to reflect the proposed once-weekly dosing in JIA patients, Pfizer is providing an amended instructions leaflet [information redacted. The instructions leaflet is included in Appendix 2. Please be aware that each pack of Enbrel includes a PI leaflet, as well as a leaflet that has the CMI on one side and detailed instructions for use on the other. These instructions include step by step guidance with pictures, and detail the correct preparation and administration technique. Clear storage instructions are provided in the CMI.	This is acceptable.
The current "patient/carer booklet" and other	Current educational materials for JIA include: "More about Juvenile Idiopathic Arthritis	The amended version of the "How to use

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
educational material should be submitted to the TGA for review prior to supply for the new indication. This information should contain clear instructions on storage, preparation and administration of etanercept. This should also include pictures describing correct administration technique, in addition to a dosing table with weight, ratios of diluents and dose. This will enhance safety regarding prescribing, administration and dose escalation.	(JIA)": brochure provided as part of the "Your Enbrel Experience" patient support program. It provides general information on disease state. A copy of this is provided in Appendix 3. "How to use your Enbrel vials for dilution": brochure provided as part of the "Your Enbrel Experience" patient support program. It provides information on Enbrel administration (see Appendix 4). An amended version of this brochure is in development and includes additional information on dosing volumes for JIA patients (to be completed by30 September 2013). "Joint Defenders" app: an interactive learning tool for iPad and iPhone platforms available for download through the Apple App Store. "Joint Defenders" provides video components of information on disease state, therapy and administration, as well as an interactive learning tool that reinforces an understanding of JIA and the importance of ongoing treatment via an educational game. The app is intended to enhance the patient experience for juvenile Enbrel patients and increase quality use of medicines outcomes. The instruction sheet for downloading the app is provided in Appendix 5.	your Enbrel vials for dilution" brochure should be submitted to the TGA for review prior to supply for the new indication.
The Delegate may wish to restrict the administration of etanercept in children aged 2 to 4 years to health care professionals only.	It is not clear as to why the RMP evaluator suggests restricting the administration of Enbrel in children aged 2 to 4 years to healthcare professionals only. The dose of Enbrel is weight based in all patients under 18 years. Therefore, children aged 2 to 4 years are not the only patients who will require their dose to be calibrated and less than the full contents of the vial given. Parents who administer Enbrel to their children are given training by a healthcare professional, on the correct use of the medicine. Furthermore, Pfizer offers a free home nurse support program to assist patients or their parents/caregivers to safely and correctly administer their Enbrel. Requiring Enbrel to be administered by a healthcare professional only in children aged 2 to 4 years would be highly impractical to the families of these children, necessitating weekly visits to their healthcare professional. Such visits might also place an additional cost burden on patients. Children in non-metropolitan areas would be most severely impacted, given that access to healthcare professional services in regional and rural areas is not as easy as in major metropolitan centres. Pfizer, therefore, does not agree with the evaluator's suggestion of administration restrictions in the 2 to 4 years age group. There is no identifiable clinical benefit in having the administration of Enbrel performed by HCPs, specifically for this age group.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
As discussed in above, two important areas of missing information specific to the JIA indication were listed as ongoing safety concerns in the global RMP Version 4.3, and additional risk minimisation measures proposed for these risks. These however are not listed in Version 5.0, and no additional risk minimisation measures assigned. The sponsor should clarify if these two areas are included in the risk minimisation plan and justify their exclusion if they have been omitted. These two areas are: Assessment of spinal mobility (paediatric patients with ERA). Clinically inactive disease and remission rates and the effectiveness of re-treatment upon disease relapse (paediatric patients with eoJIA, PsA, or ERA).	When Version 4.3 of the RMP (dated 16 August 2012) was updated to Version 5.0 (dated 12 April 2013), the sponsor converted the etanercept RMP to the new RMP template released by EMA in November 2012, and therefore moved the 2 efficacy uncertainties (that is, assessment of spinal mobility in paediatric patients with ERA, and clinically inactive disease and remission rates and the effectiveness of re-treatment upon disease relapse in paediatric patients with eoJIA, PsA, or ERA) from the safety specification section (Part II) to the new efficacy section (Part IV).	This is acceptable
A dosing table with patient weight and ratios of diluents and dose should be added to assist with correct prescribing, administration and dose escalation. This will significantly enhance safe use of etanercept.	The dosing table in the patient instructions leaflet has been amended to account for the once weekly dosing option in children. As this is included in every pack, Pfizer does not believe that the dosing table needs to be duplicated in the PI, as unambiguous dosing formulae (mg dose/kg body weight) are already included in the PI.	This is acceptable
The Delegate may wish to restrict the administration of etanercept in children aged 2 to 4 years to health care professionals only.	As previously stated Pfizer does not agree with the evaluator's suggestion of administration restrictions in the 2 to 4 years age group, and therefore does not propose to add text to the PI restricting the administration of Enbrel.	This is acceptable
In light of the most recent PSUR report (dated 27th March 2013), the risk of hepatitis B reactivation should be added to the "other adverse event" section under "Infections and infestations – Not Known", to enhance safe use of etanercept. This is in line with the current SmPC.	The Enbrel PI was updated in March 2013 to include Hepatitis B reactivation under Infections and Infestations ("frequency not known") in the Adverse Effects section. Further safety changes were submitted in July 2013. The approved text has now been added to the PI relating to this current application. Changes to the PI from the version originally submitted with this application are summarised below: CLINICAL TRIALS Juvenile idiopathic arthritis. Added a final paragraph, as requested by RMP evaluator. PRECAUTIONS. Amended subheading to read "Congestive heart failure" (submitted with Safety Related Request in July 2013). PRECAUTIONS – Use in pregnancy. Added a paragraph that was submitted as a Safety Related Request in July 2013.	This is acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	ADVERSE EFFCTS. Amended subheading to read "Malignancies and lymphoproliferative disorders" (submitted with Safety Related Request in July 2013). DOSAGE AND ADMINISTRATION Children and adolescents. Removed reference to 25 mg/mL strength (planned to be replaced by 50 mg powder for injection) and rearranged order of once weekly and twice weekly dosing options.	
A statement should be added regarding the ongoing safety concern of Myasthenia gravis (MG).	Based on review of the data in relation to myasthenia gravis, Pfizer does not consider this to be an etanercept adverse drug reaction and thus does not warrant its inclusion in the Enbrel PI.	Myasthenia gravis (MG) was reported in the latest PSUR (dated 27th March 2013) in response to the accumulation of reports of MG in the Pfizer safety database. A total of 53 case reports were identified, 47 of which were spontaneous. Of this, 37 were confirmed MG cases. 17 of these were subsequently discounted due to insufficient information, 13 "had possible alternative explanations" and 6 had no clear alternative explanation identified. Furthermore, there was inconsistent event reporting across countries. In light of this data, routine risk minimisation activities should be applied to the risk of myasthenia gravis. The Delegate may wish to include Myasthenia Gravis in the proposed Australian PI.
A statement should be added regarding the ongoing safety concern of Progressive multifocal leukoencephalomyelitis.	Based on review of the data in relation to progressive multifocal leukoencephalomyelitis, Pfizer does not consider this to be an etanercept adverse drug reaction and thus does not warrant its inclusion in the Enbrel PI.	Progressive multifocal leukoencephalomyelit is and etanercept treatment is currently under review by the TGA. A safety assessment letter was submitted to the TGA in April 2011 by Pfizer reporting 5 cases of possible PML. The sponsor concluded that there

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
		was insufficient evidence to indicate a causal associated between etanercept therapy and the risk of PML. Since this time, there have been a number of reports in the literature regarding PML and biologic therapy including etanercept (Ladizinski 2013; Graff Radford 2012; Kothary 2011). It is recommended that routine risk minimisation activities be implemented for this risk. The Delegate may wish to include PML in the proposed Australian PI.
In light of the risks of off label paediatric use, a statement should be added to the PI under "Dosage and Administration" to the effect of "No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously. There is generally no applicable use of Enbrel in children aged below 2 years in the indication juvenile idiopathic arthritis". This is also mentioned in the SmPC to enhance safe use of etanercept.	The RMP evaluator has suggested some text to be added to the Dosage and Administration section of the PI. This proposed additional text does not provide any instructional information regarding the dosage or administration of Enbrel. Pfizer believes that this information would be more appropriately located under Clinical Trials Juvenile Idiopathic Arthritis. The PI has, therefore, been amended accordingly. Please note that the final sentence proposed by the evaluator has not been included, as it refers to the use of Enbrel in an age group that is outside that proposed for the indication.	This is acceptable.
In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the consumer medicine information as follows: A dosing table with ratios of diluents and dose should be added to assist with correct prescribing, administration and dose escalation. Pictures describing injection	3.5.1. Dosing Table The dosing table in the patient instructions leaflet has been amended to account for the once weekly dosing option in children with JIA. As the patient instructions leaflet is included in every pack, Pfizer does not believe that the dosing table needs to be duplicated in the CMI, as the CMI and the Instructions for use are printed on the same pack leaflet. 3.5.2. Pictures Describing Injection Technique The patient instructions in the instructions for use leaflet includes numerous pictures to	This is acceptable

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
technique. Restriction of etanercept administration in children aged 2 to 4 years to health care professionals only.	assist the patient/carer to administer Enbrel safely and correctly. The instructions leaflet is included in every pack. Duplication of these pictures in the CMI is therefore not required. 3.5.3. Restriction of Etanercept Administration in Children Aged 2 to 4 Years to Healthcare Professionals Only As previously stated Pfizer does not agree with the evaluator's suggestion of administration restrictions in the 2 to 4 years age group, and therefore does not propose to add text to the CMI restricting the administration of Enbrel.	

VI. Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

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

Clinical

The clinical evaluator has recommended approval to extend the indication for ETN to include the treatment of additional subtypes of JIA; to lower the age limit of treatment from the currently approved 4 years of age to 2 years of age for those patients with eoJIA and pJIA; to add a once weekly dosing regimen (0.8 mg/kg, up to a maximum of 50 mg) as an alternative treatment regimen; and to amend the current PI to incorporate the internationally accepted contemporary classification of JIA by the ILAR criteria.

The clinical evaluator has reviewed the submitted data, which included:

- 1 pivotal Phase IIIb, single treatment, open label, 2 part study (Study 0881A1 3338, also known as Study B1801014).
- 1 supporting, open label extension study (Study 20021618).
- 1 Phase IV, open label registry study of 36 months duration in patients with active polyarticular or systemic JIA (Study 20021626).

The benefits noted by the evaluator included:

- 88.6% of patients achieved an ACR Pedi 30 response at Week 12, compared with 28.9% or 42.8% (ERA only) in historical placebo controls and 73.9% in historical active controls.
- Response was similar in the JIA subtypes (eoJIA, ERA, and PsA), and in each of the pre specified age brackets within the eoJIA subtype (2 to 4 years 93.3%, 5 to 11 years 90.9%, and 12 to 17 years 85.7%).

- Efficacy was maintained/improved during 96 weeks of follow up.
- Safety profile was consistent with previously reported studies in JIA and no new safety concerns.

The concerns noted by the evaluator included:

- The overall study design is not consistent with the TGA adopted EU guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis".
- The pivotal study excluded patients who were at significant risk of infection, or who had various abnormal laboratory results at baseline.

Pharmacology

No new pharmacokinetic (PK) or pharmacodynamic (PD) data was provided in this submission. No PK data for children aged 2 to less than 4 years were presented. The sponsor extrapolated the findings from patients aged 4 to 17 years collected in the previously evaluated, pivotal JIA registration study (Study 16.0016) which demonstrated increased clearance of ETN when normalised by weight, and recommended the same dosing regimen in the younger patients (0.4 mg/kg (up to 25 mg) twice weekly). In response to a Section 31 question regarding the availability of PK data for children aged 2 to less than 4 years, the sponsor acknowledged that there were no data, and reiterated that they expect the same dose regimens "to provide similar exposure to that observed in older children receiving the same dose as well as in adults receiving 25 mg BIW or 50 mg QW, where efficacy and safety have been well established. The pharmacokinetic reasoning appears to be supported by the safety and efficacy observations in these young children." Evidence was based on comparability of ETN concentrations after twice weekly dosing between JIA subjects and adult subjects with AS, and simulations conducted using a population pharmacokinetic model.

The clinical evaluator disagreed with the sponsor's argument with respect to extrapolating PK data from older children to estimate ETN dosing in younger children, citing the EMA guideline CHMP/EWP/147013/2004 "Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population" (effective 24 August 2009). This guideline states: "The pharmacokinetics in children aged 2 to 4 years is probably the least predictable within this (children aged 2 to 11 years) group." Notwithstanding this, the similarity in efficacy and safety in younger and older children is supportive of the sponsor's dosing recommendations.

PK modelling simulation using data collected in children with JIA (Study 16.0016) demonstrated that ETN 0.8 mg/kg once weekly achieved comparable drug exposure to 0.4 mg/kg twice weekly (steady state peak and trough ETN concentration 11% higher and 18% lower, respectively), albeit with a large overlap of concentration profiles.

Efficacy

Study 0881A1-3338

This was a 96 week 2 part, open label, historical control, Phase III study to evaluate the efficacy and safety of ETN in children and adolescents with eoJIA, ERA or PsA with a history of intolerance or inadequate response to a greater than or equal to 3 month course of at least 1 conventional DMARD (MTX, sulfasalazine, chloroquine or hydroxychloroquine). It was conducted at 26 centres in Europe, Australia and Latin America. Part I consisted of a 12 week active ETN treatment period primarily designed to assess efficacy, Part II consisted of a further 84 weeks of open label ETN treatment to

assess long term safety. All eligible patients received ETN 0.8 mg/kg (to a maximum dose of 50 mg) once weekly. Patients who completed Part I were eligible to enter Part II.

The primary efficacy outcome was the proportion of patients on ETN who achieved ACR Paediatric 30 (Pedi 30) response at Week 12. The result was compared to historical placebo and active control data. Efficacy data for Part II was provided in response to a section 31 request.

The overall study design is not consistent with the TGA adopted EU guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis", which states that the "parallel group design is the only acceptable means of assessing efficacy and safety". Further, the guideline nominates a randomised withdrawal study design to minimise the risk to paediatric patients of prolonged, untreated active disease, while maintaining data integrity because of the randomisation process leading into Part II. The sponsor instead stated that the open label design is consistent with the TGA adopted EU guidelines "Clinical Trials in Small Populations" (July 2006) and "Note for Guidance on Choice of Control Group in Clinical Trials" (April 2001). However the former guideline acknowledges that '*most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance. Deviation from such standards is, therefore, uncommon and should only be considered when completely unavoidable and would need to be justified'.*

The sponsor stated that: '*Due to the large amount of information available, both from clinical trials and post marketing data, on the safety and efficacy of etanercept in polyarticular course JIA subjects, it was determined that it would not be ethical to expose JIA subjects to treatment with placebo in this study. In order to still have a comparator for this study, the sponsor determined that historical controls should be used to assess the individual clinical benefit of etanercept in the overall population and in each of the JIA subtypes under study (extended oligoarticular JIA, ERA, and PsA).*'

The sponsor further stated that based on their nominated EU guidelines: '*the use of historical controls may be acceptable to demonstrate efficacy and safety, as long as adequate attention is paid to careful selection of the external control group, minimization of biases, and appropriate statistical comparisons*.'

Eligibility criteria included: age greater than or equal to 2 years but less than 17 years for eoJIA, and greater than or equal to 12 and less than 17 years for ERA and PsA; meet the ILAR criteria for the 3 subtypes of JIA being studied. The JIA had to be clinically active at screening with at least 2 active peripheral joints (that is swollen and/or limited movement with accompanying pain or tenderness). Patients were required to have a history of either inadequate response or intolerance to a greater than or equal to 3 month course of at least 1 conventional DMARD (MTX, sulfasalazine, anti malarials) at adequate dose. For the ERA subtype only, an alternative prior qualifying treatment was a greater than or equal to 1 month course of NSAID at appropriate dose. Background conventional DMARD treatment (single therapy only) could be continued on study in those receiving it in a stable dose for at least 8 weeks prior to study entry. In particular, MTX could be continued at a stable dose not exceeding 15 mg/m^2 (maximum of 20 mg/week; oral or parenteral). Continuing treatment with NSAID and low dose prednisone (no more than 10 mg/day or 0.2 mg/kg/day, whichever was less) was also permitted if the patient had received a stable dose for the 2 weeks prior to baseline. Prior treatment with any biological DMARD therapy was not allowed.

Exclusion criteria comprised 3 domains and patients meeting any 1 of the criteria were excluded:

- Co-morbidities – active infection; history of recurrent infection, immunodeficiency, blood dyscrasia, demyelinating disease, macrophage activation syndrome or pustular

psoriasis; active uveitis within 6 months of baseline; evidence of latent or previously treated tuberculosis, and any history of malignancy;

- Baseline laboratory results – haemoglobin less than 8.5 g/dL, total White Cell Count (WCC) less than 3500/mm3, neutrophil count less than 1000/mm3, Platelet count less than 125,000/mm3, ALT or AST greater than 1.5 upper limit of normal (ULN), presence of IgM Rheumatoid Factor; and positive hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody;
- Past treatments – prior treatment with any biological DMARD at any time point; prior treatment with azathioprine, cyclosporine, or leflunomide within the last 6 months; and live or attenuated vaccines within 2 months of baseline visit.

A total of 127 patients were enrolled in the study and received at least 1 dose of ETN: 60 subjects with eoJIA (including 15 patients aged 2 to 4 years, 23 aged 5 to 11 years, and 22 aged 12 to 17 years), 38 subjects with ERA, and 29 patients with PsA. Part I was completed by 122 patients (96.0%). There were 2 withdrawals each from the eoJIA and ERA subgroups, and 1 from the PsA subtype arm. Four of the 5 subject withdrawals were because of adverse events (AEs), and 1 patient in the eoJIA group prematurely discontinued because of a protocol violation.

Of the 127 patients who received ETN during Part II (mITT cohort), 109 subjects were included in the valid for efficacy (VFE) analysis (50 patients with eoJIA, 31 with ERA, and 28 with PsA). A further 13 withdrawals occurred during Part II, including 5 because of insufficient efficacy (2 subjects each in the eoJIA and ERA subgroups, and 1 subject with PsJIA), and 2 for significant protocol violations (1 in the ERA subgroup, and the other in the PsJIA cohort).

Baseline demographics: the overall mean age was 11.7 years (range of 2 to 17 years). Fifteen patients (11.8%) were aged 2 to 4 years, 23 subjects (18.1%) were aged 5 to 11 years and 89 patients (70.1%) were aged 12 to 17 years. As expected, the age and gender distribution varied with the JIA subgroup: eoJIA mean age 8.6 years, 68% female; ERA mean age 14.5 years, 21% female; PsA mean age 14.5 years, 79% female. The majority of patients were of Caucasian ethnicity (90.55%). Patients in the eoJIA group had a median baseline weight of 29.25 kg, whereas those in the other 2 JIA subtypes were older children (median baseline weight of 54.4 kg for the ERA group, and 56.6 kg for the PsA group).

Baseline disease characteristics varied with the JIA subgroup. Median disease duration was longest in patients with eoJIA (21.9 months), followed by ERA (15.7 months), and PsA (13.2 months). Patients with ERA had a numerically lower mean number of active joints at baseline (5.2) compared to subjects with PsA (7.0 joints) and eoJIA (7.6 joints). The other joint parameters (limitation of movement (LOM), pain, and swelling) showed a similar trend. Patients with eoJIA were slightly more likely to have been on baseline DMARDs (90%), than either ERA patients (84.2%), or PsA patients (79.3%). Baseline oral corticosteroids were taken by 12.6% of patients overall (eoJIA 11.7%, ERA 21.1%, and PsA 3.5%), while oral NSAIDs were taken by 53.5% overall (eoJIA 50.0%, ERA 63.2%, and PsA 48.3%).

Overall, 88.6% of patients achieved an ACR Pedi 30 response at Week 12, with comparable response rates in the JIA subtypes: PsA (93.1%), eoJIA (89.7%), and ERA (83.3%) (see Table below). These study results were compared with historical placebo response data (meta-analysis of 6 studies published by Ruperto et al 2003; ERA was also compared to a single study by Burgos-Vargas et al 2008). All odds ratios (ORs) and the lower bound of the 95% CI were greater than 1. Within the eoJIA subtype, ACR Pedi 30 response rates were comparable in each of the pre specified age brackets (2 to 4 years 93.3%, 5 to 11 years 90.9%, and 12 to 17 years 85.7%).

Table 3. ACR Pedi 30 Response Rates at Week 12 in Study 0881A1-3338 compared to Historical Placebo Control Response

	ACR Pedi 30 Response Rate		Odds Ratio (95% CI) Study 3338 vs Historical Placebo Control	
Group	Study 3338 % (95% CI)	Historical Placebo Control % (95% CI)	Individual[c]	Pooled[d]
Overall	88.6% (81.6, 93.6)	28.9% (24.0, 34.2)[a]	23.49 (12.5, 44.3)	21.80 (11.9, 40.1)
eoJIA	89.7% (78.8, 96.1)	28.9% (24.0, 34.2)[a]	26.15 (10.6, 64.2)	24.27 (10.1, 58.5)
ERA	83.3% (67.2, 93.6)	28.9% (24.0, 34.2)[a]	15.09 (6.0, 38.2)	14.00 (5.6, 34.8)
ERA	83.3% (67.2, 93.6)	42.8% (16.9, 68.8)[b]	6.67 (1.7, 26.3)	NA (single study)
PsA	93.1% (77.2, 99.2)	28.9% (24.0, 34.2)[a]	40.73 (9.4, 176.9)	37.80 (8.8, 162.4)

Abbreviations: ACR = American College of Rheumatology; CI = confidence interval; eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; mITT = modified intent to treat; NA = not applicable; Pedi = pediatric; PsA = psoriatic arthritis.
a. Meta analysis weighted estimate of placebo response rate in Ruperto et al.
b. Placebo response rate in Burgos-Vargas et al.
c. Six (6) historical studies treated individually in the logistic regression model (adjusted).
d. Pooling 6 historical studies as 1 in the logistic regression model (unadjusted).

The ACR Pedi 30 response rates were also compared with an active historical control (the initial 12 week, open label ETN treatment phase (0.4 mg/kg twice weekly) of Study 16.0016 in patients with JIA; Lovell et al, 2000). The 95% CI of each of the ORs included 1, suggesting that the ACR Pedi 30 response rate observed in Study 0881A1-3338 was comparable to that recorded in Study 16.0016 (see Table below).

Table 4. ACR Pedi 30 Response Rates at Week 12 in Study 0881A1-3338 compared to Historical Active Control Response (Study 16.0016)

	ACR Pedi 30 Response Rates		Odds Ratio (95% CI)
Group	Study 3338 % (95% CI)	Historical Active Control[a] % (95% CI)	Study 3338 vs Historical Active Control[b]
Overall	88.6% (81.6, 93.6)	73.9% (63.6, 84.3)	1.97 (0.5, 8.3)
eoJIA	89.7% (78.8, 96.1)	73.9% (63.6, 84.3)	2.00 (0.4, 9.8)
ERA	83.3% (67.2, 93.6)	73.9% (63.6, 84.3)	1.53 (0.2, 10.4)
PsA	93.1% (77.2, 99.2)	73.9% (63.6, 84.3)	2.27 (0.2, 21.3)

Abbreviations: ACR = American College of Rheumatology; CI = confidence interval; eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; mITT = modified intent to treat; Pedi = pediatric; PsA = psoriatic arthritis.
a. Etanercept study 16.0016 (Lovell et al).
b. Adjusted for covariates: baseline age, sex, duration of disease at study entry, age of disease onset, the baseline values of all 6 ACR Pedi 30 components.

The overall ACR Pedi 50/70/90/100 response rates at Week 12 were 81.1%, 70.1%, 38.7% and 31.4%, respectively, and were broadly similar in each of the JIA subtypes.

In Part II of the study, ACR Pedi 30 responses at weeks 24, 48 and 96 were comparable with, or better than, those at Week 12 and similar in each of the 3 JIA subtypes (see Table below). Within the eoJIA subtype, ACR Pedi 30 response rates were comparable in each of the pre-specified age brackets at weeks 24, 48 and 96. The overall ACR Pedi 50/70/90/100 response rates improved with time. For example, approximately twice as many subjects achieved an ACR Pedi 90 response at Week 96 (65.4%; 70 out of 107) compared to Week 12 (29.8%; 36 out of 121).

Table 5. ACR Pedi 30 Response Rates at Week 12, 24, 48, and 96 in Study 0881A1-3338

Time Point	JIA Subtype			
	eoJIA n/N (%) 95% CI	ERA n/N (%) 95% CI	PsA n/N (%) 95% CI	Total n/N (%) 95% CI
Week 12	52/58 (89.7) (78.8, 96.1)	30/36 (83.3) (67.2, 93.6)	27/29 (93.1) (77.2, 99.2)	109/123 (88.6) (81.6, 93.6)
Week 24	55/58 (94.8) (85.6, 98.9)	33/36 (91.7) (77.5, 98.2)	27/28 (96.4) (81.7, 99.9)	115/122 (94.3) (88.5, 97.7)
Week 48	55/57 (96.5) (87.9, 99.6)	31/34 (91.2) (76.3, 98.1)	26/28 (92.9) (76.5, 99.1)	112/119 (94.1) (88.3, 97.6)
Week 96	53/53 (100) (93.3, 100)	30/30 (100) (88.4, 100)	24/25 (96.0) (79.6, 99.9)	107/108 (99.1) (94.9, 100)

Abbreviations: eoJIA = extended oligoarticular juvenile idiopathic arthritis; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; CI = confidence interval; mITT = modified intent to treat. N = number of subjects randomized to study treatment; n = number of subjects with event. Percentages are calculated in reference to N.

At Week 12, 15 subjects (12.1% of 124) fulfilled the criteria for inactive disease. This outcome improved to 24.8% (30 out of 121) at Week 24, 29.7% (35 out of 118) at Week 48, and 34.0% (36 out of 106) at Week 96.

Study 20021618:

This was a long term (up to 10 years, median 6 years), open label, extension study for paediatric subjects with active DMARD refractory JIA (predominantly pJIA or sJIA) who previously participated in the initial ETN JIA treatment study (16.0016). Patients received either a single 0.8 mg/kg injection of ETN per week or 2 times 0.4 mg/kg injections (up to a maximum dose of 25 mg per injection) twice weekly 3 to 4 days apart. The primary objective of the study was to evaluate the long term safety of ETN, but efficacy outcomes were also collected as a secondary objective. Overall, 58 of 69 eligible subjects enrolled in the extension study, with 15 patients completing the 10 year study treatment period. Eleven patients withdrew because of lack of efficacy, and 5 patients discontinued because of an AE.

The main efficacy outcome was the proportion of patients on ETN who achieved an ACR Pedi 30 response at 3 months. This was achieved by 79.2% (42 out of 58) of patients. For those subjects who remained in the study, ACR Pedi 30 response rates were maintained for up to 10 years (although greater than 50% had withdrawn/discontinued by year 6). ACR Pedi 50 and 70 response rates (72% and 52%, respectively at year 1) also remained relatively stable during the 10 years of follow up.

Study 20021626

This was an open label, non-randomised, Phase IV registry study for children aged 2 to 18 years with a diagnosis of pJIA or sJIA who were receiving ETN alone (n = 103), or in combination with MTX (n = 294), or MTX alone (n = 197). The study was conducted in 32 centres (28 in US, and 4 in Canada) between April 2000 and January 2008. Patients on ETN received a single 0.8 mg/kg injection per week (up to a maximum dose of 50 mg per week). Patients receiving MTX were prescribed a minimum dose of 10 mg/m2/week (~0.3 mg/kg/week; maximum dose of 1 mg/kg/week). The primary objective of the study was to evaluate the long term safety of ETN, but efficacy outcomes were also collected as a secondary objective.

The main efficacy outcomes were Physician Global Assessment (PGA) of disease activity, joint assessment (number of active joints and number of joints with LOM) and Paediatric Quality of Life (PedsQL) collected at various time points until 36 months.

At 3 years, the mean percentage improvement in PGA of disease activity was similar across the 3 treatment groups: 60.7% for MTX, 60.9% for ETN, and 55.4% for ETN + MTX. Mean percentage improvement in active joint count at 3 years was also similar between the 3 treatment groups (57.0% for MTX, 63.2% for ETN, and 58.9% for ETN + MTX), but mean

percentage improvement in active joint count with LOM was higher in the MTX group (57.5%) compared with either group receiving ETN (23.2% for ETN, and 42.8% for ETN + MTX).

In a subgroup analysis in 47 pJIA patients aged 2 to less than 4 years, the mean percentage improvement in PGA of disease activity appeared to be higher in the 2 groups receiving ETN compared with the MTX alone group from about month 12 onwards, but the numbers were very small (for example at 3 years: 91.7% for ETN (n = 4), 89.6% for ETN + MTX (n = 12), and 66.7% for MTX (n = 5)). Similarly, the year 3 mean percentage improvement in the number of active joints was 100% for ETN (n = 4), 90.4% for ETN + MTX (n = 12), and 81.1% for MTX (n = 6). The year 3 mean percentage improvement in the number of joints with LOM was comparable across the treatment groups: 87.5% for ETN (n = 4), 80.0% for ETN + MTX (n = 12), and 91.1% for MTX (n = 6).

Safety

In study 0881A1-3338, the mean exposure to ETN was 89.1 weeks (range 1 – 100 weeks), which was similar across the JIA subtypes. This represented 215.1 patient years (PYs) of ETN exposure. Mean weekly dose of ETN was 37.9 mg (range 10 to 50 mg). Consistent with the younger age and lower weight of patients with eoJIA, they had a lower mean weekly dose of ETN (29.5 mg) compared with either the ERA (45.1 mg) or PsA (45.7 mg) patients.

In Study 20021618, the overall ETN exposure in the 58 patients was 342 PYs. In Study 20021626, drug exposure was estimated from the reported start and end dates. Mean (SD) exposure for each arm was: 1.97 (1.09) years for MTX, 2.17 (1.04) years for ETN, and 2.16 (1.02) years for ETN + MTX. The overall patient exposure in Study 20021626 to MTX was estimated to be 387.8 PYs and 859.3 PYs for ETN (alone, and in combination with MTX).

Study 0881A1-3338

In Part I, adverse event (AE) data were collected up to week 12, and included the following AEs of special interest: opportunistic infections, lymphoma, malignancy, blood dyscrasias, demyelinating disease, and autoimmune disorders. Overall 35.4% of patients reported at least 1 treatment emergent AE (TEAE), excluding infections and injection site reactions (ISRs). The system organ class (SOC) with the most AEs was Respiratory, thoracic and mediastinal disorders, (7.9%), followed by Gastrointestinal disorders, General disorders and administration site conditions, Injury, poisoning and procedural complications, Investigations, and Nervous system disorders (7.1% each). The most common individual TEAEs were: headache (5.5%), followed by fatigue, pyrexia, abdominal pain, and diarrhoea (3.1% each). No clinically meaningful differences were observed across JIA subtypes, or across the 3 age groups of subjects with eoJIA.

By the end of Part II, 73.2% of patients reported at least 1 TEAE, excluding infections and ISRs. The most common types of AE were headache (0.107 per patient year), pyrexia (0.056 per patient year), and diarrhoea (0.046 per patient year). No significant differences for the incidence and type of AEs were observed across the JIA subtypes. In the eoJIA population, AEs occurred at a higher frequency in the 2 younger cohorts (1.54 per patient year for 2 to 4 year old subjects, and 1.45 per patient year for 5 to 11 year old children) compared to older patients (1.01 per patient year for 12 to 17 year old subjects).

In Part I, treatment emergent infections were reported by 45.7% of subjects (3.33 events per PY), with the most common being: upper respiratory tract infection (14.2%), followed by pharyngitis (11.8%), rhinitis (6.3%), gastroenteritis (3.9%) and bronchitis (3.1%). No significant differences in incidence or type of infection were observed across the 3 JIA subtypes (although overall infections were numerically higher in the eoJIA patients (51.7%, 4.09 events per PY) compared with either ERA (39.5%, 2.29 events per PY) or PsA (41.4%, 3.13 events per PY) patients).

By the end of Part II, treatment emergent infections were reported by 75.6% of subjects (1.65 events per PY), with the most common being: upper respiratory tract infection (33.1%), followed by pharyngitis (25.2%), gastroenteritis (14.2%), bronchitis (10.2%) and nasopharyngitis (9.4%). No significant differences in incidence or type of infection were observed across the 3 JIA subtypes (although overall infections were numerically higher in the eoJIA patients (80.0%, 1.88 events per PY) compared with either ERA (68.4%, 0.88 events per PY) or PsA (62.1%, 1.26 events per PY) patients). In the eoJIA population, infections occurred at a higher frequency in the 2 youngest cohorts (3.31 per patient year for 2 to 4 year old subjects, and 2.25 per patient year for 5 to 11 year old children) compared to older patients (1.14 per patient year for 12 to 17 year old subjects).

Treatment emergent ISRs were reported by 10 (7.9%) subjects (0.79 events per PY) in Part I, and by 16 (12.6%) subjects (0.29 events per PY) by the end of Part II.

No subjects reported malignancy, lymphoma, demyelinating or autoimmune disease in Part I. In Part II, 4 patients developed autoimmune disorders 2 cases of uveitis, and single cases of iridocyclitis and Crohn's disease. A further 2 reports of Crohn's were considered non treatment emergent.

In Part I, 4 patients reported 4 SAEs, including 3 infections (bronchopneumonia, pyelocystitis, and gastroenteritis) and 1 case of abdominal pain. By the end of Part II, 15 patients (11.8%) reported 16 non-infectious SAEs, and 11 patients (8.7%) reported 11 serious infections. All were single types of serious infection apart from 3 cases of gastrointestinal infection. In addition, 8 subjects suffered infections considered preventable by vaccination, 7 of whom were not vaccinated. These preventable infections included 4 cases of varicella (all in young subjects with eoJIA), 2 cases of herpes zoster (1 each in the ERA and PsJIA groups), and single reports of influenza and rubella (both in the eoJIA cohort). One case of opportunistic infection was reported (latent tuberculosis). No deaths were reported in Part I or II of the study.

There were 4 discontinuations due to AEs in Part I including bronchopneumonia, pyelocystitis, asthenia and pyrexia, and fatigue, dizziness and wheezing. No additional discontinuations occurred in Part II.

Overall, 10 patients (7.9% of 127) recorded Grade 3 or 4 abnormalities of laboratory tests during Parts I and II of the study. This included 4 subjects with leucopenia (3 eoJIA, and 1 PsJIA patient), and 6 subjects had abnormalities of liver function tests (3 eoJIA, 2 ERA and 1 PsJIA patients). All liver function test (LFT) abnormalities occurred in patients taking concurrent DMARD and/or NSAID therapy. The frequency of abnormal function tests was higher in the eoJIA group (27.1%) compared to the 2 other JIA subtypes (15.8% for ERA, and 13.8% for PsJIA).

In total, 26 patients (20.5%) tested positive for anti ETN antibodies on at least 1 occasion during the study, but none tested positive for neutralizing antibodies. There was no clear correlation between the occurrence of anti ETN antibodies and the development of AEs.

Growth parameters (height, weight, BMI) did not decline during the study.

Study 20021618

AEs were collected for first year only, SAEs for duration of the study. Overall, 75.9% of patients reported at least 1 TEAE during the first year of the study. The most common non-infectious TEAEs were: ISRs reported by 11 (19%) subjects (112 AEs, 210.93 events per 100 PYs), headache (44 AEs, 82.86 events per 100 PYs), and abdominal pain (20 AEs, 37.67 events per 100 PYs).

Treatment emergent infections were reported by 75.9% of subjects (237.29 events per 100 PYs). The most common treatment emergent infections reported were upper respiratory infection (68 AEs; 128.06 events per 100 PYs), pharyngitis (9 AEs; 16.95

events per 100 PYs) and influenza syndrome (9 AEs, 16.95 events per 100 PYs). Four patients reported events of herpes zoster.

No subjects reported malignancy, lymphoma, or demyelinating disease. Three patients developed autoimmune conditions: scleroderma (n = 2) and uveitis (n = 1).

No deaths were reported, but 16 patients reported 44 SAEs during the 10 year study period. The SAEs included 11 infections, the most serious being sepsis due to Group A β haemolytic streptococcus complicated by shock, disseminated intravascular coagulopathy, purpura fulminans, respiratory distress syndrome, and ischemia of the left foot and distal leg resulting in dry gangrene requiring left foot and mid-calf amputation. The non-infectious SAEs included RA (n = 6), abdominal pain, arthralgia, and macrophage activation syndrome (n = 2 each).

There were 5 discontinuations due to AEs (arthritis flare; purpura fulminans; suspected morphea and fasciitis; post-operative wound infection; and diarrhoea, vomiting, bone disorder, and aseptic meningitis).

Three patients experienced a Grade 3 decrease in haemoglobin, but there were no Grade 3 or 4 abnormalities of LFTs reported up to month 52 of the study (data sparse after this time).

Study 20021626

Overall, 25.2% of patients on ETN, 26.5% on ETN + MTX, and 21.8% on MTX reported at least 1 AE during the registry study. The exposure adjusted rate of AEs was similar between the combined ETN treatment groups (20.8 AEs per 100 PYs) and the MTX only arm (18.3 AEs per 100 PYs). The most common AEs reported were nervous system events (ETN 8.03, ETN + MTX 6.61, and MTX 4.38 per 100 PYs). Increased alanine transaminase / abnormal liver function AEs were the most common individual AEs, and were more common in the MTX arm (2.06 AEs per 100 PYs) compared with 0.0 or 0.16 AEs per 100 PYs in the ETN and ETN + MTX arms, respectively.

Infections were reported by 19 patients 4 on ETN, 11 on ETN + MTX, and 4 on MTX. All were considered medically important (requiring hospitalisation and/or intravenous antibiotics). The overall exposure adjusted rate for infections was: 1.29 per 100 PYs for MTX, 1.78 per 100 PYs for ETN, and 2.05 per 100 PYs for ETN + MTX. The infectious AEs reported by more than 1 subject were abscess, pyelonephritis, and herpes zoster (2 patients each in the ETN + MTX arm), and infection (2 patients in the ETN only arm).

No cases of lymphoma, tuberculosis, or malignancy were reported during the study. There were no cases of demyelinating disorders in the ETN only arm or ETN + MTX arm, but there was 1 case of optic neuritis in the MTX only arm.

No deaths were recorded, but 14 patients reported 18 SAEs on MTX, 9 patients reported 16 SAEs on ETN, and 28 patients reported 38 SAEs on ETN + MTX. The most common SAEs were viral infection (0.89 per 100 PYs for ETN), headache and arthritis (both 0.63 per 100 PYs for ETN + MTX). Infections were reported separately (see above), with 1 subject (on ETN + MTX) developing Grade 4 sepsis, and 8 having Grade 3 infections (1 on MTX, 3 on ETN, and 4 on ETN + MTX).

There were 15 discontinuations due to AEs, including abnormal LFTs, arthritis flare, skin rash, headache post ETN injection, injection site reaction, overlap syndrome with juvenile dermatomyositis, and vomiting.

Risk management plan

RMP evaluation

The TGA has accepted the Etanercept Global RMP Version 5.0, dated 12 April 2013, plus the Australian specific Annex (Version: 4.3, dated 16 August 2012) for etanercept. A number of recommendations on the RMP have been made by the RMP evaluator and the sponsor should address these matters in the Pre ACPM Response and follow up where appropriate with the TGA:

- The evaluator acknowledges the sponsor's comments regarding the risks of uveitis and scleritis. However, due to the highly serious nature of these conditions, together with the current application to extend treatment to children from 2 years of age, they remain important potential risks that should be included in the list of ongoing safety concerns and specifically reported on within PSURs.
  - The sponsor provided additional clarification on this issue in a response to the second round CER and RMP Assessment Report. Uveitis and scleritis are currently listed in the PI as adverse drug reactions. Although uveitis and scleritis were removed from the RMP list of important potential risks, the sponsor states that reports of these events will continue to be monitored through routine pharmacovigilance activities, and any new information that would change the benefit risk profile would be notified to regulatory authorities and appropriate changes would be made to the PI and the RMP.
- The amended version of the "How to use your Enbrel vials for dilution" brochure should be submitted to the TGA for review prior to supply for the new indication.
- Myasthenia gravis (MG) was reported in the latest PSUR (dated 27th March 2013) in response to the accumulation of reports of MG in the Pfizer safety database. A total of 53 case reports were identified, 47 of which were spontaneous. Of this, 37 were confirmed MG cases. 17 of these were subsequently discounted due to insufficient information, 13 "had possible alternative explanations" and 6 had no clear alternative explanation identified. Furthermore, there was inconsistent event reporting across countries. In light of this data, routine risk minimisation activities should be applied to the risk of myasthenia gravis.
  - The sponsor provided additional clarification on this issue in a response to the second round CER and RMP Assessment Report. Myasthenia gravis is listed as an important potential risk in the RMP and updates are included in each annual Periodic Safety Update Report (PSUR). Thus far, they state that there is insufficient evidence of an association between MG and etanercept to support a label revision, and it is not known if the risk of MG is elevated in patients with rheumatological disorders. The sponsor will continue to monitor MG.
  - Given that there are ongoing pharmacovigilance activities addressing this issue, and that MG is not included in the EU SmPC or US label, no changes to the Australian PI are requested at present.
- Progressive multifocal leukoencephalopathy (PML) and etanercept treatment is currently under review by the TGA. A safety assessment letter was submitted to the TGA in April 2011 by Pfizer reporting 5 cases of possible PML. The sponsor concluded that there was insufficient evidence to indicate a causal association between etanercept therapy and the risk of PML. Since this time, there have been a number of reports in the literature regarding PML and biologic therapy including etanercept (Ladizinski 2013; Graff-Radford 2012; Kothary 2011). It is recommended that routine risk minimisation activities be implemented for this risk.

- The sponsor provided additional clarification on this issue in a response to the second round CER and RMP Assessment Report. Four of the 5 possible cases of PML were not confirmed cases, and the remaining confirmed case was confounded by the patient's underlying SLE disorder and long term use of systemic corticosteroids. Of the literature references mentioned, the 8 cases reported for the TNF inhibitors infliximab, etanercept, and adalimumab were all confounded by the use of other immunosuppressive therapies (2 out of 8), lack of confirmation of PML (1 out of 8), or both (5 out of 8).
- Given that there is an ongoing TGA review, ongoing pharmacovigilance activities addressing this issue, and that PML is not included in the EU SmPC or US label, no changes to the Australian PI are requested at present.

Other RMP issues were satisfactorily resolved.

Risk-benefit analysis

Delegate's considerations

Efficacy:

In the pivotal, open label, Phase III study in children and adolescents with eoJIA, ERA or PsA, etanercept has demonstrated a higher ACR Pedi 30 response at Week 12 compared to historical placebo controls, and a comparable response compared to historical active controls. ACR Pedi 30 responses at weeks 24, 48 and 96 were comparable with or better than those at Week 12, similar in each of the 3 JIA subtypes, and within the eoJIA subtype, ACR Pedi 30 response rates were comparable in each of the pre specified age brackets (2 to 4, 5 to 11, and 12 to 17 years). These results were supported by results for the secondary efficacy endpoints (ACR Pedi 50/70/90/100).

Studies 20021618 (10 year, open label extension trial) and 20021626 (registry data) were supportive of the key efficacy findings of the pivotal trial, demonstrating maintenance of ACR Pedi 30 responses for up to 10 years (although data was sparse after year 6) in paediatric subjects with active DMARD refractory JIA (predominantly pJIA or sJIA). A subgroup analysis of patients aged 2 to less than 4 years in Study 20021626 also showed that the treatment effect of ETN was comparable to that seen in older aged subjects. Efficacy was comparable in patients receiving ETN 0.8 mg/kg once weekly or 0.4 mg/kg twice weekly. Although there are methodological issues in using historical controls, the submitted data appear reasonable to support efficacy for these changes.

Safety and RMP

Etanercept has demonstrated an acceptable short term safety profile consistent with that seen for pJIA patients of a similar age (4 to 17 years) and in the adult RA population, with no new safety signals identified. There is limited long term follow up of patients with eoJIA, ERA and PsA. Infection was the most common AE in the pivotal study, with 3 infectious SAEs (bronchopneumonia, pyelocystitis, gastroenteritis) in Part I, and 11 in Part II (including 3 gastrointestinal infections). A number of cases of vaccine preventable infection were also seen (including varicella and herpes zoster). Given the comparable safety profile in the current and proposed indications, the submitted data appear reasonable to support safety.

Data deficiencies

The design of the single pivotal trial in the proposed new indications is not consistent with the TGA adopted EU guideline CPMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis". In addition to the single treatment, open label design and use of historical controls, there was a limited

number of patients recruited (n = 127), particularly in the younger age group (n = 15 aged 2 to 4 years), with limited follow up.

Conditions of registration

The following are proposed as conditions of registration:

> The implementation in Australia of the Global Risk Management Plan (RMP) for Enbrel (Version 5.0, dated 12th April 2013) and any subsequent revisions, as agreed with the TGA.

Questions for the sponsor

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

> Are any further studies being conducted in JIA using etanercept to provide further evidence of the efficacy and safety in the various JIA subtypes and patients aged 2 to 4 years?

Proposed action

There is no reason to say, at this time, that the application for Etanercept should not be approved for registration.

Request for ACPM advice

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

1. Does the open label pivotal study and use of historical controls provide sufficient and reliable safety and efficacy data, particularly in children aged 2 to 4 years to support the proposed indication?
2. Is it reasonable to extrapolate safety and efficacy data in other subtypes of JIA to support the limited results in eoJIA, ERA, and PsA?

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

Response from sponsor

Pfizer has applied to make the following changes to Enbrel (etanercept):

- Extend the indication to include additional subtypes of Juvenile Idiopathic Arthritis (JIA).
- Add once weekly dosing as an alternative dose regimen for JIA patients.
- Lower the approved age limit for polyarticular course JIA from 4 to 2 years of age.

Both the Clinical Evaluator and the TGA Delegate have recommended approval of all three aspects of this application, and Pfizer concurs with their position on the application. Pfizer's response to the TGA Delegate's Overview and Proposed Action are provided below.

Issues

Study design

The Delegate notes in the Overview under the Efficacy point:

> '*The overall study design is not consistent with the TGA adopted EU guideline CHMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis*,' which states that the '*parallel group design is the only acceptable means of assessing efficacy and safety. Furthermore, the*

guideline nominates a randomised, withdrawal study design to minimise the risk to paediatric patients of prolonged, untreated active disease, while maintaining data integrity because of the randomisation process leading into Part II."

The Delegate further notes Data Deficiencies:

'*The design of the single pivotal trial in the proposed new indications is not consistent with the TGA adopted EU guideline CHMP/EWP/422/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis*.'

Pfizer's response:

The use of an open label, single treatment study design with historical controls as comparators, as opposed to a randomised, placebo controlled withdrawal study design in Study B1801014 was agreed to with the EMA PDCO based on the following.

The EU guideline CHMP/EWP/422/04 states, '*In a paediatric study there might be ethical concerns about including a placebo arm when safe and effective…medication is readily available. They have to be balanced by the ethical concerns of accepting shortcomings due to missing placebo control. Therefore, alternatives for the design of parallel group trials should be considered*."

Etanercept is approved for the adult conditions, AS and PsA, which are analogous to juvenile ERA and PsA. In addition, it is approved for polyarticular course JIA, which is similar to eoJIA in presentation and symptoms. Finally, a study showed preliminary evidence of etanercept efficacy in these 3 subtypes (Prince et al, 2009).

Therefore, Pfizer considered that there was the potential for clinical benefit through treatment with etanercept in these 3 subtypes, and that including a placebo arm would not be ethical.

It was agreed that the patients with the 3 subtypes under study, especially the ERA and PsA subtypes, are relatively rare and, therefore, would be potentially difficult to recruit. Use of a placebo arm, even in a randomised withdrawal design, would limit the number of patients willing to participate in the study. Furthermore, as noted in the CHMP Guidelines on Clinical Trials in Small Populations (CHMP/EWP/83561/2005) and ICH Guidelines on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96), the use of historical controls may be acceptable to demonstrate efficacy and safety, as long as adequate attention is paid to careful selection of the external control group, minimisation of biases, and appropriate statistical comparisons.

Based on the above, it was agreed with the European Medicines Agency Paediatric Committee (EMA PDCO) that the following 3 historical controls would be used for comparison of the Week 12 Study B1801014 data:

- A placebo historical control for the combined population and 3 subtypes – a meta-analysis of 6 JIA studies (Ruperto et al, 2003);
- A placebo historical control for ERA subjects – a clinical study in juvenile SpA (Burgos-Vargas et al, 2008); and
- An active historical control for the combined population and 3 subtypes – the 12 week open label data from Etanercept (monotherapy) Phase III study in polyarticular course JIA (Lovell et al, 2000).

The Delegate further notes Data Deficiencies:

'In addition to the single treatment, open label design and use of historical controls, there was a limited number of patients recruited (n = 127), particularly in the younger age group (n = 15 aged 2 to 4 years), with limited follow up."

Pfizer's response:

The minimum number of subjects by JIA subtype and age group to be enrolled in Study B1801014 was agreed with the EMA PDCO. For the 2 to 4 year eoJIA group, it was agreed that a minimum of 2 subjects would be enrolled. The number of subjects to be enrolled in each of the subtypes was based on the prevalence of the 3 JIA subtypes. A 2007 report estimated that 13% to 28% of patients with JIA develop the eoJIA subtype (Ravelli et al, 2007).

Regarding the number of 2 to 4 year old subjects with eoJIA, literature reports regarding the mean age of onset of eoJIA vary widely from 3.8 to 10.25 years, and do not provide age distribution by age groups (Danner et al, 2006; Saurenmann et al, 2007; Pruunsild et al, 2007; Yilmaz et al, 2008). Although eoJIA is generally recognised as a disease of younger children, numerous other considerations were factored into the proposed minimum enrollment:

- Based upon the ILAR criteria, oligoarticular JIA is characterised as "extended" if greater than 4 active joints are affected beyond the first 6 months of disease;
- Available treatment algorithms support progressive escalation of therapy, beginning with NSAIDs and corticosteroids injections followed by a 6 month course of non-biologic DMARDs prior to initiation of an anti TNF agent. Thus, many patients would likely spend substantial amounts of time on such therapies before becoming eligible for treatment with etanercept.

Based on the factors described above, it was expected that few patients younger than 5 years of age would be candidates for biologic agents. These factors therefore limited recruitment of this age range. Although the 15 eoJIA subjects aged 2 to 4 years is a relative small sample size, the safety and efficacy data in these subjects are similar to those for the older eoJIA subjects as well as for the overall study population. In addition, up to 10 years of data will be collected across Studies B1801014 and B1801023, as described later in this response. Regarding the RMP evaluation, it is noted that the sponsor has addressed all outstanding issues with the Office of Product Review and the sponsor agrees with the Delegate's conclusions regarding the RMP evaluation.

The Delegate notes:

> *'The pivotal study excluded patients who were at significant risk of infection, or who had various abnormal laboratory results at baseline."*

Pfizer's response:

The safety-related exclusion criteria for the study were selected specifically for the protection of the subject's safety, based on known risks stated in the etanercept product labelling, as well as good medical practice. Patients with an infection associated with hospitalisation and/or parenteral antibiotics within 1 month before the baseline visit, were excluded from the study. The etanercept product labelling states that treatment should not be initiated in patients with active infections, including chronic or localised infections. This inclusion criterion was included in consideration of the vulnerable populations enrolled in the study.

Patients who had any of the laboratory abnormalities at screening, as listed in the exclusion criteria of the study report, were excluded from the study to provide clearer distinction between incident and prevalent reports of laboratory abnormalities in the study.

The Delegate has requested the following further information:

> 'Are any further studies being conducted in JIA using etanercept to provide further evidence of the efficacy and safety in the various JIA subtypes and patients aged 2 to 4 years?'

Pfizer's response:

Pfizer is currently conducting Study B1801023, which is an open label, single treatment, multi centre, 8 year extension study of Study B1801014. This study consists of 3 periods:

- An Active Treatment Period in which subjects who completed 96 weeks of active treatment with investigational product (etanercept) in Study B1801014 and are eligible, may continue investigational product in Study B1801023 for up to 8 additional years;
- A Withdrawal/Retreatment Period for subjects who either completed 96 weeks of treatment in Study B1801014 or were enrolled in the active treatment period of Study B1801023; and
- An Observational Period in which all subjects, including those withdrawn from investigational product, are to be followed for a total of 8 years from the time of initial entry into the study.

Therefore, there will be a total of up to 10 years of data collected between Study B1801014 and Study B1801023. Of the 15 subjects aged 2 to 4 years with eoJIA enrolled in Study B1801014, 14 were enrolled into Study B1801023. This currently includes 9 in the active treatment period, 1 in the withdrawal period, and 4 in the observational period.

Conclusion

In Pfizer's opinion, the data submitted by Pfizer demonstrate that Enbrel is effective in treating the additional subtypes of JIA, subject of this application, as well as in treating polyarticular JIA patients as young as 2 years of age. In addition, Pfizer believes the safety profile in these patients has been shown to be consistent with that reported in older children, for which Enbrel is already indicated. Both the clinical evaluator and the Delegate are in support of approving these aspects of the application. Pfizer also agrees with the clinical evaluator and the Delegate, that Pfizer has provided sufficient data to support the safety and efficacy of a once weekly dose regimen in treating patients with JIA.

Pfizer Australia looks forward to a favourable consideration of our application to:

- Extend the indication to include additional subtypes of JIA, such that the new JIA indication would be:
  - Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.
  - Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.
  - Active enthesitis related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.
  - Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.

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

- Add once weekly dosing as an alternative dose regimen (0.8 mg/kg up to a maximum of 50 mg, given once weekly) for JIA patients
- Lower the approved age limit for polyarticular course JIA to 2 years of age.

Advisory committee considerations

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

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Enbrel powders for injection 25 mg and 50 mg containing etanercept (rch) and 50 mg solution for injection containing etanercept (rch) to have an overall positive benefit–risk profile for the indication**;**

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years of age, who have had an inadequate response to one or more DMARDs.*
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years of age, who have had an inadequate response to, or proved intolerant to, methotrexate.*
- *Active enthesitis related arthritis in adolescents aged 12 to 17 years, who have had an inadequate response to, or proved intolerant to, conventional therapy.*
- *Active psoriatic arthritis in adolescents aged 12 to 17 years, who have had an inadequate response to, or proved intolerant to, methotrexate.*

Enbrel has not been studied in children less than 2 years.

In making this recommendation the ACPM

- Noted the relatively small numbers of children in the relevant age groups in the trials particularly noted the limited data in 2 to 4 year olds.
- Expressed some concern the extensive exclusion criteria, which may bias safety observations.

Specific advice:

The ACPM provided the following specifically requested advice:

- Does the open label pivotal study and use of historical controls provide sufficient and reliable safety and efficacy data, particularly in children aged 2 to 4 years to support the proposed indication?

The ACPM advised that the data submitted was not adequate to support the extension of indication by itself. The pivotal trial, Study 0881A1-3338, was a 96 week 2 part, open label, historical control, Phase III study and showed;

- Compared to historical controls etanercept was superior to placebo.
- In Part II of the study, which continued up to 96 weeks, responses were maintained or improved in the 3 JIA groups compared to the 12 week data.

However;

- The overall study design is not consistent with the relevant TGA adopted EU guidelines.
- The subject numbers were small.

- As 11% of the children did not complete the 96 weeks, the true response rates will be lower.
- Is it reasonable to extrapolate safety and efficacy data in other subtypes of JIA to support the limited results in eoJIA, ERA, and PsA?

The ACPM advised that extrapolation is reasonable. The product will be used infrequently by experienced clinicians so it is reasonable, in the light of the data submitted, to extrapolate on logical and previous data grounds regarding potential efficacy and the likely benefit-risk profile.

Proposed conditions of registration:

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

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

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:

- A statement in the relevant sections of the PI and of the CMI recommending varicella immunisation prior to commencement of treatment.

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

Outcome

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

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.*
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*
- *Active enthesitis related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to or, who have proved intolerant to, conventional therapy.*
- *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*

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

The full indications are now:

Enbrel is indicated for the treatment of

AdultsRheumatoid Arthritis

- *Active, adult rheumatoid arthritis (RA) in patiens who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Enbrel 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 (see CLINICAL TRIALS).*

Psoriatic Arthritis

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

Ankylosing Spondylitis

- *The signs and symptoms of active ankylosing spondylitis in adults.*

Plaque Psoriasis

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

Children and adolescents

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.*
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*
- *Active enthesitis related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to or, who have proved intolerant to, conventional therapy.*
- *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*

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

Paediatric Plaque Psoriasis

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

Specific conditions of registration applying to these goods

The Enbrel Risk Management Plan (RMP), version 5.0, dated 12 April 2013 and your correspondence of 8 January 2014, included with submission PM-2012-04135-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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