EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 January 2013
EMA/20006/2013
Committee for Medicinal Products for Human Use (CHMP)

Enbrel

etanercept

Procedure No. EMEA/H/C/000262/A46/134.1

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Rapporteur's Response Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

P46 134.1

Enbrel

EMEA/H/C/262

Marketing Authorisation Holder: Pfizer Limited

Rapporteur:	Robert Hemmings
Start of the procedure:	22.07.2012
Date of this report:	15.10.2012
Deadline for Rapporteur's AR:	16.10.2012
Deadline for CHMP member's comments:	31.10.2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Enbrel
INN (or common name) of the active substance(s):	Etanercept
MAH:	Pfizer Limited
Currently approved Indication(s)	Rheumatoid arthritis Enbrel in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. (Enbrel 25mg - Enbrel 50mg) Enbrel can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. (Enbrel 25mg - Enbrel 50mg) Enbrel is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. (Enbrel 25mg - Enbrel 50mg) Enbrel, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function. (Enbrel 25mg - Enbrel 50mg) Polyarticular juvenile idiopathic arthritis Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than 2 years. Psoriatic arthritis Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. (Enbrel 25mg - Enbrel 50mg) Ankylosing spondylitis Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. (Enbrel 25mg - Enbrel 50mg) Plaque psoriasis Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a

	contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) Plaque psoriasis Treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1). Paediatric plaque psoriasis Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants, Tumour necrosis factor alpha (TNF-α) inhibitors (L04AB01)
Pharmaceutical form(s) and strength(s):	25mg powder for solution for injection 25mg powder and solvent for solution for injection 50mg powder for solution for injection 50mg powder and solvent for solution for injection 25mg/ml powder and solvent for solution for injection for paediatric use 25 mg solution for injection in pre-filled syringe 50 mg solution for injection in pre-filled syringe
Rapporteur:	**Name:** Robert Hemmings

LIST OF ABBREVIATIONS

ANA	antinuclear antibody
AS	ankylosing spondylitis
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CRF	case report form
CRO	contract research organizations
CTC	Common Toxicity Criteria Version 2.0
CTCAE	Common Terminology Criteria for Adverse Events
DMARD	disease-modifying antirheumatic drug
GCP	Good Clinical Practice
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
JRA	juvenile rheumatoid arthritis
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PASI 50	A 50% or greater improvement (ie, decrease) in PASI score compared to baseline
PASI 75	A 75% or greater improvement (ie, decrease) in PASI score compared to baseline
PASI 90	A 90% or greater improvement (ie, decrease) in PASI score compared to baseline
sPGA	Static Physician Global Assessment (of psoriasis)
Q1 (Q3)	first quartile (third quartile)
QW	once weekly
RA	rheumatoid arthritis
SC	subcutaneous
SD	standard deviation
SE	standard error
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TNFR:Fc	tumor necrosis factor receptor
USP	United States Pharmacopeia
VZV	aricella zoster virus

I. INTRODUCTION

Follow-up Measure:

Area	Description	Due Date
Clinical	FUM 134: The MAH should submit the results of the multicentre, open-label long term safety trial (study 20050111)	6 months after the completion of the study

The data were reviewed and no update of the Product Information is required (See PVAR circulated 21.8.2012 – see section IV).

The conclusions from the PVAR were that:
The MAH has provided the requested CSR in fulfilment of P46 FUM 134.
No change to the positive benefit:risk balance for Enbrel in paediatric plaque psoriasis nor any changes to the SmPC result from the submitted data.
The MAH is requested to provide responses to the points below.

Based on the data submitted, the MAH should provide response to the following points

1. It is not clear why one case of Crohn's disease AE was considered relate to Enbrel but the other case of Crohn's disease was not considered related and the MAH is asked to comment.
2. For the 28 subjects who are continuing treatment until they reach age 18, the MAH is requested to provide the expected date for this data and commit to providing this additional information

This report addresses the responses to the two additional clarifications requested.

II. SCIENTIFIC DISCUSSION

Assessment of responses

Request 1.

It is not clear why one case of Crohn's disease AE was considered relate to Enbrel but the other case of Crohn's disease was not considered related and the MAH is asked to comment.

Response from MAH:

Relatedness of adverse events to investigational product was a determination made at the discretion of the investigator, and no information was collected on the case report form with regard to how the investigator determined relatedness. The relationship of adverse events to the investigational product was assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the investigational product?' The following descriptions were provided in the protocol to the principle investigator to help guide the decision of whether to choose "yes" or "no" as a response to this question:
No = There is no reasonable possibility that the event may have been caused by investigational product.
The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when investigational product is readministered

• does not follow a temporal sequence from administration of investigational Product

Yes = There is a reasonable possibility that the event may have been caused by investigational product. The adverse event:
• follows a temporal sequence from administration of investigational product
• is a known response to the investigational product based on clinical or preclinical data
• could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
• disappears or decreases upon cessation or reduction of dose of investigational product
• reappears or worsens when investigational product is readministered

The only obvious difference in the 2 cases is that the event that was related was classified as severe whereas the event that was not related was classified as moderate in severity. Neither event was serious and both occurred in patients with a history of psoriatic arthropathy. In summary, the Sponsor/MAH does not have any specific additional information that accounts for the investigator's assignment of relatedness for the 2 cases.

Assessment of response and conclusion

The MAH has no further information on why one case of Crohn's disease AE was considered relate to Enbrel but the other case of Crohn's disease was not considered related. Although this would have been of interest, there is no further information available and the issue will not be pursued.
Issue resolved

Request 2.
For the 28 subjects who are continuing treatment until they reach age 18, the MAH is requested to provide the expected date for this data and commit to providing this additional information.

Response from MAH:

Of the current subjects still enrolled in study 20050111, the last subject turns 18 years old in November 2017. Assuming the last subject remains in the study until this time, the MAH commits to providing the supplemental report, containing the serious adverse event and physician global assessment data for the 28 subjects, in May 2018. The completion date could be sooner if the last subject withdraws from the study before he/she reaches 18 years of age. If so, the MAH commits to providing the supplemental report 6 months after the completion date.

Assessment of response and conclusion

The MAH will provide the data in May 2018 or sooner. Issue resolved

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Recommendation**

The MAH has provided the requested CSR in fulfilment of P46 FUM 134.
No change to the positive benefit:risk balance for Enbrel in paediatric plaque psoriasis nor any changes to the SmPC result from the submitted data.

☒ **Fulfilled –** No further action required