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EMA/20004/2013
Committee for Medicinal Products for Human Use (CHMP)

Enbrel

etanercept

Procedure No. EMEA/H/C/000262/A46/145.1

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

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Rapporteur's Assessment Report for Post-Authorisation Commitments (PACs)

Enbrel
etanercept

EMEA/H/C/262
P46 145.1

Marketing Authorisation Holder: Wyeth

Rapporteur:	Robert Hemmings
Start of the procedure:	25th July 2010
Date of the report:	25th August 2010
Deadline for CHMP member's comments:	6th September 2010

I. ASSESSMENT

Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:
Response to the outstanding question following the assessment of FUM 145 (article 46)

Following the CHMP assessment report for FUM 145 (Paediatric article 46 Follow up measure 145) the final CHMP opinion was circulated on 22nd April 2010. The conclusions of the FUM 145 were:

The data from the long-term study 20021618 has shown that the safety profile for paediatric subjects is consistent with what is known for etanercept. The data submitted in accordance with Article 46 is considered satisfactory and no changes to the SPC are requested.

Long-term efficacy has been demonstrated in adults. The safety profile from this long-term open label study does not give rise to new concerns. Although the SIR for lymphomas in adults is 4.03 compared with the SEER database, this is based on 7 cases, with no control group. The ongoing pharmacovigilance relating to long-term safety with anti-TNF therapies will continue to monitor for safety signals and so no change to the SPC is required as a result of this data. No change to the positive benefit:risk ratio for etanercept follows from this FUM. The PAC is fulfilled with one outstanding question.

While it is likely that efficacy was maintained in those who remained on etanercept, it is difficult to evaluate long-term efficacy after year 6 from the paediatric data. The number of subjects for whom there was efficacy data available after year 6 constitutes a progressively smaller percentage of the patients still in the study at those time points.
The MAH is requested to explain why such little efficacy data was available in the later years of the study for the paediatric subjects.

Assessment

Response to CHMP RSI relating to study 20021618
QUESTION
While it is likely that efficacy was maintained in those who remained on etanercept, it is difficult to evaluate long-term efficacy after year 6 from the paediatric data. The number of subjects for whom there was efficacy data available after year 6 constitutes a progressively smaller percentage of the patients still in the study at those time points. The MAH is requested to explain why such little efficacy data was available in the later years of the study for the paediatric subjects.

MAH RESPONSE
The MAH acknowledges that, in the final years of study 20021618, there was a steady decrease among subjects that were initially enrolled as pediatric subjects and who had efficacy evaluations at the later time points. The number of subjects continuing on study and the number of subjects with efficacy evaluations (JRA Definition of Improvement, JRA-DOI) are presented in Table 1-1, for years 6 through 10.

Table 1-1: Subjects with efficacy evaluations (JRA-DOI) by year

Year (Month) Visit	Availability of DOI (n/N)
6 (72)	27/27
7 (84)	22/26
8 (96)	11/22
9 (108)	6/18
10 (120)	3/14

The Statistical Analysis Plan defined the following study rules for the derivation of JRADOI:

The JRA DOI was not derived if the subject joint count data were recorded on adult joint count case report forms, since the adult joint count assessment captured the number of tender/painful and swollen joints, whereas, the pediatric joint count included pain on motion (POM) and loss or limitation of motion (LOM). The JRA DOI was set to missing in this case. The JRA DOI was assessed according to the following: an improvement of at least 30% (50%, 70%, 90%, and 100%) from baseline in at least 3 of the 6 criteria of the Juvenile Rheumatoid Arthritis Core Set of Response Criteria, and a worsening of greater or equal to 30% in not more than 1 of the following 6 criteria from baseline: Physician's global assessment of disease activity, Subject's/Parent's global assessment of disease activity, number of active joints, CHAQ, CRP, and the number of joints with loss or loss of motion (LOM) plus pain and/or tenderness. No LOCF techniques were used for the JRA DOI response or its components.

As noted in Table 2-4 of the submitted Clinical Overview, Footnote "b", values of the JRA DOI components were not available for all subjects at all time points. The "N" for the JRA DOI assessments per year included those subjects who had any available disease activity measures used for the JRA DOI. Any combination of missing data from the JRA DOI components may have contributed to the low number of subjects that were evaluable.
Taking year 10 as an example, the reason for the absence of JRA-ROI for 11 of the 14 subjects remaining in the trial was that they were older than 17 years at the time of assessment, and thus their data were recorded in the adult case record form, which lacked the component data required to calculate the JRA-DOI score.
It is important to note that, as reflected in Table 2-4 of the Clinical Overview submitted with FUM 145, efficacy appeared to be maintained among those subjects with complete DOI assessments from study years 6 through 10.

Comment: The switch from the paediatric JRA assessment to the adult assessment explains the reduction over time for the older paediatric cases who remained in the study over prolonged periods. The MAH position that the percentages who complete JRA-DOI assessments continue to show evidence of efficacy is accepted. Point resolved.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

FUM 145.1
Overall Conclusion:
The MAH has addressed the clinical question arising from FUM 145, regarding the lower absolute number of patients available for efficacy assessments after year 6. The position that the older paediatric cases that were in the trial until after the age of 18 yrs had their disease activity assessed using the appropriate adult joint assessment, explains much of the reduction in numbers over time.
The MAH response is accepted.

☒ PAC fulfilled (all commitments fulfilled) - No further action required