



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

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

Humira

adalimumab

Procedure no: EMEA/H/C/000481/P46/096

Note

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



1. Introduction

On 17 August 2016, the MAH submitted a clinical study report concerning a completed paediatric study performed in Japan for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Humira and that there is no consequential regulatory action.

2. Scientific discussion

2.1. Clinical aspects

2.1.1. Introduction

The MAH submitted the final study report from the Japanese non-PASS PMOS study P12-706.

2.1.2. Clinical study

Description

Clinical study number and title

HUMIRA® 40 mg syringe 0.8mL for Subcutaneous Injection Special investigation (All-case survey) in patients with Crohn's disease

Methods

The investigation was performed as a single cohort non-interventional observational study, for the purpose of evaluating the safety and effectiveness of adalimumab in patients with Crohn's disease under actual clinical use. Patients with moderate to severe active Crohn's disease not responding to conventional treatment were included.

Adalimumab was administered by subcutaneous injections at a starting dose of 160 mg, and subsequent dose of 80 mg at week 2 and 40 mg eow from week 4.

The observation period for each subject was 24 weeks.

The primary endpoint of the study was safety as determined by the list of adverse reaction and infections.

The secondary endpoint was effectiveness evaluated by CDAI, endoscopic findings and by treating practitioners overall assessment of improvement on completion of the study or discontinuation.

Statistical tests were two-tailed with the significance level 0.05. Statistical methods used were: stepwise multivariate analyses, paired t-test, and Cochran-Armitage test. No adjustment was made for multiple centres because the number of subjects per centre was limited. The primary analysis of the primary safety and effectiveness variable was performed using Observed Case (OC).

Results

Recruitment/ Number analysed

Overall there were 1,716 patients enrolled of whom 1,693 were included in the safety analysis set and 1667 patients in the efficacy analysis set.

Baseline data

Of 1,693 patients included in the safety analysis set, 65.5% (1109/1693) were male and 34.5% (584/1693) were female. The mean age at administration was 35.5 ± 11.7 years, mean BMI was 19.9 ± 3.15 , mean morbidity period of Crohn's disease as of the first administration of adalimumab was 11.1 ± 8.0 years. The reason for use was Crohn's disease in 99.8% (1690/1693), intestinal Bechet's diseases in 0.1% (2/1693), and multiple non-specific small intestine ulcer in 0.1% (1/1693).

At baseline, 110 (6.5%) patients were between the age of 15 and 19 years and 13 (0.8%) patients were younger than 15 years. There were 54 paediatric patients under the age of 18 years ranging between 9 and 17 years of age at baseline.

During the follow-up period, 17.2% (292/1693) of the patients needed discontinuation of adalimumab therapy due to lack of efficacy (37.0%, 108/292), adverse events (28.4%, 83/292), no visit (including hospital transfer) (16.8%, 49/292), patient request (12.7%, 37/1693), and other reasons (5.1%, 15/292).

CHMP comment

No baseline characteristics, demographic data, medical history or reasons for discontinuations have been presented for the paediatric population.

Safety results

During the observation period, 527 adverse drug reactions were reported by 360 patients (21.3%). One hundred twenty-six (126) serious adverse drug reactions were reported by 96 patients (5.7%). 196 serious AEs were reported by 147 (8.7%) patients. Forty-five (45) cases reported by 44 patients were serious infections (2.3%).

Of the 54 paediatric patients fifteen experienced a total of 19 AEs. The most common AEs were CD and upper respiratory tract inflammation which were reported twice, respectively. Three SAEs (CD (2), blood creatine phosphokinase increased) were reported in 2 patients. Five infections were reported (pneumonia, nasopharyngitis, infectious mononucleosis, herpes zoster, influenza) which all were non-serious and which completely resolved or improved during the observation period. No deaths, malignancies, TB, or demyelinating disorder occurred in paediatric patients.

CHMP comment

No new safety issues were identified in the paediatric population included in the study.

Efficacy results

The changes in CDAI scores from baseline to Week 24 in 1667 patients in the effectiveness analysis set, CDAI scores (mean \pm SD) changed from 204.3 ± 105.7 at Week 0 to 142.9 ± 90.4 at Week 4, 142.7 ± 93.8 at Week 8, and 149.1 ± 100.9 at Week 24. CDAI scores at each evaluation time point were significantly lower than the score at Week 0 ($p < 0.0001$, paired t-test).

CHMP comment

Efficacy results have been presented for the whole population included but not for the paediatric population of interest.

2.1.3. Discussion on clinical aspects

Although no new safety issues have been identified in the paediatric population included in the study no data has been presented on the characteristics of the included children or on the efficacy of the treatment in this population. For an evaluation of the benefit risk in the studied population such data should be submitted.

Secondary round

Baseline data paediatric population

Of the 54 paediatric patients included in the study (9 to 18 years of age), the proportion of males was 61 % (33/54 patients).

The largest proportion of patients at baseline had CD of the ileum (72 %) and colon (59 %).

All paediatric patients had received either 5-aminosalicylic acid (92.6%; 50/54 patients), steroids (18.5%; 10/54), or immunosuppressants¹ (11.1%; 6/54) for Crohn's disease prior to this study.

Efficacy results

At week 24, CDAI scores were available from 31 patients. Of these 67.7% (21/31 patients) achieved clinical remission (CDAI < 150).

Treatment discontinuation before the end of observation period, 24 weeks, occurred in 10 pediatric patients. Reasons for the discontinuation were "inadequate response" in 6 patients, "no visit" in 2 and "adverse events" in 2 patients. For 3 of the 6 subjects with an inadequate response at week 24, CDAI scores were < 150 at week 4 but increased thereafter. For 3 patients with an inadequate response there were no CDAI score available. The adverse events that were the causes for discontinuations concerned Liver disorder in one patient and Crohn's disease and Blood creatine phosphokinase increased in one.

2.1.4. Updated discussion on clinical aspects

The requested efficacy data have been submitted. Efficacy was shown in the pediatric population and no new safety concerns were identified.

3. Overall conclusion and recommendation

Overall conclusion

The MAH's conclusion that the submitted paediatric study does not influence the benefit risk for Humira and that there is no consequential regulatory action, is supported.

Recommendation

Fulfilled: No regulatory action required.