30 June 2015
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Procedure Management and Committees Support 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/P46/087

Note

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

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Introduction

On 29 May 2015, the MAH submitted a completed paediatric study for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study was performed in an adult Japanese population. However, the definition of “adult” in Japan differs to that from in Europe and for each of the four studies the minimum age requirement for enrolment was 15 years of age. As such, 3 subjects of what are defined in Europe as “paediatric” patients (i.e. less than 18 years of age) were enrolled.

A short critical expert overview has also been provided. The MAH stated that the submitted paediatric studies do not influence the benefit risk for Humira and that there is no consequential regulatory action.

This report contains the assessment of this study report, with focus on the paediatric patients.

1. Scientific discussion

1.1. Information on the pharmaceutical formulation used in the study

40 mg/0.8 mL syringe for subcutaneous injection.

1.2. Clinical aspects

1.2.1. Introduction

Humira was approved in Japan for treatment of rheumatoid arthritis (RA) in patients showing an inadequate response to conventional therapy, in April2008. One of the conditions of approval of Humira by Japanese regulatory authority (Health, Labour and Welfare Ministry (MHLW)) was request to conduct a large-scale Post Marketing Observational Study (PMOS) to investigate the long-term safety of Humira, particularly associated with the development of infections and malignant tumors.

1.2.2. Clinical study

Clinical study number and title

P12-070:

Special Investigation (Long-term Treatment in Patients with Rheumatoid Arthritis)

Description

Study P12-070 was a single-cohort, non-interventional observational study with objective to collect information on the safety and effectiveness of HUMIRA during a 3-year period for the treatment of RA, to clarify the following:

1) Incidence of adverse drug reactions (ADRs) in the clinical setting

2) Incidence of infections and malignant tumors in the clinical setting

3) Factors affecting the safety and effectiveness of HUMIRA treatment

Study population /Sample size

Patients who had completed the preceding 24-week PMOS (all-case PMOS) were enrolled in this study.

Patients with "Presence" of the below items 1) and 2) were suitable for the study registration.

1) Presence/absence of Humira treatment at the beginning of the survey.

2) Presence/absence of Health Assessment Questionnaire (HAQ) or Modified HAQ (MHAQ) evaluation at baseline.

In Study P12-070 patients were followed up from week 24 to 3 years of treatment. Information on the safety and effectiveness of HUMIRA treatment was collected once every 6 months, using an electronic data capture system or printed case report forms (CRFs).

The following information was collected at the different time points:

1) The history of anti-TNF therapy, Humira treatment, concomitant drug information, including disease-modifying antirheumatic drugs (DMARDs), biologics and glucocorticoids, surgical treatment for RA, effectiveness evaluation (Disease Activity Score 28 4 ESR (DAS28-4 ESR) and MHAQ, and adverse events were collected in CRF once every 6 months from 24 weeks to 3 years after the initiation of Humira.

2) After discontinuation of HUMIRA, the presence or absence of malignant tumors, tuberculosis, serious infection, death, or other adverse events were collected using the Follow-up Questionnaire Form every 6 months to 3 years after the initiation of Humira

Outcomes/endpoints

Primary Endpoint

- Safety:
    - Incidence of ADRs

Secondary Endpoints

- Safety:
    - Factors that might affect the safety oflong-term treatment ofRA with Humira
    - Incidence of malignant tumors and infection
- Effectiveness:
    - Evaluation ofDAS28-4 ESR
    - Evaluation of disease activity by MHAQ
    - Factors that might affect the effectiveness of long-term treatment of RA with Humira

Results

Recruitment / Number analysed

Of the 508 patients included in the safety analysis set, 3 patients were enrolled in the study as < 18 years of age. One patient was enrolled with age of 15 years while two patients were 17 years at enrollment.

Efficacy results

Among the 3 patients enrolled in the study as < 18 years of age, one patient has been excluded from effectiveness analysis set. The following effectiveness results were reported for two subjects enrolled as < 18 yrs. Seventeen years old female patient reported DAS28-4(ESR) of 6.2 at baseline, 2.7 at week 4, 3.7 at week 12, and 4.3 at study discontinuation. The MHAQ result for this patient was reported as 1.6 at baseline and 0.8 at discontinuation. Fifteen years old female patient reported DAS28- 4(ESR) of 5.2 at baseline, 2.9 at week 4, 1.6 at year-1, 1.6 at year-1.5, 1.8 at Year-2, and 2.4 at study discontinuation.

Safety results

Among the 3 patients enrolled in the study as < 18 years of age the following safety events were reported for 1 patient, a 15 years old female that developed nonserious event of skin eruption (urticarial) with causal relationship to study drug assessed as possible with the outcome reported as recovered, and non-serious event of eosinophil count increased with causal relationship assessed as possible and with outcome reported as recovered.

1.2.3. CHMP´s discussion on clinical aspects

Study P12-070 was performed in an adult Japanese population, but due to diverging definitions of adults there were patients included in the study that according to the European definition are regarded as paediatrics.

There were 3 paediatric patients included in the study. One of these experienced a non-serious event of urticaria and eosinophilia, with a possible causal relationship to the drug. The patient recovered.

Due to the limited numbers of paediatric patients in the study, no firm conclusions can be drawn regarding efficacy and safety in the paediatric population. No information indicating any new safety issues has emerged.

2. CHMP's overall conclusion and recommendation

Overall conclusion

The presented data does not change the benefit risk for adalimumab in the paediatric approved indications. No changes are warranted in the SmPC.

Recommendation

No further action required.

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.