13 December 2018
EMA/907573/2019
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/P46/110

Note

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

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1. Introduction

On 24 September 2018, the MAH submitted a completed paediatric study for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study P13-170 PMOS Special Investigation (Long-term treatment CD patients) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

HUMIRA 40 mg Syringe 0.8 mL for Subcutaneous Injection

2.3. Clinical aspects

2.3.1. Introduction

In EU Adalimumab (Humira) is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. In paediatric CD (within EU): Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Safety and effectiveness of adalimumab for CD patients has been investigated in Western patients in three studies: two induction studies (Study M02-403 and Study M04-691) and one maintenance study (Study M02-404). Similar results were obtained in Japanese clinical studies (induction therapy: Study M04-729, maintenance therapy: Study M06-837). The application to add the CD indication to the Humira label in Japan was made in September 2009, and the indication was approved in October 2010. The investigation described in this document was performed after approval for the purpose of evaluating the safety and effectiveness of HUMIRA under actual clinical practice conditions.

This surveillance study was conducted as a post-approval commitment following the approval of CD, per the Pharmaceuticals and Medical Devices Agency's (PMDA) requirement for such studies when new compounds or new indications are approved.

Dosage and Administration of Crohn's Disease in Japan

The initial dose of adalimumab for adult Crohn's Disease patients is 160 mg as subcutaneous injection. The initial dose is followed by 80 mg 2 weeks later. Four weeks after the initial dose begin a maintenance dose of 40 mg every other week. The dose may be increased to 80 mg administered eow when the effect of treatment with 40 mg eow is decreased.

The MAH submitted a final report for:

- Study P13-170; Long-term treatment CD patients

2.3.2. Clinical study

Study P13-170; Long-term treatment CD patients

Description

Study design

This was a single-arm, multicentre, prospective cohort study (post marketing observational study). The observation period was up to 3 years.

This study was conducted from November 2011 to March 2017. The enrollment period of subjects was from November 2011 to October 2013.

Methods

Objective(s)

This investigation was to be conducted to obtain the following information regarding the use of Humira 40 mg Syringe 0.8 mL for Subcutaneous Injection, on the safety (especially profile of malignant tumours and serious infections) and effectiveness in patients with Crohn's disease who are receiving Humira for an extended period of time.

Study population /Sample size

A total of 511 patients were enrolled. Among the enrolled patients, case report forms were not collected from 7 patients, so there were 504 patients whose data in case report forms were assessable.

From the 504 patients for whom case report forms were obtained, 389 patients were evaluable for the safety analysis, after the exclusion of a total of 115 patients as follows (more than one reason could be provided for exclusion): 2 patients treated with Humira before the contract for the survey ("treated before contract") were excluded, 111 patients who were overdue for the time frame for registration (14 days) defined in the protocol ("violation of registration criteria: deviation from registration period"), 3 patients with malignancy before the registration ("violation of protocol criteria: malignancy"). A total of 310 patients were evaluable for the efficacy analysis, after 79 patients ("efficacy assessment impossible") were excluded from the 389 patients who made up the safety analysis set.

Among the 389 patients included in the safety analysis set, there was 1 patient under 15 years old (14years old), 17 patients between 15 and 17 years old, 366 patients between 18 and 64 years old, and 5 patients over 65 years old.

Table 1 Dose and Exposure Duration of Adalimumab in the paediatric Population in Study P13-170

No.	Sex	Age	Dose (mg)*	Duration (Days)
1	Male	17	160→80→40	846
2	Male	17	160→80→40	1093
3	Male	17	160→80→40	1093
4	Male	17	160→80→40	1093
5	Male	16	160→80→40	1093
6	Male	17	160→80→40	158
7	Male	14	160→80→40	1093
8	Male	16	160→80→40	1093
9	Female	17	160→80→40	1093
10	Female	17	160→80→40	967
11	Female	15	160→80→40	1093
12	Female	17	160→80→40	1013
13	Female	15	160→80→40	1093
14	Female	15	160→80→40	115
15	Male	15	160→80→40	72
16	Male	16	160→80→40→160**→80→40→80***	1093
17	Female	17	160→80→40	1093
18	Male	15	160→80→40	1093
			Mean	904.8
			SD	358.9
			Median	1093.0

* Dosage and administration of Crohn's disease in Japan.

The initial dose of adalimumab for adult Crohn's Disease patients is 160 mg as subcutaneous injection. The initial dose is followed by 80 mg 2 weeks later. Four weeks after the initial dose begin a maintenance dose of 40 mg every other week. The dose may be increased to 80 mg administered eow when the effect of treatment with 40 mg eow is decreased.

** Reintroduced for symptom recurrence.

*** Increased due to lack of efficacy.

Treatments

Humira as described above.

Outcomes/endpoints

Primary Endpoints Related to Safety

Number of patients with adverse events [Time Frame: Up to Year 3]

Secondary Endpoints Related to Efficacy

1. Crohn's Disease Activity Index [Time Frame: Up to Year 3]

2. Work Productivity and Activity Impairment Questionnaire [Time Frame: Up to Year 3]

3. C-reactive Protein [Time Frame: Up to Year 3]

4. Endoscopy [Time Frame: Up to Year 3]

Statistical Methods

N/A

Results

Recruitment/ Number analysed

Adalimumab was administered for 793.4 ± 402.8 (Mean ± SD), 1093.0 days (median) in the safety population.

Persistence rate at 52 weeks was 61.7%; patients discontinued adalimumab due to several reasons.

Efficacy results

CDAI Remission Rate at the Final Assessment (CDAI < 150)

310 patients were included in the efficacy analysis set after 79 patients ("efficacy assessment impossible") were excluded from the 389 patients who made up the safety analysis set. Overall, 212 of the 310 patients included in the efficacy analysis (68.4%) were in remission (CDAI < 150) at their final visit.

15 paediatric patients were included in the efficacy analysis set after 3 patients ("efficacy assessment impossible") were excluded from the 18 paediatric patients who were included in the safety analysis set. 11 of the 15 paediatric patients included in the efficacy analysis (73.3%) were in remission (CDAI < 150) at their final visit.

Safety results

Incidences of ADRs

Among the 389 patients included in the safety analysis set, 157 adverse reactions were noted in 105 patients; the percentage of patients who experienced adverse reactions during the study was 26.99%.

Common adverse reactions by system organ class of adverse reactions (MedDRA SOC: ≥ 10 patients) and their incidence rates were "infections and infestations" (9.51%, 37/389), "gastrointestinal disorders" (6.94%, 27/389), "general disorders and administration site conditions" (3.86%, 15/389), "skin and subcutaneous tissue disorders" and "Lab tests" (3.60%, 14/389 each).

Common adverse reactions by preferred term (MedDRA PT: ≥ 5 cases) and their incidence rates were "Crohn's disease" (2.57%, 10/389), "upper respiratory tract inflammation," "Nasopharyngitis," and "C-reactive protein increased" (1.54%, 43/389 each).

Serious ADRs

Of the 389 patients in the safety analysis set, 53 serious adverse reactions were noted in 43 patients, the incidence rate of serious adverse reactions was 11.05% (43/389).

Common adverse reactions by system organ class (MedDRA SOC: ≥ 10 patients) and their incidence rates were "gastrointestinal disorders" (4.88%, 19/389), and "infections and infestations" (4.37%,

17/389) and the common serious adverse reaction by preferred term (MedDRA PT: ≥ 5 patients) and its incidence rate was "Crohn's disease" (1.29%, 5/389).

Paediatric population

Across the paediatric population (N = 18), a total of 15 adverse events (AEs) were noted in 9 paediatric patients (50.0%). The age range of 9 paediatric patients with AEs was 16.1 years old. The age of the paediatric patients with AEs were: 3 patients at 15 years old, 2 patients at 16 years old, and 4 patients at 17 years old. A total of 14 non-serious adverse events and 1 serious adverse event (SAE) were observed, which corresponded to an overall observed rate of 30.43 events (E)/100 patient-treatment years (PTYs) and 2.17 E/100 PTYs, respectively.

Case: Fracture (SAE)

A 15-year-old male with a history of CD, enteral nutrition treatment for an unknown duration, who had received Humira (160 mg, 80 mg and 40 mg) for approximately 2 months, experienced a bone fracture due to traumatic injury. Humira was discontinued due to the surgery, and the reporting physician did not consider the event related to Humira. The event resolved with surgery.

The single cases of "mycoplasmal tracheobronchitis" and "pneumonia" are described below.

Case: Mycoplasmal tracheobronchitis

A 17-year-old female with a history of CD, who had received Humira (160 mg, 80 mg and 40 mg) for approximately 2 years and 8 months, experienced pyrexia, runny nose and cough. The diagnosis of mycoplasmal tracheobronchitis was confirmed with a chest x-ray. Humira was discontinued due to the event and an antimicrobial agent administered for 1 week. The event outcome was improved.

Case: Pneumonia

A 16-year-old male with a history of CD, enteral nutrition treatment for an unknown duration, who had received Humira (160 mg, 80 mg and 40 mg) for approximately 2 years and 4 months, experienced pyrexia and cough. The influenza test was negative; the diagnosis of pneumonia was confirmed with a chest x-ray. Antimicrobial agents were administered for 10 days. The event outcome was improved.

Table 2 AE and SAE Rate per 100 PTY in the paediatric Population

	Serious adverse events		Non-serious adverse events	
N	18		18	
Events	1		14	
Total Years	46.00			
100 PTY	2.17		30.43	
PT term	Events	100 PTY	Events	100 PTY
Pancreatic enzymes increased	0	0.00	1	2.17
Upper respiratory tract inflammation	0	0.00	1	2.17
Constipation	0	0.00	1	2.17
C-reactive protein increased	0	0.00	2	4.35
Anal fistula	0	0.00	1	2.17
Pyrexia	0	0.00	1	2.17
Tracheobronchitis mycoplasmal	0	0.00	1	2.17
Fracture	1	2.17	0	0.00
Pneumonia	0	0.00	1	2.17
Headache	0	0.00	1	2.17
Cough	0	0.00	1	2.17
Crohn's disease	0	0.00	1	2.17
Stomatitis	0	0.00	1	2.17
Injection site reaction	0	0.00	1	2.17

CHMP's comment:

The safety results in this study are considered to be in line with the known safety profile for adalimumab. The safety profile in the small group of 18 paediatric patients did not differ from the overall known safety profile. It is agreed that the serious adverse event with a fracture is not related to adalimumab treatment.

2.3.3. Discussion on clinical aspects

MAH Discussion

Safety

In this surveillance study, the safety profile of Humira in CD remained similar to that established in the controlled clinical trials in adult patients with CD; no new safety signals were observed and the incidence rate of adverse events in adult and paediatric patients did not increase. The adverse events of special interest as determined in the study protocol did not reveal any new risks.

Efficacy

Efficacy was comparable to that seen in the controlled clinical studies, including in patients below 18 years of age.

The findings of this post marketing observational study support the conclusion that adalimumab is effective for the treatment of CD in Japanese patients, and that efficacy is sustained over time. There were no new safety signals observed, and the data are consistent with the known safety profile of adalimumab in adult and paediatric CD and the other approved indications.

Although the approved CD indication in Japan is for adults, the regulatory agency requested that all patients, i.e., including paediatric patients, should be included in this study. Paediatric patients in Japan are defined as < 15 years of age whereas in the Western world, the age cut-off is usually 18 years. In this surveillance study, 1 patient was below the age of 15, and 18 patients in total were below 18 years of age. No specific safety findings were seen in those patients.

3. CHMP overall conclusion and recommendation

Overall conclusion

There were no new safety signals revealed in this study. In the small group of 18 paediatric patients the efficacy and safety profile was in line with earlier experience and in line with the description in the SmPC.

The benefit/risk ratio of adalimumab for the treatment of CD remains unchanged.

Recommendation

☒ **Fulfilled:**

No regulatory action required.