London, 18 October 2018
EMA/CHMP/777619/2018
Committee for Medicinal Products for Human Use (CHMP)

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/P46/108

Note

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

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1. Introduction

On 29 July 2018 the MAH submitted data available from patients less than 18 years of age, recruited in study P12-764, 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

Marketing approval for Humira in Ankylosing spondylitis (AS) was obtained in the EU in June 2006 and in the US in July 2006.

In Japan, the indication of AS was applied for approval in October 2009, and was approved in October 2010.There was an instruction as the condition for approval of the additional indication of AS: "Since the number of clinical trial subjects in Japan is very limited, the background information of patients using this drug should be kept track of by conducting a use-results survey in all cases until data for a certain number of cases are accumulated after marketing, and data on the safety and effectiveness of this drug should be obtained early and necessary measures for the proper use of this drug should be taken". Therefore, this surveillance was conducted. It is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Humira 40mg for subcutaneous administration

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study;" Special Investigation (All Cases Investigation in Patients With Ankylosing Spondylitis)"

2.3.2. Clinical study P12-764:

Special Investigation (All Cases Investigation in Patients With Ankylosing Spondylitis)

Description

The study P12-764 was a single-arm, multicenter, prospective cohort study (post marketing observational study). The observation period was 24 weeks.

Methods

Objectives

The following parameters of safety and efficacy in patients with AS receiving Humira were investigated:

1. ADRs unexpected from PRECAUTIONS (especially clinically significant adverse drug reactions)

2. Incidence and conditions of occurrence of adverse drug reactions in the clinical setting
3. Factors that may affect the safety and effectiveness of Humira.

Important items of investigation were development of infections, tuberculosis, malignant tumor, administration site reactions, autoimmune diseases, pancytopenia, demyelinating disease, congenital heart failure, and interstitial pneumonia.

Study design

The study was designed as a non-interventional observational study. The study employed a central registration system to reduce possible selection bias.

This surveillance was conducted from October 2010 to May 2017. The registration period of subjects was from 10 October 2010 to 28 May 2015.

Study population /Sample size

Inclusion Criteria

Patients receiving Humira for the treatment of AS after the approval of the indication were to be all enrolled.

Exclusion Criteria

Contraindications according to the Package Insert:

- Patients who have serious infections
- Patients who have tuberculosis
- Patients with a history of hypersensitivity to any ingredient of Humira
- Patients who have demyelinating disease or with a history of demyelinating disease
- Patients who have congestive cardiac failure

Treatments

The "Dosage and Administration" in the package insert is "The usual adult dose is 40 mg of adalimumab (genetical recombination) given by subcutaneous injection once in 2 weeks. If the response is inadequate, the dose may be increased up to 80 mg per time." As described below, adalimumab was used according to the dosage/administration in most cases. In addition, 11 subjects had dosing intervals increased to 40 mg/3 weeks or 40 mg/4 weeks per time.

The proportion of dosage/administration "40 mg/2 weeks" was 93.7% (371/396) and the proportion of "initial dose 40 mg/2 weeks and subsequently 40 mg/2 weeks or 80 mg/2 weeks" was 1.3% (5/396).

Assessor's comment: The vast majority of patients administered Humira 40 mg eow. It is assumed that this was the dosing of the included paediatric subjects as well, however, this information was not provided, which is a shortcoming.

Outcomes/endpoints

Primary Endpoints

(Safety)

- The number and percentage (%) of patients who reported any adverse drug reactions (ADR) during this study.
- The number and percentage (%) of patients who reported any ADRs classified according to background factors (Demographics, Treatment Factors, Concomitant medications etc.).
- Profile of ADRs before and after increase in Humira dose.
- Adverse events (AE) occurring during or after the treatment period.
- List of cases of serious AEs.
- Errors in administration during self-injection.

Secondary Endpoint

(Effectiveness)

- The percentage (%) of overall improvement by physicians at 12 weeks and 24 weeks.
- Change in BASDAI from baseline to 24weeks.
- The number and percentage (%) of patients achieving "improvement"; overall improvement by physicians at last evaluation, classified according to background factors (Demographics, Treatment Factors, Concomitant medications etc.).

Statistical Methods

This was an observational study; therefore, the analyses will primarily involve the generation of descriptive summary statistics.

Results

Recruitment/ Number analysed

403 subjects were registered. 396 subjects were included in safety analysis and 374 subjects were included in efficacy analysis.

There were 8 young subjects (18 years of age or younger), of which 6 were paediatric patients under 18 years of age who participated in this study.

Baseline data

Efficacy results

In the 374 subjects included in efficacy analysis, the overall improvement rating "Markedly improved or improved" was seen in 89.5% (257/287) at 12 weeks after the start of treatment and 91.0% (292/321) at 24 weeks after the start of treatment.

Assessor's comment*:* No efficacy data for the 6 paediatric patients were provided. This is acceptable.

Safety results

In the 396 subjects included in safety analysis, there were 144 reports of adverse drug reactions in 101 subjects, and the incidence rate of adverse drug reactions was 25.51% (101/396). The rate was not higher than 97.56% (40/41), than the incidence rate of ADRs by the time of approval.

In the 396 subjects included in safety analysis, there were 15 reports of serious adverse drug reactions in 15 subjects, and the incidence rate of serious adverse drug reactions was 3.79%. Events for which 2 or more reports were made were 2 reports of "Bronchitis" (outcome: resolved) in 2 subjects.

Two out of 8 young subjects, ranging in age from 15 to 18, (25.0%) experienced AEs. None of these subjects experienced SAEs.

Table 1. List of Patients the Age of 18 and Under

No.	Sex	Age	Discontinuation, Present/ Absent	Disease Name (MedDRA PT Term)	Seriousness	Causal Relationship	Outcome
1	F	17	Absent	Nasopharyngitis	Nonserious	Unrelated	Improved
2	M	18	Absent	Injection site reaction	Nonserious	Related	Improved
3	F	18	Absent				
4	M	17	Absent				
5	M	17	Absent				
6	F	15	Absent				
7	M	16	Absent				
8	M	16	Absent				

Assessor's comment: It appears that 2 of the 8 young subjects were in fact 18 years old, and thus 6 paediatric patients were included. None of these was younger than 15 years old. Of these, 1 experienced a nasopharyngitis and 1 an injections site reaction.

2.3.3. Discussion on clinical aspects

Study P12-764 was an observational study in Japanese patients with ankylosing spondylitis. The objectives were to confirm efficacy and safety in Japanese subjects with active AS. The study included almost 400 subjects, of which 8 young subjects ranged in age from 15 to 18 years. Of these young subjects, 6 were considered paediatric (3 subjects were 17, 2 were 16 and 1 was 15 years of age). Two of these young subjects experienced one AE each, one nasopharyngitis and one injection site reaction. None of these subjects experienced SAEs.

The MAH concludes that the small number of paediatric patients enrolled limits interpretation of the data from the patient population. There were no new safety signals observed and the data are consistent with the known safety profile of adalimumab.

The Rapporteur notes that no information on the dosing of these subjects has been provided, which is a shortcoming. However, it is assumed that they received 40mg sc. every other week, like the vast majority of the adult subjects included in the study. Since the low number of subjects (six paediatrics)

precludes any conclusions on safety to be drawn it does not seem meaningful to request clarification on this point, and this issue is not further pursued.

It is agreed with the MAH that no new safety signals that warrant changes in the safety information regarding children have emerged in this study.

3. Rapporteur's overall conclusion and recommendation

The data that can be extracted from the 6 paediatric subjects are very limited. However, it is agreed with the applicant that no data that changes the B/R balance of the product or warrants changes to the PI or RMP has been retrieved. No further actions are required.

☒ Fulfilled:

No regulatory action required.