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/P46/098

Note

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


This surveillance was conducted in compliance with the New Drug Re-examination Guideline (MFDS notification No. 2015-79) in Korea.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The Post-Marketing Observational Study P14-362 in Korean patients with Juvenile idiopathic arthritis (JIA) is a stand-alone study. The study population included 28 subjects, 13 subjects were <18 years.

1.2. Information on the pharmaceutical formulation used in the study

Humira was to be administered in accordance with the approved SmPC.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report(s) for: P14-362, Post-Marketing Surveillance of Humira Injection in Korean JIA Patients under the "New-Drug Re-examination.

Humira (Adalimumab) is an anti-TNF monoclonal antibody. Humira was first approved by the Food and Drug Administration (FDA) for the treatment of the subjects with RA in the United States (US) in December 2002 and in the 15 European Adalimumab Union (EU) countries in September 2003, and 10 EU accession countries in May 2004. To date, Humira is approved in 90 countries worldwide. There currently approved European SmPC includes two JIA indications: Polyarticular juvenile idiopathic arthritis and Enthesitis-related arthritis. In Korea, Humira was approved for polyarticular juvenile idiopathic arthritis on 10 August 2012 and subsequently approved for enthesitis-related arthritis (ERA) on 14 December 2015.

1.3.2. Clinical study P14-362

Methods

Objective(s)

The objective of this surveillance is to evaluate the following items regarding the safety profile of Humira for JIA patients in normal medical practice:

1. Serious adverse event • adverse drug reaction
2. Unexpected adverse event • adverse drug reaction
3. Already known adverse drug reaction
4. Non-serious adverse drug reaction
5. Adverse events profile resulting from drug misuse, drug abuse or drug interaction
6. Other information related to the product's safety and effectiveness (including the influence to the laboratory value)

**Study design**

This study was conducted at the institutions which provide a written agreement to AbbVie Korea, and where the use of Humira for JIA was following their normal medical practice setting. Pediatric patients who were prescribed Humira as per physician's medical judgment were registered to the study and be administered Humira in accordance with the approved SmPC.

Patients were observed for a minimum of 3 months following first dose of Humira Injection.

It was planned to include all patients who were treated with Humira until the planned number of cases were collected to obtain meaningful data on safety profile including TB incidence in the early stage of the study conduction. Once this surveillance had been initiated in an institution, physicians were recommended to include/recruit all patients who were prescribed Humira. An evaluable patient was a patient who had been administered Humira at least once and had safety information at subsequent visits (or telephone contact, correspondence). Drop-out patients were also considered for safety evaluation, if the safety information was obtained by follow-up contact. If there was loss of follow-up, the reason was recorded.

Once the study agreement had been in place, the surveillance was initiated at the site. The enrollment method changed from consecutive method to non-consecutive method, thus all subjects who were prescribed Humira were enrolled during the surveillance period at each site.

**Study population /Sample size**

Physician referred to the product market authorization (label) for inclusion and exclusion criteria.

**Inclusion Criteria**

1. Patients from 2 years of age who were diagnosed with polyarticular juvenile idiopathic arthritis (JIA) or patients from 6 years of age who were diagnosed with enthesitis-related arthritis (ERA).
2. Polyarticular juvenile idiopathic arthritis (JIA) patients for whom the response to previous disease-modifying anti rheumatic drug therapy had been inadequate.
3. Patients who give written authorization form to use their personal and health data from legal parents or representative.

**Exclusion Criteria**

Patient with any of the following was not registered in this surveillance:

1. Patients with known hypersensitivity to Humira or any of its excipients.
2. Patients who is participating on other clinical trials.

**Variables; baseline characteristics, treatments and outcomes/endpoints**

Basic demographics (patient initials, age, sex, name of institution, department and physician) were taken and recorded.
Diagnosis and medical history including previous TB history or vaccination were taken and recorded and included: weight, height, date of JIA diagnosis, duration of symptoms, previous therapy history including DMARD, NSAIDs and steroids history.

PPD skin test was performed and recorded. Chest x-ray interpretation result was taken and recorded.

Patients were administered Humira Injection as per the package label. Concomitant medications, including TB prophylaxis regimen, NSAIDs, steroids, were recorded and included: generic name (brand name in case of combination drug), total daily dose, length of administration (start date and end date), and indication(s).

Presence of adverse event(s), type of adverse event(s), onset, end date, severity, causality assessment by physician on the adverse event(s), action taken, outcome, were captured, whether it is related to the drug or not, during the study (after informed consent or first administration of Humira) and for 70 days following the last scheduled administration of Humira Injection.

Patients were eligible for effectiveness evaluation if treated with Humira for 12 (± 4) weeks and had effectiveness data (i.e., Active joint status [0 – 68] data at inclusion and at 12 (± 4) weeks post-treatment, Investigator's global assessment and Parent's global assessment data at 12 (± 4) weeks post-treatment) as below. However, for the patients treated previously with Humira Injection before inclusion, the effectiveness information shall be collected according to the following:

- When administration period of Humira Injection is 12 weeks or less: Active Joint status (0 - 68) data prior to the first administration and at 12 weeks (± 4 weeks) post-treatment, Investigator’s global assessment and Parent’s global assessment information at 12 weeks (± 4 weeks) post-treatment
- When Humira has been administered for more than 12 weeks: a) Active Joint status (0 - 68) data prior to the first administration and at 12 weeks (± 4 weeks) after the first administration, b) Active Joint status (0 - 68) data at inclusion and at 12 weeks (± 4 weeks) following the initiation of surveillance, Investigator’s global assessment and Parent’s global assessment at 12 weeks (± 4 weeks) following the initiation of surveillance

Active joint status

Changes in active joint count between before the administration of Humira and approximately 12 (±4) weeks after the administration of Humira were recorded on the case report form.

Physician’s global assessment

Physician’s global assessment of the disease was taken and recorded approximately 12 (± 4) weeks following the administration of Humira Injection (Improved, Not changed, Aggravated, Not assessable).

Parent’s global assessment

Parent’s global assessment for effectiveness was taken and recorded approximately 12 (± 4) weeks following the administration of Humira Injection (Improved, Not changed, Aggravated, Not assessable).

Study size

At least 600 subjects were to be collected for surveillance to meet the local regulatory requirements, but number of subjects was adjusted to 26 subjects based on the following:
1. Significantly low incidence and prevalence of polyarticular JIA

According to the applicant, there are no exact data relating to prevalence of JIA in Korea. Total number of patients of all ages who was reported to Health Insurance Review & Assessment Service (HIRA) with 'M08 (Juvenile Arthritis)' in 2014 is only 3,559 patients. Only two subtypes among the seven types of Juvenile Arthritis are polyarticular JIA, but there is no specific information on the number of patients of polyarticular JIA. If excluded other subtypes of JIA and considered the age, the prevalence in Korea is estimated to be very low. Also, there is no data of prevalence for age in Korea related to enthesitis-related arthritis (ERA) but according to reference that pediatric enthesitis-related arthritis (ERA) population is about 10% of total JIA population. It is worldwide known as very limited patient population incidence rate between 12.8 and 93.4 per 100,000. Although there are racial/regional differences, annual incidence of JIA in children below 15 years of age is 13.9 patients per 100,000 and prevalence of JIA is 113 patients per 100,000 according to the report from Western region. Considering racial differences, the prevalence in Asian is reported significantly lower than in European (JIA relative risk European 1.25 vs Asian 0.41).

2. Humira is not a primary therapeutic agent for JIA.

The applicant states that according to the HIRA data, total number of patients who was prescribed Humira for JIA is only about 21 patients in 2013, 38 patients in 2014.

3. Difficulties in obtaining guardians consents

JIA is indicated for pediatric patients, it is difficult to get pediatric patients' consents from their parents. Therefore, it was expected to enroll 28 subjects.

**CHMP comment:**

The reasons for the adjusted number of enrolled subjects are acknowledged.

**Statistical Methods**

The safety analysis data set includes all subjects who have received at least one administration of Humira after initiation of surveillance and have follow-up for the safety information.

The effectiveness analysis data set includes all subjects who have been administered Humira and received Humira for not less than 12 (± 4) weeks or more and for whom effectiveness evaluation parameters have been recorded.

The number and percentage of subjects reporting overall adverse events/adverse drug reactions were tabulated and by system organ class and preferred term. The number and percentage of subjects reporting any serious and unexpected (unlabeled) adverse events/adverse drug reactions were tabulated in a similar fashion.

To investigate the factors affecting the safety and effectiveness, the number and percentage of subjects were also classified by various background factors (e.g., demographic factors, treatment factors such as medical history, dosing and administration, concomitant medications, starting of administration before/after the contract date, etc.) and tabulated. If adverse event rate or effectiveness data of the subject who administrated Humira before/after the contract date was statistically significant, it was planned to be divided into subgroups and presented it in the separate category.
Student's one sample t-test, Student's paired t-test or Wilcoxon's signed rank test was conducted on continuous variables according to pre-normality test. For categorical variables, comparison was made by conducting Chi-square test or Fisher's exact test.

<table>
<thead>
<tr>
<th>CHMP comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>The methods are relevant to the study design and results should be viewed as descriptive in nature. Due to the low number of patients included is not meaningful to evaluate background factors affecting the results.</td>
</tr>
</tbody>
</table>

**Results**

**Study period**

The Post-Marketing Surveillance (PMS) study period is from 10 August 2012 through 09 August 2016 based on the date which Humira obtained MFDS approval for extension of JIA indication. The first patient was enrolled on 15 May 2014, and the last visit of the last patient was completed on 29 April 2016.

**Recruitment/ Number analysed**

This PMS was conducted by 11 investigators at 10 sites and The Case Report Forms (CRFs) were retrieved from 28 subjects from 9 study sites during the PMS study period. Nine subjects who didn't have active joint count values at baseline or 12 weeks (2 subjects among those didn't have Physician's global assessment, and Parent's global assessment values as well) were excluded from effectiveness analysis.

**Baseline data**

Among 28 safety evaluation subjects, 14/28 subjects were male. The mean age was 17.68 (± 5.69) years old, and ranged from 8.00 to 34.00 years old, and 64.29% (18/28 subjects) were 10 to less than 19 years old.

The mean duration of JIA symptoms was 101.15 (± 96.85) months ranging from 4.00 months to 408.00 months. The subjects with history of anti-rheumatic therapy including DMARD, NSAIDs and steroids were 92.86% (26/28 subjects). Prior to treatment with Humira, 92.31% (24/26 subjects) had been treated with MTX, 69.23% (18/26 subjects) with Sulfasalazine, 57.69% (15/26 subjects) with Etanercept, 26.92% (7/26 subjects) with Hydroxychloroquine, 19.23% (5/26 subjects) with others, 15.38% (4/26 subjects) with Leflunomide and Abatacept each, and 3.85% (1/26 subjects) with cyclosporine.

Those with past and current medical history were 46.43% (13/28 subjects), and none of the subjects had presence of renal disease, hepatic disease, and allergic history. Those with concomitant medication were 85.71% (24/28 subjects). The most common past/current medical history was uveitis which included 21.43% (6/28 subjects). None of the subjects had presence of active Tuberculosis (TB) history and previous TB History. One subject performed treatment of latent TB. Antineoplastic and immunomodulating agents were listed as concomitant medication in the majority of cases.

The subjects were categorized into 'before participation' when Humira has been administered more than 12 weeks at participation, and had additionally collected past safety and effectiveness data. The subjects were categorized as 'after participation' otherwise. The subjects included in 'before participation' were 53.57% (15/28 subjects), and 'after participation' were 46.43% (13/28 subjects).
The mean length of treatment was 535.04 (± 438.33) days and ranged from 65.00 days through 1,971.00 days. Humira treatment at the last administration was on-going for 92.86% (26/28 subjects). The reason for discontinue/termination of Humira administration was in both cases 'Lack of drug effect.

**Efficacy results**

Active joint count before/after Humira administration on 19 effectiveness evaluation subjects was investigated during baseline visit and following visit. The mean active joint count at baseline visit was 9.63 (± 8.43) and ranged from 0.00 through 30.00. The mean active joint count at following visit was 3.58 (± 6.28) and ranged from 0.00 through 28.00. The mean decrease at baseline visit and following visit was 6.05 (± 6.65), nominal p-value < 0.0001.

Parent's global assessment was 100% (19/19 subjects) 'Improved,' and the Physician's global assessment was 94.74% (18/19 subjects) 'Improved and 5.26% (1/19 subjects) 'Not changed.

In the total effectiveness assessment, 63.16% of patients (12/19) were categorized as "Improved" and 36.84% of patients (7/19) were categorized as "Not Improved.

**CHMP comment**

The results are consistent with previous results indicating efficacy of Humira in the treatment of JIA. However, the generalizability and the conclusions that can be made from the study are limited due to the small population. Efficacy results were summarized by the applicant according to various background factors. However, due to the low number of patients included in this study, it is not meaningful to evaluate how these background factors affect the results.

**Safety results**

A total of 8 adverse events (AEs) in 6 subjects (21.43%) were reported from 28 safety evaluation subjects during this study period. There was one serious adverse event; The Subject had erythema 68 days after Humira was first administered, and was hospitalized from seven days later for 2 days. The symptoms resolved and the subject recovered. Of the adverse events reported during the study period, the unexpected adverse event 'Joint swelling' that was not listed in the product label occurred in one subject.

The most frequently reported adverse event was 'Influenza,' in 3 subjects and the remaining 5 AEs were back pain, joint swelling, erythema, urticaria, and pyrexia which were each reported by a single subject. The outcome of adverse events in 7/8 cases was 'recovered,' and the remaining case had an outcome of 'recovering.

There were 13 pediatric patients under the age of 18 years who participated in this study.

Two of these patients (15.4%) experienced a total of 2 AEs. One pediatric patient (7.7%) experienced back pain, which was considered an adverse drug reaction, and 1 pediatric patient (7.7%) experienced a SAE of erythema, which was not considered an adverse drug reaction.

**CHMP comment**

The number or pattern of AEs reported does not cause any concern given the indication and the investigated age group. Incidence of Adverse Events by different background factors (demographics, medical history and Humira treatment) was summarized but the groups included too few individuals for any meaningful conclusions to be made regarding the association between these factors and the risk of developing different AEs.
1.3.3. Discussion on clinical aspects

The generalizability and the conclusions that can be made from the study are limited due to the small population (28 included subjects, 13 subjects <18 years), especially as the results on effectiveness is based on only 19 patients, which means 32% of the data missing. However, the results are not in conflict with previous results indicating efficacy of Humira in the treatment of JIA and no new safety concerns have emerged. Thus it is agreed with the applicant that the data does not change the benefit/risk of Humira and no updates of the SmPC are warranted.

2. Overall conclusion and recommendation

Overall conclusion and Recommendation

The benefit risk is unchanged and no updates of the SmPC are warranted.

☒ Fulfilled:

No regulatory action required.