EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines 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/P46/01388/1

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	26 May 2025	26 May 2025
☐	CHMP Rapporteur AR	30 June 2025	3 June 2025
☐	CHMP comments	14 July 2025	n/a
☐	Updated CHMP Rapporteur AR	17 July 2025	n/a
☒	CHMP outcome	24 July 2025	24 July 2025

Table of contents

1. Introduction

On 8 May 2025, 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 P20-251 'Post-marketing observational study for Humira in patients diagnosed with Pyoderma Gangrenosum (PG)' is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study drug (Humira) was not provided by the MAH; investigators used commercially available Humira for this study.

2.3. Clinical aspects

2.3.1. Introduction

This procedure concerns submission of the final study report under Article 46 of a post-marketing observational study (Study P20-251) for Humira in patients diagnosed with Pyoderma Gangrenosum (PG) in Japan to fulfil the "Drug Use-Result Survey" regulatory requirement in Japan. In Japan, Humira had previously been approved in various indications, and received approval for the treatment of PG. Humira is the only drug approved for the treatment of PG in Japan. For regulatory approval of Humira for treatment of patients with PG, an open-label, single arm, multicenter Phase 3 trial (M16-119, NCT03311464) was conducted in Japan, and it evaluated the efficacy and safety of Humira in the treatment of active ulcer(s) in Japanese PG subjects.

Pyoderma Gangrenosum is not an approved indication for Humira in the EU.

According to the MAH, Pyoderma Gangrenosum (PG) is a rapidly progressive disease characterized by deep ulcers, predominantly in the lower extremities. PG presents painful, single or multiple lesions, with several clinical variants, in different locations, with a nonspecific histology, which makes the diagnosis challenging and often delayed. Comorbidities of PG include rheumatoid arthritis, inflammatory bowel disease, acute myeloid leukaemia, and Takayasu's arteritis. PG is clinically classified into five types including ulcerative (classic), bullous, pustular, vegetative and peristomal types. Among them, ulcerative type PG is most common, in which the PG lesion rapidly enlarges with central deep ulceration and undermined borders. In Japan, the estimated incidence of PG is roughly 3.0/1 million per year and many PG patients are 50 to 70 years of age.

The safety profile of Humira in Study M16-119 was according to the MAH similar to that in previous studies. However, the study included a limited number of PG patients (22 patients) and targeted only a certain subset of PG type. This non-interventional Post Marketing Observational Study M20-251 was designed to evaluate safety and effectiveness of Humira in PG patients in the real-world setting, with a particular focus on the incidence proportion of infection reported as adverse drug reactions (ADRs).

The MAH submitted a final report for:

- P20-251 'Post-marketing observational study for Humira in patients diagnosed with Pyoderma Gangrenosum (PG)'

2.3.2. Clinical study

P20-251 – Post-marketing observational study for Humira in patients diagnosed with Pyoderma Gangrenosum (PG)

Description

Study P20-251 was an unblinded, prospective, non-interventional, non-comparative postmarketing surveillance conducted in accordance with good post-marketing study practice Ministerial Ordinance of the Pharmaceuticals and Medical Devices Agency of Japan. PG patients who were prescribed Humira as per investigator's medical judgment in accordance with the approved label in Japan were registered in a multicenter, central registration system. Subjects were followed for safety and effectiveness evaluation up to 52 weeks following the first dose of Humira. Data was collected via registration form and case report form completed by participating physicians based on routine medical records.

The study drug (Humira) was not provided by the MAH; investigators used commercially available Humira for this study. Investigators prescribed Humira to the subjects according to the package insert of Humira. Humira self-injection was allowed if investigators completed with the required measure explained on the package insert.

Methods

Outcomes/endpoints

The primary study endpoint was incidence proportion of all infections reported as ADR during observation period.

Results

Two patients less than 18 years of age were included in the safety analysis population.

Of the 67 patients in the safety analysis set, the mean age was 61.9 years, 50.7% were male, 53.7% were ≥ 65 years, and 92.5% had ulcerative type of PG. Efficacy analysis set was 60 patients. Of these, 27 (45%) patients received treatment for 52 weeks, mean treatment duration was 253.5 days.

Efficacy results

The proportion of subjects who achieved PGA (Physician's Global Assessment) 0 or 1 [95% CI] at week 52 was 59.3% [38.8, 77.6] (16/27 subjects), and the proportion of subjects who achieved PGA (target lesion) 0 or 1 [95% CI] was 65.4% [44.3, 82.8] (17/26 subjects).

The proportion of patients who achieved IIA (Investigator Inflammation Assessment) score 0 for both erythema and border elevation [95% CI] was 50.0% [29.9, 70.1] (13/26 patients).

The mean VRS (Verbal Rating Scale) score [standard deviation] was 1.8 [0.9] at the start of treatment, 0.6 [0.7] at Week 26, 0.5 [0.5] at Week 52, and 0.8 [1.0] at the discontinuation of treatment, suggesting that this drug improved pain.

Recurrences of ulcers were not observed in any patient during the observation period in this survey.

Based on the above, a certain tendency toward improvement in clinical symptoms was observed at Week 52 of administration of Humira according to the MAH.

Paediatric Data

Two patients less than 18 years of age were included in the safety analysis population, neither of whom reported ADRs.

Case information for the two patients is provided below.

6-10-year-old, male

This patient weighed <45 kg, had the disease for 1 year and had 10 lesions in total. The subject had no past medical history and had comorbidities of a neurodevelopmental disorder and ulcerative colitis. Prior medications (oral or injectable) for PG included predonine 6 mg/day, cyclosporine, biological agents, acetaminophen, and ibuprofen. Concomitant medications (oral or injectable) included acetaminophen and ibuprofen. No adverse events were reported for this subject.

16 -<18-year-old, female

This patient had the disease for 1 year and had 2 lesions in total (weigh was not reported). The subject had no past medical history and comorbidities. Prednisolone 20 mg/day was reported as a prior and concomitant medication. No adverse events were reported for this subject.

Safety results

The occurrence status of ADRs included 22 ADRs in 14 patients, including 12 ADRs of infections in 10 patients.

Seven events of serious infection were reported as ADRs in 6 patients. The events were pneumonia, urinary tract infection, Fournier's gangrene, pyelonephritis, sepsis, tuberculosis, and cytomegalovirus enterocolitis in 1 patient each.

According to the MAH, no new safety signals were identified from the above, confirming that the treatment of PG by the use of Humira is manageable in daily medical practice. The MAH continues to monitor the occurrence of known ADRs such as serious infections.

Conclusions by the MAH

No new safety signals were identified. The results from Study P20-251 support the safety and effectiveness of Humira for patients with PG in daily practice in Japan. The safety results are consistent with the current safety profile as described in the Humira product label, the benefit-risk profile of Humira is unchanged, and no updates to the Humira Summary of Product Characteristics have been proposed due to the results of this study.

2.3.3. Discussion on clinical aspects

Two patients less than 18 years of age were included in the safety analysis population. Pyoderma Gangrenosum is not an approved indication for Humira in the EU.

Study P20-251 was an unblinded, prospective, non-interventional, non-comparative postmarketing surveillance conducted in accordance with good post-marketing study practice Ministerial Ordinance of the Pharmaceuticals and Medical Devices Agency of Japan. PG patients who were prescribed Humira as

per investigator's medical judgment in accordance with the approved label in Japan were registered in a multicenter, central registration system. Subjects were followed for safety and effectiveness evaluation up to 52 weeks following the first dose of Humira. Data was collected via registration form and case report form completed by participating physicians based on routine medical records.

The primary study endpoint was incidence proportion of all infections reported as ADR during observation period.

Of the 67 patients in the safety analysis set, the mean age was 61.9 years, 50.7% were male, 53.7% were ≥ 65 years, and 92.5% had ulcerative type of PG.

Of the two patients less than 18 years of age included in the safety analysis population, neither reported ADRs.

6-10-year-old, male

This patient weighed <45 kg, had the disease for 1 year and had 10 lesions in total. The subject had no past medical history and had comorbidities of a neurodevelopmental disorder and ulcerative colitis. Prior medications (oral or injectable) for PG included predonine 6 mg/day, cyclosporine, biological agents, acetaminophen, and ibuprofen. Concomitant medications (oral or injectable) included acetaminophen and ibuprofen. No adverse events were reported for this subject.

16 -<18-year-old, female

This patient had the disease for 1 year and had 2 lesions in total (weigh was not reported). The subject had no past medical history and comorbidities. Prednisolone 20 mg/day was reported as a prior and concomitant medication. No adverse events were reported for this subject.

No new safety signals were identified by the MAH. The benefit-risk of Humira is unchanged and no update to the Summary of Product Characteristics has been proposed because of these data. This is supported by the CHMP.

3. CHMP overall conclusion and recommendation

Two patients less than 18 years of age were included in the safety analysis population. Pyoderma Gangrenosum is not an approved indication for Humira in the EU. No new relevant findings of clinical efficacy or safety were observed in the performed post-marketing non-interventional study of subjects with Pyoderma Gangrenosum in Japan. The submission of this data under Article 46 is acknowledged and appreciated. No update to the Product Information is required based on the reported study. The benefit-risk balance for Humira remains unchanged and positive.

☒ **Fulfilled:**

No regulatory action required.