18 December 2013
EMA/CHMP/758439/2013
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Humira (adalimumab)

Procedure No. EMEA/H/C/000481/II/0125

Marketing authorisation holder (MAH): AbbVie Ltd.

## Note

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

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# 1. Background information on the procedure

## *1.1. Requested Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 19 September 2013 an application for a variation.

This application concerns the following medicinal product:

| Medicinal product: | International non-proprietary name: | Presentations: |
|---|---|---|
| Humira | adalimumab | See Annex A |

The following variation was requested:

| **Variation requested** | | **Type** |
|---|---|---|
| C.I.13 | Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | II |

Submission of the final clinical study report for M10-444 (data up to Week 120): Compassionate use study of adalimumab in children 2 to < 4 years old or age 4 and above weighing less than 15 kg with active juvenile idiopathic arthritis (JIA) in order to fulfil the requirement of article 46 of the paediatric regulation.

The requested variation did not propose amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: K Dunder

## *1.2. Steps taken for the assessment*

| | |
|---|---|
| Submission date: | 19 September 2013 |
| Start of procedure: | 20 October 2013 |
| Rapporteur's preliminary assessment report circulated on: | 28 November 2013 |
| CHMP opinion: | 19 December 2013 |

# 2. Scientific discussion

## *2.1. Introduction*

Adalimumab (Humira) is a recombinant human immunoglobulin (IgG1) monoclonal antibody that neutralizes the biological function of TNF. Humira is indicated for treatment of moderate to severe active rheumatoid arthritis (RA), active and progressive psoriatic arthritis (PsA), severe active ankylosing spondylitis (AS), Axial spondyloarthritis without radiographic evidence of AS, severe active Crohn's disease (CD), moderate to severe active ulcerative colitis (UC) and moderate to severe chronic plaque psoriasis (Ps). In the EU, adalimumab was approved for children 13 to 17 years of age on 25 August 2008, for children 4 to 12 years of age on 18 March 2011, and for children 2 to 4 years of age on 25 February 2013.

As part of Paediatric Investigation Plan (PIP) requirement of the European Medicines Agency, AbbVie conducted Study M10-144 to collect safety, efficacy, and pharmacokinetic (PK) data in up to 30 subjects 2 to < 4 years of age and subjects ≥ 4 years of age that weigh < 15 kg with moderately to severely active polyarticular or polyarticular course JIA. The interim CSR Clinical Study Report was submitted as part of the variation (EMEA/H/C/481/II/102 approved on 25/02/201325/02/2013) to extend the indication for adalimumab as a treatment for paediatric subjects with moderately to severely active polyarticular JIA from 4 to 17 years to 2 to 17 years. As part of the response to the CHMP's Request for Supplementary Information received during review of this variation, further safety and efficacy data up to Week 60 were submitted in November 2012.

The final clinical study report for this study has now been provided presenting data from up to 120 weeks treatment. This AR will discuss the safety aspects of this study. Since the interim report from 60 Weeks treatment was thoroughly reviewed within the approval process of variation 102, focus will be on the final part of the study.

## *2.2. Clinical Safety aspects*

### 2.2.1. Methods – analysis of data submitted

The primary objective of the phase 3b, open-label (OL), multicenter study M10-444 *'Compassionate Use Study of Adalimumab in Children 2 to < 4 Years Old or Age 4 and Above Weighing Less Than 15 kg with Active Juvenile Idiopathic Arthritis (JIA)'* was to evaluate the safety of adalimumab, specifically the incidence of serious adverse events (SAEs) and adverse events (AEs). The secondary objectives of the study were to collect pharmacokinetic (PK) data (including anti-adalimumab antibody analysis [AAA] for analysis) and to evaluate the effectiveness of adalimumab in these paediatric subjects.

A total of 32 subjects were enrolled at 14 study sites in the United States, France, the Czech Republic, and Germany. The first subject first visit was 24 March 2009 and the last subject last visit was 21 March 2013. All subjects had study visits at Screening, Baseline, and at Weeks 2, 4, 8, 12, 16, 20, and 24. Visits beyond Week 24 occurred every 12 weeks until subjects reached 4 years of age and attained a body weight ≥ 15 kg (US) or for a maximum of 1 additional year after subjects reached 4 years of age and attained a body weight ≥ 15 kg to allow transition to an appropriate treatment (EU).

Eligible subjects were aged 2 to < 4 years old at Screening with moderately to severely active polyarticular JIA or polyarticular course JIA or age ≥ 4 and weighing < 15 kg with moderately to severely active polyarticular JIA or polyarticular course JIA. A total of 29 subjects (90.6%) were in the active joint count for 73 joints (AJC73) ≥ 5 category, with a mean Baseline AJC73 of 10.0 ± 7.47. Thirty-one subjects (96.9%) were RF negative (rheumatoid factor < 12 IU/mL) with a Baseline mean of 10.2 ± 1.24. The majority of subjects (19 subjects [61.3%]) had a Baseline C reactive protein (CRP) value within the normal range (i.e., < 0.9 mg/dL) with a mean value of 1.6 ± 2.43. Subjects were judged by the investigator to be in generally good health, had normal cardiopulmonary and normal neurological examination results, and had a negative purified protein derivative test (PPD) at Screening. Subjects in the EU were also to have previously failed, had an insufficient response to, or been intolerant to 1 or more disease modifying anti rheumatic drug.

### 2.2.2. Results

All subjects received ≥ 1 dose of adalimumab (ITT). A total of 26 subjects (81.3%) completed the study and 6 subjects (18.8%) prematurely discontinued from the study (1 subject before Week 24 and 5 subjects after Week 24). Two subjects discontinued study drug because of an AE.

The minimum intended treatment period for all enrolled subjects was 24 weeks. Mean duration of exposure to adalimumab was 515.3 ± 245.33 days (median = 575.0 days). All subjects received at least 57 days of adalimumab treatment, with a maximum exposure to adalimumab of 910 days.

**Results**

Adverse events

**Table 1 Overview of subjects with TEAEs and TEAEs per 100 Patient-Years (ITT)**

| | Adalimumab | |
|---|---|---|
| TEAE | Number (%) of Subjects N = 32 | Events (E/100 PYs) PYS = 45.1 |
| Any TEAE | 29 (90.6) | 217 (481.2) |
| TEAE at least possibly drug related as assessed by the investigator[a] | 11 (34.4) | 22 (48.8) |
| Severe TEAE | 6 (18.8) | 6 (13.3) |
| Serious TEAE | 5 (15.6) | 5 (11.1) |
| TEAE leading to discontinuation | 2 (6.3) | 2 (4.4) |
| Death | 0 | 0 |

a. Relationship to study drug, as assessed by investigator, Note: A TEAE is any AE with onset on or after first dose of study drug and up to 70 days after last day of study drug. An AE with unknown severity is counted as severe. An AE with unknown relationship to study drug is counted as drug-related. E/100PY = events per 100 patient years

More than 90% of subjects reported at least 1 TEAE (217 events, 481.2 events per 100 patient-years [E/100PYs]) and 2 subjects (6.3%) reported a TEAE that led to discontinuation from the study. The majority of subjects reported TEAEs that were nonserious and considered by the investigator to be mild or moderate in severity and not related or probably not related to study drug.

**Table 2** **TEAEs reported by ≥ 5% of subjects by decreasing frequency and events per 100 PYs by primary MedDRA PT (ITT)**

| | Adalimumab | |
|---|---|---|
| MedDRA PT | Number (%) of Subjects N = 32 | Events (E/100PYs) PYs = 45.1 |
| Any TEAE | 29 (90.6) | 217 (481.2) |
| Nasopharyngitis | 8 (25) | 11 (24.4) |
| Pyrexia | 7 (21.9) | 11 (24.4) |
| Bronchitis | 6 (18.8) | 7 (15.5) |
| Cough | 6 (18.8) | 11 (24.4) |
| Rhinorrhea | 6 (18.8) | 7 (15.5) |
| Upper respiratory tract infection | 6 (18.8) | 11 (24.4) |
| Juvenile arthritis | 5 (15.6) | 10 (22.2) |
| Otitis media | 5 (15.6) | 9 (20.0) |
| Vomiting | 5 (15.6) | 5 (11.1) |
| Diarrhea | 4 (12.5) | 4 (8.9) |
| Gastroenteritis | 4 (12.5) | 4 (8.9) |
| Rash | 4 (12.5) | 5 (11.1) |
| Rhinitis | 4 (12.5) | 5 (11.1) |
| Ear infection | 3 (9.4) | 4 (8.9) |
| Pharyngitis | 3 (9.4) | 6 (13.3) |
| Pharyngitis Streptococcal | 3 (9.4) | 3 (6.7) |
| Sinusitis | 3 (9.4) | 3 (6.7) |
| Acute tonsillitis | 2 (6.3) | 4 (8.9) |
| Arthropod bite | 2 (6.3) | 4 (8.9) |
| Body temperature increased | 2 (6.3) | 3 (6.7) |
| Cystitis | 2 (6.3) | 2 (4.4) |
| Gastroenteritis viral | 2 (6.3) | 2 (4.4) |
| H1N1 influenza | 2 (6.3) | 2 (4.4) |
| Headache | 2 (6.3) | 2 (4.4) |
| Pneumonia | 2 (6.3) | 2 (4.4) |
| Uveitis | 2 (6.3) | 2 (4.4) |
| Varicella | 2 (6.3) | 2 (4.4) |

Note: A TEAE is any AE with onset on or after first dose of study drug and up to 70 days after last day of study drug.
E/100PY = events per 100 patient-years

The majority of subjects reported TEAEs that were considered by the investigator to be not related or probably not related to study drug. A total of 11 subjects (34.4%) had events that were considered by the investigator to be at least possibly related to study drug. Six subjects reported events that were considered by the investigator to be probably related to study drug (injection site reaction, injection site pain, injection site pruritus, injection site rash, injection site swelling, cystitis, and juvenile arthritis). Rash was the most frequently reported TEAE that was considered by the investigator to be at least possibly related to study drug (2 subjects, 6.3%).

**Table 3** **Summary of relationship and TEAEs at least possibly related to study drug by MedDRA PT (ITT)**

| Relationship MedDRA PT | Number (%) of Subjects Adalimumab N = 32 |
|---|---|
| Any AE | 29 (90.6) |
| Not related | 10 |
| Probably not related | 8 |
| Possibly related | 5 |
| Probably related | 6 |

| | |
|---|---|
| At least possibly related | |
| Any AE | 11 (34.4) |
| Rash | 2 (6.3) |
| Bronchitis | 1 (3.1) |
| Cystitis | 1 (3.1) |
| Ear infection | 1 (3.1) |
| Injection site pain | 1 (3.1) |
| Injection site pruritus | 1 (3.1) |
| Injection site rash | 1 (3.1) |
| Injection site reaction | 1 (3.1) |
| Injection site swelling | 1 (3.1) |
| Juvenile arthritis | 1 (3.1) |
| Laryngitis | 1 (3.1) |
| Otitis media | 1 (3.1) |
| Pharyngitis | 1 (3.1) |
| Pharyngitis streptococcal | 1 (3.1) |
| Pneumonia | 1 (3.1) |
| Pyrexia | 1 (3.1) |
| Upper respiratory tract congestion | 1 (3.1) |
| Viral pharyngitis | 1 (3.1) |

Note: A TEAE is any AE with onset on or after first dose of study drug and up to 70 days after last day of study drug. Table depicts most related adverse event for each preferred term, as assessed by the investigator.

Serious adverse events

Five subjects (15.6%) reported an SAE during the study. The SAEs that were reported were dental caries, gastroenteritis rotavirus, juvenile arthritis, type 1 diabetes mellitus, and varicella. These SAEs were considered by the investigator to be not related or probably not related to study drug.

Deaths

No deaths were reported during the study.

AEs of special interest

Of all AEs of special interest, events were seen in the following categories: treatment emergent infections, injection site reaction related events, allergic reactions, and hematologic disorders.

*Treatment emergent infections*

Twenty-five subjects (78.1%) reported at least 1 treatment emergent infection during the study. Three subjects had serious infections (1 report each of dental caries, gastroenteritis rotavirus, and varicella). These events were considered by the investigator to be mild to moderate in severity and not related to study drug. The most frequently reported infections were nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, gastroenteritis, and rhinitis. All other infections were reported by < 10% of subjects (not more than 3 subjects). No subjects prematurely discontinued from study drug as a result of an infection

*Injection Site Reaction-Related TEAEs*

A total of 4 subjects (1 subject reported 2 events) reported treatment-emergent injection site reaction-related events. These events were considered by the investigator to be mild in severity and probably related to study drug. The events resolved and the subjects continued in the study.

*Allergic Reaction, Including Angioedema/Anaphylaxis*

Two subjects (6.3%) reported an allergic reaction-related TEAE.

- One was a 2-year-old female from North Africa who experienced an event of intermittent urticaria on Day 631 that lasted for 17 days. The event was considered by the investigator to be mild in severity and not related to study drug.
- The second case was a 3-year- old white male who experienced an event of rash on his trunk, back, abdomen, and face on Day 12 that lasted 11 days. The event was considered by the investigator to be mild in severity and possibly related to study drug.

*Hematologic Disorders, Including Pancytopenia*

Two subjects (6.3%) reported a treatment-emergent hematologic disorder during the study.

- One subject was a 2-year-old white female who experienced an event of microcytic anemia on Day 253 that was ongoing as of Day 757. The event was considered by the investigator to be mild in severity and not related to study drug.
- The second subject was a 2-year-old Asian female who experienced an event of decreased platelet count on Day 506. The event was considered by the investigator to be severe and not related to study drug. The reported event was considered resolved after a repeat test was performed by a local hospital laboratory and the results for platelet count were within normal range.

The following TEAEs of special interest were not reported during the study:

- malignancies
- lupus-like reactions or systemic lupus erythematosus
- demyelinating disorder
- vasculitis
- reported re-activation of hepatitis B
- diverticulitis
- intestinal perforation
- intestinal stricture
- liver failure or other liver events
- myocardial infarction (MI)
- pulmonary embolism
- CVA
- treatment-emergent worsening/new onset of psoriasis
- an adalimumab administration-related medication error
- Stevens-Johnson syndrome
- erythema multiforme
- congestive heart failure (CHF)
- interstitial lung disease

- pancreatitis
- sarcoidosis
- progressive multifocal leukoencephalopathy or reversible posterior leukoencephalopathy syndrome
- amyotrophic lateral sclerosis (ALS)
- treatment-emergent TB
- seizure disorder
- antiphospholipid syndrome and associated auto-antibodies
- CPK elevations that were assessed as severe by the investigator

Secondary study endpoints included PK data, change from Baseline in laboratory findings, individual indicators of efficacy (physical function of the Disability Index of Childhood Health Assessment Questionnaire [DICHAQ], Parent's Global Assessment of subject's overall disease activity, Parent's Assessment of Pain, Physician's Global Assessment of Disease Activity, joint assessments, CRP, and the Child's Health Questionnaire [CHQ-PF50]) and the proportion of subjects with Paediatric American College of Rheumatology (PedACR) 30/50/70/90 responses.

Approximately 6 to 20 subjects in the US (including Puerto Rico) and EU were to be assessed for PK from blood draws at Baseline, Week 12, and Week 24. PK blood draws were obtained only from those who consented to this procedure. Week 24 PK data collected from 15 study subjects indicated that mean serum adalimumab trough concentrations achieved a steady-state of 6 to 8 µg/mL at Week 12 and Week 24. Steady state serum adalimumab concentrations were comparable to subjects who were > 4years old.

Clinical Laboratory Evaluation

*Hematology*

**Table 4 Number (%) of subjects whose hematology laboratory values changed from high or normal and low or normal baseline to low or high maximum values**

| Hematology Parameter | n/N (%) | |
|---|---|---|
| | Change from High/Normal to Low | Change from Low/Normal to High |
| Hemoglobin | 0 | 4/31 (12.9) |
| Hematocrit | 0 | 10/31 (32.3) |
| Red blood cell count | 0 | 3/31 (9.7) |
| Platelet count | 0 | 12/18 (66.7) |
| White blood cell count | 0 | 6/30 (20.0) |
| Neutrophils | 0 | 9/26 (34.6) |
| Lymphocytes | 0 | 18/22 (81.8) |
| Monocytes | 0 | 9/30 (30.0) |
| Eosinophils | 1/28 (3.6) | 4/29 (13.8) |
| Basophils | 0 | 0 |

Notes: Baseline is defined as the last observation prior to the first dose of study drug.
Low: Less than lower limit of normal
Normal: Within normal range
High: Greater than the upper limit of normal
n/N = number of subjects out of total subjects

*Chemistry*

**Table 5 Number (%) of subjects whose chemistry laboratory values changed from high or normal and low or normal baseline to low or high maximum values (ITT)**

| | n/N (%) | |
|---|---|---|
| **Chemistry Parameter** | **Change from High/Normal to Low** | **Change from Low/Normal to High** |
| ALT | 0 | 2/28 (7.1) |
| AST | 0 | 6/28 (21.4) |
| AP | 0 | 1/28 (3.6) |
| Total bilirubin | 0 | 0 |
| Creatinine | 0 | 0 |
| BUN | 0 | 4/28 (14.3) |
| Uric acid | 0 | 0 |
| Inorganic phosphate | 0 | 2/29 (6.9) |
| Calcium | 0 | 11/26 (42.3) |
| Sodium | 0 | 2/30 (6.7) |
| Potassium | 0 | 0 |
| Glucose | 0 | 9/29 (31.0) |
| Albumin | 0 | 7/30 (23.3) |
| Total protein | 0 | 4/30 (13.3) |
| Cholesterol | 0 | 4/15 (26.7) |
| Triglycerides | 0 | 8/30 (26.7) |
| Albumin/globulin ratio | 0 | 0 |
| BUN/creatinine ratio | 0 | 0 |
| CRP | 0 | 6/18 (33.3) |
| Carbon dioxide | 0 | 0 |
| Globulin | 0 | 0 |
| RF | 0 | 0 |

Notes: Baseline is defined as the last observation prior to the first dose of study drug.
Low: Less than lower limit of normal
Normal: Within normal range
High: Greater than the upper limit of normal
n/N = number of subjects out of total subjects

No shifts in total bilirubin, creatinine, uric acid, potassium, albumin/globulin ratio, BUN/creatinine ratio, carbon dioxide, globulin, or RF laboratory values were observed. No subjects who had a high or normal chemistry laboratory value experienced a shift to a low value.

Two subjects had at least 1 clinical significant abnormality in their chemistry laboratory values. These subjects developed a CTC toxicity grade ≥ 3 chemistry value for a single laboratory measurement during the OL period that resolved before the end of the study. One subject had hypernatremia and 1 subject had hyperglycemia. Neither subject discontinued because of abnormal chemistry laboratory values.

Two subjects had potentially clinically significant abnormalities in their liver function tests. Neither subject discontinued early from the study because of their abnormal liver function test. One resolved during the study, the second was ongoing as of Day 336.

A small shift in ALT and AST values from < 1.5 × ULN to ≥ 1.5 – < 3.0 × ULN was observed for 1 subject each.

*ANA and Anti-dsDNA*

No shifts were observed in final ANA or anti-dsDNA values.

*Anti adalimumab antibodies (AAA)*

A single subject out of 15 tested was found to be anti-adalimumab antibody (AAA) positive; therefore, it was not possible to evaluate the effect of AAA on safety and efficacy or to compare AAA+ rates with other studies.

Vital Signs, Physical Findings

The mean change from Baseline in heart rate and body temperature was within normal range for children 2 to 4 years of age. There was a 5.6 ± 1.55 kg mean change from Baseline in weight, indicating the subjects were growing. No subjects discontinued from study drug because of abnormal vital signs.

**Summary of MAH´s discussion and conclusion**

Safety results from this study demonstrated that adalimumab administered subcutaneously eow is generally safe and well-tolerated for up to 120 weeks of treatment in subjects 2 to < 4 years of age and subjects ≥ 4 years of age weighing < 15 kg, with moderately to severely active polyarticular JIA or polyarticular course JIA. No deaths occurred during this study. More than 90% of subjects (217 events, 481.2 E/100PYs) reported at least 1 TEAE and the majority of subjects reported TEAEs that were considered by the investigator to be mild to moderate in severity and not related or probably not related tostudy drug. Five subjects (15.6%) reported an SAE during the study and these SAEs were considered by the investigator to be not related or probably not related to study drug. The TEAEs of special interest that were considered by the investigator to be at least possibly related to study drug were injection site reaction and allergic reaction (rash).

Results of the efficacy endpoints demonstrated that adalimumab administered subcutaneously eow over 120 weeks reduced JIA disease activity in this population. A PedACR30/50 response was achieved by at least 80% of subjects, the majority of subjects achieved a PedACR70 response, and at least one-third of subjects achieved a PedACR90 response. A decrease was observed for all joint assessments, including TJC75, SJC66, POM75, LOM69, and AJC73, and the greatest change occurred from Week 60 through at least Week 84, although the number of subjects decreased to nearly 50% during those weeks. A decrease was also observed for CRP and CRP levels decreased to within the normal range at Weeks 72 and 84.

The primary and secondary objectives for this study were met. The data presented in this clinical study report demonstrate that adalimumab therapy up to 120 weeks was effective for treatment of moderately to severely active polyarticular or polyarcticular course JIA in subjects 2 to < 4 years of age or age ≥ 4 weighing < 15 kg. Adalimumab was generally safe and well-tolerated in these populations and the safety profile throughout the study was consistent with profiles in older paediatric patients with JIA from previous adalimumab clinical trials. No new safety signals were observed. In addition, adalimumab dosing, based on the height and weight of young children, was feasible and appropriate for this population.

## 2.2.3. Discussion

The final report from the Study M10-144 has been submitted. The primary study endpoint, measured over the course of the study, was the incidence of SAEs and AEs in polyarticular JIA subjects 2 to < 4 years old and subjects ≥ 4 years weighing < 15 kg.

In total 32 patients have been enrolled and received Humira, representing a cumulative exposure to Humira of 45.1 patient years (PYs). All subjects received at least 57 days of adalimumab treatment, with a maximum exposure to adalimumab of 910 days. 26 patients completed the study. Six subjects (18.8%) prematurely discontinued from the study (1 subject before Week 24 and 5 subjects after

Week 24). Two subjects discontinued study drug because of an AE, in both cases nonserious flare of juvenile arthritis.

No deaths were reported in the study. Five subjects (15.6%) reported an SAE during the study. The SAEs that were reported were dental caries, gastroenteritis rotavirus, juvenile arthritis, type 1 diabetes mellitus, and varicella. These SAEs were considered by the investigator to be not related or probably not related to study drug. They were all presented and evaluated within the 60 weeks interim analysis reviewed within the variation II/102 procedure. No additional SAEs have been reported during the last 60 weeks of the study.

By the time of the 60 Weeks interim analysis 22 subjects (68.8%) had reported at least 1 treatment emergent infection. At the end of the study 3 additional subjects had experienced this. This is not unexpected. No additional cases of serious infections have emerged since the Week 60 report.

Nine subjects reported 11 other TEAEs of special interest. The TEAEs of special interest that were reported were oral candidiasis (1), allergic reaction (2), hematologic disorders (2), and injection site reaction (4). These reports are not unexpected and are in line with the known safety profile of Humira.

PK-data were collected through week 24. The results were provided and assessed within the variation 102 procedure.

Overall, no new safety signal has been identified from the data submitted. Results were in line with the known safety profile of Humira and did not warrant a change to the product information.

### *2.3. Risk management plan*

No updated Risk Management Plan was submitted within this variation procedure. The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information.

### *2.4. Changes to the Product Information*

The MAH proposed no changes to the Product Information (PI), to which the CHMP agreed.

## 3. Overall conclusion and impact on the benefit/risk balance

No new safety concerns have been raised within this study. The safety profile observed up to Week 120 was in line with the known safety profile of adalimumab and the safety in older paediatric patients with JIA from previous adalimumab clinical trials. No update of the SmPC was warranted. The CHMP concluded that the presented results do not impact the positive benefit/risk balance of adalimumab in the approved indications when used in accordance with the recommendations of the Product Information.

## 4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| Variation accepted | | Type |
|---|---|---|
| C.I.13 | Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | II |

Submission of the final clinical study report for M10-444(data up to Week 120): Compassionate use study of adalimumab in children 2 to < 4 years old or age 4 and above weighing less than 15 kg with active juvenile idiopathic arthritis (JIA) in order to fulfil the requirement of article 46 of the paediatric regulation. No change to the product information was required.

The requested variation did not proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.