10 November 2016
EMA/CHMP/676652/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0154

Note

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

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List of abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse event
AESI	Adverse event of special interest
AN	Abscess and inflammatory nodule
BID	Twice a day
BMI	Body mass index
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
DB	Double-blind
DLQI	Dermatology Life Quality Index
eow	Every other week
EU	European Union
ew	Weekly
GCP	Good Clinical Practice
HiSCR	Hidradenitis Suppurativa Clinical Response
HS	Hidradenitis suppurativa
ICH	International Conference on Harmonization
ITT	Intent-to treat
LS	Least squares
MTX	Methotrexate
NRS	Numeric rating scale
pbo	Placebo
SAE	Serious adverse event
SC	Subcutaneous
TNF	Tumour necrosis factor
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Ltd. submitted to the European Medicines Agency on 29 March 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adolescents from 12 years of age with hidradenitis suppurativa for Humira; as a consequence, sections 4.1, 4.2, 5.1 and 5.2, of the SmPC are updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0121/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0121/2013 was completed. The PDCO issued an opinion on compliance for the PIP P/0121/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Kristina Dunder CHMP Co-Rapporteur: N/A

PRAC Rapporteur: Ulla Wändel Liminga

Timetable	Actual dates
Submission date	29 March 2016
Start of procedure	23 April 2016
CHMP Rapporteur's preliminary assessment report circulated on	17 June 2016
CHMP Rapporteur's updated assessment report circulated on	14 July 2016
Request for supplementary information and extension of timetable adopted by the CHMP on	21 July 2016
MAH's responses submitted to the CHMP and PRAC on	10 September 2016
CHMP & PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	11 October 2016
PRAC RMP advice and assessment overview adopted by PRAC on	27 October 2016
CHMP Opinion	10 November 2016

2. Scientific discussion

2.1. Introduction

Humira contains adalimumab, a recombinant human monoclonal antibody that neutralizes the biological function of TNF. The product is currently approved for treatment of several conditions, e.g. rheumatoid arthritis (RA), Crohn's disease (CD), active ulcerative colitis (UC) and chronic plaque psoriasis (Ps). Humira is also approved for use in paediatrics in all of these indications, with the lowest age limit being 2 years in polyarticular juvenile idiopathic arthritis.

A variation application for an extension of the indication of Humira to adults with active moderate to severe hidradenitis suppurativa (HS) was approved on 28 July 2015 (procedure EMEA/H/C/481/II/137). The current application is a type II variation application to extend the indication for Humira also to the use in adolescents from 12 years of age with HS.

HS is a serious, chronic, inflammatory skin disease of the hair follicle that usually presents with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, such as the axillary, inguinal and anogenital regions. The disease is characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and ooze purulent drainage and lead to scarring. HS is associated with several complications like the development of anal, urethral and rectal strictures and fistulas. Scarring and fibrosis can lead to contractures and limitations in limb mobility. HS has a severely negative impact on quality of life, which is often worse compared to other skin diseases.

Prevalence and similarities between HS in adolescents and adults

Since no EU-based population sampling has been utilized to assess the prevalence of HS, data from a large insured administrative database in the US were used to determine the prevalence of HS in 2009 in the EU Paediatric Investigation Plan (PIP) P/0121/2013 for the use of adalimumab in HS. The overall prevalence of HS was 0.19% (7,472 patients diagnosed with HS out of 3,950,936 patients continuously eligible in 2009). The prevalence of HS in the paediatric population was found to be less than one-fifth of that in the adult population. The prevalence of HS in the adult population was 0.23% (7,162 adult patients diagnosed with HS out of 3,157,445 adult patients). In comparison, the prevalence of HS in the paediatric population was 0.04% overall (310 paediatric patients diagnosed with HS out of 793,491 paediatric patients). Of these patients, the prevalence among infants less than 2 years of age was 0.00%,

the prevalence among prepubescent children between 2 and 11 years of age (inclusive) was 0.00% (12 children diagnosed with HS out of 433,354 total children sampled), and the prevalence among adolescents between 12 and 17 years of age (inclusive) was 0.09% (298 adolescents diagnosed with HS out of 328,634 total adolescents sampled).

A questionnaire-based survey of hospital-identified HS patients in the United Kingdom (UK) found the mean age of onset of HS to be 21.8 years, the mean duration from onset to maximal severity to be 6.4 years, and that the severity of HS generally increases over several years. Onset of HS typically occurs in the second or third decade of life. The virtual absence of HS in children below the age of 12 suggests that hormonal factors and puberty may play an important role in its pathogenesis.

There is virtually no literature available on adolescents with HS due to the rarity of the disease in this population; however, review of the available literature provides no suggestion that the key clinical features of HS are distinguishable in adolescents and adults. One source indicates that HS in children and adolescents generally shares the same overall presentation of characteristic clinical features of HS observed in adults (i.e., inflammatory nodules, abscesses, draining fistulas, and scarring). In support of this assertion, in the approved EU adalimumab HS PIP, the EMA agreed with the extrapolation analyses from adults to adolescents with HS based on the similarity of HS disease in these populations. Therefore, it would appear that HS development in adolescence represents the same disease process seen in adulthood, similar to other inflammatory skin disorders that affect both adolescents and adults, such as chronic plaque Ps. The impact of HS on quality of life observed in adults (pain and discomfort from physical symptoms, social stigma, and long term psychological impact, including depression and anxiety) is profound and expected to also greatly impact adolescents with HS.

There are no published case reports describing use of adalimumab in adolescent HS patients.

Treatment options for moderate to severe HS in the paediatric population

No therapeutic studies have been published in paediatric subjects with HS. As a consequence, current treatments are driven primarily by expert opinion, case reports, and/or extrapolation of treatments used in adult patients. Treatment of HS in this population depends largely on the extent and activity of disease, and possible endocrine co-morbidities and obesity should be considered in determining appropriate treatment.

The primary aim of medical treatment in HS is to control inflammation and reduce symptoms, most notably pain. Therapies used for HS include medical treatments (e.g., systemic combination therapy with clindamycin and rifampicin, intralesional triamcinolone, systemic cyclosporine, anti-androgen treatment in females, metformin, and systemic retinoids), surgical treatments (radical excision, marsupialization, and deroofing), and laser treatment (CO2 laser and Nd:YAG laser). Evaluation of the effectiveness of these interventions is difficult because efficacy has not been rigorously established using adequately sized controlled trials with validated instruments, or controlling for severity of disease. In addition, none of the medical treatments are approved for use in HS and several have the potential for major toxicities e.g. oral retinoids and anti-androgens.

Surgical and laser treatment can be associated with significant post-procedure morbidities, including pain and scarring that may further restrict limb mobility, and a considerable percentage of these patients who undergo surgical or laser treatment for their HS experience persistent disease due to inadequate removal of involved tissue at the surgical site or due to the presence of disease at sites other than where surgery has been performed.

Understanding of the pathogenesis of HS has progressed rapidly in the last several years. The fact that adalimumab, a monoclonal antibody against the pro-inflammatory cytokine TNF-α, has proven efficacy in

treating adult HS confirms that TNF plays an important role in the pathogenesis of the disease; however, treatment efficacy in adolescent patients with HS has not been tested. Most experts believe that bacterial infection is a secondary event in the disease process, and that antibiotics do not cure the disease but may relieve symptoms through either an antibacterial or an anti-inflammatory effect.

Until recently, the only published guidelines for the management of HS were national guidelines from Germany and the Netherlands, and there were no formal widely accepted treatment guidelines for HS either in the adult or the paediatric literature. However, treatment guidelines for HS were recently published in the EU. The guidelines concluded, "It is recommended that HS is treated based on the subjective impact and objective severity of the disease. Locally recurring lesions can be treated surgically, whereas medical treatment either as monotherapy or in combination with surgery is more appropriate for widely spread lesions. Medical therapy may include antibiotics and immunosuppressants." These guidelines also do not provide details specific to adolescents or children.

In moderate to severe HS in adolescent and adult patients alike, a multifaceted approach may be adopted, where surgical therapy is used to remove the chronic components of HS which are not expected to respond to medical therapy (e.g., scarring, fistulas, and sinus tracts), and long-term systemic medical therapy is used to treat the acute or sub-chronic manifestations of HS (e.g., abscesses and inflammatory nodules).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment update is included in this application which was considered acceptable by the CHMP.

In accordance with the CHMP guideline EMA Ref. EMEA/CHMP/SWP/4447/00 entitled ‘Guideline on the Environmental Risk Assessment of Medicinal Products for Human use’, proteins are exempted because they are unlikely to result in a significant risk to the environment. Adalimumab (Humira) is a human anti-human TNFα monoclonal antibody (IgG1) - a composite of 100% human antibody sequences.

2.3. Clinical aspects

2.3.1. Introduction

GCP

No new clinical trials were submitted in support of this variation application. The clinical studies referred to have been previously evaluated in other submissions.

Since the overall prevalence of HS is low (<1%) and the prevalence of HS in the paediatric population is even lower (less than one-fifth of that in the adult population), the conduct of clinical studies in paediatric HS patients was not considered feasible by the MAH. Hence, the present application is based on extrapolation, using PK-PD modelling and simulation.

The application for the HS indication in adults was based on data from four studies (Studies M10-467, M11-810, M11-313, and M12-555).

The extrapolation of the indication hidradenitis suppurativa (HS) from adult patients to adolescents is

based on:

- Determination of adalimumab exposure response relationship using population PK-PD modeling based on data from the initial double-blinded period of Phase 3 studies (Studies M11-313 and M11-810) in adult HS patients.
- Use of the previously developed adalimumab paediatric population PK model (pJIA, ERA Enthesitis-related arthritis, paediatric Ps, and paediatric CD) to determine a dosing regimen in adolescent HS patients that will achieve serum adalimumab concentrations similar to those observed in adult HS patients.

2.3.2. Pharmacokinetics

Pharmacokinetics in the target population (Adolescents with HS) has not been studied. Instead the MAH has carried out a pooled population PK analysis to describe the dose-exposure relation in children and adolescents.

Data from paediatric Ps (Study M04-717), JIA (Studies DE038 and M10-444), ERA (Study M11-328), and paediatric CD (Study M06-806) were used to develop the paediatric population PK model. Data from all subjects (age 2 – 18 years) enrolled into the 5 paediatric studies that received adalimumab and had at least one adalimumab concentration above the lower limit of quantitation were included in the population PK analysis (N = 524).

The final paediatric population PK model was a one-compartment model with first-order absorption and elimination, combined additive and proportional residual error model, and exponential inter-individual variability terms on CL/F and V2/F. The stepwise forward selection backward elimination covariate selection process resulted in AAA status, BSA, baseline albumin, and methotrexate co-administration as significant covariates on adalimumab CL/F and BSA as a significant covariate on adalimumab V2/F. The final model parameter estimates are presented in the table below.

Table 1. Final model parameter estimates

		Bootstrap Results N = 990		
Parameter	**Model Results**	**Mean**	**Median**	**95% Confidence Interval**
CL/F (L/day)	0.248	0.247	0.247	0.233 – 0.263
V_2/F (L)	4.71	4.73	4.73	4.50 – 5.00
K_a (1/day)	0.463	0.484	0.468	0.378 – 0.771
Proportional error	0.226	0.247	0.227	0.164 – 0.593
Additive error	1.36	1.25	1.32	0.013 – 1.65
DE038 Residual error	0.923	0.926	0.924	0.747 – 1.12
M10-444 Residual error	1.97	1.89	1.93	0.832 – 2.74
M06-806 Residual error	0.953	0.940	0.947	0.602 – 1.16
M11-328 Residual error	0.652	0.643	0.643	0.387 – 0.902
AAA on CL/F (Week 2)	5.73	5.97	5.85	4.67 – 7.79
BSA on V_2/F	1.80	1.80	1.80	1.64 – 1.95
BSA on CL/F	1.18	1.18	1.18	1.02 – 1.33
ALB on CL/F	–1.11	–1.10	–1.11	–1.41 – (–0.767)
MTX on CL/F	0.784	0.787	0.785	0.723 – 0.864
ETA1 (EXP on CL/F)	0.206	0.203	0.203	0.168 – 0.245
ETA2 (EXP on V_2/F)	0.063	0.061	0.061	0.024 – 0.092

ETA = Inter-individual variability

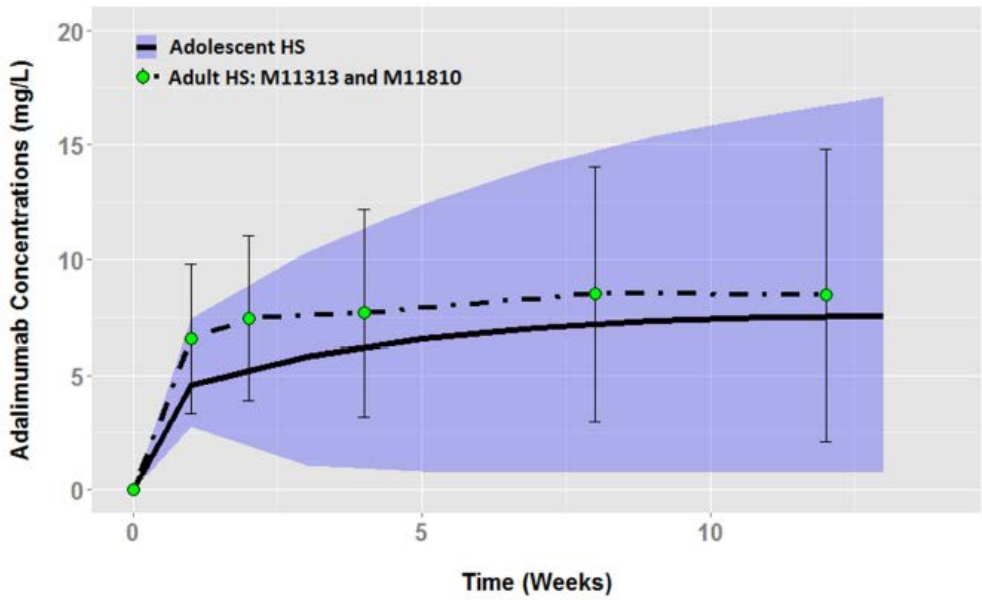
Cross reference: Study M04-717 PK report (R&D/13/1067)

Simulation of adalimumab exposure in adolescent HS patients

The final paediatric population PK model was used to simulate serum adalimumab exposure in adolescent HS subjects. Before conducting the PK simulations, subject demographics (weight, BSA, age, albumin) for adolescent HS subjects were extrapolated based on data from adolescent Ps subjects (Study M04-717). Baseline albumin levels and BSA distribution in adolescent HS subjects were assumed to be similar to those observed in adolescent Ps subjects enrolled in Study M04-717 (Median [range]: Albumin: 4.8 g/dL [3.9 – 5.4 g/dL], BSA: 1.68 [1.29 – 2.29]). This assumption was based on the observation of similar distribution of albumin and BSA between adult Ps and HS subjects in the Phase 3 studies. A 6.5% AAA+ rate was assumed for adolescent HS subjects similar to that observed in adult HS subjects receiving at least one dose of adalimumab in Phase 3 trials. Although methotrexate use was a significant covariate on adalimumab CL/F in the final paediatric population PK model, the effect of its co-administration was not included in the adolescent HS simulations since it is not an approved treatment for HS and was not used in the adult HS Phase 3 trials. A dataset including 458 virtual adolescent HS subjects was created (similar number of subjects to adult PK dataset) and 100 replicates were simulated in NONMEM for a total number of simulated subjects of 45,800. A weight-based dose of 0.8 mg/kg eow was first simulated similar to the approved dose in paediatric Ps subjects. Given the expected weight range for adolescent HS subjects (≥ 35 kg) based on observed weight distribution in adolescent Ps subjects (38 – 108 kg), a 40 mg eow fixed dose for all subjects was also simulated and results were compared to those obtained after 0.8 mg/kg eow dosing.

Simulated adalimumab concentrations in adolescent HS subjects (summarized as median and 90% prediction interval) were compared to those observed in adults in Phase 3 studies (Studies M11-313 and M11-810) to determine a dosing regimen for adolescent subjects that would achieve serum concentrations similar to those observed in adults. The result is shown in the figure below.

Figure 1. Simulated adalimumab concentrations in adolescent HS subjects (summarized as median and 90% prediction interval) were compared to those observed in adults in Phase 3 studies (Studies M11-313 and M11-810)

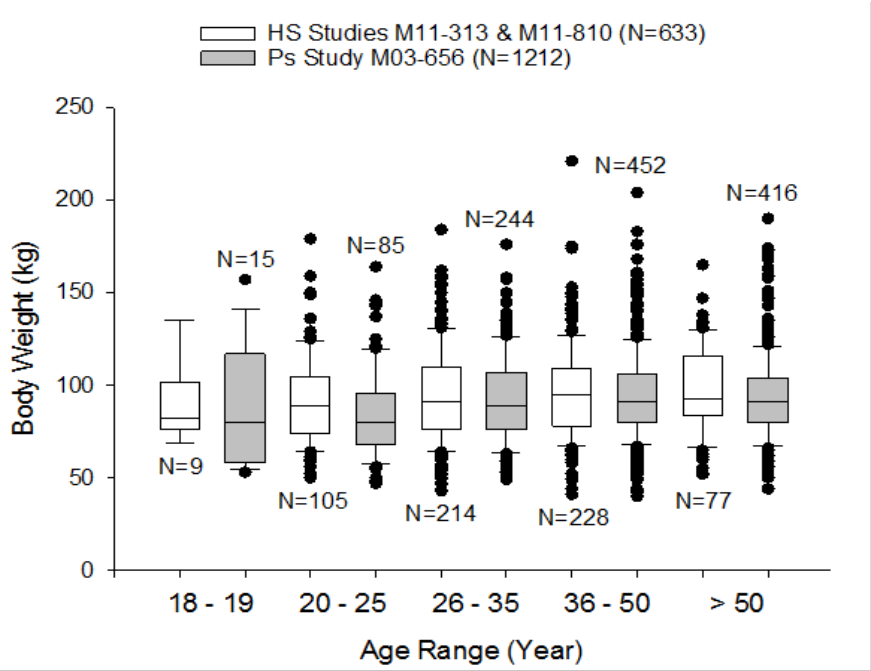


To address the CHMP comment on the appropriateness of the use of the paediatric Ps population demographics for adolescent HS in the PK extrapolations, the MAH compared the body weight (BW) of the

adult subjects in the two disease population (HS and Ps) across different age groups enrolled in the Phase 3 studies (Studies M11-313 and M11-810 for adult HS and Study M03-656 for adult Ps) and also between the adolescent HS subjects (12 – 17 years) from the ongoing HS Disease Based Registry and adolescent Ps subjects (12 – 17 years) in Study M04-717.

As shown in Figure below, BWs are comparable between adult HS and adult Ps subjects across different age groups. The BW of subjects in the two disease populations was also comparable in the younger adult subjects (18 – 19 years) in both populations, suggesting that the BW of the two populations would be expected to be generally comparable in the adolescent age group.

Figure 2. Comparison of Body Weight between Adult HS (Studies M11-313 and M11-810) and Adult Ps Subjects (Study M03-656)



In 62 adolescent HS patients (12 – 17 years) from the ongoing HS Disease Based Registry (H13 – 147), the median (range) BW was 75 kg (42 – 145 kg), which is higher than the observed weight distribution in adolescent Ps subjects (12 – 17 years) in Study M04-717 (60 kg [38 – 108 kg]). However, a difference of 15 kg in the median BW between the two populations would result in only a small increase of approximately 12% in the predicted median adalimumab clearance values in adolescent HS patients. These data suggest that the plasma exposure in adolescent HS patients is expected to be similar to those obtained by extrapolation from the adolescent Ps population.

As part of the application, the CHMP also raised a concern regarding the proposed posology. Indeed, the Applicant proposed a different posology in HS patients 12 to 18 years of age compared to the adult patients. A maintenance dose of 40 mg every other week was suggested instead of the adult 40 mg every week regimen. Further, the adult induction dose regimen (adalimumab 160 mg at Week 0 and 80 mg at Week 2) was not included in the suggested posology for adolescents.

A similar posology as in several other paediatric indications, in which no loading dose is recommended, was proposed by the MAH. However, in Crohn´s disease (which has a similarly intense dosing schedule at

initiation of therapy as for HS in adults), loading dose regimens are recommended both in paediatric patients and in adults.

In the CHMP's opinion, there was an obvious risk of underdosing with the proposed regimen. Indeed, the dose proposed is a flat dose (40 mg for all patients) and it is expected that the weight range can be rather wide in the intended age range 12-17 years. Based on this, there is a concern that particularly patients in the upper age range (16-17 years), especially those who are obese, will achieve a too low exposure with the proposed posology.

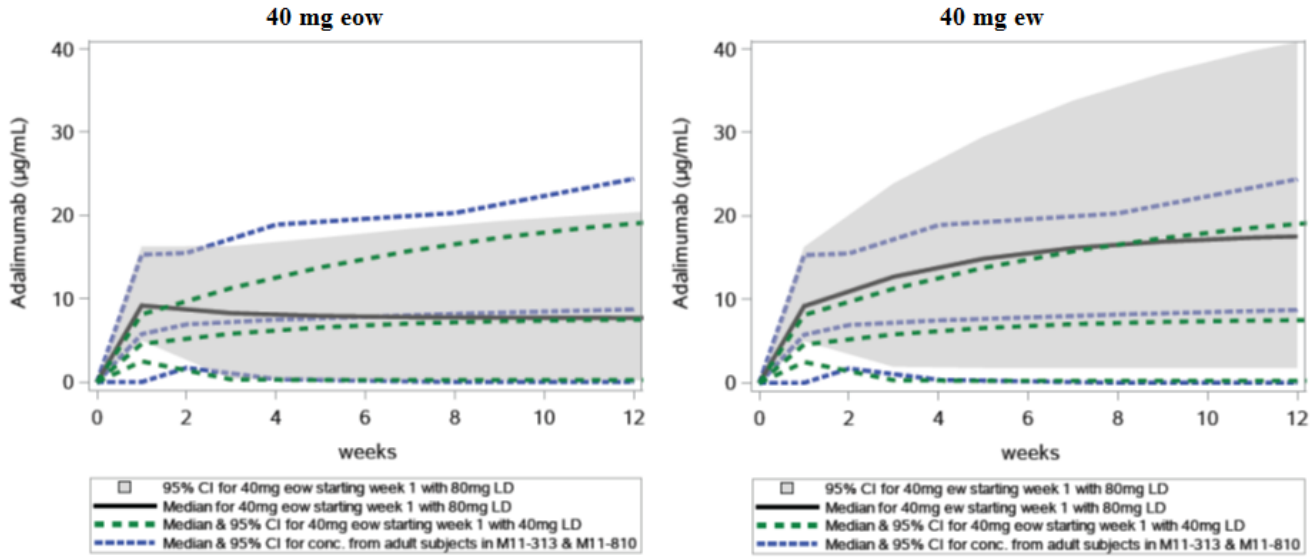
Based on the concerns raised by the CHMP, the Applicant has proposed a revised proposal for dosing of Humira in adolescent HS subjects together with the following justifications:

Induction Dose Evaluation

The proposed posology included a dosing regimen of 40 mg every other week (eow) with the first two doses given weekly, to try to achieve steady state concentrations early in treatment. Based on concerns raised by CHMP, the MAH has further evaluated the use of a higher induction dose at Week 0, followed by the proposed maintenance dose of 40 mg eow in adolescent HS patients starting at Week 1 as shown in Figure below (left panel). The use of an induction dose of 80 mg at Week 0 helps achieve adalimumab steady-state concentrations more rapidly compared with a 40 mg induction dose. The simulated (median and 90% prediction interval) steady-state concentrations after an induction dose of 80 mg followed by 40 mg eow starting at Week 1 in adolescent HS subjects were similar to the adalimumab concentrations observed in adult HS subjects in Phase 3 studies (Studies M11-313 and M10-810) and were slightly higher when compared to the originally proposed induction dose of 40 mg at Week 0. These results demonstrate that the use of an induction dose of 80 mg followed by 40 mg eow starting at Week 1 is an appropriate dosing regimen to achieve similar steady-state concentrations in adolescent HS subjects in a similar time frame to those observed in adult HS subjects, especially at earlier time points.

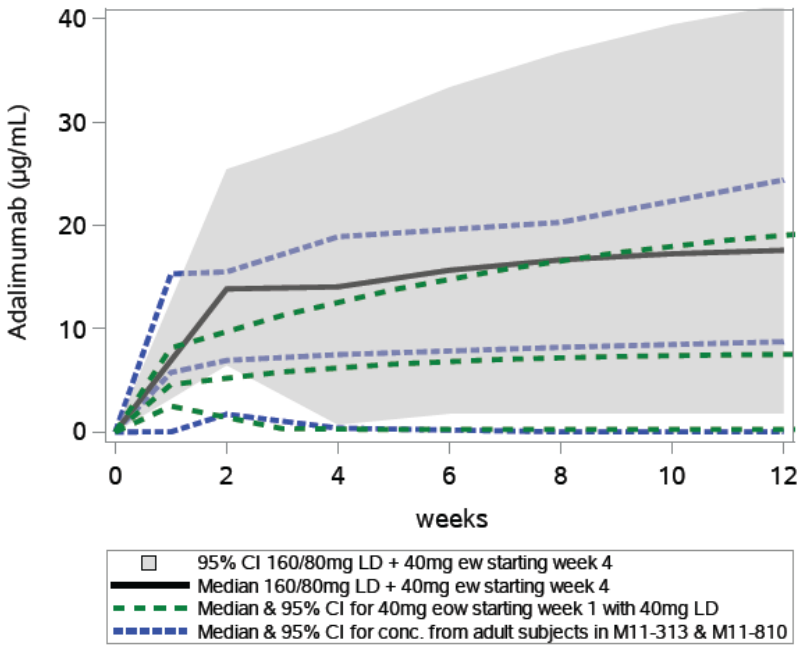
The use of a maintenance dose of 40 mg every week (ew) in adolescent subjects were predicted to result in higher adalimumab concentrations in adolescent HS subjects compared to those observed in adult HS subjects (Figure below, right panel). The use of a higher loading dose of 160 mg at Week 0 and 80 mg at Week 2 followed by 40 mg ew starting at Week 4 (similar to the dose regimen approved in adult HS subjects) would similarly result in overexposure in adolescent HS subjects when compared to adult and is not regarded as an appropriate dose in adolescents with HS.

Figure 3. **Simulated Serum Adalimumab Concentrations in Adolescent HS Subjects with an 80 mg Induction Dose at Week 0 and 40 mg eow (left) or 40 mg ew (right) Maintenance Dosing Beginning at Week 1 and Observed Serum Adalimumab Concentrations in Adult HS Subjects from Studies M11-313 and M11-810**



Note: The blue dashed lines represent the median and 95% confidence interval of observed adalimumab concentrations in adult HS subjects in Phase 3 studies (Studies M11-313 and M11-810). Black solid lines and grey shaded area represent the median and 95% prediction interval for simulated concentrations in adolescent HS subjects following an induction dose of 80 mg SC at Week 0 and 40 mg eow (left) or 40 mg ew (right) starting at Week 1. Green dashed lines represent the median and 95% prediction interval for simulated concentrations in adolescent HS subjects following an induction dose of 40 mg SC at Week 0 and 40 mg eow starting at Week 1.

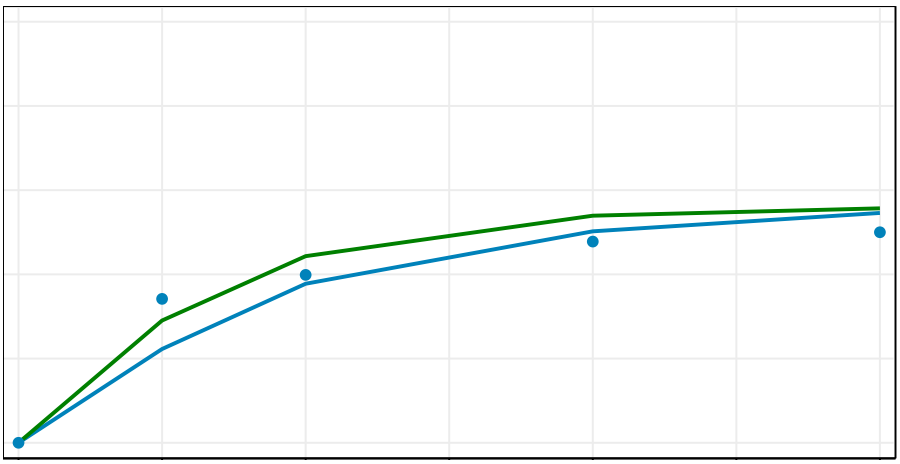
Figure 4. Simulated Serum Adalimumab Concentrations in Adolescent HS Subjects with an Induction Dose of 160 mg at Week 0 and 80 mg at Week 2 followed by 40 mg ew Maintenance Dosing Beginning at Week 4 and Observed Serum Adalimumab Concentrations in Adult HS Subjects from Studies M11-313 and M11-810



Note: The blue dashed lines represent the median and 95% confidence interval of observed adalimumab concentrations in adult HS subjects in Phase 3 studies (Studies M11-313 and M11-810). Black solid line and grey shaded area represent the median and 95% prediction interval for simulated concentrations in adolescent HS subjects following an induction dose of 160 mg at Week 0, 80 mg at Week 2 and 40 mg ew starting at Week 4. Green dashed lines represent the median and 95% prediction interval for simulated concentrations in adolescent HS subjects following an induction dose of 40 mg SC at Week 0 and 40 mg eow starting at Week 1.

The simulated serum adalimumab concentrations following an induction dose of 80 mg at Week 0 and 40 mg eow starting at Week 1 in adolescent HS subjects were subsequently used together with the population PK/PD model to simulate HiSCR response rate in adolescent HS subjects for the 80 mg induction dose regimen and compared with those predicted under the originally proposed 40 mg induction dose regimen and observed HiSCR response rates in adult HS subjects. As shown in the figure below, the predicted HiSCR response rate in adolescents under the 80 mg induction dose regimen was similar to the overall response rate observed in Phase 3 studies (Studies M11-313 and M11-810) in adult subjects, especially at Week 2. The use of an induction dose of 80 mg is expected to achieve a higher HiSCR response rate in adolescent HS subjects earlier when compared to the induction dose of 40 mg, consistent with the PK differences observed with the two dosing regimens at earlier time points. The simulated HiSCR rate in adolescent HS subjects further confirms the appropriateness of the use of an induction dose of 80 mg along with the proposed maintenance regimen of 40 mg eow starting at Week 1.

Figure 5. Simulated HiSCR Response Rates in Adolescent HS Subjects with an 80 mg Induction Dose at Week 0 and 40 mg eow Maintenance Dosing Beginning at Week 1 and Observed HiSCR Response Rates in Adult HS Subjects from Studies M11-313 and M11-810



Note: Solid lines represent median of predicted HiSCR response rates in adolescent HS subjects following an induction dose of 40 mg (blue) or 80 mg (green) SC at Week 0 and 40 mg eow starting at Week 1. Blue circles represent observed HiSCR response rate in adult HS subjects in the Phase 3 Studies (Studies M11-313 and M11-810).

Supporting Data for 30 kg Lower Weight Limit

The lowest weight observed in adolescent HS patients from the ongoing HS Disease Based Registry (Study H13-147) was 42 kg. In addition, there was only 1 subject with BW below 40 kg among the adolescent Ps subjects (12 – 17 years) in the Paediatric Ps Study M04-717 (BW of 38 kg). Based on these

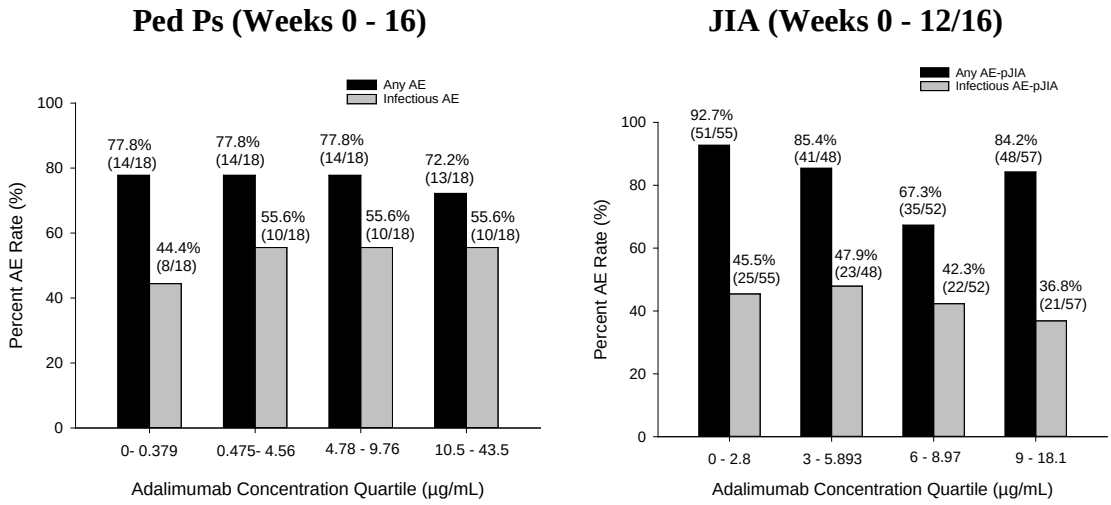
data, the epidemiology of HS, and the general understanding that HS most commonly develops in patients in their early 20s, it appears very unlikely that an HS subject would weigh less than 30 kg. Therefore, the MAH proposed as part of the application a lower weight limit of 30 kg for use of adalimumab in adolescent HS subjects. Providing simple dosing instructions reduces label complexity and potential for dosing errors.

It is also important to ensure that the adolescent HS patients weighing 30 – 40 kg are not overexposed under the proposed dose of 40 mg eow. Due to the limited availability of demographic information in adolescent Ps subjects in Study M04-717 weighing < 40 kg (only one subject), use of the population PK model to predict adalimumab concentrations for subjects 12 – 17 years of age weighing 30 – 40 kg will have limited confidence. Therefore, the MAH has utilized the demographic data from paediatric Ps subjects (below 12 years of age) from Study M04-717 to estimate the predicted adalimumab exposures in subjects in the weight range of 30 – 40 kg who would receive 40 mg eow under the proposed dosing regimen.

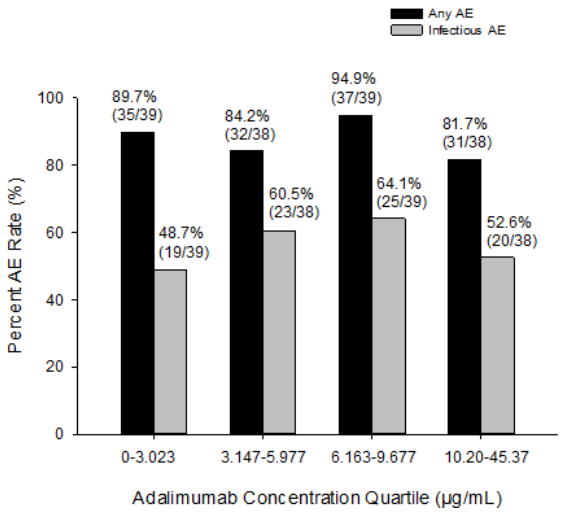
The median (95% Prediction Interval) for the simulated serum trough concentrations in subjects with BW of 30 – 40 kg was predicted to be 8.02 µg/mL (0.19 – 24.9 µg/mL). These values are comparable to the adalimumab exposures expected in adolescent HS subjects with BW > 40 kg and are within the concentration range observed in other studies with adalimumab in paediatric populations, including paediatric Crohn's disease (CD), paediatric Ps, and juvenile idiopathic arthritis (JIA).

The use of the proposed dosing regimen in adolescent HS subjects weighing 30 – 40 kg is further supported by the data showing that there is no apparent relationship between adalimumab concentrations and adverse event (AE) rates in paediatric patients with Ps (Study M04-717), JIA (Studies M10-444, M11-328 and DE038), and CD (Study M06-806), as shown in the figure below.

Figure 6. Relationship Between Adalimumab Concentrations and Risk of AEs in Paediatric Subjects with Ps (Top Left), JIA (Top Right) and CD (Bottom)



CD Maintenance Phase (Weeks 4 - 52)



Note: Data are from JIA Studies DE038, M10-444, and M11-328, paediatric Ps Study M04-717, and paediatric CD Study M06-806.

Concern for Underdosing in Older Adolescent HS Subjects

The MAH further evaluated the appropriateness of the proposed dose of 40 mg eow for all patients (≥ 30 kg) by comparing the predicted adalimumab steady state concentrations in adolescent HS subjects across different BW ranges. Body weight ranges were selected for this analysis, since body weight is a better predictor of adalimumab pharmacokinetics than age. The predicted adalimumab steady-state concentrations in adolescent HS subjects were also compared to those observed in adult HS subjects in the Phase 3 studies (Studies M11-313 and M11-810).

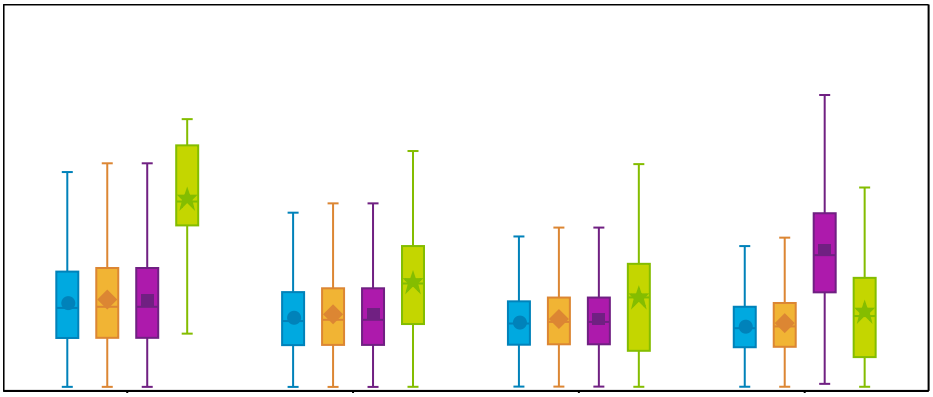
In addition, PK simulations were performed for an increase in dosing frequency for patients with a BW ≥ 90 kg to address the concern of potential low exposures in the upper age/weight range. This upper weight cut-off was selected based on the observed median BW in adult HS subjects in the Phase 3 studies (93 kg). In addition, a BW cut-off of 90 kg allowed for the evaluation of predicted adalimumab concentrations in the heaviest patients to address the concern that older, heavier patients are more likely to be under-dosed. Under this potential dosing regimen, patients with BW in the range of 30 – < 90 kg would receive an induction dose of 80 mg at Week 0 followed by 40 mg eow starting at Week 1 and patients weighing ≥ 90 kg would receive an induction dose of 80 mg at Week 0 followed by 40 mg ew starting at Week 1 (similar to the maintenance dose approved in adult HS subjects).

As shown in the Figure below, the predicted adalimumab steady state trough concentrations were comparable across all BW bins in adolescent HS subjects following the proposed dosing regimen of 80 mg at Week 0 and 40 mg eow starting at Week 1. The predicted concentrations of adalimumab following the 40 mg eow dosing regimen in adolescent HS subjects were also comparable to those observed in adult HS subjects in the respective weight groups with the exception of the subjects in the lowest BW bin (≤ 38 – < 60 kg); however, the sample size in adult HS subjects in this weight range was small (N = 8). These results demonstrate the appropriateness of the flat dosing regimen of 40 mg eow for all adolescent HS patients and that the risk of underdosing is unlikely with this proposed regimen across all weight groups.

The use of a more frequent dosing regimen of 40 mg ew in adolescent HS patients weighing ≥ 90 kg would result in higher exposures in these patients when compared to the use of 40 mg eow dosing in these patients. The predicted concentrations in the adolescent HS patients weighing ≥ 90 kg would also be

higher than those observed in adult subjects in the same weight group (Figure below, purple bar for patients weighing ≥ 90 kg). Based on these results, the more frequent dosing regimen of 40 mg ew would be predicted to result in similarly higher exposures in patients across all the weight ranges.

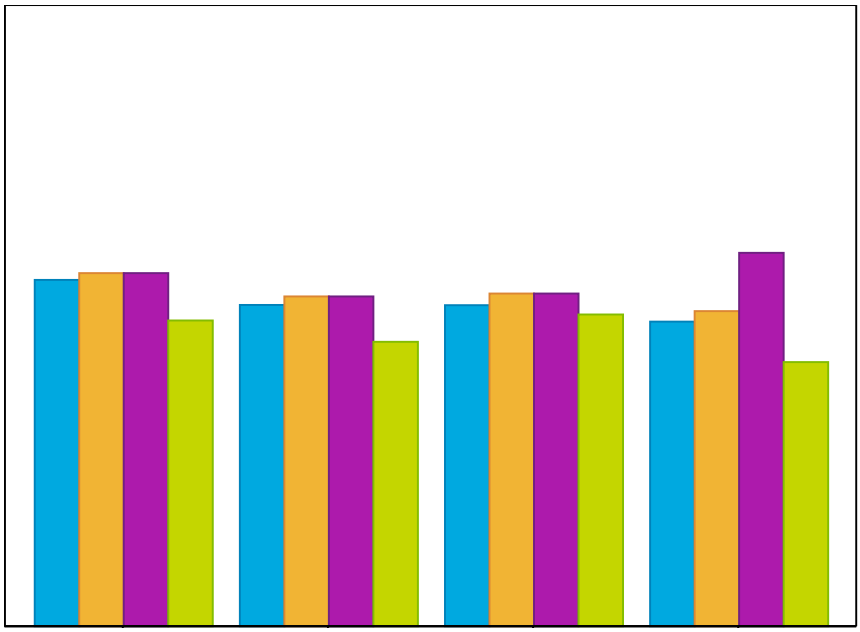
Figure 7. Simulated Adalimumab Trough Concentrations in Adolescent HS Subjects Following Different Dosing Regimens Compared to Observed Concentrations in Adult HS Subjects by Body Weight Categories



Note: Data represent predicted adalimumab steady state trough concentrations in adolescent HS subjects following 40 mg at Week 0 and 40 mg eow starting at Week 1 (blue bar), 80 mg at Week 0 and 40 mg eow starting at Week 1 (orange bar), 80 mg at Week 0 and 40 mg eow (for patients < 90 kg) or 40 mg ew (for patients ≥ 90 kg) starting at Week 1 (purple bar), and observed adalimumab steady state trough concentrations in adult HS subjects in Phase 3 Studies M11-313 and M11-810 receiving 160 mg at Week 0 followed by 80 mg at Week 2, and 40 mg ew starting at Week 4 (green bar).

To further confirm the appropriateness of the proposed dose of 40 mg eow for all patients (≥ 30 kg), the MAH compared the predicted HiSCR response rates in adolescent HS subjects across different BW bins following the different dosing regimens. As shown in the figure below, the predicted HiSCR response rates were comparable across the different BW bins in adolescent HS subjects following an induction dose of 80 mg at Week 0 and 40 mg eow starting at Week 1, and were also comparable to those observed in adult HS subjects (who received 40 mg ew) in the respective weight groups. The use of a more frequent dosing regimen of 40 mg ew in adolescent HS patients weighing ≥ 90 kg is predicted to result in modest improvement in efficacy in these patients when compared to the use of 40 mg eow dosing (Figure below, purple bar for patients ≥ 90 kg).

Figure 8. Simulated HiSCR Response Rates in Adolescent HS Subjects following Different Dosing Regimens Compared to Observed HiSCR Response Rates in Adult HS Subjects by Body Weight Categories



Notes: Data represent predicted HiSCR response rates in adolescent HS subjects following 40 mg at Week 0 and 40 mg eow starting at Week 1 (blue bar), 80 mg at Week 0 and 40 mg eow starting at Week 1 (orange bar), 80 mg at Week 0 and 40 mg eow (for patients < 90 kg) or 40 mg ew (for patients ≥ 90 kg) starting at Week 1 (purple bar), and observed HiSCR response rates in adult HS subjects in Phase 3 Studies M11-313 and M11-810 receiving 160 mg at Week 0 followed by 80 mg at Week 2, and 40 mg ew starting at Week 4 (green bar).

The HiSCR response rates in Studies M11-313 and M11-810 represent the primary efficacy endpoints in adult HS subjects in the Phase 3 Studies.

Based on these results, the MAH considers that the proposed flat dose regimen of 80 mg at Week 0 followed by 40 mg eow starting at Week 1 is an appropriate dosing regimen for the overall adolescent HS population.

In addition, the MAH acknowledges that patients mature at different rates/ages and that certain adolescent patients may be more similar to adults in their handling of adalimumab and associated benefit:risk balance. Considering that 40 mg ew dosing has demonstrated clinically important advantages when compared with 40 mg eow dosing for the treatment of HS in adults, the MAH proposed the option to increase dosing to 40 mg ew in patients not responding adequately to Humira 40 mg eow.

The proposed addition to the posology of a 40 mg ew dosing regimen in adolescent HS patients with inadequate response to treatment with 40 mg eow dosing is supported by safety data in paediatric patients with CD that support the approved option in the EU Summary of Product Characteristics (SmPC) to increase maintenance dosing frequency to 40 mg ew in paediatric patients with severe CD weighing ≥ 40 kg who experienced insufficient response to the recommended 40 mg eow dosing regimen.

This option to increase dosing frequency in paediatric CD patients was approved based on the results of Study M06-806, a multi-center, randomized, DB, safety, efficacy, and PK study designed to evaluate the efficacy of 2 adalimumab dosage regimens in the induction and maintenance of clinical remission in paediatric subjects with moderate to severe CD between the ages of 6 and 17 inclusive.

It should be noted that at least 60% of all subjects in this study population used concomitant immunosuppressant (IMM) medications (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) during the study (Study M06-806; table below), and that these medications affect the safety profile of adalimumab in this study, as reflected by an increase in the overall proportion of subjects experiencing AEs compared to studies in other paediatric indications.

In Study M06-806, after receiving open-label (OL) induction therapy at a dose based on their Baseline BW, all subjects were randomized by their BW at Week 4 to either the Low-Dose or High-Dose eow DB maintenance regimens, as shown below.

Subject Weight	Low Dose	High Dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Subjects who received DB ew dosing were also evaluated from a safety standpoint. Although the number of study subjects receiving 40 or 20 mg ew dosing was relatively small compared to the number receiving 40 or 20 mg eow dosing, overall safety profiles, as represented by the proportion of subjects with AEs, were similar between dosing regimens. An increased incidence of severe AEs and serious AEs (SAEs)/100 PYs in subjects receiving adalimumab ew versus eow dosing was mainly due to a higher number of CD (flare or worsening) events reported as a severe AE or SAE. It should be noted that no SAEs at least possibly related to adalimumab were reported in subjects receiving ew dosing and that the incidence of AEs at least possibly related to adalimumab was very similar between subjects receiving ew or eow dosing.

Table 2. Overview of AEs in Paediatric CD Study M06-806 – DB eow and DB ew Maintenance Periods

	High-Dose Adalimumab 40 or 20 mg			
	eow N = 93 PYs = 54.1		ew N = 35 PYs = 12.1	
Subjects with:	**n (%)**	**E (E/100 PY)**	**n (%)**	**E (E/100 PY)**
Any AE	86 (92.5)	507 (937.2)	28 (80.0)	132 (1090.9)
At least possibly drug related[a]	39 (41.9)	111 (205.2)	10 (28.6)	25 (206.6)
Severe AE	19 (20.4)	27 (49.9)	9 (25.7)	13 (107.4)
SAE	22 (23.7)	24 (44.4)	9 (25.7)	13 (107.4)
Leading to discontinuation of study drug	15 (16.1)	20 (37.0)	5 (14.3)	7 (57.9)
Any at least possibly drug-related SAEs[a]	1 (1.1)	1 (1.8)	0	0
Infectious AEs	56 (60.2)	99 (181.1)	16 (45.7)	24 (198.3)
Serious infections	5 (5.4)	5 (9.2)	3 (8.6)	4 (33.1)
Malignancies	0	0	0	0
Lymphomas	0	0	0	0
NMSC	0	0	0	0
Malignancies (excluding NMSC and lymphomas)	0	0	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0	0	0
Injection site reactions	9 (9.7)	25 (46.2)	4 (11.4)	7 (57.9)
Opportunistic infections (excluding TB)	1 (1.1)	1 (1.8)	0	0
Congestive heart failure	0	0	0	0
Demyelinating disease	0	0	0	0
Hepatic-related AEs	4 (4.3)	5 (9.2)	1 (2.9)	1 (8.3)
Allergic reactions	6 (6.5)	8 (14.8)	1 (2.9)	1 (8.3)
Lupus-like syndrome	0	0	0	0
Hematologic-related AEs	9 (9.7)	11 (20.3)	3 (8.6)	3 (24.8)
Fatal AEs	0	0	0	0
Deaths[b]	0	0	0	0

a. As assessed by investigator.

b. Includes non-treatment-emergent deaths.

Note: An AE during the eow DB Maintenance Period is any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug. An AE during the ew DB Maintenance Period is any AE with an onset date on or after the first ew DB dose and prior to OL dose or up to 70 days after the last dose of study drug if subject discontinued prematurely from the DB ew period.

Cross reference: Study M06-806 Final CSR (R&D/10/605) Table 108, Table 109 (submitted in Sequence Number 0080)

2.3.3. Pharmacodynamics

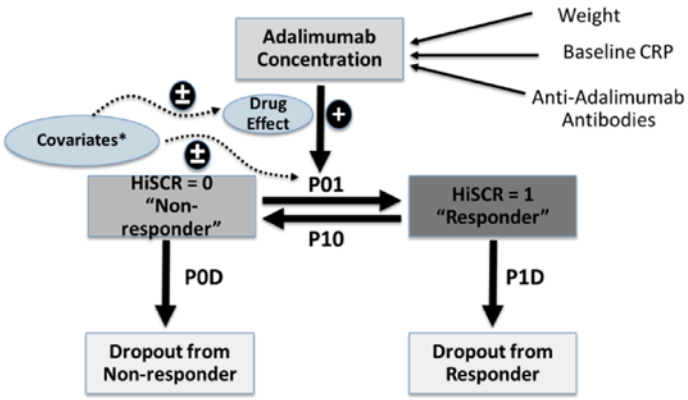
No new pharmacodynamics data is submitted.

2.3.4. PK/PD modelling

Serum adalimumab concentrations and Hidradenitis Suppurativa Clinical Response (HiSCR) response rates from Period A of the Phase 3 Studies M11-313 and M11-810 were used to develop a continuous time Markov Chain PKPD model for adalimumab in adult HS subjects. In addition, adalimumab exposure-response relationship during the first 12 weeks of treatment in the OLE Study M12-555 was evaluated using serum adalimumab concentrations and HiSCR response rates.

Individual PK parameters were generated from the previously developed population PK model (Studies M10-467, M11-313, and M11-810) and were then applied as the input functions of the PD model to describe the relationship between adalimumab exposure and efficacy. A continuous time Markov Chain modeling approach was employed to describe the time course of adalimumab concentration effect on achievement of HiSCR. The schematic of the model is shown in the figure below.

Figure 9. Description of time course of adalimumab concentration effect on achievement of HiSCR



[NB the parameter names in the model schematic are different from the parameter names used in tables and text; K01 corresponds to P01 in the model schematic, etc.]

The transition states of the Markov chain were defined as: No Response = State 0, Achieving HiSCR = State 1, and Dropout = State D.

Baseline Sartorius score was found to influence the rate of transition from HiSCR non-responder to responder status. Higher baseline Sartorius scores resulted in a lower rate of transition and hence a lower probability of achieving HiSCR. This effect was independent of adalimumab treatment and affected both treatment arms equally. No significant covariates were identified on the drug effect parameter [PREF, "Drug effect" and capital greek letter theta 1 used interchangeably]. The functional form of the covariate effects on the K01 parameter is shown below

$$K_{01} = \frac{10^{\theta_2}}{day} \cdot (1 + PREF \cdot Conc.) \left(\frac{SART\_BL}{105}\right)^{\theta_6}$$

Parameter estimates obtained from the final Markov model are shown in in the table below. [NB the parameter estimates are on the log scale]

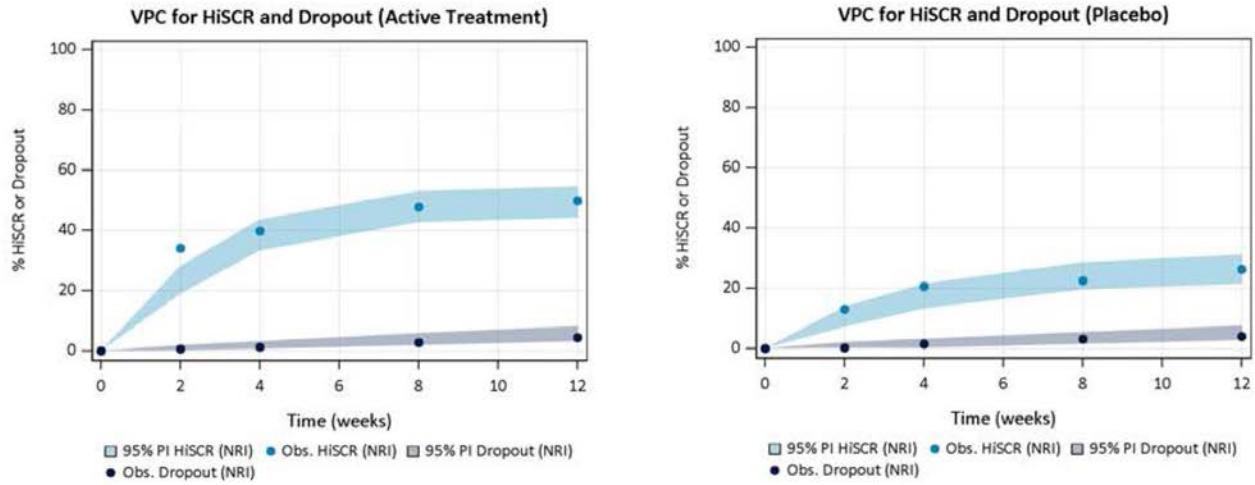
Table 3. Parameter estimates obtained from the final Markov model

Parameter	Population Estimate (RSE%)	95% Confidence Interval
θ_1 "Drug Effect"	–0.655 (14.4)	–0.839 to –0.471
θ_2 "K_{01}"	–2.050 (2.34)	–2.143 to –1.957
θ_3 "K_{10}"	–1.730 (2.72)	–1.823 to –1.637
θ_4 "K_{0D}"	–3.220 (3.66)	–3.451 to –2.989
θ_5 "K_{1D}"	–3.090 (4.92)	–3.388 to –2.792
θ_6 "SART_BL"	–0.534 (19.5)	–0.738 to –0.330

RSE = Relative Standard Error; θ_1 to θ_6 were included in the model using a power function (e.g., $10^{\theta 1}$).
Cross reference: PKPD Report R&D/15/1084

The ability of the model to describe the percentage of HiSCR response and dropout over time was evaluated by use of Visual Predictive Check, VPC (see below). Although the model slightly underpredicted the HiSCR response rate at Week 2, it accurately predicted HiSCR response rates for all subsequent study visits.

Figure 10. Ability of the model to describe the percentage of HiSCR response and dropout over time evaluated by use of Visual Predictive Check, VPC



2.3.5. Discussion on clinical pharmacology

Clinical studies in adolescents with HS have not been performed and no data is available on the efficacy, safety or exposure in this population. In order to extrapolate the efficacy of adalimumab from the source population (adult HS) to the target population (adolescent HS) it is assumed that the relation between dose, exposure and response is similar in adults and adolescents.

The exposure to adalimumab in adolescent HS patients has not been determined. PK data obtained in children and adolescents in other indications (pJIA, ERA, paediatric Ps, and paediatric CD) has been integrated in a population PK model. The drug disposition (distribution and elimination) is not different between indications according to the model. The influential factors are anti-drug antibodies (AAA), body size, serum albumin level and concomitant methotrexate treatment. With respect to adolescent HS patients, the model does not provide any reason to expect different exposure compared to other paediatric indications. Thus, the pooled paediatric PK model is adequate for the purpose of simulation of exposure in adolescents with HS.

Efficacy and exposure data are available from clinical studies in adult HS patients. These data have been integrated in an exposure-response model which used to simulate the response to a different posology in adolescents. Since only one dose level was studied in the adult patients, the modelled exposure-response needs to be interpreted with caution due to the risk of confounding factors.

It should be noted that the main support /arguments in this application are based on the fact that the new target population is fairly similar to the adult population and that the plasma adalimumab exposure seems to be reasonably well matched to the adult exposure in HS. The modelling approach is appreciated and valuable as supportive evidence for extrapolation.

Adolescent psoriasis vs. adolescent HS patients for PK extrapolations

In adults, psoriasis and HS patients had rather similar body weights across different age groups. In adolescents, HS patients tended to have higher body weights compared with psoriasis patients, based on a HS Disease based registry. A 15 kg body weight difference was expected to result in an approximately 12% higher CL of adalimumab in adolescent HS patients, which may not be of large relevance for the overall conclusions.

As part of the application, the CHMP raised a concern regarding the proposed posology. In the CHMP's opinion, there was an obvious risk of underdosing with the proposed regimen. Based on the concerns

raised by the CHMP, the Applicant has proposed a revised proposal for dosing of Humira in adolescent HS subjects together with a justification; the CHMP assessment is as follows:

Induction dose evaluation

The lack of a loading dose (LD) regimen in adolescent HS patients as compared to adult HS patients was questioned by the CHMP. In the response, the Applicant has provided simulations of different regimens, with and without an LD, with a similar LD regimen as in adults (160 mg + 80 mg) and with an every other week (eow) vs. every week (ew) maintenance dose regimen. Based on these simulations, an LD regimen with an 80 mg dose was found the best match the adult exposure, as observed in the pivotal adult HS studies.

With the dose regimen approved in adults (160 mg week 0, 80 mg week 2 and 40 mg ew from week 4), adolescent HS patients were predicted to achieve higher adalimumab concentrations compared with adults. Similarly, an every week (ew) maintenance dose regimen was predicted to result in higher exposure compared with adults.

Based on the simulations, using exactly the same dosing regimen in adolescent HS patients as in adult HS patients was claimed to result in overexposure in the overall adolescent group (12-18 years). However, within this group, there can be large differences between a 12-year old and a 17-year old patient, for instance in body weight. There may also be young HS patients (12-13 years) with a high body weight. Nevertheless, a more cautious initiation of therapy (LD 80 mg instead of 160 mg + 80 mg) may be sensible in adolescents, but with a possibility to increase the maintenance dose to the adult 40 mg ew dose, if needed.

Lower weight limit cut-off of 30 kg

It was considered adequate to include a lower weight limit in the posology and a cut-off of 30 kg has been suggested by the Applicant. Indeed, providing simple dosing instructions reduces label complexity and potential for dosing errors. It is agreed that it seems unlikely that an HS subject would weigh less than 30 kg. From predictions based on paediatric psoriasis patients, it seems unlikely that HS patients in the weight range 30-40 kg would be at risk of achieving too high exposures.

Concern for underdosing in older adolescent HS subjects

Considering the risk of underdosing, the Applicant has also introduced a statement that the dose may be increased from 40 mg eow to 40 mg ew in case of insufficient response in older adolescent HS subjects. This proposal was supported by different simulations of adalimumab concentrations across different weight spans. It is difficult to understand why the predicted exposure in adolescent HS subjects changes only minimally across weight categories, while the exposure in adult HS subjects is more clearly related to body weight. Based on the simulations, the Applicant does not propose an adult posology in all “old” adolescent HS patients, but has introduced the possibility to increase the dose to the adult maintenance dose (40 mg ew) in case of insufficient response. Use of a 40 mg ew regimen in adolescents has some support from use in paediatric Crohn´s disease, albeit with limited data from clinical trials. It is, however, agreed that there is precedent to allow patients with insufficient response to 40 mg eow to increase dosing to 40 mg ew, e.g. in adult patients with RA and Ps and paediatric patients with CD. It is also agreed that any obvious relationship between adalimumab dose or exposure with safety has not been observed. A somewhat higher incidence of severe AEs and SAEs/100 PYs in subjects receiving adalimumab ew versus eow dosing was observed, but was mainly due to a higher number of CD flares or worsening events. Hence, the proposed possibility to increase the dose is endorsed by the CHMP.

2.3.6. Conclusions on clinical pharmacology

As a result of the CHMP's assessment, the MAH has updated the proposed posology for adolescent HS subjects as follows:

- Introduction of a weight limit for adolescents from 12 years of age, weighing at least 30 kg
- Introduction of a dose of 80 mg at Week 0
- Possibility to increase the dosing frequency to 40 mg every week in adolescent patients with inadequate response to 40 mg eow

The revised dosing regimen is considered acceptable to the CHMP.

2.4. Clinical efficacy

As mentioned above, no new clinical trials were submitted to support the extension of the indication to include adolescents with HS. The application is based on modelling and simulation, with extrapolation of efficacy and safety of adalimumab from adults with HS and extrapolation of PK data from other paediatric indications for adalimumab to adolescents with HS.

2.4.1. Dose response study(ies)

No information about dose response of adalimumab in adolescents with HS is available. The proposed dose is based on modelling and simulation, described and assessed in the Clinical Pharmacology section.

2.4.2. Main study(ies)

No studies with adalimumab in adolescents with HS are available. The approval of the HS indication in adults was based on data from four studies, of which Studies M11-810 and M11-313 were pivotal. These were both multi-center, randomized, double-blind, placebo-controlled, 2-period studies with the aim to determine the clinical safety and efficacy of adalimumab compared to placebo in subjects with moderate to severe HS.

Both studies included an initial 12-week double-blind treatment period and a subsequent 24-week double-blind treatment period. In both studies, a loading dose regimen was used, with adalimumab 160 mg at Week 0, 80 mg at Week 2 followed by 40 mg ew or matching placebo starting at Week 4. In the second part of the studies, subjects in the adalimumab arm were re-randomized to receive adalimumab 40 mg ew (i.e. continue with 40 mg ew treatment), adalimumab 40 mg eow (i.e. reduced dosing frequency) or matching placebo (i.e. withdrawal of active treatment). The primary end-point in both studies was the "Hidradenitis Suppurativa Clinical Response", HiSCR, developed by the applicant. HiSCR is defined as at least a 50% reduction in the AN (abscess and inflammatory nodule) count with no increase in abscess count and no increase in draining fistula count, at Week 12 relative to baseline.

The main results of the HS studies in adults are summarized in the table below, for reference.

Summary of Efficacy for studies M11-313 and M11-810 (adult studies in HS)

Title: A Phase 3 Multicenter Study of the Safety and Efficacy of ADA in Subjects with Moderate to Severe Hidradenitis Suppurativa					
Study identifier	M11-313 (PIONEER I) and M11-810 (PIONEER II)				
Design	Phase 3 multicenter, randomized, DB, PBO-controlled studies of the safety and efficacy of ADA in subjects with moderate to severe HS				
	Duration of main phase:		Period A, 12 weeks		
Hypothesis	Superiority				
Treatment groups (N=307 for M11-313; N=326 for M11-810)	Placebo		12 weeks n=154 for M11-313 n=163 for M11-810		
	ADA ew		160 mg at week 0, 80 mg at week 2, 40 mg ew starting at week 4 until week 12, 12 week of treatment, SC n=153 for M11-313 n=163 for M11-810		
Endpoints and definitions	Primary endpoint	HiSCR	Proportion of subjects achieving HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to baseline at Week 12.		
	First secondary ranked endpoint (SRE)	AN0, 1 or 2	Proportion of subjects achieving inflammatory nodule and abscess count of 0, 1, or 2 at Week 12, among subjects with Hurley Stage II at baseline (it was considered too strict to be applied to subjects with Hurley stage III).		
	Second SRE	NRS30	Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at Week 12 among subjects with Baseline skin pain NRS (numerical rating scale) ≥ 3.		
	Third SRE	Modified Sartorius score	Change in modified Sartorius score from Baseline to Week 12.		
Database lock	M11-313: 5 February 2014; M11-810: 23 May 2014				
Results and analysis					
Analysis description	**Primary analysis**				
Analysis population and time point description	ITT-A (N=307 for M11-313; N=326 for M11-810)				
Descriptive statistics and estimate variability	Study	M11-313		M11-810	
	Treatment group	PBO	ew	PBO	ew

	Number of subjects		154	153	163	163
	Primary endpoint	**HiSCR**%	26.0	41.8	27.6	58.9
	SRE	**AN0, 1 or 2** %	28.6	28.9	32.2	51.8
		NRS30 %	24.8	27.9	20.7	45.7
		Modified Sartorius score	-15.7	-24.4	-9.5	-28.9
Effect estimate per comparison	**Primary endpoint**		Comparison groups	PBO *vs* EW		
			Test statistic	Cochrane-Mantel-Haenszel (CMH) test, statistical test was 2-tailed with the significance level 0.05.		
			P-value	M11-313 P=0.003* M11-810 P<0.001*		
	SRE		Comparison groups	PBO *vs* EW		
			Test statistic	Cochrane-Mantel-Haenszel (CMH) test, statistical test was 2-tailed with the significance level 0.05.		
			P-value	M11-313 P=0.961 (AN0,1 or 2) P=0.628 (NRS30) P=0.124 (Sartorius) M11-810 P=0.010* (AN0,1 or 2) P<0.001* (NRS30) P<0.001* (Sartorius)		

2.4.3. Discussion on clinical efficacy

The application for Humira in the adults HS indication was supported by two adequately designed and performed phase 3 studies in subjects with moderate to severe HS. Both studies met the primary efficacy end-point (Hidradenitis Suppurativa Clinical Response, HiSCR), albeit with different size of the effect vs. placebo (42% and 59%, respectively, for HiSCR at week 12 vs. 26-27% for placebo). For the three, ranked secondary end-points, only one study (M11-810) met all these endpoints. In contrast, none of

these end-points achieved statistical significance in the second study (M11-313), although most outcomes were numerically in favour of adalimumab ew. Other secondary end-points in both studies generally mirrored the results of the primary and ranked secondary end-points. Outcomes related to patient-reported Quality of Life showed an effect of adalimumab vs. placebo, e.g. for DLQI.

Thus, it was concluded that the efficacy of adalimumab in adults with moderate to severe HS was deemed clinically relevant, including positive outcomes related to patient-reported QoL. The indication approved in adults is a second line indication, in patients with an inadequate response to conventional systemic HS therapy. A second line indication is presently applied for adolescents.

No new clinical trials were submitted to support the extension of the indication to include adolescents with HS. The application is based on modelling and simulation, with extrapolation of efficacy and safety of adalimumab from adults with HS and extrapolation of PK data from other paediatric indications for adalimumab to adolescents with HS.

2.4.4. Conclusions on the clinical efficacy

The use of PK and PKPD modelling to extend the adult HS indication to adolescents is considered the best option available considering the very low prevalence of HS in adolescents and is also in accordance with the PIP for Humira in HS. Even if the condition is rare, in particular in the adolescent group, it does exist in adolescents and well-studied treatments are overall few in HS. Hence, the CHMP endorsed from an efficacy perspective the indication in HS for adolescents.

2.5. Clinical safety

No clinical data are available on the use of Humira in adolescents with HS. In the assessment of the adults HS indication, it was concluded that the safety profile of adalimumab in HS did not appear different from what that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE. The rate or severity of infections, including SSTIs, with Humira in HS did not give cause for concern in comparison with the experience in other indications. For AESI other than infections, no new or unexpected findings were overall observed in the HS studies; however, several events of worsening/new onset psoriasis were reported. Serious AEs were reported in 11% of subjects (e.g. anemia, cellulitis, ectopic pregnancy, hidradenitis, non-cardiac chest pain, palpitations, pilonidal cyst, pneumonia, postoperative wound infection, sepsis). Two deaths on adalimumab were reported in the HS clinical studies; none of which were considered related to adalimumab.

Adalimumab has a well-established safety profile based on clinical trial and post-marketing data gained in multiple indications for more than 10 years. As of 31 December 2015, adalimumab has been evaluated in more than 33,000 subjects in clinical trials. The estimated cumulative post-marketing patient exposure since the international birth date (31 December 2002) through 31 December 2015 is approximately 4.3 million patient years.

In the EU, adalimumab is approved for the treatment of paediatric patients with pJIA (> 2 years), ERA (≥6 years), CD (≥6 years), and Ps (>4 years). The incidence of treatment emergent AESI is similar across these paediatric indications. In addition, the safety profile across these paediatric indications is similar or consistent with the expected rates due to underlying disease and has not revealed any new safety signals compared with adults.

To comply with the US FDA's post-marketing requirement for TNF-α blockers, the MAH performs enhanced safety surveillance for reports of malignancy in paediatric, adolescent, and young adult patients (≤30 years of age). Cumulative malignancy data in paediatric patients treated with adalimumab for varying diseases also do not reveal any new signals in the paediatric patient population.

As discussed previously, the CHMP was of the opinion that a posology for adolescents more in line with the adult HS posology seems more adequate. Based on that, the MAH was asked to provide and discuss available safety data for adalimumab when a loading dose regimen is used in paediatric patients, e.g. based on data from Crohn's disease for which a loading dose is applied also in paediatric patients.

The MAH proposed to update the recommended posology for adolescent HS patients (from 12 years of age and weighing at least 30 kg) to include an 80 mg induction dose at Week 0, followed by a 40 mg eow maintenance dosing regimen starting at Week 1.

The proposed induction dosing regimen for the adolescent HS indication is supported by safety data in paediatric CD subjects from 6 years of age in which similar or higher induction doses were used (Study M06-806). The approved recommended dosing regimen for the paediatric CD indication is based on this safety data.

The recommended induction dosing regimen for paediatric CD subjects weighing < 40 kg is 40 mg at Week 0 followed by 20 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen of 80 mg at Week 0 and 40 mg at Week 2 can be used. The typical recommended induction dose regimen for paediatric subjects ≥ 40 kg with moderately to severely active CD is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen of 160 mg at Week 0 and 80 mg at Week 2 has also been approved for treatment.

The paediatric CD dosing regimen, including induction dosing, was approved based on the results of Study M06-806. In Study M06-806, all subjects received OL induction therapy at a dose based on their Baseline BW: 160 mg at Week 0 and 80 mg at Week 2 for subjects weighing ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects weighing < 40 kg.

With regard to AEs in this study, in general, proportions of subjects reporting AEs in the 2 induction dosing groups were similar (Table below).

Table 4. Overview of AEs in Paediatric CD Study M06-806 – OL Induction Period by Dose Group and Body Weight

	OL Induction Period, n (%) Any Adalimumab	
	80/40 mg Doses (BW < 40 kg at Baseline) N = 69	**160/80 mg Doses (BW ≥ 40 kg at Baseline) N = 123**
Any AE	33 (47.8)	68 (55.3)
At least possibly drug-related[a]	10 (14.5)	29 (23.6)
Severe AE	3 (4.3)	7 (5.7)
SAE	2 (2.9)	4 (3.3)
Leading to discontinuation of study drug	1 (1.4)	0
At least possibly drug-related SAE[a]	0	0
Infectious AE	8 (11.6)	19 (15.4)
Serious infections	1 (1.4)	1 (0.8)
Malignancies	0	0
Lymphomas	0	0
Non-melanoma skin cancer (NMSC)	0	0
Malignancies (excluding NMSC and lymphomas)	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0
Injection site reactions	7 (10.1)	15 (12.2)
Opportunistic infections	0	0
Congestive heart failure	0	0
Demyelinating disease	0	0
Hepatic-related AEs	0	0
Allergic reactions	0	1 (0.8)
Lupus-like syndrome	0	0
Hematologic-related AEs	1 (1.4)	2 (1.6)
Fatal AEs	0	0
Deaths[b]	0	0

a. As assessed by the investigator.

b. Includes non-treatment-emergent deaths.

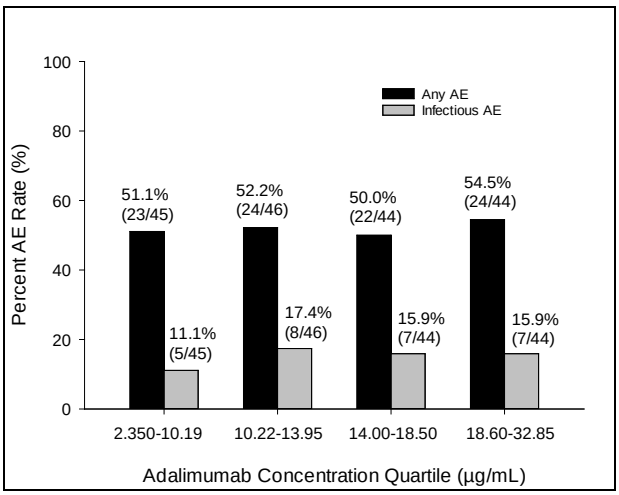
Note: An AE has an onset date on or after the first induction dose and prior to DB dose and up to 70 days after the last dose of study drug if subject discontinued prematurely from the Induction period.

Cross reference: Study M06-806 Final CSR (R&D/10/605) Table 69 (submitted in Sequence Number 0080)

Since the dose regimens including an 80 mg or 160 mg induction dose at Week 0 were generally well tolerated, and since the higher induction dose is used on Day 1 in the approved adult HS indication, it would follow that the 80 mg induction dose would be appropriate from a safety standpoint as proposed for the adolescent HS indication.

Moreover, the use of an induction dose regimen in adolescent HS subjects is also supported by exposure-safety analyses during the induction phase of paediatric CD Study M06-806. As shown in Figure below, there is no apparent relationship between adalimumab concentration and total AE and infectious AE rates in paediatric CD subjects receiving induction dosing across a large range of adalimumab concentrations. It should be noted that an 80 mg induction dose is used for paediatric CD patients weighing between 30 and 40 kg.

Figure 11. Relationship Between Adalimumab Concentrations and Risk of AEs in Paediatric Subjects with CD in the Induction Phase of Study M06-806 (Weeks 0 – 4)



2.5.1. Discussion on clinical safety

Adalimumab has been approved for more than 10 years and its safety profile is well characterized at this stage, with infections and risks related to malignancies being well-known risks. The proposed dosing schedule for Humira in adult HS is quite high, and HS is one of the highest dosed indications for Humira. Still, the safety profile of adalimumab in the adult HS studies did not appear different from what that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE. This included the rate or severity of infections, including SSTIs.

As mentioned above, no clinical data are available in adolescents with HS. Hence, extrapolation is made from use in other indications.

Adalimumab is approved for use in children and adolescents in other indications, e.g. for the treatment of paediatric patients with pJIA (> 2 years), ERA (≥6 years), CD (≥6 years), and Ps (>4 years). The maximal dosing regimens (40 mg eow) are similar to that proposed for adolescent HS. However, in paediatric CD, an intense loading dose regimen (160 mg + 80 mg) and maintenance dose (40 mg ew) may be used in certain cases. The incidence of treatment emergent AESI was found similar across these paediatric indications and no new safety signals compared with adults have been identified.

At the CHMP's request, the Applicant presented safety data in paediatric CD subjects from 6 years of age in which similar or higher induction doses were used. No unexpected safety findings were observed in this group and no apparent relationship between adalimumab exposure and total AE or infectious AE rates in paediatric CD subjects was observed. The extent of paediatric data is rather limited; however, the safety data from adult indications also supports the intense loading dose regimen and a 40 mg ew regimen.

2.5.2. Conclusions on clinical safety

The safety profile of Humira in adolescent HS is likely not to be substantially different for this age group and indication compared with those already approved. Humira can be used in children as young as 2 years in other indications, so there is experience from use in paediatric patients. The target group for this indication is adolescents 12-17 years old, thus, not a very young population, so large differences vs. adults are not expected.

The experience of use of high loading dose regimens in paediatric patients is not large; however, no unexpected safety findings were observed in in paediatric CD subjects from 6 years of age in which similar or higher induction doses were used and no apparent relationship between adalimumab exposure and total AE or infectious AE rates in paediatric CD subjects was observed.

Use of a 40 mg ew regimen in adolescents has sufficient support from use in paediatric Crohn´s disease, albeit with limited data from clinical trials. In addition, sufficient reassurance is given from the use of Humira 40mg ew in adult patients with RA and Ps with insufficient response to 40 mg eow.

In addition, no relationship between adalimumab dose or exposure with safety has not been observed.

In conclusion, the safety profile in this new indication with the revised regimen is acceptable to the CHMP.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.1.1 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.1.1 with the following content:

Safety concerns

Identified risks:

- Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and TB;
- Reactivation of hepatitis B;
- Pancreatitis;
- Lymphoma;
- HSTCL;
- Leukaemia;
- NMSC;
- Melanoma;
- Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin);
- Demyelinating disorders (including MS, GBS and optic neuritis);
- Immune reactions (including lupus-like reactions and allergic reactions);

- Sarcoidosis;
- CHF;
- MI;
- CVA;
- ILD;
- Pulmonary embolism;
- Cutaneous vasculitis;
- SJS and erythema multiforme;
- Worsening and new onset of Ps;
- Haematologic disorders;
- Intestinal perforation;
- Intestinal stricture in CD;
- Liver failure and Other Liver Events;
- Elevated ALT levels;
- Autoimmune Hepatitis; and
- Medication errors and maladministration.

Potential risks:

- Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma);
- Vasculitis (non-cutaneous);
- PML;
- RPLS;
- ALS;
- Adenocarcinoma of colon in UC patients;
- Infections in infants exposed to adalimumab in utero;
- Medication errors with paediatric vial; and
- Off-label use.

Missing information

- Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications;
- Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA;
- Pregnant and lactating women;

- Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA.
- Long-term safety data in the treatment of adults with HS.
- Long-term safety data in the treatment of adults with uveitis.

Pharmacovigilance plan

	Milestone/ Exposure	Milestones/ Calendar Time	Study Status
Ongoing Pharmacovigilance Actions			
Annual interim data from Registry for CD patients (Study P06-134)		Reporting February through 2015	Ongoing
Registry for CD patients (Study P06-134)	6 years	Final report August 2016	Ongoing
Annual interim data from Registry for pedCD patients (Study P11-292)		Reporting August through 2023	Ongoing
Registry for pedCD patients (Study P11-292)	10 years	TBD	Ongoing
Annual interim data from Registry for Ps patients (Study P10-023)		Reporting February through 2022	Ongoing
Registry for Ps patients (Study P10-023)	10 years	Final Report February 2023	Ongoing
Evaluation of treatment interruptions with the Ps registry (Study P10-023)	10 years	February 2023	Ongoing
Annual interim data from Registry for pJIA patients (Study P10-262)		Reporting August through 2024	Ongoing
Registry for pJIA patients (Study P10-262)	10 years	Final Report September 2024	Ongoing
Evaluation of treatment interruptions with the pJIA registry (Study P10-262)	10 years	September 2024	Ongoing
Support Rheumatoid Arthritis National Registry in Germany (RABBIT) until the end of 2017	NA	Reporting February through 2017 (Biennially)	Ongoing

	Milestone/ Exposure	Milestones/ Calendar Time	Study Status
(Biannual summary report)			
Support Rheumatoid Arthritis National Registry in United Kingdom (BSRBR) until 2017	NA	TBD	Ongoing
Support Rheumatoid Arthritis National Registry in Sweden (ARTIS) until 2015	NA	TBD	Ongoing
Long-term HS data (Study M12-555)		4Q2016	Ongoing
Long-term uveitis data (Study M11-327)		4Q 2018	Ongoing
Planned Pharmacovigilance Actions			
Annual Interim data from Registry for UC (Study P11-282)		Reporting August through 2019	Planned
Biannual Interim data from Registry for UC (Study P11-282)		Reporting August from 2019 through	Planned
Registry for UC patients (Study P11-282)	10 years	TBD	Planned

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risk		
Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB	Labelling	To educate prescribers and patients about the risk of serious infections associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Reactivation of hepatitis B	Labelling	None proposed.
Pancreatitis	Labelling	None proposed.
Lymphoma	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
HSTCL	Labelling	To educate prescribers and patients about the risk of

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Leukaemia	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
NMSC	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Melanoma	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Merkel cell carcinoma (Neuroendocrine carcinoma of the skin)	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Demyelinating disorders	Labelling	To educate prescribers and patients about 1) the risk of demyelinating disorders associated with the use of Humira, and 2) the underlying risk of demyelinating disorders associated with uveitis, particularly intermediate uveitis: • Patient Alert Card • HCP Educational Material.
Immune reactions (including lupus-like reactions and allergic reactions)	Labelling	None proposed.
Sarcoidosis	Labelling	None proposed.
CHF	Labelling	To educate prescribers and patients about the risk of CHF associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
MI	Labelling	None proposed.
Cerebrovascular accident	Labelling	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Interstitial lung disease	Labelling	None proposed.
Pulmonary embolism	Labelling	None proposed.
Cutaneous vasculitis	Labelling	None proposed.
SJS	Labelling	None proposed.
Erythema multiforme	Labelling	None proposed.
Worsening and new onset of Ps	Labelling	None proposed.
Haematologic disorders	Labelling	None proposed.
Intestinal perforation	Labelling	None proposed.
Intestinal stricture in CD	Labelling	None proposed.
Liver failure and other liver events	Labelling	None proposed.
Elevated ALT levels	Labelling	None proposed.
Autoimmune hepatitis	Labelling	None proposed.
Medication errors and maladministration	Labelling	None proposed.
Important potential risk		
Other malignancies (except lymphoma, HSTCL, leukaemia, NMSC, and melanoma)	Labelling	To educate prescribers and patients about the risk of malignancies associated with the use of Humira: • Patient Alert Card • HCP Educational Material.
Vasculitis (non-cutaneous)	The SmPC currently contains no text regarding vasculitis (non-cutaneous).	None proposed.
Progressive multifocal leukoencephalopathy (PML)	The SmPC currently contains no text regarding PML.	None proposed.
Reversible posterior leukoencephalopathy syndrome (RPLS)	The SmPC currently contains no text regarding reversible posterior leukoencephalopathy syndrome.	None proposed.
Amyotrophic lateral sclerosis (ALS)	The SmPC currently contains no text regarding reversible ALS.	None proposed.
Adenocarcinoma of colon in UC patients	Labelling	None proposed.
Infection in infants exposed to adalimumab in utero	Labelling	None proposed.
Medication errors with paediatric vial	Labelling	None proposed.
Off-label use	The SmPC currently contains no text regarding off-label use.	None proposed.
Missing Information		
Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver	Labelling	None proposed.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications		
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD and pedERA	Labelling	None proposed.
Pregnant and lactating women	Labelling	None proposed.
Remission-withdrawalretreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and JIA	The SmPC currently contains no text regarding remission withdrawal-retreatment in nr-axSpA or episodic treatment in Ps, CD, UC, and JIA.	None proposed.
Long-term safety information in the treatment of adults with HS	Labelling	None proposed.
Long-term safety information in the treatment of adults with uveitis	Labelling	None proposed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes to the section 4.1 are highlighted below; for full changes please refer to the Product information.

Hidradenitis suppurativa (HS)

Humira is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults ***and adolecents*** ~~*patients*~~***from 12 years of age*** *with an inadequate response to conventional systemic HS therapy* ***(see sections 5.1 and 5.2)****.*

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

“No additional consultation with target patient groups is included in this application, since the changes to the package leaflet proposed are minimal, and similar to information already presented in the package leaflet for the adult hidradenitis suppurativa indication and other indications.”

3. Benefit-Risk Balance

Benefits

Beneficial effects

HS is a serious, chronic, inflammatory skin disease of the hair follicle that usually presents with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, such as the axillary, inguinal and anogenital regions. The disease is characterized by recurrent inflamed nodules and abscesses, which may rupture to form fistulas and ooze purulent drainage and lead to scarring. HS is associated with several complications like the development of anal, urethral and rectal strictures and fistulas. Scarring and fibrosis can lead to contractures and limitations in limb mobility. HS has a severely negative impact on quality of life, which is often worse compared to other skin diseases.

Humira (adalimumab) was approved in the HS indication in adults in 2015. There are few randomized, controlled trials of medical therapies or other interventions in the treatment of HS. Thus, treatments vary widely and are not well characterized. These include medical treatments (e.g. systemic therapy with clindamycin and rifampicin, tetracyclines, intralesional triamcinolone and others), surgical treatments and laser treatment.

The application for Humira in the adults HS indication was supported by two adequately designed and performed phase 3 studies in subjects with moderate to severe HS. Both studies met the primary efficacy end-point (Hidradenitis Suppurativa Clinical Response, HiSCR), albeit with different size of the effect vs. placebo (42% and 59%, respectively, for HiSCR at week 12 vs. 26-27% for placebo). Thus, it was concluded that the efficacy of adalimumab in adults with moderate to severe HS was deemed clinically relevant, including positive outcomes related to patient-reported QoL. The indication approved in adults is a second line indication, in patients with an inadequate response to conventional systemic HS therapy. A second line indication is presently applied for adolescents.

To prevent the risk of overdosing, a loading dose regimen in adolescents of 80mg has been proposed by the MAH. The MAH has also proposed to introduce the possibility to increase the dose to the adult maintenance dose (40 mg ew) in case of insufficient response. This dosing regimen is considered satisfactory by the CHMP.

Uncertainty in the knowledge about the beneficial effects

The current application relates to an extension of the adult HS indication to include adolescents from the age of 12 years with HS. This application is based solely on extrapolation and no clinical data are available in adolescents with HS. In order to use an extrapolation approach, it has to be assumed with reasonable certainty that the PK/PD relationship is similar in adults and adolescents. Due to the rarity of the condition, there is limited information to support this view; however, since the condition seems to occur mainly after onset of puberty and likely has a hormonal component, it seems reasonable that the condition is similar in adolescents and adults.

Risks

Unfavourable effects

Adalimumab has been approved for more than 10 years and its safety profile is well characterized at this stage, with infections and risks related to malignancies being well-known risks. The proposed dosing schedule for Humira in adult HS is quite intense, and HS is one of the highest dosed indications for Humira. Still, the safety profile of adalimumab in the adult HS studies did not appear different from what

that previously observed with adalimumab in other indications, except for rather frequent reporting of hidradenitis as an AE. This included the rate or severity of infections, including SSTIs.

Adalimumab is approved for use in children and adolescents in other indications, e.g. for the treatment of paediatric patients with pJIA (> 2 years), ERA (≥6 years), CD (≥6 years), and Ps (>4 years). The maximal dosing regimens (40 mg eow) are similar to that proposed for adolescent HS. However, in paediatric CD, an intense loading dose regimen (160 mg + 80 mg) and maintenance dose (40 mg ew) may be used in certain cases. The incidence of treatment emergent AESI was found similar across these paediatric indications and no new safety signals compared with adults have been identified.

Uncertainty in the knowledge about the unfavourable effects

As mentioned above, no clinical data are available in adolescents with HS. Hence, the safety profile in the population targeted in this extension application is based on extrapolation from use in other indications.

The experience of use of high loading dose regimens in paediatric patients is not large; however, no unexpected safety findings were observed in in paediatric CD subjects from 6 years of age in which similar or higher induction doses were used and no apparent relationship between adalimumab exposure and total AE or infectious AE rates in paediatric CD subjects was observed.

Use of a 40 mg ew regimen in adolescents has sufficient support from use in paediatric Crohn´s disease, albeit with limited data from clinical trials. In addition, sufficient reassurance is given from the use of Humira 40mg ew in adult patients with RA and Ps with insufficient response to 40 mg eow.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The use of PK and PKPD modelling to extend the adult HS indication to adolescents is considered the best option available considering the very low prevalence of HS in adolescents and is also in accordance with the PIP for Humira in HS. Even if the condition is rare, in particular in the adolescent group, it does exist in adolescents and well-studied treatments are overall few in HS.

To prevent the risk of overdosing, a loading dose regimen in adolescents of 80mg has been proposed by the MAH. The MAH has also proposed to introduce the possibility to increase the dose to the adult maintenance dose (40 mg ew) in case of insufficient response. This dosing regimen is considered satisfactory by the CHMP.

From a safety perspective, the safety profile isn't expected to be substantially different for this age group and indication compared with those already approved. Humira can be used in children as young as 2 years in other indications, so there is experience from use in paediatric patients. The target group for this indication is adolescents 12-17 years old, thus, not a very young population, so large differences vs. adults are not expected. No specific safety issues are foreseen for this new target group. Use of a loading dose regimen and an every week posology (if needed) has support from safety data in other indications. In addition, no relationship between adalimumab dose or exposure with safety has been observed.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The current application relates to an extension of the adult HS indication to include adolescents from the age of 12 years with HS. This application is based solely on extrapolation and no clinical data are available in adolescents with HS.

To prevent the risk of overdosing, a loading dose regimen in adolescents of 80mg has been proposed by the MAH. The MAH has also proposed to introduce the possibility to increase the dose to the adult maintenance dose (40 mg ew) in case of insufficient response. This dosing regimen is considered satisfactory by the CHMP.

No specific safety issues are foreseen for this new target group. Use of a loading dose regimen and an every week posology (if needed) has support from safety data in other indications.

In conclusion, the CHMP considers that the benefit-risk is positive for this extension of indication in hidradenitis suppurativa for adolescents from 12 years of age.

4. Recommendations

Outcome

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**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adolescents from 12 years of age with hidradenitis suppurativa for Humira; as a consequence, sections 4.1, 4.2, 5.1 and 5.2, of the SmPC are updated. The Package Leaflet and the RMP (version 12.1.1) are updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and RMP (final version 12.1.1).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0121/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment of adolescents from 12 years of age with hidradenitis suppurativa for Humira; as a consequence, sections 4.1, 4.2, 5.1 and 5.2, of the SmPC are updated. The Package Leaflet and the RMP (version 12.1.1) are updated in accordance.

Summary

Please refer to the published Assessment Report Humira H-481-II-154-AR.