London, 23 June 2005
Product name: **HUMIRA**
Procedure number: **EMEA/H/C/481/II/21**

SCIENTIFIC DISCUSSION

1 Introduction

Adalimumab is a recombinant human immunoglobulin (IgG_1) monoclonal antibody containing human peptide sequences that binds to human Tumor Necrosis Factor (TNF) and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

When this application was submitted, Humira (adalimumab) was approved for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to other disease modifying anti-rheumatic drugs (DMARDs).

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterised by progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction until enough damage occurs to interfere with function of the joint.

Studies have demonstrated the potential benefit of early treatment with anti-TNF inhibitors alone or in combination with methotrexate (MTX) for recently diagnosed RA subjects.

The MAH submitted one pivotal study, Study DE013 (PREMIER), to demonstrate the safety and efficacy of adalimumab + MTX combination therapy in the treatment of moderately to severely active RA in adult subjects who were recently diagnosed (< 3 years) and who had not been previously treated with MTX.

Based on this study, the MAH proposed an extension of the indication for Humira to include treatment of recently diagnosed patients with moderately to severely active RA who have not been previously treated with MTX.

The MAH proposed to amend the text of the SPC, sections 4.1, 4.8 and 5.1 with the results from the DE013 study, and to update the PL accordingly.

2 Clinical aspects

To support the new indication “treatment of early RA”, the MAH submitted a single pivotal phase 3 study, DE013 (PREMIER).

2.1 Clinical efficacy

Study DE013

The PREMIER study was a prospective multi-centre randomised, double-blind, active comparator-controlled, parallel-groups study comparing adalimumab given every second week with methotrexate (MTX) given weekly and the combination of adalimumab and MTX administered over 2 years in patients with early rheumatoid arthritis.

Methods

Study Population

Adults ≥ 18 years with a diagnosis of active RA as defined by the 1987-revised ACR (American College of Rheumatology) criteria (≥ 8 swollen joints out of 66 joints assessed and ≥ 10 tender joints out of 68 joints assessed) with disease duration < 3 years. Subjects were not to have received previous treatment with MTX, cyclophosphamide, cyclosporin, azathioprine, or more than two other DMARDs.
The study population of Study DE013 had an average duration of RA since diagnosis of 0.8 years. The study population was MTX-naïve and most (67.5%) had not previously received any DMARD for the treatment of their RA. Eighty-three percent (83%) of the subjects were rheumatoid factor (RF) positive.

The mean tender joint count was 31.6 and the mean swollen joint count was 21.6. The overall activity score, as measured by the DAS28, was 6.3, indicating high disease activity.
The mean age was 52 years and 74.5% of subjects were female.

Treatments

Subjects were randomised 1:1:1 to one of three treatment groups:

- adalimumab 40 mg every other week (eow) sc (adalimumab + placebo weekly);
- adalimumab 40 mg eow together with weekly MTX; or
- weekly MTX (MTX + placebo eow).

Adalimumab + Placebo Escalation/De-escalation:
The dosing interval of the blinded parenteral study medication was to be decreased from eow to weekly in subjects who failed to respond, or who lost their response, on or after 16 weeks of treatment. Failure to respond was defined as not reaching an ACR20 response compared to baseline on two consecutive visits at least two weeks apart. The individual dose of the blinded oral study medication was to have been optimised (i.e the highest tolerated dose was to be administered for at least 6 weeks)

MTX + Placebo Escalation/De-escalation**:**
Oral MTX was started at 7.5 mg/week and was to have remained at this dose for four weeks. In the presence of any remaining swollen joints, the dose was increased to 15 mg from Week 5 forward for an additional 4 weeks and to a total of 20 mg from Week 9 forward (completed by Week 26).
In cases of more typical MTX toxicities, the dose of MTX was reduced to ≥7.5 mg/week. If MTX was required to be reduced below 7.5 mg/week, subjects should be withdrawn from the study. MTX reduction was predefined in relation to ALT increases. Study medication was also to be withdrawn if AST or ALT remained elevated (≥2 X ULNl) despite MTX dose reduction. This was also applicable if AST or ALT remained elevated 1.5-2 X ULN for more than 12 weeks.

Outcomes/Endpoints

The primary objective was to examine the efficacy and safety of adalimumab in combination with MTX *vs.* MTX monotherapy in the treatment of early RA. If this primary objective was met, a second primary analysis was to be performed to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression as measured by change from Baseline in modified Total Sharp Score (TSS) at Week 52.

Additional objectives included an assessment of the role of the study treatments in the therapy of subjects with early RA using other secondary efficacy parameters.

Efficacy Variables

Primary Efficacy Variables
The two primary efficacy endpoints were:
1. Proportion of subjects who achieved an ACR50 response at Week 52 between adalimumab + MTX combination therapy and MTX monotherapy; and
2. Change from Baseline in modified Total Sharp Score (TSS) between adalimumab + MTX combination therapy and MTX monotherapy at Week 52.

If primary endpoint number 1 was met, the second primary endpoint was to be analysed to investigate whether adalimumab + MTX combination therapy is superior to MTX monotherapy in the inhibition of radiographic progression.

ACR50 Responder Criteria
Subjects were considered to have an ACR50 'responder' status if the following three criteria were met:
≥50% improvement from Baseline in TJC and in SJC and in three of the following five parameters:
a. Patient's Assessment of Pain (VAS).
b. Patient's Global Assessment of Disease Activity (VAS).
c. Physician's Global Assessment of Disease Activity (VAS).
d. Subject's self-assessment of physical function (Disability Index of the HAQ).
e. Acute phase reactant value (CRP).

The secondary Efficacy Variables included assessment of ACR20, ACR50, and ACR70; HAQ; SF-36, DAS28, TSS, ACR-N at various time points throughout the study.

Regarding the modified Total Sharp Score at week 52, the CHMP requested additional justification on why analysis of inter- and intra-reader reliability was not conducted, and on the chosen cut-off value for the modified Total Sharp score and its clinical relevance.

The MAH provided additional information explaining the inter-reader agreement. Additionally, justification was provided on the fact that no specific cut-off value for minimal clinically important change in TSS was predefined. Evolution of mean change in TSS from baseline provided acceptable support of superiority of adalimumab *vs.* MTX. As for ACR, all data support that adalimumab should, preferentially, be used with MTX.

The MAH was further asked to explain the reasons why TSS was missing for 66 patients in the adalimumab+MTX group, and 85 in the MTX arm. The MAH informed that the primary reason for different percentages of missing x-rays was the different discontinuation rates for the two groups. At the end of 104 weeks there were 65 subjects who prematurely terminated in the adalimumab + MTX combination therapy group and 88 from the MTX monotherapy group. Comparable percentages terminated from each group due to adverse events (AEs) (11.9% and 7.4% in the adalimumab + MTX and MTX groups, respectively) as well as other reasons for early termination. However, the one exception was termination due to lack of efficacy, which was less common in the adalimumab + MTX combination therapy group (4.9%) than the MTX monotherapy group (17.9%). While this difference was pronounced at Week 52 when the primary analysis was performed, the overall early discontinuation rates and missing x-rays were comparable between the groups at Week 52. Hence the MAH considered that the evaluation of the co-primary endpoint was still valid.
The CHMP noted that the level of missing data was higher than optimal. However, it appeared reasonable that the much more frequent loss of X-rays from the MTX arm due to discontinuation for lack of efficacy argues against bias in favour of adalimumab. It was considered unlikely that any sensitivity analysis would change conclusions reached previously.

Results

Patients disposition

A total of 799 subjects received at least one injection of study medicinal product and were analysed. Overall, a total of 539 subjects completed 2 years: 169 (65.8%) who received MTX monotherapy, 167 (60.9%) who received adalimumab monotherapy, and 203 (75.7%) who received adalimumab + MTX combination therapy.

Overall, a total of 260 subjects prematurely terminated the study: 88 (34.2%) who received MTX monotherapy, 107 (39.1%) who received adalimumab monotherapy, and 65 (24.3%) who received adalimumab + MTX combination therapy. Subject disposition at Week 52 was comparable to that observed at Week 104.

Overall the disease activity seems to reflect a population of moderate to severe active disease. Disposition of patients including terminated patients reflect the intended use of the combination therapy up to 2 year.

Efficacy results

Adalimumab + MTX combination therapy was compared to MTX monotherapy and adalimumab monotherapy using two co-primary endpoints: the proportion of subjects who achieved ACR50 response at 52 weeks and the change from Baseline in modified Total Sharp Score (TSS) after 52 weeks. The chosen primary endpoints and respective timepoints are consistent with regulatory guidance. Study DE013 was in compliance with GCP and the Declaration of Helsinki, and utilised current standard research approaches regarding design, conduct, and analysis.

The results of primary and secondary endpoints are presented in the Tables below.

Table 1. ACR Responses

ACR Responses (percent of patients)						
Response	**MTX n=257**	**Humira n=274**	**Humira/MTX n=268**	**p-value[a]**	**p-value[b]**	**p-value[c]**
ACR 20						
Week 52	62.6%	54.4%	72.8%	0.013	<0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	<0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	<0.001	<0.001	0.317
Week 104	42.8%	36.9%	59.0%	<0.001	<0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	<0.001	<0.001	0.656
Week 104	28.4%	28.1%	46.6%	<0.001	<0.001	0.864

a. p-value is from the pairwise comparison of methotrexate monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test.

b. p-value is from the pairwise comparison of Humira monotherapy and Humira/methotrexate combination therapy using the Mann-Whitney U test

c. p-value is from the pairwise comparison of Humira monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Table 2. Change in Modified Total Sharp Score from Baseline at Weeks 52 and 104 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[a]	p-value[b]
Week 52					
Baseline (mean ± SD)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 52 (mean ± SD)	27.6 ± 24.6	21.8 ± 19.7	19.4 ± 19.9		
Change at Week 52 (mean ± SD)	5.7 ± 12.7	3.0 ± 11.2	1.3 ± 6.5	<0.001	0.002
Week 104					
Baseline (mean ± SD)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 104 (mean ± SD)	32.3 ± 30.0	24.3 ± 23.2	20.0 ± 20.5		
Change at Week 104 (mean ± SD)	10.4 ± 21.7	5.5 ± 15.8	1.9 ± 8.3	<0.001	<0.001

Note: An increase in modified TSS is indicative of disease progression and/or joint worsening. In contrast, no change in modified TSS represents a halting of disease progression and a decrease represents improvement.

Note: Primary analysis imputation used for missing data.

a. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

b. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

Table 3. Subjects With No Worsening in Modified TSS and Components from Baseline at Weeks 52 and 104 (All Randomized Subjects)[a]

	MTX (N = 257)		Adalimumab (N = 274)		Adalimumab + MTX (N = 268)			
	N	n (%)	N	n (%)	N	n (%)	p-value[b]	p-value[c]
Modified TSS								
Week 52	257	96 **(37.4)**	274	139 **(50.7)**	268	171 **(63.8)**	<0.001	0.002
Week 104	257	86 **(33.5)**	274	122 **(44.5)**	268	164 **(61.2)**	<0.001	<0.001
Erosion score								
Week 52	257	111 (43.2)	274	165 (60.2)	268	190 (70.9)	<0.001	0.009
Week 104	257	104 (40.5)	274	143 (52.2)	268	184 (68.7)	<0.001	<0.001
JSN score								
Week 52	257	145 (56.4)	274	174 (63.5)	268	208 (77.6)	<0.001	<0.001
Week 104	257	123 (47.9)	274	166 (60.6)	268	194 (72.4)	<0.001	0.004

JSN: joint space narrowing

Note: Primary analysis imputation was used for missing data.

a. No worsening defined as change from Baseline as ≤ 0.5.

b. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

c. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

Of the subjects who completed the 2-year double-blind period of the study, only 13 (4.9%) subjects in the adalimumab + MTX combination group withdrew due to a primary reason of unsatisfactory

therapeutic effect compared to 52 (19.0%) subjects in the adalimumab monotherapy group and 46 (17.9%) subjects in the MTX monotherapy group.

The CHMP requested supplementary information. The MAH was asked to submit the results for the clinical endpoints ACR20 response at 6 months and AUC ACR-N from 0-6 months. The MAH submitted the requested data and results from AUC ACR N at 6 months were shown statistically significantly in favour of the combination group compared with monotherapy. ACR20 was not significantly different at 6 months but ACR 50 was accepted as a more stringent level of efficacy.

The CHMP requested supplementary information on how many patients required dose escalation and how this affected efficacy (or safety) and a further justification on the dosing regimen proposed. The MAH informed that the proportion of patients who dose escalated and had a response at Weeks 52 and 104 was similar for all three treatment groups. In addition, the number (%) of subjects achieving a response after dose escalation at these timepoints was small for ACR20, ACR50, and DAS28 < 2.6. Thus, patients for whom the dose was escalated had only a small contribution to the outcome of efficacy endpoints at Weeks 52 and 104. The MAH provided data that show that 40 mg eow is the appropriate dose for this patient population, and that dose escalation may be beneficial for a very small proportion of patients only. Thus, there is no reason to recommend a dose escalation of adalimumab, as only a very small proportion of patients would benefit from this. Consequently, the recommended dose of adalimumab is 40 mg e.o.w.

Discussion on clinical efficacy

Efficacy at week 52 and 104 is in favour of the combination of adalimumab and MTX v.s. both the monotherapy options as measured by the primary endpoints ACR50 and x-ray score. The CHMP also noted that secondary efficacy variables indicate similar efficacy with the two monotherapies and the combination is statistically significantly superior to both, as measured with ACR20/50/70, ACR-N and as major clinical response.

However, the CHMP noted that adalimumab monotherapy seems to have greater efficacy than MTX monotherapy on X-ray outcomes but not on signs and symptoms. The MAH was requested to further explain this. After the submission of supplementary information from the MAH, it was concluded that adalimumab in combination with MTX is more effective than adalimumab monotherapy, and that this option is the one to be recommended primarily in the SPC. However, for patients who do not tolerate MTX, adalimumab monotherapy might be an alternative, which is also reflected in the SPC.

A comparison of all efficacy endpoints following one and two years of treatment for the combination of adalimumab + MTX therapy demonstrates the persistence of response throughout the study, e.g as evident by the ACR 70 response which was maintained for six continuous months. Following 104 weeks of treatment, 48.5% (130/268) of subjects who received adalimumab + MTX combination therapy achieved a major clinical response, thereby demonstrating the persistence of response over two years. The results of efficacy analyses do not indicate any loss of efficacy over time for the adalimumab treatment groups.

2.2 Clinical safety

Patient exposure

The extent of exposure is presented in the Table 4 below. With regard specifically to adalimumab exposure, all subjects randomized to either the adalimumab + MTX combination therapy group or the adalimumab monotherapy group received adalimumab for at least four weeks. Longer durations of exposure to adalimumab were seen in those subjects treated with adalimumab + MTX combination therapy (e.g., 221 of 268 subjects [82.5%] received adalimumab for greater than 52 weeks) than in those subjects treated with adalimumab monotherapy (e.g., 195 of 274 subjects [71.2%] received adalimumab for greater than 52 weeks).

Table 4. Extent of Exposure and Cumulative Exposure (Safety Analysis Set)

	MTX (N = 257)	**Adalimumab (N = 274)**	**Adalimumab + MTX (N = 268)**
Duration of Treatment (days)			
N	257	274	268
Mean ± SD	575.2 ± 244.6	545.1 ± 258.4	621.7 ± 216.7
Median	728.0	727.0	729.0
Range (min-max)	1.0 – 773.0	1.0 – 749.0	1.0 – 807.0
Adalimumab Exposure, n (%)	N/A		
<= 4 weeks	N/A	274 (100)	268 (100)
>4 weeks	N/A	271 (98.9)	264 (98.5)
>12 weeks	N/A	256 (93.4)	257 (95.9)
>26 weeks	N/A	225 (82.1)	244 (91.0)
>52 weeks	N/A	195 (71.2)	221 (82.5)
>76 weeks	N/A	179 (65.3)	213 (79.5)
>104 weeks	N/A	135 (49.3)	174 (64.9)

N/A: Not applicable

Adverse events

All subjects who received at least one dose of study medication were included in the safety analysis (MTX monotherapy = 257, adalimumab monotherapy = 274, adalimumab + MTX combination therapy = 268).

The overall incidences of treatment-emergent Adverse events reported across the three treatment groups were comparable: MTX monotherapy (95.3%), adalimumab monotherapy (95.6%) and adalimumab + MTX combination therapy (97.8%).

There were 11.3% (29 of 257) of subjects in the MTX monotherapy group, 13.9% (38 of 274) of subjects in the adalimumab monotherapy group, and 12.7% (34 of 268) of subjects in the adalimumab + MTX therapy treatment group who discontinued study medicinal product due to an AE.

The overall percentage of infectious Adverse events was higher in the adalimumab + MTX combination group (77.2%) than in the MTX (68.1%) or adalimumab (67.5%) monotherapy groups. This difference was statistically significant (p = 0.020) and the pair wise comparisons between each monotherapy arm and the combination therapy arm were also statistically significant. The overall percentage of serious infectious Adverse events was 4.9% in the adalimumab + MTX, 2.7% in the MTX group, and 1.1% in the adalimumab treatment groups; the differences were statistically significant (p = 0.033).

The most frequent (>5% of subjects in any treatment group) treatment-emergent infectious Adverse events were nasopharyngitis, upper respiratory tract infection, pharyngitis, sinusitis, herpes simplex, urinary tract infection, bronchitis, and influenza.

Serious adverse events, malignancies and deaths

a) Serious adverse events

The most common serious infectious Adverse events reported by subjects among the three treatment groups were pneumonia, septic arthritis, and cellulitis.

There was one case of tuberculosis reported in the adalimumab + MTX combination therapy arm.

There were no demyelinating events reported.

One case of a lupus-like reaction was reported in Study DE013 by a subject who received adalimumab monotherapy.

Two subjects had serious adverse events coded as heart failure, one in each of the monotherapy arms.

b) Malignancies

Table 5. Number (%) of subjects with neoplasms occurring in two or more subjects in any treatment group

Adverse Event System Organ Class Preferred Term	**MTX (N= 257)**	**Adalimumab (N = 274)**	**Adalimumab + MTX (N =268)**
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)			
Basal Cell Carcinoma	**0**	**0**	**2 (0.7)**

No statistically significant difference was observed in the percentage of subjects with malignancies, overall (p = 0.807) or excluding non-melanoma skin cancers (p = 0.727), across treatment groups Treatment-emergent malignancies, including skin cancers, were reported by 15 subjects (5 of 257 subjects [2.0%] in the MTX monotherapy group, 4 of 274 subjects [1.5%] in the adalimumab monotherapy group, and 6 of 268 subjects [2.2%] in the adalimumab + MTX combination therapy group). Treatment-emergent malignancies excluding non-melanoma skin cancers were reported by 10 subjects (4 of 257 subjects [1.6%] in the MTX monotherapy group, 4 of 274 subjects [1.5%] in the adalimumab monotherapy group, and 2 of 268 subjects [0.8%] in the adalimumab + MTX combination therapy group). One lymphoma was observed (in the MTX monotherapy arm).

c) Deaths

A total of six deaths (0.7% of 799 subjects) were reported over the two-year double-blind period of the study. Four of these deaths occurred in the adalimumab arm and one each occurred in the MTX and combination arms.

Table 6. Subjects with Adverse Events Leading to Death (Safety Analysis Set)

Subject No.	Sex	Age	Treatment Group	Days on Drug at Onset	Duration of AE	Serious Adverse Event Preferred Term	Study Drug Relationship[a]
160-06	M	58	MTX	25	21	Lobar Pneumonia NOS	POS
032-14[b]	M	78	adalimumab	476	280	Colon Cancer Stage IV	UNLIKE
060-02	M	74	adalimumab	539	57	Hepatic Necrosis	POS
067-12	F	48	adalimumab	611	1	Death NOS	POS
160-07	M	78	adalimumab	50	6	Metastases to Liver	POS
025-05	F	61	adalimumab + MTX	378	553	Ovarian Cancer NOS	POS

NOS: Not otherwise specified

a. According to the Investigator.

b. These subjects were diagnosed during the study, but did not experience death until after study discontinuation.

Study Drug Relationship: UNLIKE = unlikely to be related; POS = possibly related.

Laboratory findings

Statistically significant differences between the mean changes in the adalimumab + MTX combination therapy group and the MTX monotherapy group were observed for 5 of the 19 clinical chemistry parameters (alkaline phosphatase, AST, bilirubin, CK, and cholesterol).
Of these five parameters, three were liver function tests. Relative to the MTX monotherapy group, the adalimumab + MTX combination therapy group showed a greater mean decrease in alkaline phosphatase (-21.8 IU/l vs. –11.8 IU/ l). The adalimumab + MTX combination therapy group had greater mean increases in AST (2.5 IU/ l vs. 1.5 IU/ l) and total bilirubin (2.2 µmol/ l vs. 1.4 µmol/ l).
The other two chemistries that were significantly different between the adalimumab + MTX combination therapy group and the MTX monotherapy group were cholesterol (0.5 mmol/ l vs. 0.2 mmol/ l) and CK (10.9 IU/ l vs. 4.9 IU/ l).

Discussion of clinical safety

The CHMP concluded that the adverse event profile was similar to the one previously seen in the currently approved indication. However, a tendency towards more infections in the combination therapy group was found, which was not considered surprising.

The CHMP noted that antibody data were lacking and should be submitted. In particular long-term effects with monotherapy should be discussed and described in relation to antibody findings. In a request for supplementary information the MAH provided data from the initial submission for RA that show that the presence of antibodies to adalimumab is higher in monotherapy, 12%, versus 1% in combination therapy. Antibody status among non-responders and those with relapse was evaluated. Both antibody positive and negative patients were found in these groups, with a majority of the negative, and thus no clear correlation to non-response was found. Since data from responders on monotherapy was not presented, the antibody profile in this population is unknown. Interruption of dose was not possible to evaluate as the number of patients was too low.

Furthermore, the CHMP noted the tendency towards increased levels in the Liver Function Tests, in the adalimumab+MTX combination group. The MAH was requested to submit further documentation to demonstrate any possibly treatment-related changes throughout the duration of the trial and comment as to the possible mechanism of these changes. Additionally, the MAH was asked to discuss the need for monitoring of liver enzymes during treatment with adalimumab. The MAH submitted supplementary information and detailed that the data presented on liver function tests and hepatic events do not indicate

any new alarming findings. Monitoring of hepatic enzymes is mandatory during treatment with MTX. However, specific monitoring of hepatic events due to treatment with adalimumab is not considered necessary. The CHMP agreed with the justification.

3. Overall Discussion and benefit/risk assessment

The overall risk/benefit of treatment in patients with RA with a disease duration up to 3 years without previous methotrexate therapy, is in favour of methotrexate and adalimumab given in combination. Adalimumab in monotherapy is similar to MTX in monotherapy. Existing clinical data demonstrate that combination of antiTNF therapy and MTX is superior to MTX or antiTNF monotherapy for both clinical and radiological outcomes. This is supported by the data submitted for adalimumab.

Taking into account ACR, clinical remission and TSS data, it appears reasonable to conclude that adalimumab monotherapy could be an alternative to MTX. However, adalimumab should preferentially be used with MTX. Therefore, the indication should recommend the combination of MTX and adalimumab. However, as for the already approved RA indication, a possibility to treat patients who are intolerant to MTX should be possible. The proposed indication is: "*Humira in combination with methotrexate, is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.*"

A full description of the PREMIER data, including all three-treatment arms, is of value for the prescriber, to allow for a benefit/risk assessment for the treatment of the individual patient. Thus, the CHMP requested that the results from combination therapy as well as the two-monotherapy groups should be described in section 5.1 of the SPC.

No unknown safety signals have been found in the submitted study; although elevated hepatic enzymes were more common in the MTX + adalimumab monotherapy compared with both monotherapy arms.

The CHMP recommended that follow-up programmes be continued.

CONCLUSION

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and the Package Leaflet.

The CHMP adopted on 23 June 2005 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.