



European Medicines Agency

London, 18 October 2007

Product name: Remicade

Procedure number: EMEA/H/C/240/II/100

SCIENTIFIC DISCUSSION

Introduction

Infliximab is a chimeric human-murine IgG1 κ monoclonal antibody, which binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF) α and inhibits the functional activity of TNF α .

Remicade (infliximab) is currently approved for the treatment of rheumatoid arthritis (RA), adult and paediatric Crohn's disease (CD), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis and ulcerative colitis (UC).

PsA is a chronic, inflammatory, usually rheumatoid factor (RF)-negative arthritis associated with psoriasis. According to EU guidance for treating PsA, psoriasis is prevalent in 1% to 3% of the population. Estimates of those psoriasis patients who develop PsA vary widely (6%-42%). Affecting men and women equally, PsA typically appears between the ages of 30 and 50 years. PsA usually involves multiple peripheral joints, the axial skeleton, sacroiliac joints, fingernails, and entheses. The presentation of PsA has been categorised into 5 overlapping clinical patterns, which include oligoarthritis, polyarthritis, arthritis of distal interphalangeal (DIP) joints, spondylitis, and arthritis mutilans. More than one-half of the patients with PsA may have evidence of erosions on X-rays, and up to 40% of the patients may develop severe, erosive arthropathy.

The MAH (marketing authorisation holder) applied to change the PsA indication, adding that infliximab has been shown to improve physical function and inhibit the progression of structural damage of active arthritis, as measured by X-ray.

The current approved dose of infliximab for treating active and progressive PsA is 5 mg/kg, administered at weeks 0, 2, and 6, followed by a maintenance regimen q8 (every 8) weeks. Infliximab may be administered in combination with methotrexate (MTX) or as monotherapy in patients who are intolerant to MTX or have a contraindication to the use of MTX. The same dosing regimen is supported by additional data demonstrating inhibition of structural damage.

Clinical aspects

The clinical development program for infliximab for the treatment of PsA consisted of 2 controlled clinical trials, IMPACT (study P02114) and IMPACT II (study C0168T50).

Study P02114 (IMPACT)

Design: An investigator-initiated, multicentre study in subjects with PsA and peripheral polyarticular arthritis who had failed at least 1 disease modifying antirheumatic drug (DMARD). This study was conducted at 9 study centres in Austria, Canada, England, Germany, and the US. The study design included a 16-week, randomised, double-blind, placebo-controlled treatment (Stage I), followed by a 34-week, open-label treatment period (Stage II).

Objectives: The primary objective was to study efficacy (ACR20¹) of infliximab compared with placebo at week 16 and to determine safety of infliximab. Secondary objectives were to follow response of skin involvement, percentage ACR20 over time, and ACR50 and 70, Disease activity score (DAS), Psoriatic arthritis response criteria (PsARC), AUC percentage, ACR improvement (ACRn), and change in joint scores at week 16 and week 50.

Diagnosis and Main Criteria for Inclusion: Subjects had to be 18 years of age or older with a diagnosis of active PsA with peripheral polyarticular involvement and at least one of the following: Distal phalangeal (DIP) involvement, polyarticular arthritis, with absence of rheumatoid nodules and

¹ ACR, American College of Rheumatology response criteria. The ACR response criteria were developed for RA. The ACR20 criteria is defined as a $\geq 20\%$ reduction in the tender joint count, a $\geq 20\%$ reduction in the swollen joint count and a $\geq 20\%$ reduction in 3 of 5 additional measures: a) patient assessment of pain, b) patient global assessment of disease activity, c) physician global assessment of disease activity, d) disability index of the health assessment questionnaire (HAQ) and, e) acute phase reactant.

presence of psoriasis, arthritis mutilans or asymmetric peripheral arthritis, negative RA-factor, at least 6 months since diagnosis. Subjects should have had at least 1 DMARD failure. If on a DMARD, the dose must have been stable since 4 weeks. Corticosteroids were allowed if stable <10mg/day.

Number of Subjects: The study initially enrolled 104 subjects, of whom 87 completed year 1. Seventy eight (78) subjects continued treatment in year 2.

Treatment:

Stage I: subjects were randomly assigned to receive 5 mg/kg infliximab or placebo infusions at weeks 0, 2, 6, and 14.

Stage II: subjects on placebo initially and at weeks 16, 18, were crossed over to receive 5 mg/kg infliximab at weeks 22, 30, 38, and 46. Subjects who had been receiving infliximab received infusions of placebo at weeks 16 and 18 (to maintain the blind) and infusions of infliximab at weeks 22, 30, 38, and 46. All subjects were followed until week 50. Thereafter subjects joined the open label long-term extension to 2 years.

Study C0168T50 (IMPACT 2)

Design: A multicentre, randomised, double-blind, placebo-controlled trial for 24 weeks, with 2 parallel treatment groups (placebo and infliximab 5 mg/kg) of subjects with active polyarticular PsA. After week 24, placebo patients were switched to infliximab, although they could enter early escape already at week 16. Subjects could dose escalate at week 38. All subjects received treatment up to week 46.

Objectives: The primary objective was to evaluate the efficacy of infliximab in subjects with active PsA by assessing reduction in signs and symptoms of arthritis and prevention of structural damage. The major secondary objectives were to evaluate the efficacy of infliximab in: 1) achieving ACR 20 sustained response, 2) achieving the PsARC, 3) clearing psoriatic skin lesions, and 4) improving quality of life in subjects with PsA.

Number of Subjects: Two hundred subjects (planned) were randomised in a 1:1 ratio to infliximab 5 mg/kg (n = 100) or placebo (n = 100).

Diagnosis and Main Criteria for Inclusion: Subjects had to be 18 years of age or older with a diagnosis of active, polyarticular (5 or more joints involved) peripheral PsA for at least 6 months prior to the first infusion, and with an inadequate response to current or previous DMARD or NSAID (non-steroidal anti-inflammatory drug) therapy. Diagnosis of PsA must have included the presence of active psoriasis. Concomitant MTX at stable doses was permitted, but not required.

Mode of Administration Infliximab 5 mg/kg was infused at weeks 0, 2, 6, 14, 22, 30, 38, and 46; at weeks 16, 18, 22, 30, 38, and 46 for placebo subjects who entered early escape, and at weeks 24, 26, 30, 38, and 46 for placebo subjects who crossed over to infliximab. Infliximab 10 mg/kg was infused at weeks 38 and 46 for subjects who dose escalated.

Efficacy: The primary endpoints were the proportion of subjects with ACR 20 response at week 14 (not further addressed within the current assessment as not relevant to the claimed extension of indication) and the change from baseline in the total modified *van der Heijde* modified Sharp (vdH-S)² score at week 24. In addition, other secondary endpoints and exploratory endpoints related to structural damage were evaluated. Maintenance of responses for signs and symptoms of arthritis, physical function, skin disease, and quality of life endpoints were summarised through week 54.

² The vdH-S score is a detailed scoring method evaluating erosions, joint space narrowing, (sub)luxation, ankylosis, gross osteolysis, and pencil in cup phenomena.

Clinical efficacy

Radiographic assessments

In IMPACT, radiographic images of the hands and feet were taken at baseline, week 50 and week 98 in the long-term extension. The radiographs of all subjects were scored by 2 independent readers for joint erosion and joint space narrowing (JSN) based on the vdH-S score (*van der Heijde et al, 1992*) modified by the addition of hand DIP joints. In addition, the readers assessed the radiographs for PC ("pencil in cup" deformity) and GO (gross osteolysis), radiographic features characteristic of PsA. The erosion scores for the hand region and the foot region were a summation of the erosion scores in 40 joints of the hands and 12 joints of the feet. Erosions for each hand joint were scored from 0 to 7, and in the feet from were scored 1 to 10 (0 = no erosion in both case). The JSN scores (from 0 to 4, where 0 indicated no/normal JSN) for the hand region and the foot region were a summation of the JSN scores in 40 joints of the hands and 12 joints of the feet. The total PsA-modified vdH-S score was calculated as the sum of erosion and JSN scores from the hand and foot regions averaged by the 2 readers; ranging from 0-528.

In IMPACT 2, structural damage was assessed by the change from baseline in the total modified vdH-S score at weeks 24, 54 and at the time of study termination if the study termination occurred more than 8 weeks from the last radiograph. Erosions for each hand joint were scored from 0 to 7, and in feet from 0-12 (0 = no erosion). JSN was scored from 0 to 4 (0 indicates no/normal JSN). The total modified vdH-S score was calculated as the sum from the hand and foot regions, ranging from 0-528.

Radiographic analyses

Smallest detectable difference (SDD) and smallest detectable change (SDC)

In IMPACT 2, radiographic progression at week 24 was defined as a worsening from baseline in the modified vdH-S score that was greater than the smallest detectable difference (SDD) based on the limits of agreement (*Lassere et al, 1999*), defined as the 95% confidence limits of the difference between the 2 observed changes for the same subject and was calculated as $2.77 \times$ within subject standard deviation of the change score (*Bland and Altman, 1996*). Change from baseline at week 24 was used to calculate the SDD. SDD is related to repeatability. SDC is the 95% confidence limits of the difference between a subject's observed change and true change (*Bland and Altman, 1996*). The SDC is SDD divided by square root of 2 (*van der Heijde et al, 2005*) and was calculated as $1.96 \times$ within subject standard deviation of the change score. Change from baseline at week 24 was used to calculate the SDC.

The CHMP considered that use of the modified vdH-S score for the evaluation of the X-rays was acceptable. It was noted that there is less knowledge about the 'natural' progression rate in PsA, but that it appears to be more variable than in RA. Thus, the CHMP considered it to be even more important in this indication to have a placebo group which progresses, to demonstrate reduced rate of structural damage.

Estimates of progression rate before start of treatments

For IMPACT, the MAH estimated the average annual progression rate in radiographic damage before treatment with the study agent, based on calculations considering the duration of PsA symptoms in years. The MAH claimed that estimating progression from the start of symptoms rather than the date of diagnosis is a conservative approach and takes into account radiographic progression that may have occurred prior to diagnosis. Table 1 presents a summary of the average annual progression rates in total modified vdH-S score prior to the study and during the study (to week 98) and shows the difference between the prestudy progression rate and the progression rate observed during the study.

Table 1 Summary of average annual progression rate in total modified vdH-S score prior to and during study; evaluable subjects

	Group I	Group II	Total
Subjects randomized	52	52	104
Subjects evaluable	23	20	43
Average annual progression rate			
Prior to study	23	20	43
Mean $\pm$ SD	3.15 $\pm$ 3.62	8.72 $\pm$ 23.00	5.74 $\pm$ 15.94
Median	1.65	2.24	2.00
IQ range	(0.89, 3.81)	(0.29, 6.25)	(0.40, 5.15)
Range	(0.00, 14.29)	(0.00, 104.00)	(0.00, 104.00)
95% confidence interval	(1.27, 4.25)	(1.24, 6.7)	(1.58, 4.07)
During study	23	20	43
Mean $\pm$ SD	0.02 $\pm$ 3.89	1.38 $\pm$ 5.40	0.65 $\pm$ 4.65
Median	0.00	0.00	0.00
IQ range	(-1.29, 0.26)	(-0.53, 1.25)	(-0.81, 0.28)
Range	(-8.52, 10.27)	(-4.60, 18.64)	(-8.52, 18.64)
95% confidence interval	(-0.91, 0.43)	(-0.8, 1.08)	(-0.55, 0.5)
Difference between Prior to and During study	23	20	43
Mean $\pm$ SD	3.13 $\pm$ 6.10	7.34 $\pm$ 20.84	5.09 $\pm$ 14.85
Median	1.21	1.49	1.47
IQ range	(0.14, 8.27)	(0.12, 6.56)	(0.13, 8.02)
Range	(-7.90, 15.65)	(-18.64, 89.93)	(-18.64, 89.93)
95% confidence interval	(0.53, 5.8)	(0.71, 7.31)	(0.98, 4.93)

The CHMP noted that there is limited insufficient knowledge on the relation between progression rate, and duration of disease (occurrence of symptoms and/or diagnosis), and if the progression rate is linear. There was a clear difference in the estimated average annual progression rate prior to the study in the two groups (e.g. mean 3.1 ± 3.6 and 8.7 ± 23), despite the fact that groups were fairly well balanced at study start. The MAH justified the chosen starting point and the CHMP reiterated that to analyse the estimated annual progression rate before and at the end of infliximab treatment by dividing baseline PsA modified vdH-S score by the number of years of PsA symptom duration does not seem very reliable but rather a limited comparator.

Results

IMPACT

Radiographs were obtained from 90 of the 104 subjects enrolled in IMPACT. Of the 90 subjects who had radiographs obtained, 71 subjects had evaluable radiographs of both hands and feet at both baseline and week 50. Group I was the placebo/infliximab group, Group II received infliximab throughout the study. The Tables 2 to 4 below show main results from this study.

Table 2 Number of subjects with no worsening in modified van der Heijde modified Sharp score at baseline and Week 50; randomized subjects (excluding Subject 505)

	Group I	Group II	Combined
Subjects randomized	51	52	103
Total modified vdH-S score			
n	33	37	70
Subjects with no worsening	28 (84.8%)	31 (83.8%)	59 (84.3%)
p-value		0.903	
Erosion score			
n	33	37	70
Subjects with no worsening	30 (90.9%)	31 (83.8%)	61 (87.1%)
p-value		0.374	
JSN score			
n	33	37	70
Subjects with no worsening	28 (84.8%)	35 (94.6%)	63 (90.0%)
p-value		0.175	

Table 3 Summary of change from baseline in total modified vdH-S score to Week 98, by anatomic region; evaluable subjects

	Group I	Group II	Total
Subjects randomized	52	52	104
Subjects evaluable	23	20	43
Change from baseline at Week 98			
Hands total score			
Median (95% CI)	0.00 (-1.50, 0.25)	0.00 (-1.25, 1.50)	0.00 (-1.11, 0.25)
Mean $\pm$ SD	-1.05 $\pm$ 4.21	2.17 $\pm$ 8.71	0.45 $\pm$ 6.80
Feet total score			
Median (95% CI)	0.00 (-0.50, 0.50)	0.00 (0.00, 0.50)	0.00 (-0.25, 0.25)
Mean $\pm$ SD	0.93 $\pm$ 4.51	0.43 $\pm$ 1.70	0.70 $\pm$ 3.47
Both hands and feet total score			
Median (95% CI)	0.00 (-1.75, 1.00)	0.00 (-1.50, 2.00)	0.00 (-1.00, 1.00)
Mean $\pm$ SD	0.03 $\pm$ 7.30	2.60 $\pm$ 10.04	1.23 $\pm$ 8.67

Table 4 **Number of subjects with no worsening in modified vdH-S score at Week 98; evaluable subjects**

	Group I	Group II	Total
Subjects randomized	52	52	104
Subjects evaluable	23	20	43
Subjects with no worsening in			
Total modified vdH-S score	19 (82.6%)	14 (70.0%)	33 (76.7%)
Erosion score	20 (87.0%)	15 (75.0%)	35 (81.4%)
JSN score	19 (82.6%)	15 (75.0%)	34 (79.1%)

The CHMP considered the value of IMPACT being limited for several reasons. Firstly, X-rays were only available from a limited number of subjects. Secondly the duration of the placebo treatment was short (16 weeks), and there were no X-rays taken until week 52; thus when subjects had received infliximab for either 52 or approximately 36 weeks. Therefore, it was not possible to estimate the number of patients with no progression during placebo treatment. This is a shortcoming as, at week 50, a very high percentage of the patients, 85% in Group I and 84% in Group II had no progression in the total vdH-score. Finally, the reference to annual progression rate prior to study start was considered of a limited value. Nevertheless, the fact that the progression rate during study period was generally small is supportive of an effect. Also the limited numbers of severe X-ray findings and no occurrence of new severe damage were considered reassuring. Still, there is no possibility to, based on these data, assess the magnitude of the effect, or to find out who is responding or progressing. The year 2 data are even more limited (in total 43 subjects on infliximab). X-ray films were missing for a number of subjects, as the study protocol indicated that X-rays were “possibly taken” at week 98.

IMPACT 2

The MAH indicated that in IMPACT 2, there was a significant difference in the distribution of change from baseline in total modified vdH-S score at week 24 for the infliximab group compared with the placebo group (see Table 5 below). At Year 1, the infliximab group had significantly less progression of structural damage compared with the placebo group that consisted of subjects who had crossed over to infliximab treatment at 6 months.

The CHMP noted that the placebo controlled data at week 24 indicated fewer subjects with progression in the infliximab group (3/100) compared with the placebo group (12/100). Very few subjects appeared to progress in the active treatment period, from week 24 to week 54 (7/200). However, the CHMP considered that a proper evaluation of IMPACT 2 results was difficult due to the lack of historical data as well as the limited placebo-controlled period of the study.

Table 5 Key radiographic efficacy endpoints - IMPACT 2 and IMPACT

	<u>IMPACT 2</u>		<u>IMPACT</u>		<u>Year 2</u>
	<u>Placebo</u>	<u>Infliximab</u>	<u>Placebo</u>	<u>Infliximab</u>	<u>Combined</u> <u>Infliximab</u>
Subjects randomized	100	100	52	52	78
n	100	100	33	37	43
Radiographic Outcomes					
Change from baseline in total modified vdH-S score					
Week 24					
Mean	0.82	-0.70	NA	NA	NA
Median	0.00	0.00	NA	NA	NA
Year 1 /Year 2					
Mean	0.53	-0.94	-1.95	-1.52	1.23
Median	0.00	0.00	-0.50	-0.50	0.00
Proportion of subjects with radiographic progression greater than the SDC					
Week 24	12.0%	3.0%	NA	NA	NA
Year 1/Year 2	4.0% ^a	3.0% ^a	0%	2.7%	9.3%

^a Proportion with radiographic progression from Week 24 through Week 54.

Subgroup Analyses in IMPACT2 related to Structural Damage

The CHMP noted that there was a tendency towards less effect in the asymmetric arthritis group, i.e. the more typical PsA patients. A thorough subgroup analysis (including symmetric versus asymmetric arthritis) in relation to radiographic results was requested. The subgroup analyses were submitted for IMPACT 2, as no data were collected in IMPACT on PsA subtypes (see table 6 below). Based on the data presented, the placebo group progressed least in the asymmetric subgroup, while a slightly higher rate of progression was seen in the other subgroups. In the infliximab groups, there was no progression in any subgroup. However, this period is too short to adequately assess the effects of infliximab on progression of joint damage, since the progression rate in the placebo group is uncertain, and there is insufficient data on the natural progression rate in PsA. On the other hand, some support may be gained from RA, where more convincing data are available, from 2 years treatment with infliximab. Given that the symmetric PsA shows greatest resemblance with RA, and the PsA data are more convincing in the symmetric patients, it may be accepted to include reduction of rate of progression into section 4.1 of the summary of product characteristics (SPC).

Table 6

Change from baseline in total PsA mvdH-S score														
Median of the differences between treatment groups of the change from baseline in modified vdH-score at week 24 and week 54 and associated 95% confidence intervals for subgroups defined by baseline disease characteristics; randomised subjects														
	Placebo n	Placebo mean	Placebo median	Placebo minimum	Placebo maximum	Infliximab n	Infliximab mean	Infliximab median	Infliximab minimum	Infliximab maximum	Median Difference	Lower	Upper	pval
Week 24														
All subjects	100	0.82	0.00	-4.50	12.68	100	-0.70	0.00	-15.00	4.00	0.00	0.00	0.50	< 0.001
Arthritis involving DIPs	22	1.97	0.00	-2.00	12.68	26	-0.40	0.00	-4.50	3.50	0.50	0.00	2.00	0.017
Asymmetric peripheral arthritis	22	0.30	0.00	-4.50	5.57	18	-0.86	0.00	-8.50	1.00	0.50	0.00	1.50	0.052
Polyarticular arthritis	48	0.72	0.00	-1.08	9.77	53	-0.77	0.00	-15.00	4.00	0.00	0.00	0.50	0.005
Week 54														
All subjects	100	0.53	0.00	-6.13	12.12	100	-0.94	0.00	-29.00	3.00	0.00	0.00	0.49	0.001
Arthritis involving DIPs	22	1.22	0.00	-6.13	10.00	26	-0.66	0.00	-4.50	1.00	0.50	0.00	1.83	0.057
Asymmetric peripheral arthritis	22	0.64	0.00	-1.00	9.00	18	-0.41	0.00	-3.00	1.00	0.00	0.00	1.01	0.109
Polyarticular arthritis	48	0.32	0.00	-3.50	12.12	53	-1.31	0.00	-29.00	3.00	0.00	0.00	0.11	0.045

Pencil-in-cup Deformity (PC) and Gross Osteolysis (GO) (both studies)

The modified vdH-S scoring method incorporates separate assessments for 2 types of severe erosive processes associated with PsA: PC deformity, in which an osseous surface on the proximal bone of a joint protrudes into the expanded surface of the distal bone, and GO, which is characterized by gross destruction of the bone.

In IMPACT 2, few subjects had evidence of these severe erosive processes at baseline and there was little change in the number of joints with or without PC and GO at week 24 or week 54. Also in IMPACT, there was little change in the number of joints with or without PC and GO from baseline at week 98 in either group. None of the subjects without PC or GO at baseline were found to have developed these conditions at the week 98 follow-up. Overall, these data support slow progression in all subjects

Conclusion on efficacy:

Documentation to support the sought indication included data from two studies, IMPACT and IMPACT 2. The value of IMPACT was considered limited for several reasons. Firstly, X-rays were only available from a limited number of subjects. Secondly, in IMPACT, no X-ray evaluation was performed at the end of the placebo period of 16 weeks. Therefore, it was not possible to estimate the number of patients with no progression during placebo treatment. This is a shortcoming as at week 50, a very high percentage of the patients, 85% in Group I and 84% in Group II had no progression in the total vdH-score. Furthermore, the estimated annual progression rate prior to study start was very uncertain.

IMPACT 2 provided placebo controlled data at week 24. This period is too short to adequately assess the effects of infliximab on progression of joint damage, since the progression rate in the placebo group is uncertain, and there is insufficient data on the natural progression rate in PsA. Nevertheless, available data indicated that there were fewer subjects who progressed in the infliximab group (3/100) compared with the placebo group (12/100) at week 24. Very few appear to progress in the active treatment period, from week 24 to week 54 (7/200). Subgroup analyses were provided. At week 24, it appears that the placebo group progressed least in the asymmetric subgroup, while a slightly higher rate of progression was seen in the other subgroups. In the infliximab groups, there was no progression in any subgroup. Given that the symmetric PsA shows greatest resemblance with RA, where more convincing data are available, and the PsA data are more convincing in the symmetric patients, the CHMP accepted the inclusion of wording into section 4.1.

Clinical safety

The safety in the performed studies had been assessed within previous variation procedures, and in assessments of PSURs. There were no new data that altered previously adopted conclusions.

Risk management plan

The MAH argued that there was no need for a RMP to be provided for the current variation application. The CHMP agreed with this approach, and noted that the MAH is currently working on a RMP for infliximab, which will be submitted later this year.

Overall conclusion and benefit/risk assessment

Remicade has previously been approved for the treatment of RA, AS and PsA/psoriasis. These inflammatory conditions are to some extent similar with joint involvement and development of structural damage of varying severity and degree. Besides inflammatory control, reduction of the structural damage is one of the main goals of treatment.

Benefit

Documentation to support the sought indication included data from two studies, IMPACT and IMPACT 2. The value of IMPACT was considered limited and considered of insufficient value to warrant inclusion in the SPC.

IMPACT 2 provided placebo controlled data at week 24, indicating fewer subjects with progression in the infliximab group (3/100) compared with the placebo group (12/100). Very few appear to progress in the active treatment period, from week 24 to week 54 (7/200). However, as historical data as well as placebo-controlled data are limited, a proper evaluation of IMPACT 2 results was considered difficult.

Subgroup analyses were submitted for three groups; arthritis involving DIPs, asymmetrical peripheral arthritis, and polyarticular arthritis. Data were collected in the study specifically for “polyarticular arthritis” and “asymmetrical peripheral arthritis”, which correspond to “symmetric polyarthritis” and “oligoarticular arthritis”, respectively. Consequently, it is assumed that patients not having asymmetric disease, had symmetric disease.

Looking at the X-ray data at weeks 24, it appears that the placebo group progressed least in the asymmetric subgroup, while a slightly higher rate of progression was seen in the other subgroups. In the infliximab groups, there was no progression in any subgroup. However, this period was considered too short to adequately assess the effects of infliximab on progression of joint damage, since the progression rate in the placebo group is uncertain, and there is insufficient data on the natural progression rate in PsA. On the other hand, some support may be gained from RA, where more convincing data are available, from 2 years treatment with infliximab. Given that the symmetric PsA shows greatest resemblance with RA, and the PsA data are more convincing in the symmetric patients, it was accepted to include some wording into section 4.1.

Data on physical function were assessed within variation II-73, which resulted in wording in section 5.1 of the SPC. The application to include ‘improvement of physical function’ also in section 4.1 was therefore agreed.

Risk

No new safety data were submitted in this application.

Benefit-Risk Balance

Overall, the benefit /risk balance for the treatment of PsA remains positive.

CONCLUSION

On 18 October 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the SPC and package leaflet.