London, 23 June 2005
Product name: **HUMIRA**
Procedure number: **EMEA/H/C/481/II/22**

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 neutralises 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).

Psoriatic arthritis (PsA) is a chronic inflammatory disorder of the joints and skin, and is characterised by the association of arthritis and psoriasis. The goal of PsA treatment is to improve the joint manifestations of the disease, inhibit the structural damage to joints, improve the disability associated with the disease, improve the skin lesions, and improve the quality of life. Therapy for PsA is directed at controlling the inflammatory process. Studies with other medicinal products have demonstrated the potential benefit of treatment with anti-TNF inhibitors for psoriatic arthritis subjects.

The Marketing Authorisation Holder (MAH) submitted a clinical development program to demonstrate the safety and efficacy of adalimumab alone or in combination with disease modifying anti-rheumatic medicinal products in the treatment of psoriatic arthritis. It consisted of two placebo-controlled Phase 3 clinical studies (M02-518 and M02-570) and an interim report of the open-label long-term extension study (M02-537).

The MAH proposed to amend the text of the SPC, sections 4.2, 4.8 and 5.1 with the results from the M02-518, M02-570 and M02-537 studies, and to update the Package Leaflet accordingly.

2 Clinical aspects

To support the introduction of the new indication “psoriatic arthritis”, the MAH submitted 3 studies, 2 pivotal studies (M02-518, M02-570) and the interim report of one open label long-term extension study (M02-537).

2.1 Clinical pharmacology

The clinical pharmacology (pharmacokinetics/pharmacodynamics) and immunogenicity of adalimumab have been characterised in healthy subjects as well as in rheumatoid arthritis (RA) patients. The data has been provided in previous submissions for RA, therefore, separate clinical pharmacology studies in patients with PsA were not conducted.

An adalimumab dose of 40 mg every other week (eow) was selected for use in all PsA studies based on studies in RA where 1380 subjects received adalimumab in four placebo-controlled RA studies. Consequently, 40 mg eow was the proposed dose for the treatment of PsA subjects.

The CHMP requested further information on the dose and posology schedule chosen by the MAH, considering that it had been extrapolated from studies on rheumatoid arthritis (RA) and not specifically determined in PsA. The MAH provided a justification based on the same pattern of treatments, same mechanism of action and similar efficacy evaluations between RA and PsA. The CHMP noted that ideally, dose finding studies would have been desirable. However, the current experience from trials with Humira, mainly in RA, including the early RA data having been under assessment at the same time, gives sufficient support that the doses tested in PsA are adequate.

2.2 Clinical efficacy

Study M02-518

Study M02-518 was a multicentre, randomised, double-blind, placebo-controlled study, stratified by methotrexate (MTX) use and extent of psoriasis, designed to compare the effects of adalimumab at a dose of 40 mg administered subcutaneously (sc) eow *vs.* placebo for a 24- week treatment period. This study evaluated the effectiveness and safety of adalimumab either alone or in combination with concomitant MTX in subjects with moderately to severely active PsA who have had an inadequate response or intolerance to NSAID therapy.

Study M02-570

Study M02-570 was a multicentre, randomised, double-blind, placebo-controlled, stratified by DMARD use, designed to compare the effects of adalimumab at a dose of 40 mg administered subcutaneously (sc) eow *vs.* placebo for a 12- week treatment period. This study evaluated the effectiveness and safety of adalimumab either alone or in combination with any concomitant DMARD (except cyclosporine or tacrolimus) in subjects with moderately to severely active PsA who had an inadequate response to DMARD therapy.

Study M02-537

Study M02-537 was a multicentre, uncontrolled, open-label, continuation study in subjects completing Study M02-518 or Study M02-570, with or without concomitant DMARDs. This study was submitted in order to provide evidence of the long-term effectiveness of adalimumab in the treatment of PsA in subjects who completed either pivotal study. This study was ongoing at the time of the present submission and the results of an interim analysis with a data cut-off of the week 24 visit in the open label extension study or a date of 17 May 2004 were presented.

Methods

Study Population

Adults of 18 years of age or older with a diagnosis of PsA that was moderate to severely active (as defined by ≥3 swollen joints and ≥3 tender or painful joints), that had active cutaneous lesions of chronic plaque psoriasis or a documented history of chronic plaque psoriasis. The primary difference between the inclusion criteria for the two studies was that in M02-518 subjects were required to have an inadequate response to NSAID therapy, and in M02-570 subjects were required to have an inadequate response to DMARD therapy. With respect to concomitant therapy during the studies, M02-518 subjects were allowed to be on stable doses of MTX (but other DMARDs were excluded) while M02-570 subjects were allowed to be on stable doses of any DMARD.

The CHMP requested supplementary information on the treated subpopulation that was on concomitant MTX, which the MAH provided. The CHMP considered that the heterogeneity of the population would not bias in favour of demonstrating response to adalimumab *vs.* placebo, which was shown in all subsets. Additionally, PsA is a very heterogeneous disease, and it is not considered feasible to conduct clinical trials in a sufficient number of patients in all subpopulations and with possible concomitant treatment strategies. The CHMP noted that the indication is restricted to patients failing on previous DMARD, which should give sufficient recommendation as to when to start adalimumab.

Treatments

In the controlled studies, adalimumab was evaluated by assessing five aspects of PsA using the endpoints arthritic manifestations, structural damage, disability, skin manifestations and quality of life.

Duration of treatment with adalimumab in all PsA studies up to the chosen cut-off date was as presented in the table 1.

Table 1. Duration of Treatment (All Studies)

	Adalimumab (N = 395)
	Duration of Treatment [a] (days)
Mean ± SD	182.7 ± 89.14
Median	172
Range (min-max)	15 – 354
	Duration of Treatment [b] (n, %)
≤4 weeks	395 (100.0)
>4 weeks	385 (97.5)
>12 weeks	335 (84.8)
>24 weeks	185 (46.8)
>36 weeks	91 (23.0)
>48 weeks	1 (0.3)
>60 weeks	0

a. Duration of treatment = last dose date - first dose date + 15.
b. Duration of treatment = last dose date – first dose date +1.

Outcomes/Endpoints

The primary efficacy variable was the ACR20 response at Week 12 in M02-518 and M02-570. Study M02-518 also included the inhibition of disease progression as assessed by change from baseline in modified total Sharp score on X-rays of the hands and feet at Week 24 as an additional co-primary efficacy variable.

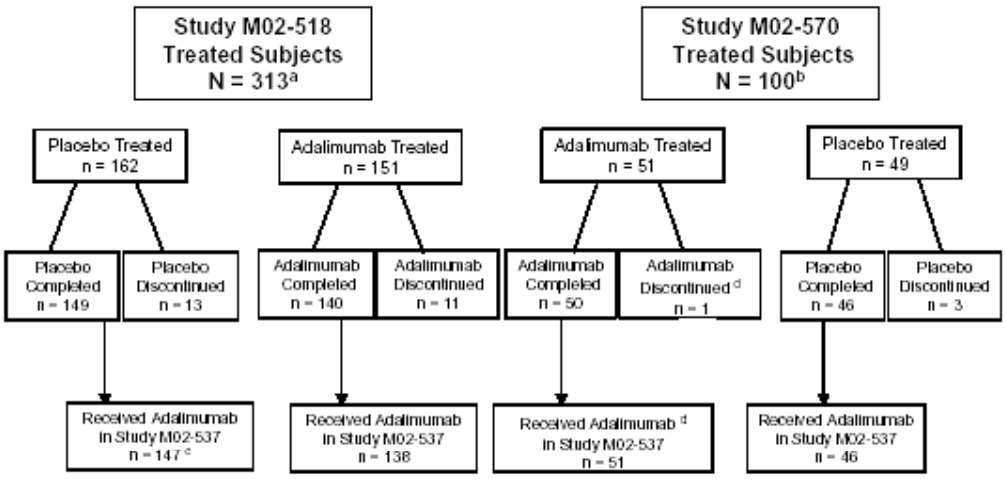
A number of secondary efficacy endpoints were included, relating to Psoriatic Arthritis Response Criteria (PsARC), ACR, PASI, and quality of life assessments. The overall design and efficacy variables of the two pivotal studies were similar.

Results

Patients disposition

The overall subject disposition is displayed in the figure 1.

Figure 1. Overall Subject Disposition (All Studies)



a. Two subjects (518-0163 and 518-4503) were randomized to adalimumab treatment but did not receive study drug.
b. Two subjects (570-0155 and 570-1151) were randomized to adalimumab treatment but did not receive study drug.
c. Subject 518-4801 enrolled in Study M02-537, but never received adalimumab.
d. Subject 570-1451 received adalimumab in Study M02-570, discontinued from Study M02-570, but was permitted to enroll in Study M02-537.

Efficacy results

The CHMP considered that the following analyses were relevant for the efficacy assessment of this application.

(1) Arthritic manifestations

The ACR20 response at week 12 was 58% for adalimumab vs. 14% for placebo ($p<0.001$) in Study M02-518 and 39% for adalimumab vs. 16% for placebo in Study M02-570. In study M02-518 the PsARC response was 62% for adalimumab *vs.* 26% for placebo at Week 12 ($p<0.001$) and 60% for adalimumab *vs.* 23% for placebo at Week 24 ($p<0.001$).

(2) Disability

The reduction in the secondary endpoint of the Disability Index of the HAQ in Study M02-518 was -0.4 units for adalimumab vs. -0.1 units for placebo at Week 12 and Week 24 ($p<0.001$). The reduction in the Disability Index of the HAQ in Study M02-570 was –0.3 units for adalimumab vs. –0.1 units for placebo ($p=0.024$) at Week 12.

(3) Quality of life

At Week 12, adalimumab was statistically superior to placebo in six of the eight individual SF-36^{TM} domains in Study M02-518, and in four of the eight domains in Study M02-570. Improvement was demonstrated also by the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale Score, and the Dermatology Life Quality Index (DLQI).

(4) Other endpoints

Skin manifestations: The CHMP considered that the number of patients (n= 16), with a PASI score ≥10 (a score relevant for moderate to severe psoriasis), was insufficient to draw definite conclusions. Thus, efficacy on skin symptoms of psoriasis should be shown separately, and these data were not considered further for the efficacy assessment.

Disease Progression: The CHMP noted the data on disease progression. However, a period of 24 weeks was considered too short to allow an assessment of this parameter, and thus, these data were not considered further in the efficacy assessment.

Discussion on clinical efficacy

Efficacy in patients with mainly moderately active psoriatic arthritis has been shown with adalimumab up to 24 weeks, and seems clinically relevant with respect to the percentage of ACR responders compared with placebo. The duration of the studies is limited and an open label continuation study is ongoing. Approximately 50% of the patients had concomitant MTX. The number of patients treated with other DMARDs is very low. The percentage of responders within the monotherapy/combination therapy groups is similar at weeks 12 and 24 and there is a tendency towards better efficacy in patients with higher inflammatory activity, based on the CRP levels. However, a relatively low level of CRP was accepted for inclusion (>1.5 mg/dl) in the studies and the difference between the chosen levels of comparison, i.e. 2 mg/dl might be questioned.

The CHMP noted that data on the maintenance of the effect or increase of disease activity after stopping treatment should have been submitted. The MAH provided supplementary documentation, however, the data are too limited for further conclusions.

In relation to the ongoing study, a tendency towards tapering of effect was observed in the 48-week evaluation, among the limited number of patients (40) available at this time point. This indicates the need for long-term efficacy data. Moreover, the CHMP noted that antibody data was lacking. Available data on longer-term treatment are currently too limited to draw any conclusions on persistence of efficacy. A dose escalation to adalimumab 40 mg every week was performed only in a small group of patients, which does not allow any conclusions to be drawn.

2.3 Clinical Safety

Patient exposure

The mean exposure for the 395 subjects in all PsA studies combined was 183 days (median exposure 172 days).

Table 2. Premature Discontinuation and Primary Reason for Discontinuation (Controlled Studies)

	Study M02-518		**Study M02-570**		**Combined**	
	Placebo (N = 162) n (%)	**Adalimu-mab (N = 151) n (%)**	**Placebo (N = 49) n (%)**	**Adalimu-mab (N = 51) n (%)**	**Placebo (N = 211) n (%)**	**Adalimu-mab (N = 202) n (%)**
Completed Week 12[a,b]	155 (95.7)[a]	144 (95.4)[a]	46 (93.9)	50 (98.0)	201 (95.3)[b]	194 (96.0)[b]
Completed Week 24	149 (92.0)	140 (92.7)	NA[c]	NA[c]	149 (70.6)	140 (69.3)
Early Discontinuation	13 (8.0)	11 (7.3)	3 (6.1)	1 (2.0)	16 (7.6)	12 (5.9)
Adverse Event	1 (0.6)	3 (2.0)	1 (2.0)	1 (2.0)	2 (0.9)	4 (2.0)
Withdrew Consent	5 (3.1)	3 (2.0)	0 (0.0)	0 (0.0)	5 (2.4)	3 (1.5)
Lost to Follow-up	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Abnormal Laboratory Value(s)	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)
Abnormal Test Procedure Event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory Therapeutic Event	4 (2.5)	1 (0.7)	1 (2.0)	0 (0.0)	5 (2.4)	1 (0.5)
Protocol Violation	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Administrative Problems	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.6)	1 (0.7)	1 (2.0)	0 (0.0)	2 (0.9)	1 (0.5)

a. For subjects who prematurely discontinued, the date of assessment on the study drug CRF must have been after the upper bound of the Week 12 window (*i.e.,* Study Day 99).

b. Including the subjects in Study M02-570 who completed the study and the subjects in Study M02-518 who completed Week 12. For subjects who prematurely discontinued Study M02-518, the date of assessment on the study drug CRF must have been after the upper bound of the Week 12 window (*i.e.,* Study Day 99).

c. Study M02-570 was a 12-week study.

Adverse events

The number and percentage of patients who experienced treatment-emergent Adverse events is reported in table 3.

Table 3. Overview of Subjects Who Experienced Treatment − Emergent Adverse Events (Controlled Studies)

	M02-518			M02-570			Combined		
Treatment-Emergent[a] Adverse Event[b] Category	**Placebo (N = 162) n (%)**	**Adalimumab 40 mg eow (N = 151) n (%)**	**p-value[c]**	**Placebo (N = 49) n (%)**	**Adalimumab 40 mg eow (N = 51) n (%)**	**p-value[c]**	**Placebo (N = 211) n (%)**	**Adalimumab 40 mg eow (N = 202) n (%)**	**p-value[c]**
Any AE	130 (80.2)	122 (80.8)		39 (79.6)	27 (52.9)	0.006**	169 (80.1)	149 (73.8)	
Any at least possibly drug-related AE	47 (29.0)	64 (42.4)	0.018*	14 (28.6)	14 (27.5)		61 (28.9)	78 (38.6)	0.038*
Any severe AE	11 (6.8)	5 (3.3)		4 (8.2)	2 (3.9)		15 (7.1)	7 (3.5)	
Any SAE	7 (4.3)	5 (3.3)		2 (4.1)	1 (2.0)		9 (4.3)	6 (3.0)	
Any AE leading to discontinuation of study drug	5 (3.1)	6 (4.0)		2 (4.1)	1 (2.0)		7 (3.3)	7 (3.5)	
Any infectious AE	64 (39.5)	68 (45.0)		16 (32.7)	9 (17.6)		80 (37.9)	77 (38.1)	
Any serious infectious AE	1 (0.6)	1 (0.7)		1 (2.0)	0 (0.0)		2 (0.9)	1 (0.5)	
Any AE of malignancy (including lymphoma)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Deaths	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

**, * Statistically significant at the p = 0.01 and 0.05 levels, respectively.

a. Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug.

b. Subjects may be counted in more than one AE category.

The most common adverse events, defined as those occurring in >5% of subjects treated with adalimumab in all studies, were upper respiratory infections, nasopharyngitis, injection site reactions and sinusitis which are similar to other performed studies with adalimumab.

Table 4. Number (%) of Subjects with Treatment -Emergent Adverse Events Occurring in >=5% of Subjects (All Studies)

Adverse Event Preferred Term[a,b]	Adalimumab (N = 395) n (%)
Any Adverse Event	**293 (74.2)**
Upper respiratory tract infection	52 (13.2)
Nasopharyngitis	35 (8.9)
Injection site reaction	25 (6.3)
Sinusitis	21 (5.3)

a. Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug. Only AEs occurring in ≥5% of subjects are presented.

b. More than one AE category per subject possible.

Serious adverse events, malignancies and deaths

(a) Serious adverse events

Serious adverse events were reported in the controlled studies in 6 adalimumab treated patients (meningitis, diverticulitis, convulsions aggravated, renal calculus, toe arthrodesis and nasal septum disorder). In the placebo group there were nine patients with 13 serious events (e.g. pericarditis, pulmonary embolism, cerebrovascular accident, coronary artery disease aggravated).

An additional 12 serious events have occurred so far in the open label extension. Events judged to be at least possibly related were rhabdomyolysis and renal failure in a 30-year-old male. Other events of interest were myocardial infarction (female 55 years old), pulmonary embolism (female 65 y), and acute pancreatitis (female 59 y).

No event of tuberculosis (tb)/granulomatous infections, demyelinating disease, immunologic reaction, lupus-like reaction, congestive heart failure was found.

The overall incidence of infections was 38.1% on adalimumab and 37.9% on placebo.

(b) Malignancies

Prostate cancer was diagnosed in a male 64 years old on day 83 of treatment, and a Non-Hodgkin´s lymphoma in a 79 y old male on day 4. This malignancy was diagnosed after a single dose of adalimumab and in retrospect was apparent on a radiographic study that predates adalimumab administrations. These treatment-emergent malignancies were judged to be probably not-related to study treatment. A non-melanoma skin cancer occurred in a 38-year-old female.

(c) Deaths

There were no deaths reported in the three PsA studies.

Laboratory findings

For the two studies combined, liver abnormal function tests occurred in 4.0% of adalimumab-treated subjects and in 0.5% of placebo-treated subjects (p = 0.018).
Alanine aminotransferase increased occurred in 3.0% of adalimumab-treated subjects and 0% placebo-treated subjects (p = 0.013). This trend was also observed in Study M02-518, but not in Study M02-570.

In the 12 adalimumab-treated subjects with ALT increases of □3 x ULN in Study M02-518, 11 were on concomitant potential hepatotoxic products or had other potential causes of the elevation. Two adalimumab-treated subjects prematurely discontinued from the study (one due to isoniazid pancreatitis and one due to abnormal laboratory values). Five adalimumab-treated subjects had transient increases that resolved on continued therapy, and one had resolution during follow-up after discontinuation of study drug and isoniazid. Of the six adalimumab-treated subjects who had elevated ALT values at completion of M02-518, four entered open-label extension Study M02-537.

Table 5. Number (%) of Subjects with ALT Elevations >=1.5xULN by Methotrexate Use (Controlled Studies)[a]

	M02-518		M02-570		Combined	
	Placebo (N = 162) n (%)	**Adalimumab 40 mg eow (N = 151) n (%)**	**Placebo (N = 49) n (%)**	**Adalimumab 40 mg eow (N = 51) n (%)**	**Placebo (N = 211) n (%)**	**Adalimumab 40 mg eow (N = 202) n (%)**
With concomitant MTX, n^b/N^c (%)	10/81 (12.3%)	26/77 (33.8%)	3/23 (13.0%)	1/24 (4.2%)	13/104 (12.5%)	27/101(26.7%)
Without concomitant MTX, n^b/N^c (%)	9/81 (11.1%)	12/74 (16.2%)	3/26 (11.5%)	4/27 (14.8%)	12/107 (11.2%)	16/101 (15.8%)
Total, n/N (%)	19/162 (11.7%)	38/151 (25.2%)	6/49 (12.2%)	5/51 (9.8%)	25/211 (11.8%)	43/202 (21.3%)

a. Subject is considered to have an elevation of ALT ≥1.5xULN if Baseline value was <1.5xULN and any value of ≥1.5xULN occurred during the study or if ALT was between 1.5xULN and 3xULN at Baseline and any value of ≥3xULN occurred during the study.

b. Number of subjects with an ALT ≥1.5xULN.

c. Total number of subjects within subgroup.

Safety in special populations

Analyses of overview Adverse events parameters by various intrinsic factors did not indicate any clinically relevant differences for males *vs.* females, subjects <65 years *vs.* those ≥65 years, Caucasians *vs.* non-Caucasian, or subjects with <10 years of PsA *vs.* those with ≥10 years of PsA.
Analyses of overview Adverse events parameters by extrinsic factors did not indicate any clinically relevant differences for subjects with DMARD use at baseline *vs.* those without, subjects with oral corticosteroid use at baseline *vs.* those without, subjects with alcohol use at baseline *vs.* those without, or subjects with tobacco use at baseline *vs.* those without.
No subject in the PsA clinical program became pregnant as of the data cut-off.

Discussion on clinical safety

The safety profile of adalimumab is similar to that previously known from anti-TNF therapy. However, further close monitoring of e.g. serious infections including tb and malignancies are of importance when new groups of patients are introduced to anti-TNF therapy. The MAH described the programs for educational efforts to prevent tb and for monitoring of malignancies.

The CHMP noted the increased incidence of liver enzyme elevations. The MAH was asked to discuss these data and to discuss whether monitoring of hepatic enzymes should be performed during treatment, in particular in patients with PsA. The MAH submitted supplementary information which does 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.

3. Overall Discussion and benefit/risk assessment

Efficacy of Adalimumab has been shown in patients with an inadequate response to previous DMARDS/NSAIDs and mainly moderately active psoriatic arthritis. With respect to the percentage of ACR responders compared with placebo, efficacy seems clinically relevant. There is a tendency towards better efficacy in patients with higher inflammatory activity, based on the CRP levels, which is in line with active disease.

Approximately 50% of the patients were on concomitant MTX at randomisation. The number of patients treated with other DMARDs is very low and is not sufficient to ensure safe use concomitantly with adalimumab and should therefore not be included in the indication.

The percentage of responders within the monotherapy/combination therapy groups, are similar at weeks 12 and 24. A tendency towards a decrease in efficacy was found among the limited number of patients (n=40) followed up to one year in the open-label continuation study. Thus, a possible tapering of effect in the open label study strengthens the need for more long-term proof of continuing effect.

Safety in patients with PsA is similar to the previously approved indication, with the exception of elevated hepatic enzyme levels. However, no alarming hepatic events or safety signals were reported in the PsA studies.

As already known, there is a risk for serious infections, including opportunistic infections and tb and educational efforts are important. The MAH has proposed educational programs. Malignancies continue to be followed as well as other events of concern, as per normal PSUR procedures.

In conclusion, the CHMP recommended that the indication proposed by the MAH "*reducing signs and symptoms of psoriatic arthritis"* should be changed to *"Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate".*

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.