European Medicines Agency

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ASSESSMENT REPORT FOR RAPTIVA

International non-proprietary name/Common name: (efalizumab)

Procedure No. EMEA/H/C/542/II/19

Variation Assessment Report as adopted by the CHMP with
All information of a commercially confidential nature deleted

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Introduction

Efalizumab is a recombinant humanized monoclonal antibody produced in genetically engineered Chinese Hamster Ovary cells. It is an IgG kappa immunoglobulin, containing human constant region sequences and murine light- and heavy-chain complementary determining region sequences. Raptiva is a selective immunosuppressor that alters T-lymphocyte function and may affect host defences against infections. Efalizumab is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA.

Following the assessment of PSUR 5, the CHMP requested the Marketing Authorisation Holder (MAH) to perform a comprehensive benefit-risk (B-R) re-assessment including a critical discussion of safety and efficacy outcomes of cumulative post-marketing safety information and of all Raptiva clinical trials completed after the original Marketing Authorisation Application (MAA) procedure.

With the submission of the benefit/risk re-evaluation, the MAH applied for an update of Section 4.4 "Special Warnings and Precautions for Use" of the Summary of Product Characteristics (SPC) with a rewording of the discontinuation guidance (based on integrated assessment of studies ACD2391g, HUPS300, 25180, 25300), Section 4.8 "Undesirable Effects" with an update of information on overall incidence of adverse events (based in particular on studies ACD2243g, ACD2391g, ACD2601g, 25161,25300, 24011 and safety analyses based on the overall clinical database) and Section 5.1 "Pharmacodynamic Properties" with an update of the clinical particulars (based on integrated assessment of studies ACD2243g, ACD2391g, ACD2601g, 25300, 24011). Sections 2 and 3 of the Package Leaflet (PL) have been updated accordingly.

Clinical aspects

The safety and efficacy of Raptiva in moderate to severe plaque psoriasis patients have been demonstrated in five randomized, double-blind, placebo-controlled trials (n=1742). In all 5 studies, patients randomized to the Raptiva group achieved better responses than placebo on the primary endpoint which was statistically significant.

During the original MAA procedure, interim reports of study 24011 and ACD2243g were submitted to the EMEA in December 2003 and April 2004. Final clinical study reports of these two studies have since become available as well as final study results for study 25300, 25161, 25030, ACD2244g, ACD2391g and ACD2601g, ACD2782g and HUPS300. Additional safety data from studies for other indications were also included in the safety database.

In the studies, the endpoint was expressed as the proportion of patients with ≥75% improvement in the Psoriasis Area and Severity Index (PASI) score (relative to baseline) and/or proportion of subjects with predefined response on the physician global assessment (PGA).

Clinical efficacy

The following studies are in support of the efficacy of Raptiva in the authorised indication:

Study 24011 was a Phase III trial whose primary efficacy objective was to compare efalizumab 1 mg/kg subcutaneously (SC) once a week for 12 weeks with placebo in patients with moderate to severe plaque psoriasis. A secondary objective of this study was to evaluate the efficacy of efalizumab during the extended treatment and re-treatment periods. In the double-blind (DB) treatment period, patients were randomised 2:1 to receive efalizumab 1 mg/kg or matching placebo SC once a week for 12 weeks. Patients with a PASI 75 response at First Treatment (FT) Week 12 then entered an Observation period of up to 24 weeks. At the end of the Observation period, or if relapse or clinical need for re-treatment was noted patients entered a 12-week open Re-treatment (RT) period, during which they received efalizumab 1 mg/kg subcutaneously once a week.

The median time to relapse (> 50% loss of response) among PASI 75 responders at 12 weeks was 58 days (n=164). None of these patients experienced a worsening of disease to 125% of baseline PASI. Re-treatment of week 12 responders who had relapsed led to PASI 75 and PASI 50 response rates of 47.6% and 77.9% respectively. Patients who did not reach a PASI 75 response (PASI 50-74 responders & non-responders) entered a 12-week extended (ET) treatment period immediately after the FT period. In these patients approximately 50% of PASI 50-74 responders achieved a PASI 75 response at 24 weeks, while <15% of FT period non-responders did so.

Table 1: Study 24011: PASI 75 Response at 24 weeks for PASI 50-74 Responders and Non-Responders at Week 12 (FT on Efalizumab)

	PASI 75 responders amongst previous PASI 50-74 responders		**PASI 75 responders amongst previous Non-responders**	
	N	n (%)	N	n (%)
All patients	118	56 (47.5)	188	24 (12.8)

In study 25300, patients had the possibility to stop treatment after Week 12 and enter an Observation period lasting up to 8 weeks. A total of 135 Week 12 responders entered the Observation period. Consistent with the data from study 24011, median time to relapse was 56 days. Among the 113 patients who chose to be retreated with efalizumab after the Observation period, response was similar to that observed during the FT period: mean (SD) PASI score at RT Week 12 was 7.03 (5.47) as compared to a RT baseline value of 19.27 (8.17).

Study ACD2391g was a Phase III trial whose primary efficacy objective was to assess the rate of response at 24 weeks in patients originally randomised to receive 1.0 mg/kg/wk SC efalizumab for 12 weeks in study ACD2390g. PASI 75 response at 24 weeks was determined relative to Day 0 of study ACD2390g. Of the 117 patients who were PASI 50-74 responders at Week 12, 58 (49.6%) became PASI 75 responders at Week 24. Approximately 19% of patients who were non-responders at Week 12 became PASI 75 responders at Week 24 (24 out of the 127 non-responders).

In study 25300, 853 of 1255 patients (68%) had PGA ratings of good or better at week 12 (95% CI: 65% and 70.5%). A PASI 75 response rate of 36% (451 patients) was observed at week 12. All efficacy results were consistent with the primary endpoint. Of note the response rate in patients (n=232) who were refractory to all three major systemic treatments (i.e. cyclosporin, methotrexate, and PUVA) was 61% versus 69% in patient not refractory for any of these (p=0.03).

The MAH updated Section 5.1 of the SPC to reflect the data on time to relapse in the target population and other clinical particulars (see paragraph 3.3 Changes to the Product Information).

Clinical studies in special populations

Study ACD3753g was a randomised, double-blind, placebo-controlled Phase IV trial in patients with moderate to severe plaque psoriasis involving the hands and/or feet, with or without pustules and with or without psoriasis at other sites. The study consisted of a 12-week treatment regimen of efalizumab 1.0 mg/kg/wk or placebo, followed by a 4-week observation period. The primary efficacy endpoint was the proportion of patients with a Physician's Global Assessment of Hand and/or Foot Psoriasis (PGA [hand/foot]) rating of 0, 1 or 2 ("Clear", "Almost Clear" or "Mild") at Week 12/Day 84. In the Intention to treat (ITT) population, 46.2% of patients receiving efalizumab achieved response compared with 17.9% of patients receiving placebo (24 of 52 and 5 of 28 patients respectively; difference in proportions 28.3; p=0.015; 95%CI: 8.7, 47.9). It is noted that the PGA [hand/foot] is not a thoroughly validated endpoint.

Studies 25300 and 25161 provided supportive evidence for the efficacy of efalizumab in hand and foot psoriasis. These studies did not require patients to have any hand and/or foot involvement, but assessment of hand and/or foot psoriasis using the Palmoplantar Pustulosis Area and Severity Index (PPPASI) was a tertiary endpoint. PPPASI was analysed in the subgroups of patients who had baseline scores above zero. Median percent improvement in PPPASI 69.4% (n=247) in study 25300 and 100% (m=19) in study 25161 respectively.

The CHMP noted that no special claims with respect to efficacy in hand foot psoriasis is made. This was agreed and in principle this is already covered in the current indication referring to second line treatment of moderate to severe chronic plaque psoriasis.

Clinical safety

Sixteen new studies have become available since registration. The overall clinical safety database for efalizumab now includes more than 7000 patients (>6000 receiving efalizumab and >1400 receiving placebo), including more than 6500 patients with psoriasis, providing an exposure to efalizumab of approximately 2800 patient-years and an exposure to placebo of >300 patient-years.

Currently, the main safety information in the SPC comes from the 12-week placebo-controlled studies and the PSURs. The new studies provide relevant information in the following areas that should be reflected in the SPC:

• Safety data on long-term treatment for up to 3 years (studies ACD2243g, ACD2391g, ACD2601g and 25161).

• Safety data in the target population for up to 24 weeks of treatment (studies 24011 and 25300).

The MAH proposed the inclusion of the long-term data to some of the safety information already present in Section 4.8, under "Additional Information".

Concerning *leucocytosis* and *lymphocytosis*, the expected pharmacodynamic (PD) effect already observed in the short-term studies was observed in study ACD2243g. The MAH proposed that the information regarding the PD effect that reaches a plateau and does not increase beyond the FT period should be reflected in the SPC In Section 4.8 under "Additional Information". The CHMP agreed with the MAH's proposal (See paragraph 3.3 Changes to the Product Information).

Concerning *thrombocytopenia*, a small and gradual decrease in mean platelet counts was seen over the 3 years of treatment in study ACD2243g. There appeared to be no clinical sequelae associated with this decrease, and mean platelet counts remained within the normal range throughout the study. The MAH agreed with the CHMP to update Section 4.8 to reflect these long term data.

Concerning *hypersensitivity* and *allergic disorders*, 9 patients in study ACD2243g (2.6%) developed anti-efalizumab antibodies during the study. Due to the low incidence of antibody formation, no correlation can be established between the presence of antibodies and AE rates.

Hypersensitivity-related adverse events were uncommon, and the rate of such events decreased over time (9.8% or 33 of 338 patients for FT and less than 6.6% or 19 of 290 patients for the remaining 12-week periods of the study). In study ACD2601g, hypersensitivity-related AEs were observed in 6.6%, 3.7%, 4.5% and 2.1% of patients in the successive 12-week periods (42 of 635, 21 of 567, 23 of 509 and 10 of 479 patients respectively), suggesting that there is no increase in such events over long-term treatment.
The MAH agreed with the CHMP to update Section 4.8 to reflect these long term data.

An indirect comparison of the incidence densities in the long-term studies vs the 12-week studies showed no increase in risk of any event examined, with exception of non-melanoma skin cancer (NMSC). Standardised incidence ratio did not show evidence of an increase risk of cardiovascular events or overall malignancies with efalizumab compared to the expected incidences in a general psoriasis population. There was however some increase in the incidence of NMSC and infections. The data of malignancies and infections have been included in Section 4.8 of the SPC (see paragraph 3.3 Changes to the Product Information).

In March 2008 the CHMP requested the MAH to perform, a meta-analysis of clinical trial data related to malignancies.
The MAH discussed that they have performed a statistical analysis of clinical trial data related to malignancies.
The pooled analyses included data from a total of 29 clinical trials in which patients were treated with efalizumab or placebo: the studies have been assigned either to Cohort A (which includes studies involving up to 12 weeks of treatment) or to Cohort B (which includes all long-term studies, with exposure greater than 12 weeks and up to 3 years). A third cohort (Cohort C) has been created and includes data up to 12 weeks from all studies. The 12-week cut-off for this third cohort has been chosen to allow fair comparison to placebo, for which the maximum exposure is 12 weeks.
As an external reference population, the moderate-to-severe psoriasis population from the UK-based General Practice Research Database (GPRD) was used. In total 95,069 psoriasis patients above the age of 20 years were identified, of which 4070 (4.28%) were classified as having severe psoriasis. This is the population considered as the reference population for these analyses.

Table 2 below shows the Incidence per 100 patient years and the standardised incidence ratio.
Signal work-up of malignancies shows that the data presented cannot exclude that there might be an increase over time driven by Non-Melanoma Skin Cancer (NMSC), namely squamous cell carcinoma. The risk of developing lymphoma or lymphoproliferative disorders does not seem to increase over time.

Table 2: Incidence Densities and Odds Ratios in the 12-Week Cohort A, Incidence Densities in the Longer-Term Cohort B (>12 Weeks to 144 Weeks) and SIR

	12-Week Treatment (Cohort C)		Long term (up to 144 Weeks (Cohort B)	
	Incidence per 100 patient-years (95%CI)		Incidence per 100 patient-years (95%CI)	SIR*
	Efalizumab	Placebo	Efalizumab	Observed / Expected
Malignancies	0.63 (0.29, 1.20)	1.03 (0.21, 3.00)	1.44 (1.08, 1.87)	NC
NMSC	0.35 (0.11, 0.82)	0.69 (0.08, 2.47)	0.88 (0.60, 1.23)	3.90 (2.89, 5.18)
Melanoma	0.07 (0, 0.39)	0 (0, 1.26)	0.05 (0.01, 0.20)	2.13 (0.38, 6.72)
Lymphomas / leukaemias	0.07 (0, 0.39	0 (0, 1.26)	0.11 (0.03, 0.27)	NC
Others	0.14 (0.02, 0.51)	0.34 (0.01, 1.90)	0.42 (0.24, 0.69)	1.11 (0.73, 1.63)

* the SIR shown here is the one in the original submission

Taking into account all the limitations of the meta-analysis and the available data indicating some risk of NMSC, malignancies will have to be monitored.
The MAH committed to continue monitoring the safety of the product in order to better identify the incidence profile of rare events such as severe infections and lymphoproliferative disorders.

Conclusions and Benefit / Risk Assessment

The efficacy data provided with this variation has shown that the discontinuation of treatment may cause a recurrence or exacerbation of psoriasis especially in patients not responding to treatment and that tapering the dose of efalizumab is not effective in decreasing the incidence of psoriasis-related events. Section 4.4 of the SPC has been updated to reflect this information. Also, information about time to relapse after treatment discontinuation and effect of efalizumab re-treatment in patients with PASI 75 response after 12 weeks especially provided by Study IMP24011 has shown that approximately half of the patients (46.8%) who were partial responders (50% to 74% improvement on PASI, similar to PGA good) after 12 weeks of Raptiva treatment achieved a PASI 75 response at week 24. Additionally, long-term treatment data showed that half of the patients treated for more than 1 year were PASI 75 responders. Section 5.1 has been updated accordingly.

Concerning safety, long term data from study ACD2243g in relation to and lymphocytosis and thrombocytopenia confirmed that the pharmacodynamic (PD) effect already observed in the short-term studies. Section 4.8 has been updated to reflect that the PD effect reaches a plateau and does not increase beyond the FT period.
Concerning thrombocytopenia, a small and gradual decrease in mean platelet counts was seen over the 3 years of treatment in study ACD2243g within the normal range was observed. Also, over long term treatment, the frequency of hypersensitivity-related adverse events did not increase. These findings have been included in Section 4.8.
Since the placing of the market of Raptiva, the following reactions were added to the SPC: septic meningitis, infections (including opportunistic infections as tuberculosis), immune related haemolytic anaemia, antibodies during vaccinations, interstitial pneumonitis, arthritis, erythema multiforme, inflammatory polyradiculoneuropathy, and facial palsy. Other possible signals are tuberculosis, progressive multifocal leukoencephalopathy, lymphomas and other malignancies, and liver disorders. However, data from long-term studies confirm the current safety profile of efalizumab.

The CHMP concluded that the benefit-risk of Raptiva remains positive for the population in the approved indication.

Changes to the Product Information

Summary of Product Characteristics

New text is marked as underlined; deleted text is marked as ~~strikethrough~~

Section 4.4 'Special warnings and precautions for use'

Psoriasis
During treatment with Raptiva, cases of exacerbation of psoriasis, including pustular, erythrodermic, and guttate subtypes, have been observed (see section 4.8). In such cases, it is recommended to discontinue treatment with Raptiva.
~~Abrupt d~~Discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis including erythrodermic and pustular psoriasis, especially in patients not responding to treatment. Gradual reduction of dose or frequency does not appear to be beneficial.

Discontinuation
Management of patients discontinuing Raptiva includes close observation. In case of recurrence or exacerbation of disease, as well as in patients who discontinue Raptiva and are non-responders, the treating physician should institute the most appropriate psoriasis treatment as necessary. In case re-treatment with Raptiva is indicated the same guidance should be followed as under Posology and method of administration. Re-treatment may be associated with lower or inadequate response to Raptiva than in the earlier treatment periods. Therapy may be continued only in those patients who respond adequately to treatment.

The CHMP considered these changes to be acceptable since they provide specific new information.

Section 4.8 'Undesirable effects'

The MAH proposed the following update of Section 4.8:

Additional Information

Long-term exposure:
Analysis following long-term use in a cohort of ~~158~~339 patients (study ACD 2243g) with moderate to severe psoriasis receiving Raptiva 1 mg/kg/week ~~for 108 weeks~~ , of which 166 patients have been treated for more than 2 years and up to 3 years, did not show any noteworthy differences in frequency of adverse events as compared to 12 weeks of exposure to Raptiva. ~~Safety data beyond 12 weeks in the target population are not yet available.~~ The safety profile of Raptiva remains acceptable over long term, up to 3 years. Most events were mild to moderate, with no apparent increase over time in the incidence of serious events and events leading to discontinuation. Long-term use of Raptiva did not reveal any common unexpected AE.

Pooled safety analysis:
The incidence of serious infections and malignancies in the Raptiva clinical trial database of 29 studies was evaluated up to 12 weeks in comparison to placebo and over long term treatment in 15 of these 29 studies of > 12 weeks and up to 144 weeks duration (Table1).

Table 1 Incidence per 100 patient years (95% CI) in the short term cohort (<12 weeks treatment) and in the longer-term cohort (>12 weeks to 144 weeks)			
	Short term cohort (<12 week treatment) *		Longer Term Cohort (>12 to 144 weeks) **
	Raptiva (n = 5509)	Placebo (n = 1242)	Raptiva (n = 4709)
Serious infections	2.82 (2.01; 3.83)	1.37 (0.37; 3.50)	1.83 (1.43; 2.32)
Malignancies	0.56 (0.24; 1.10)	1.03 (0.21; 3.00)	1.39 (1.04; 1.81)
* pooled analysis of 29 studies ** pooled analysis of 15 studies			

The CHMP considered the proposed addition of the text '*The safety profile of Raptiva remains acceptable over long term, up to 3 years. Most events were mild to moderate, with no apparent increase over time in the incidence of serious events and events leading to discontinuation. Long-term use of Raptiva did not reveal any common unexpected AE*' to be not acceptable since it can be regarded to be a commercial claim.

In addition, the CHMP was of the opinion that the information presented in the table is relevant for this section, but should be described in words (e.g. the incidence of malignancies appear to increase with treatment duration).

The MAH agreed with the CHMP to revise the text as follows:

Additional Information

Long-term exposure:
Analysis following long-term use in a cohort of ~~158~~ 339 patients with moderate to severe psoriasis receiving Raptiva 1 mg/kg/week ~~for 108 weeks~~, of which 166 patients have been treated for more than 2 years and up to 3 years, did not show any noteworthy differences in frequency of adverse events as compared to 12 weeks of exposure to Raptiva. ~~Safety data beyond 12 weeks in the target population are not yet available.~~

The MAH also agreed with the CHMP to amend Section 4.8 with the inclusion of data on thrombocytopenia as follows:

'Leucocytosis and lymphocytosis: in large placebo-controlled and in long-term clinical studies, between 40 and 50% of patients developed sustained asymptomatic lymphocytosis during Raptiva therapy. All values were between 2.5 fold and 3.5 fold the ULN (Upper Limit of Normal). Lymphocyte count returned to baseline after therapy discontinuation. Slight elevation in absolute neutrophil count and eosinophil count were observed but in a smaller proportion of patients.

Thrombocytopenia: in the combined safety database of 3291 Raptiva-treated patients at the time of approval, there were nine occurrences (0.3%) of thrombocytopenia with less than 52,000 cells per µl reported. Four of these patients had clinical signs of thrombocytopenia. Based on available platelet count measurements, the onset of platelet decline was between 8 and 12 weeks after the first dose of Raptiva in 5 patients, but occurred later in the other patients. In one patient, thrombocytopenia occurred 3 weeks after treatment discontinuation. ~~The platelet count nadirs occurred between 12 and 72 weeks after the first dose of Raptiva.~~ Over long term treatment up to 3 years, a small and gradual decrease in mean platelet counts within the normal range was observed. In the same population two cases of severe thrombocytopenia (0.6%) of rapid onset were observed (See section 4.4).

Hypersensitivity and allergic disorders: in large placebo-controlled clinical studies, the percentage of patients experiencing an adverse event suggestive of hypersensitivity, including urticaria, rash and allergic reactions was slightly higher in the Raptiva group (8%) than in the placebo group (7%). (See section 4.4). Over long term, hypersensitivity-related adverse events did not increase.

Infections: other therapies that alter T-lymphocyte function have been associated with increased risk of developing serious infections. In placebo controlled clinical trials, infection rates in Raptiva-treated patients was approximately 27.3% versus 24.0% in placebo-treated patients. In the target population studied in study IMP24011, the infection rate in Raptiva-treated patients was approximately 25.7% versus 22.3% in placebo-treated patients.
As regards serious infections ~~In both controlled and uncontrolled studies~~, the overall incidence in both controlled and uncontrolled studies of up to 12 weeks ~~of hospitalisations for infections~~ was ~~1.6~~ 2.8 per 100 patient-years for Raptiva-treated patients compared with ~~1.2~~ 1.4 per 100 patient-years for placebo-treated patients. The most frequent serious infections were pneumonia, cellulitis, infections not otherwise specified and sepsis. Over long term treatment, the incidence of serious infection was 1.8 per 100 patient years. (See section 4.4).

Class adverse reactions

Neoplasms benign and malignant: a higher rate of malignancies has been associated with therapies affecting the immune system. In placebo controlled clinical trials, the overall incidences of malignancy (the majority of which were non-melanoma skin cancers) were similar in Raptiva-treated patients and in placebo-treated patients. In addition, the incidences of specific tumours in Raptiva patients were in line with those observed in control psoriasis populations. ~~Among psoriasis patients who received Raptiva at any dose, the overall incidence of malignancies of any kind was 1.7 per 100 patient-years for Raptiva-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Experience with Raptiva has not shown evidence of risk of developing malignancy exceeding that expected in the psoriasis population.~~
There was no evidence of an increased risk of any particular malignancy over time with the exception of non-melanoma skin cancer (0.3 vs. 0.9 per 100 patient-years, short term and long term treatment, respectively) (See section 4.4).

The CHMP found this change acceptable however the MAH was recommended to revise the SPC in accordance with the current SPC guideline at the next renewal in order to make the additional information more easily accessible to the prescribing physicians (i.e. reactions reported are not included in the adverse reactions table).

Section 5.1 Pharmacodynamic properties

The MAH proposed to summarise the long term efficacy data in Section 5.1 as follows:

'Clinical efficacy
The efficacy of Raptiva versus other systemic therapies in patients with moderate to severe psoriasis has not been evaluated in studies directly comparing Raptiva with other systemic therapies. The present results of Raptiva versus placebo ~~in these patients~~ over 12 weeks of treatment indicate a ~~modest efficacy of~~ response to Raptiva (in terms of PASI 75 response rate) in 22% to 39% of patients (see Table ~~2~~3). Long term open label, uncontrolled studies indicate efficacy of Raptiva (in terms of PASI 75 response rate) in 35% to 50% of patients (Table 5). Based on the clinical development data generated (see Table ~~1~~2) and ~~limited~~ long-term experience (Table 5), Raptiva is recommended for use in patients as defined in section 4.1.'

[….]

~~Table 3~~
~~Summary of Overall Patient Exposure from Clinical Trials~~

~~Treatment duration completed~~	~~24 weeks~~	~~48 weeks~~	~~96 weeks~~	~~108 weeks~~
~~Number of Patients~~	~~1053~~	~~221~~	~~171~~	~~158~~

~~Long term data up to 108 weeks have been obtained in an uncontrolled study in 158 patients with moderate to severe psoriasis (ACD2243g) (See Table 3 above). About 72% of the patients (122 of 170) in the cohort were PASI 75 responders. When all the drop outs of the maintenance cohort were considered as non responders, the PASI 75 responder rate was 42% (122 of 290 patients).~~

Long-term treatment:
Data from extended treatment (more than 12 weeks) have been obtained from 4311 patients in open label uncontrolled studies. Over 600 patients have been treated for more than 1 year (studies ACD2391g, ACD2601g and ACD2243g) including 166 patients treated for more than 2 years and up to 3 years (Table 4).

Table 4
Summary of Overall Patient Exposure from Clinical Trials

Treatment duration completed	More than 12 weeks	More than 24 weeks	More than 1 year	More than 2 years
Number of Patients	4311	1418	617	166

Study ACD2391g was an open-label extension of the placebo controlled trial ACD2390g. A PASI 75 response rate of 44% was observed at 24 weeks of continuous Raptiva treatment (Table 5).

Study ACD2601g was the open label extension of the placebo controlled trial ACD2600g. PASI 75 response rate was 41% at Week 60 (Table 5).

Study ACD2243g, an open label uncontrolled study, provided data on the continuous treatment with Raptiva up to 3 years. After an initial 12 week treatment period, only patients achieving at least PASI 50 and an OLS of at least mild were allowed to continue treatment (n=290; 86%). In the Intent-to-Treat analysis (n=339), the PASI 75 response rate was 41% at Week 12 and was maintained during the study with a 46% response rate at Week 144 (Table 5). Additionally, a PASI 90 response rate was observed in approximately 30% of patients at 3 years.

Table 5 PASI 75 response rate (%)over time (Intent-to-Treat analysis)			
	ACD2390g/2391 g (n=369)	2600g/2601g (n= 450)	2243g (n=339)
Week 12	27%	24%	41%
Week 24	44%	35%	44%
Week 36		44%	48%
Week 48		45%	49%
Week 60		41%	50%
Week 72			48%
Week 84			48%
Week 96			47%
Week 108			48%
Week 120			50%
Week 132			48%
Week 144			46%

The CHMP considered the proposed text to be unacceptable since the figures are already presented in the table 1 and 2 of Section 5.1. Additionally, the figures presented in the text above are a range of responder rates over the short term studies which do not reflect the different populations and different study design. Therefore, the MAH was requested to present an estimate of PASI75 responders that summarise all studies. Also the efficacy results based on open label long tem studies are biased because only those who benefit continue.

Overall, the CHMP agreed on the relevance of the presented long term study data however recommended that Section 5.1 should be concise in terms of information to the treating doctors and agreed with the MAH to include the following text:

'Clinical efficacy

The efficacy of Raptiva versus other systemic therapies in patients with moderate to severe psoriasis has not been evaluated in studies directly comparing Raptiva with other systemic therapies. The present results of Raptiva versus placebo ~~in these patients~~ over 12 weeks of treatment with different populations indicate a ~~modest efficacy of~~ PASI 75 response to Raptiva in 22% to 39% of patients (see Table 2).
Based on the clinical development data generated (see Table 1) and ~~limited~~ long-term experience, Raptiva is recommended for use in patients as defined in section 4.1.'

[….]

'Long-term treatment:
Data from extended treatment (more than 12 weeks) have been obtained from 4311 patients in open label uncontrolled studies. Over 600 patients have been treated for more than 1 year including 166 patients treated for more than 2 years and up to 3 years. Approximately half of the patients treated for more than 1 year were PASI 75 responders (when all dropouts were considered as non-responders).'

The MAH also proposed the following changes:

'Time to relapse (≥50% loss of improvement) was evaluated in Study ACD2058g and IMP 24011 for patients who were classified as responders (≥75% improvement on PASI) after 12 weeks of treatment. The median time to relapse among PASI responders ranged from ~~59~~58 to 74 days following the last Raptiva dose in the initial treatment period.

In study IMP24011, approximately half of the patients (46.8%) who were partial responders (50% to 74% improvement on PASI, similar to PGA good) after 12 weeks of Raptiva treatment achieved a PASI 75 response at week 24.'

The CHMP considered the proposed changes to be acceptable.

Patient Leaflet

The MAH has revised the PL in line with the SPC. The word 'abruptly' has been removed from sections 2 and 3.

Take special care with Raptiva:
[…]
- If you discontinue Raptiva treatment ~~abruptly~~ (and this applies especially to patients not responding to treatment) your psoriasis may significantly worsen. Your doctor may wish to monitor you and provide effective treatment.

If you stop using Raptiva:
If you discontinue treatment with Raptiva ~~abruptly~~ without substitution treatment, your psoriasis may significantly worsen. (See "Take special care with Raptiva")

In addition, the MAH took the opportunity to update the whole list of Local Representatives in section 6.

Conclusion

On 24 April 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.