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February 2007

Dear Colleague

Updated Prescribing Information for
Raptiva® 100 mg/ml powder and solvent for solution for injection
(active ingredient: efalizumab).

In December 2006, the Marketing Authorisation Holder of Raptiva reviewed isolated cases of acute peripheral neuropathies occurring in patients receiving Raptiva. Up to the end of 2006, three cases of Guillain-Barré Syndromes or related disorders occurring in patients receiving Raptiva had been reported during the post-marketing surveillance as well as two cases of transverse myelitis. Compared to the current exposure to Raptiva, the reporting rate appears higher than what would be expected in the general population, suggesting a possible association between these cases and the administration of Raptiva. In all cases of acute inflammatory polyradiculoneuropathy for which this information was available, the patients recovered after discontinuation of Raptiva. Following discussion with the competent authorities, the Raptiva Summary of Product Characteristics (SPC) has been updated to include this information. A copy of the revised text adopted by the European Commission on 23rd February 2007 is enclosed.

The additional text in SPC section 4.4 (Special warnings and precautions for use) is as follows:

Cases of inflammatory polyradiculoneuropathy have been observed in post-marketing surveillance in patients receiving Raptiva (see section 4.8). Patients have recovered after discontinuation of Raptiva, therefore Raptiva should be stopped following the diagnosis of inflammatory polyradiculoneuropathy.

In SPC section 4.8 (Undesirable effects) the following has been added in the table under "Nervous system disorders" with frequency "not known":

*Inflammatory polyradiculoneuropathy**
** Events identified during postmarketing surveillance*

and in section 4.8 body text:

Inflammatory polyradiculoneuropathy: isolated cases have been observed during post-marketing surveillance. (See section 4.4).

The physicians should consider the occurrence of such an event if patients present neurological symptoms during a treatment with Raptiva.

Vat Registered No. GB 301648388
Registered in England No. 1192915

Overall, the benefit/risk profile of Raptiva remains favourable.

Call for reporting

Physicians are reminded to continue to report adverse reactions in accordance with Irish yellow card spontaneous reporting scheme.

Communication information

If you have further questions on this issue, please contact Medical Information at the above address or telephone on 00 44 208 818 7373.

An updated copy of the Raptiva Summary of Product Characteristics is attached.

Yours sincerely,

Dr Gillian Shepherd MD MRCP

Medical Director

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Raptiva®▼ 100 mg/ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains a retrievable amount of 125 mg of efalizumab.
Reconstitution with the solvent yields a solution containing efalizumab at 100 mg/ml.

Efalizumab is a recombinant humanized monoclonal antibody produced in genetically engineered Chinese Hamster Ovary (CHO) cells. Efalizumab is an IgG1 kappa immunoglobulin, containing human constant region sequences and murine light- and heavy-chain complementary determining region sequences.

Excipients: 2.5 mg polysorbate 20, 3.55 mg histidine, 5.70 mg histidine hydrochloride monohydrate, 102.7 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is a white to off white cake.
The solvent is a clear, colourless liquid.

The pH of the reconstituted solution is 5.9 – 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 ciclosporin, methotrexate and PUVA (see section 5.1 – Clinical Efficacy).

4.2 Posology and method of administration

Treatment with Raptiva should be initiated by a physician specialised in dermatology.

An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight (maximum single dose should not exceed a total of 200 mg). The volume to be injected should be calculated as follows:

Dose	Volume to be injected per 10 kg body weight
Single initial dose: 0.7 mg/kg	0.07 ml
Subsequent doses: 1 mg/kg	0.1 ml

The duration of therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better). For discontinuation guidance see section 4.4.

Children and adolescents (< 18 years)
Raptiva is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Use in the elderly (≥ 65 years)
The dosage and administration schedule in the elderly should be the same as for adults (see also section 4.4).

Patients with renal or hepatic impairment
No studies have been conducted in patients with renal or hepatic impairment. Raptiva should be used with caution in this patient population.

Method of administration
Raptiva is for subcutaneous injection. Injection sites should be rotated.
For instructions for use see section 6.6.

After proper training in the reconstitution and injection technique, patients may self-inject with Raptiva, if their physician determines that this is appropriate.

4.3 Contraindications

Hypersensitivity to efalizumab or to any of the excipients.
Patients with history of malignancies.
Patients with active tuberculosis and other severe infections.
Patients with specific forms of psoriasis like guttate, erythrodermic or pustular psoriasis as sole or predominant form of psoriasis.
Patients with immunodeficiencies.

4.4 Special warnings and precautions for use

Effects on the immune system

a) Infections
Raptiva is a selective immunosuppressor that alters T-lymphocyte function and may affect host defences against infections. It has the potential to increase the risk or severity of infections, e.g. tuberculous pneumonia and reactivate latent chronic infections.
Patients developing an infection during treatment with Raptiva should be monitored and according to severity Raptiva should be discontinued. In a patient with history of clinically significant recurring infections, Raptiva should be used with caution.

b) Vaccinations
Limited data are available on the effects of vaccination. Neo-vaccinations given during treatment with Raptiva may induce antibody levels lower than those observed in non-treated

subjects, but the clinical significance of this is unknown. Patients should not receive live and live-attenuated vaccines while on Raptiva therapy. Before vaccination, treatment with Raptiva should be withheld for 8 weeks and can resume 2 weeks after vaccination (See Section 4.5).

c) Malignancies and lymphoproliferative disorders
It is not yet known whether or not Raptiva can increase the risk of lymphoproliferative disorders or other malignancies in psoriasis patients. Raptiva should be discontinued if a malignancy develops while the patient is on treatment (see sections 4.3 and 4.8).
Raptiva has not been studied in combination with immunosuppressive systemic antipsoriasis medicinal products. Therefore, combination therapies with these products are not recommended (see section 4.5).

Immune-mediated haemolytic anaemia
In post-marketing surveillance, isolated cases of severe haemolytic anaemia have been reported during treatment with Raptiva. In such circumstances, Raptiva should be discontinued.

Thrombocytopenia
Thrombocytopenia may occur during Raptiva treatment and may be associated with clinical signs such as echymoses, spontaneous bruising or bleeding from muco-cutaneous tissues. If these manifestations occur, efalizumab should be stopped immediately, a platelet count should be performed and appropriate symptomatic treatment should be instituted immediately (see section 4.8).
Platelet counts are recommended upon initiating and periodically while receiving Raptiva treatment. It is recommended that assessments be more frequent when initiating therapy (e.g., monthly) and may decrease in frequency with continued treatment (e.g., every 3 months).

Inflammatory polyradiculoneuropathy
Cases of inflammatory polyradiculoneuropathy have been observed in post-marketing surveillance in patients receiving Raptiva (see section 4.8). Patients have recovered after discontinuation of Raptiva, therefore Raptiva should be stopped following the diagnosis of inflammatory polyradiculoneuropathy.

Hypersensitivity and allergic reactions
As with any recombinant product, Raptiva is potentially immunogenic. Consequently, if any serious hypersensitivity or allergic reaction occurs, Raptiva should be discontinued immediately and appropriate therapy initiated (see sections 4.3 and 4.8).

Arthritis
Cases of arthritis have been observed during treatment or after discontinuation of Raptiva. It is recommended to discontinue Raptiva if arthritis occurs during treatment.

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 discontinuation of treatment may cause a recurrence or exacerbation of plaque psoriasis including erythrodermic and pustular psoriasis.

Discontinuation
Management of patients discontinuing Raptiva includes close observation. In case of recurrence or exacerbation of disease, 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.

Special patient populations
No differences in safety or efficacy were observed between elderly (≥ 65 years) patients and younger patients. As there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.
Raptiva has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients. See section 4.8 regarding the effects on the hepatic function.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal drug interaction studies performed with Raptiva.

Limited data are available on the effects of vaccination in patients receiving Raptiva. In a study of 66 patients with moderate plaque psoriasis, immune responses during and after Raptiva treatment were investigated. Following booster vaccination with tetanus toxoid (recall antigen), the ability to mount an immune response to the tetanus toxoid was preserved in those patients undergoing Raptiva therapy. After 35 days of treatment with Raptiva, the proportion of subjects treated with efalizumab with positive skin test reactions to *Candida* was significantly reduced compared with the placebo group. Antibody response to an experimental neo-antigen (ØX174) was reduced during Raptiva therapy, but began to normalize 6 weeks after discontinuation of Raptiva therapy and did not demonstrate tolerance induction. A pneumococcal vaccine administered 6 weeks after discontinuation of Raptiva yielded normal results. Neo-vaccinations given during treatment with Raptiva may induce antibody levels lower than non-treated subjects, but the clinical significance of this is unknown.
Patients should not receive live and live-attenuated vaccines during Raptiva treatment (See section 4.4).

Given the mechanism of action of efalizumab, its effects on the immune system may be potentiated by systemic immunosuppressives commonly used for the treatment of psoriasis (see section 4.4).

Raptiva has been used in combination with topical corticosteroids in psoriasis patients without any untoward effects nor with any observable significant beneficial effect of the combination therapy above monotherapy with efalizumab.

4.6 Pregnancy and lactation

Pregnancy
In general, immunoglobulins are known to cross the placental barrier. There are no adequate data from the use of efalizumab in pregnant women. Animal studies indicate an impairment of the immune function of the offspring (see section 5.3).

Pregnant women should not be treated with Raptiva.
Women of childbearing potential have to use appropriate contraception during treatment.

Lactation
Excretion of efalizumab in human milk has not been investigated, however immunoglobulins are expected to be excreted in human milk. Moreover, an antibody analogue of efalizumab was shown to be excreted in milk of mice. Women should not breastfeed during treatment with Raptiva.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on the pharmacological mechanism of action of efalizumab, the use of Raptiva is not expected to affect patient's ability to drive and use machines.

4.8 Undesirable effects

The most frequent symptomatic adverse drug reactions (ADRs) observed during Raptiva therapy were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia. In large placebo-controlled clinical studies, these reactions were observed in approximately 41% of Raptiva-treated patients and 24% in placebo-treated patients over 12 weeks of treatment. After initiation of therapy, these reactions were generally less frequent and occurred at similar rates to that seen in the placebo group from the third and subsequent weekly injections.
Antibodies to efalizumab were detected in only 6% of patients. In this small number of patients no differences were observed in pharmacokinetics, pharmacodynamics, clinically noteworthy adverse events or clinical efficacy.

Adverse events (Preferred Terms) in the overall population studied clinically with Raptiva are listed below by frequency of occurrence and by MedDRA System Organ Class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Very common (>1/10)	Common (>1/100, <1/10)	Un-common (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)	Not known
Infections and infestations						Aseptic meningitis*. Severe Infections*.
Blood and the lymphatic system disorders	Leukocy-tosis and lymphocy-tosis		Thrombo-cytopenia			Immune mediated haemolytic anaemia*
Immune system disorders		Hyper-sensitivity reactions				
Nervous system disorders						Inflamma-tory poly-radiculone-uropathy*
Respiratory, thoracic and mediastinal disorders						Interstitial pneumoni-tis*
Skin and subcutaneous tissue disorders		Psoriasis	Urticaria			Erythema multiforme*
Musculoskeletal and connective tissue disorders		Arthralgia Arthritis / Psoriatic arthritis (exacerba-tion/flare)				
General disorders and administration site conditions	Flu-like symptoms including fever, headaches, chills, nausea and myalgia	Back pain, Asthenia	Injection site reactions			
Investigations		Elevation of alkaline Phospha-tase, Elevation of ALT				

* Events identified during postmarketing surveillance

The safety profile in the target population as defined in section 4.1 is similar to the safety profile in the overall population treated during clinical development of Raptiva as presented above.

Analysis following long-term use in a cohort of 158 patients with moderate to severe psoriasis receiving Raptiva 1 mg/kg/week for 108 weeks 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.

Additional Information

Leucocytosis and lymphocytosis: in large placebo-controlled 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, 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. (See section 4.4)

Psoriasis: in the first 12 weeks of placebo-controlled studies, the rate of psoriasis adverse events was 3.2% in the Raptiva-treated patients and 1.4% in the placebo-treated patients. Among 3291 patients in the combined safety database, 39 patients presented an erythrodermic or pustular psoriasis (1.2%). Seventeen of these events occurred after discontinuation of Raptiva, while 22 occurred during treatment. In the cases occurring during treatment, most of these events (16/22) occurred in patients presenting no response to Raptiva. Cases occurring after discontinuation were observed both in patients responding or not responding to Raptiva treatment.

Arthritis / Psoriatic arthritis: in the first 12 weeks of placebo-controlled studies, arthritis and exacerbation or flare of arthritis were observed in 1.8% of Raptiva-treated patients and placebo-treated patients. In these studies, the incidence of other types of arthritis-related adverse events were similar between the Raptiva and placebo groups.

Flu-like symptoms: in large placebo-controlled clinical studies, approximately 20% of patients in excess of placebo reported flu-like symptoms including headaches, chills, fever, nausea and myalgia. The percentage of patients reporting flu-like symptoms was greatest with the first injection and decreased by more than 50% with the second injection. These symptoms diminished thereafter to a percentage comparable to that of patients treated with placebo. Headache was the most frequent of the flu-like symptoms. None of those events was serious and less than 5% were considered severe. Overall less than 1% of patients discontinued therapy because of acute flu-like symptoms.

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).

Elevation of alkaline phosphatase: in large placebo-controlled clinical studies approximately 4.5% of patients developed sustained elevation of alkaline phosphatase throughout Raptiva

therapy compared to 1% in placebo patients. All values were between 1.5 fold and 3 fold the ULN, and returned to baseline levels after therapy discontinuation.

Elevation of ALT: about 5.7% of patients developed elevation in ALT during Raptiva therapy compared to 3.5% in placebo. All occurrences were asymptomatic and values above 2.5 fold ULN were not more frequent in the Raptiva group than in the placebo group. All values returned to baseline levels upon therapy discontinuation.

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. In both controlled and uncontrolled studies, the overall incidence of hospitalization for infections was 1.6 per 100 patient-years for Raptiva-treated patients compared with 1.2 per 100 patient-years for placebo-treated patients. The most frequent serious infections were pneumonia, cellulitis, infections not otherwise specified and sepsis. (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. (See section 4.4)

Inflammatory polyradiculoneuropathy: isolated cases have been observed during post-marketing surveillance. (See section 4.4).

4.9 Overdose

In a clinical study, where subjects were exposed to higher doses of efalizumab (up to 10 mg/kg intravenous), one subject receiving 3 mg/kg intravenous dose experienced hypertension, chills, and fever on the day of study drug dosing, which required hospitalization. Another subject who received 10 mg/kg intravenous dose experienced severe vomiting following administration of efalizumab, which also required hospitalization. Both occurrences fully resolved without any sequelae. Doses up to 4 mg/kg/week subcutaneously for 10 weeks have been administered without any toxic effect.

There is no known antidote to Raptiva or any specific treatment for Raptiva overdose other than withholding treatment and patient observation. In case of overdose, it is recommended that the patient be monitored under close medical care and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressive agents, ATC code: L04AA21

Mechanism of action
Efalizumab is a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of LFA-1 (lymphocyte function-associated antigen-1), a leukocyte cell surface protein.

By this mechanism, efalizumab inhibits the binding of LFA-1 to ICAM-1, which interferes with T lymphocytes adhesion to other cell types. LFA-1 is present on activated T lymphocytes, and ICAM-1 is up-regulated on endothelial cells and keratinocytes in psoriasis plaques. By preventing LFA-1/ICAM binding, efalizumab may alleviate signs and symptoms of psoriasis by inhibiting several stages in the immunologic cascade.

Pharmacodynamic effects
In studies using an initial dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg, efalizumab maximally reduced expression of CD11a on circulating T lymphocytes to approximately 15-30% of pre-dose baseline values and saturated CD11a to <5% of baseline available CD11a binding sites. The full effect was seen 24 to 48 hours after the first dose, and was maintained between weekly doses. Within 5 to 8 weeks following the 12th and final dose of efalizumab administered at 1.0 mg/kg/wk, CD11a levels returned to within a range of ±25% of baseline values.

Another pharmacodynamic marker, consistent with the mechanism of action of efalizumab, was the increase in the absolute counts of circulating leukocytes observed during efalizumab treatment. Increased absolute counts were apparent within 24 hours of the first dose, remained elevated with weekly dosing, and returned to baseline after treatment cessation. The largest increase occurred in the absolute count of circulating lymphocytes. In clinical trials, mean lymphocyte counts approximately doubled relative to baseline in subjects receiving 1.0 mg/kg/wk of Raptiva. The increase included CD4 T-lymphocytes, CD8 T-lymphocytes, B-lymphocytes, and natural killer (NK) cells, although NK cells and CD4 cells increased less relative to other cell types. At a dose of 1.0 mg/kg/wk subcutaneous efalizumab, lymphocyte levels returned to within 10% of baseline by 8 weeks post last dose.

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 indicate a modest efficacy of Raptiva (in terms of PASI 75 response rate) (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.

Failure on prior systemic therapies is defined as insufficient response (PASI < 50 or PGA less than good), or worsening of disease in patients while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the 3 major systemic therapies as available.

The safety and efficacy of Raptiva in moderate to severe plaque psoriasis patients has been demonstrated in five randomized, double-blind, placebo-controlled trials at the recommended dose (n=1742). There are no comparative data with Raptiva versus other systemic psoriasis therapies. The largest study IMP24011 (n=793) included patients (n=526) who were not controlled by, contraindicated to, or intolerant to two or more systemic therapies as judged from the patients' histories of psoriasis treatment. In all studies, the primary endpoint was the proportion of patients with a ≥ 75% improvement in the Psoriasis Area and Severity Index score (a PASI 75 response) relative to baseline when assessed one week after a 12-week treatment course. Secondary endpoints included the proportion of subjects who achieved a rating of Minimal or Clear on a static global assessment by the physician, the Overall Lesion Severity (OLS), the proportion of patients with a ≥ 50% improvement in PASI score (a PASI 50 response) relative to baseline after 12 weeks of treatment, the time-course of mean PASI percentage improvement from baseline, improvement in the Dermatology Life Quality Index (DLQI), Psoriasis Symptom Assessment (PSA), the Physician's Global Assessment (PGA) of change, change in the PASI thickness component, and change in the body surface area affected.

In all five studies, patients randomized to the Raptiva group achieved statistically significantly better responses than placebo on the primary endpoint. The same results were confirmed in patients that were unsuitable for other systemic therapies (study IMP24011) (see Table 1 below).

Table 1
Primary Endpoint: Proportion of Subjects with ≥75% improvement in PASI after 12 weeks of Treatment (PASI 75)

		Efalizumab [a]	
Patient population IMP24011	Placebo	1.0 mg/kg/wk	Treatment Effect [95% CI]
All patients	4% (n=264)	31% (n=529) [b]	27% [22%, 32%]
Patients who are not controlled by, contraindicated to, or intolerant to two or more systemic therapies *	3% (n=184)	30% (n=342) [b]	27% [21%, 32%]

[a] p-values compared efalizumab with placebo using logistic regression including baseline PASI score, prior treatment for psoriasis and geographical region as covariates.
[b] p<0.001.
* As judged from the patients' histories of psoriasis treatments

In all five studies, patients randomized to the Raptiva dose group achieved statistically significantly better responses than placebo on the primary endpoint (PASI 75 response) (see Table 2 below) and on all the secondary efficacy endpoints.

Table 2
Primary Endpoint: Proportion of Subjects with ≥75% improvement in PASI after 12 weeks of Treatment (PASI 75)

		Efalizumab [a]	
Study	Placebo	1.0 mg/kg/wk	Treatment Effect [95% CI]
ACD2390g *	4% (n=187)	27% (n=369) [b]	22% [16%, 29%]
ACD2058g	2% (n=170)	39% (n=162) [b]	37% [28%, 46%]
ACD2059g *	5% (n=122)	22% (n=232) [b]	17% [9%, 27%]
ACD2600g *	3% (n=236)	24% (n=450) [b]	21% [15%, 27%]
IMP24011 *	4% (n=264)	31% (n=529) [b]	27% [22%, 32%]

[a] IMP24011: p-values compared efalizumab with placebo using logistic regression including baseline PASI score, prior treatment for psoriasis and geographical region as covariates.
Other studies: p-values compared each efalizumab group with placebo using Fisher's exact test within each study.
[b] $p<0.001$.
* The efalizumab used in the study is the Genentech manufactured product

Time to relapse (≥50% loss of improvement) was evaluated in Study ACD2058g 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 to 74 days following the last Raptiva dose in the initial treatment period.

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).

5.2 Pharmacokinetic properties

Absorption:
After subcutaneous administration of efalizumab peak plasma concentrations are reached after 1-2 days. Comparison with intravenous data indicated an average bioavailability of about 50% at the recommended dose level of 1.0 mg/kg/wk subcutaneous.

Distribution:
Steady state was achieved at week 4. At the 1 mg/kg/wk dose level (with an initial dose of 0.7 mg/kg the first week), mean efalizumab plasma trough values were 11.1±7.9 µg/ml. Measurements of volume of distribution of the central compartment after single intravenous doses were 110 ml/kg at dose 0.03 mg/kg and 58 ml/kg at dose 10 mg/kg.

Biotransformation:
The metabolism of efalizumab is through internalisation followed by intracellular degradation as a consequence of either binding to cell surface CD11a or through endocytosis. The expected degradation products are small peptides and individual amino acids which are eliminated by glomerular filtration. Cytochrome P450 enzymes as well as conjugation reactions are not involved in the metabolism of efalizumab.

Elimination:
Efalizumab is cleared by nonlinear saturable elimination (dose dependent). Mean steady state clearance is 24 ml/kg/day (range 5-76 ml/kg/day) at 1 mg/kg/week subcutaneous.
The elimination half-life was about 5.5-10.5 days at 1 mg/kg/week subcutaneous. T_{end} at steady state is 25 days (range 13-35 days). Weight is the most significant covariate affecting efalizumab clearance.

Non-linearity:
Efalizumab shows dose-dependent nonlinear pharmacokinetics which can be explained by its saturable specific binding to cell surface receptors CD11a. It appeared that the receptor mediated clearance of efalizumab was saturated when plasma efalizumab concentrations were above 1 µg/ml.

Through population pharmacokinetic analysis, weight was found to affect efalizumab clearance. Covariates as baseline PASI, baseline lymphocyte count and age had modest effects on clearance; gender and ethnic origin had no effect. The pharmacokinetics of efalizumab in paediatric patients have not been studied. The effect of renal or hepatic impairment on the pharmacokinetics of efalizumab has not been studied.

Antibodies to efalizumab were detected in only 6% of patients evaluated. In this small number of patients no differences were observed in either pharmacodynamic or pharmacokinetic parameters.

5.3 Preclinical safety data

Efalizumab does not cross-react with CD11a from species other than humans and chimpanzees. Therefore, conventional non-clinical safety data with the medicinal product are limited and do not allow for a comprehensive safety assessment. Inhibitory effects were observed on the humoral and T-cell dependent immune responses. In pups of mice treated with an antibody analogue of efalizumab, a decrease in T-cell dependent immunity was observed up to at least 11 weeks of age. Only at 25 weeks of age was this decrease no longer significant.
Otherwise, the effects observed in non-clinical studies could be related to the pharmacology of efalizumab.

No lymphomas were observed following 6 months treatment with an antibody analogue of efalizumab in a 6 months study with p53 +/+ wild type mice.
No teratogenic effects were seen in mice during organogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Polysorbate 20
Histidine
Histidine hydrochloride monohydrate
Sucrose

Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, an immediate use is recommended (see also section 6.4).

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Store in the original package in order to protect from light.

From a microbiological point of view, the product should be used immediately after first opening and reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. Physico-chemical stability of the reconstituted product has been shown for 24 hours at 2°C to 8°C.

6.5 Nature and contents of container

Powder:
Colourless type I glass vial with a butyl rubber stopper, and aluminum seal fitted with a flip-off plastic cap.
Solvent:
Type I glass pre-filled syringe.

Raptiva is available in:
Packs of 1 vial of powder, 1 pre-filled syringe of solvent, 1 needle for reconstitution and 1 needle for injection.

Packs of 4 vials of powder, 4 pre-filled syringes of solvent, 4 needles for reconstitution and 4 needles for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Raptiva is for single use only.

One vial of Raptiva should be reconstituted with the solvent before use. Reconstitution of the single-use vial with 1.3 ml of the supplied water for injections yields approximately 1.5 ml of solution to deliver 100 mg per 1 ml of Raptiva. The maximum retrievable dose is 125 mg per 1.25 ml of Raptiva.

The solution should reconstitute in not more than 5 minutes. The reconstituted solution is a clear to slightly opalescent, colourless to pale yellow solution, and should not be administered if it contains particles or is not clear.

Detailed instructions for use are provided in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Ltd.
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Raptiva – 1 vial EU/1/04/291/001
Raptiva – 4 vials EU/1/04/291/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2004

10. DATE OF REVISION OF THE TEXT

February 2007

LEGAL STATUS

POM

NAME AND ADDRESS OF DISTRIBUTOR IN UK

Serono Ltd
Bedfont Cross
Stanwell Road
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