

**ANNEX I**  
**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 the severity of infections, e.g. tuberculous pneumonia, and reactivate latent, chronic infections e.g. JC virus infection.

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.

The use of Raptiva may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). One case of JC virus infection resulting in PML has been reported in post-marketing surveillance in a patient with psoriasis receiving Raptiva (see section 4.8).

Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML (such as impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes). If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. If any doubt exists, further evaluation, including Magnetic Resonance Imaging (MRI) scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC viral DNA and repeat neurological assessment, should be considered. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of Raptiva must be permanently discontinued.

##### 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.

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.

#### Special patient populations

No differences in safety or efficacy were observed between elderly ( $\geq 65$  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 ( $\phi$ X174) 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)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Very rare (<1/10,000)	Not known
<b>Infections and infestations</b>						Aseptic meningitis*, Severe infections*, JC virus infection resulting in progressive multifocal leukoencephalopathy*
<b>Blood and the lymphatic system disorders</b>	Leuko- cytosis and lympho- cytosis		Thrombo- cytopenia			Immune mediated haemolytic anaemia*
<b>Immune system disorders</b>		Hyper- sensitivity reactions				
<b>Nervous system disorders</b>			Facial palsy (Bell's palsy)			Inflammatory polyradiculo- neuropathy*
<b>Respiratory, thoracic and mediastinal disorders</b>						Interstitial pneumonitis*
<b>Skin and subcutaneous tissue disorders</b>		Psoriasis	Urticaria			Erythema multiforme*
<b>Musculoskeletal and connective tissue disorders</b>		Arthralgia Arthritis / Psoriatic arthritis (exacerbation/ flare)				
<b>General disorders and administration site conditions</b>	Flu-like symptoms including fever, headaches, chills, nausea and myalgia	Back pain, Asthenia	Injection site reactions			
<b>Investigations</b>		Elevation of alkaline Phosphatase, 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.

### Additional Information

#### Long-term exposure:

Analysis following long-term use in a cohort of 339 patients with moderate to severe psoriasis receiving Raptiva 1 mg/kg/week, 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. 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  $\mu$ l 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. 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).

#### 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). Over long term treatment, the frequency of hypersensitivity-related adverse events did not increase.

#### 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.

As regards serious infections, the overall incidence in both controlled and uncontrolled studies of up to 12 weeks was 2.8 per 100 patient-years for Raptiva-treated patients compared with 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.).

JC virus infection resulting in PML has been reported in post-marketing surveillance in a patient with psoriasis receiving Raptiva (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.

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).

##### 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  $\pm 25\%$  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 over 12 weeks of treatment with different populations indicate a 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 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  $\geq 75\%$  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  $\geq 50\%$  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 (see Table 1 below).

Table 1 Primary Endpoint: Proportion of Subjects with $\geq 75\%$ improvement in PASI after 12 weeks of Treatment (PASI 75)			
Patient population IMP24011	Placebo	Efalizumab <sup>a</sup>	
		1.0 mg/kg/wk	Treatment Effect [95% CI]
All patients	4% (n=264)	31% (n=529) <sup>b</sup>	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) <sup>b</sup>	27% [21%, 32%]
<sup>a</sup> p-values compared efalizumab with placebo using logistic regression including baseline PASI score, prior treatment for psoriasis and geographical region as covariates.			
<sup>b</sup> 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 $\geq 75\%$ improvement in PASI after 12 weeks of Treatment (PASI 75)			
Study	Placebo	Efalizumab <sup>a</sup>	
		1.0 mg/kg/wk	Treatment Effect [95% CI]
ACD2390g *	4% (n=187)	27% (n=369) <sup>b</sup>	22% [16%, 29%]
ACD2058g	2% (n=170)	39% (n=162) <sup>b</sup>	37% [28%, 46%]
ACD2059g *	5% (n=122)	22% (n=232) <sup>b</sup>	17% [9%, 27%]
ACD2600g *	3% (n=236)	24% (n=450) <sup>b</sup>	21% [15%, 27%]
IMP24011 *	4% (n=264)	31% (n=529) <sup>b</sup>	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 ( $\geq 50\%$  loss of improvement) was evaluated in Study ACD2058g and IMP 24011 for patients who were classified as responders ( $\geq 75\%$  improvement on PASI) after 12 weeks of treatment. The median time to relapse among PASI responders ranged from 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.

#### 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).

## **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  $11.1 \pm 7.9$   $\mu\text{g/ml}$ . 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.  $T_{\text{end}}$  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  $\mu\text{g/ml}$ .

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**

4 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 aluminium 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 EasyMIX adapter for reconstitution and 1 needle for injection.

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

Packs of 12 vials of powder, 12 pre-filled syringes of solvent, 12 EasyMIX adapters for reconstitution and 12 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 NUMBERS

EU/1/04/291/001  
EU/1/04/291/002  
EU/1/04/291/003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 20 September 2004

**10. DATE OF REVISION OF THE TEXT**

Medicinal product no longer authorised

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURING AUTHORISATION  
HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH  
RELEASE**

Name and address of the manufacturer(s) of the biological active substance

Genentech, Inc.  
1 DNA Way, South San Francisco, CA 94080-4990  
USA

Name and address of the manufacturer(s) responsible for batch release

Merck Serono S.p.A.  
Via L. Einaudi 11,  
00012 Guidonia Montecelio (Rome)  
Italy

**B CONDITIONS OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON  
THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex 1: Summary of Product Characteristics, section 4.2)

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.



Medicinal product no longer authorised

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE****BOX OF 4 VIALS AND 4 PRE-FILLED SYRINGES****BOX OF 12 VIALS AND 12 PRE-FILLED SYRINGES****1. NAME OF THE MEDICINAL PRODUCT**

Raptiva 100 mg/ml powder and solvent for solution for injection  
Efalizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial of powder contains a retrievable amount of 125 mg of efalizumab.

**3. LIST OF EXCIPIENTS**

Polysorbate 20, histidine, histidine hydrochloride monohydrate and sucrose.  
Solvent: water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial of powder for solution for injection.  
1 pre-filled syringe of 1.3 ml solvent.  
1 EasyMIX adapter for reconstitution.  
1 needle for injection.

4 vials of powder for solution for injection.  
4 pre-filled syringes of 1.3 ml solvent.  
4 EasyMIX adapters for reconstitution.  
4 needles for injection.

12 vials of powder for solution for injection.  
12 pre-filled syringes of 1.3 ml solvent.  
12 EasyMIX adapters for reconstitution.  
12 needles for injection.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Subcutaneous use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

Use immediately after reconstitution.

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

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

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard any unused solution.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER**

EU/1/04/291/001

EU/1/04/291/002

EU/1/04/291/003

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

raptiva 100 mg/ml

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS****RAPTIVA 100 mg/ml VIAL LABEL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Raptiva 100 mg/ml  
Powder for solution for injection  
Efalizumab  
Subcutaneous use

**2. METHOD OF ADMINISTRATION****3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Batch

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

125 mg retrievable

**6. OTHER**

<b>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</b> <b>SOLVENT PRE-FILLED SYRINGE LABEL</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</b>
--

Solvent for use with Raptiva  
Water for injections

<b>2. METHOD OF ADMINISTRATION</b>
------------------------------------

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Batch

<b>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</b>
--

1.3 ml in pre-filled syringe

<b>6. OTHER</b>
-----------------

Medicinal product no longer authorised

#### **B. PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### **Raptiva 100 mg/ml powder and solvent for solution for injection Efalizumab**

**Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Raptiva is and what it is used for
2. Before you use Raptiva
3. How to use Raptiva
4. Possible side effects
5. How to store Raptiva
6. Further information

## **1. WHAT RAPTIVA IS AND WHAT IT IS USED FOR**

Raptiva is a systemic psoriasis medicine. Systemic therapies are medicines taken orally or administered by injection and thus will be present in and affect the whole body.

Raptiva is a medicine containing efalizumab, made by means of biotechnology. It is produced by genetically engineered mammalian cells. Efalizumab is a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other specific proteins of the human body. Efalizumab reduces inflammation of the psoriatic lesions which results in improvement of the affected areas of the skin.

#### **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.

This restriction of the indication of Raptiva is based on the present efficacy data and limited long-term experience with Raptiva.

## **2. BEFORE YOU USE RAPTIVA**

Ask your doctor or pharmacist for advice before taking any medicine.

#### **Do not use Raptiva:**

- If you are allergic (hypersensitive) to efalizumab or any of the other ingredients of Raptiva.
- If you have or have had any cancer.
- If you have active tuberculosis or other severe infections. Symptoms that might indicate that you have an infection are fever, wounds, feeling tired, dental problems, a bad cough that lasts longer than 2 weeks, pain in the chest or coughing up blood or sputum.
- If you have forms of psoriasis other than plaque psoriasis (for instance other more severe forms of psoriasis, as diagnosed by your doctor).
- If you have been diagnosed as having a disorder of your immune system.

It is important that you tell your doctor if you have had or you have any of the above.



**Take special care with Raptiva:**

- If you experience hypersensitivity or allergic reactions such as overall body itching, hives, skin flushing or rash tell your doctor immediately or go to the local casualty.
- You might get infections more easily. If you develop a new infection or notice any new or sudden change in thinking, balance, strength, talking, walking or vision, please contact your doctor. He/she will determine whether to monitor your treatment or whether it is necessary for you to stop using Raptiva.
- If you develop cancer while undergoing treatment, please contact your doctor who will determine if it is necessary for you to stop using Raptiva.
- If you develop signs and symptoms associated with anaemia (a reduction in red blood cells which can make the skin pale and cause weakness or breathlessness) while undergoing treatment, please contact your doctor who will determine if it is necessary for you to stop using Raptiva.
- If you develop any of the signs and symptoms associated with a decrease in blood platelets, such as easy bleeding from the gums, bruising or pinpoint red spots on the skin, please tell your doctor immediately. He/she will determine whether to monitor your treatment or whether it is necessary for you to stop using Raptiva.
- Some patients had reactions including headache, fever, nausea and vomiting within two days of each of the first two injections. These reactions were largely mild to moderate. If you notice that any of these reactions do not vanish after the second injection, tell your doctor.
- If you discontinue Raptiva treatment (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 experience a worsening of your psoriasis or you develop arthritis, please inform your doctor. He/she will determine whether to stop using Raptiva or continue treatment with closer observation.
- If you are going to receive any vaccine, please check with your doctor. You must not receive certain types of vaccines during Raptiva treatment. It may be necessary to discontinue Raptiva treatment 8 weeks before a vaccination.
- If your weight changes unexpectedly, please contact your doctor. He/she will calculate the correct dosage based on your new weight.

Tell your doctor if you have renal or hepatic impairment.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Please check with your doctor if you are planning to receive any vaccine (see “Take special care with Raptiva”).

When taking Raptiva you might be more vulnerable to infections (see Take special care with Raptiva) this effect might be enhanced by other medicines that are used to treat psoriasis and that also make you more vulnerable to infections. Please check with your doctor if you receive other medicines to treat your psoriasis.

Raptiva can be used in combination with topical corticosteroids.

**Pregnancy**

It is not known whether Raptiva can cause harm to your baby if you are pregnant or whether it can affect your ability to become pregnant. Therefore, if you are pregnant, consult with your doctor immediately.

If you are a woman of childbearing potential, you are advised not to become pregnant and to use adequate contraception while using Raptiva.

**Breast-feeding**

It is possible that efalizumab is excreted in human milk. If you are breastfeeding, your doctor will advise you either to discontinue breastfeeding or to discontinue Raptiva while breastfeeding.

### **Driving and using machines**

The use of Raptiva is not expected to affect your ability to drive and use machines.

## **3. HOW TO USE RAPTIVA**

Always take Raptiva exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

### **Dosing for adults (18-64 years) and the elderly ( $\geq 65$ years)**

The usual dose is an initial single injection of 0.7 mg/kg followed by weekly injections of 1.0 mg/kg. Your doctor will tell you how much you should inject. The duration of therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment, your doctor will discuss with you the extent of your response to treatment.

### **Method and route of administration**

Raptiva is injected just under the skin (subcutaneous). It is for single use only. The injection can be self-administered or given by another person, for example a family member or your doctor. You should continue to inject Raptiva as long as instructed to do so by your doctor.

The vial of powder is designed to be reconstituted (mixed) with the solvent.

If you administer Raptiva, please read the following instructions carefully and follow them step by step:

- Wash your hands. It is important that your hands and items you use be as clean as possible.
- Take the Raptiva out of the refrigerator and lay out on a clean surface everything you need:
  - one vial containing the Raptiva powder
  - one pre-filled syringe containing the solvent
  - one EasyMIX adapter for reconstitution
  - two alcohol swabs
  - one needle for subcutaneous injection, and
  - a sharps container
- Remove the protective cap from the Raptiva vial and from the solvent pre-filled syringe. Wipe the top of the vial with an alcohol swab.
- Holding the EasyMIX outer cover, carefully peel back and remove the protective film using the tab. This will expose a plastic spiked end that you will use to pierce the vial. You should not touch this area.
- Holding the EasyMIX outer cover, place it on top of the vial, then press down so that the plastic spiked end pierces the rubber stopper on the vial.
- Ensure the EasyMIX adapter is firmly attached to the vial, before removing the outer cover.



- Pull off the cap covering the pre-filled syringe tip.
- Attach the pre-filled syringe containing the solvent to the EasyMIX adapter with a 'push and twist' action.

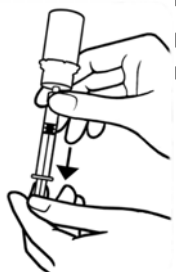


- Very slowly push down on the syringe plunger to inject all the solvent into the Raptiva vial.
- Without removing the syringe, gently rotate the vial to dissolve the medicine in the solvent.

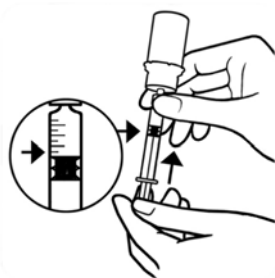


**Do not shake** (Shaking will cause foaming of the Raptiva solution). Generally reconstitution takes less than 5 minutes. After the powder has dissolved, check the resulting solution for particles and discoloration. The reconstituted solution should be clear to pale yellow and free of particles. No other medicines should be added to the solution containing Raptiva and Raptiva should not be reconstituted with other solvents.

- Turn the vial upside down, with the syringe still attached. Withdraw the solution slowly into the syringe, taking more than the dose you need. Some foam or bubbles may remain in the vial. With the syringe still attached to the vial, check the syringe for air bubbles.
- Gently tap the syringe to make any bubbles rise to the top of the syringe.



- Gently push the plunger up until the dose to be given remains in the syringe. This will also push the bubbles out of the syringe and into the vial. If you eject too much Raptiva back into the vial, simply repeat the drawing up process and continue.



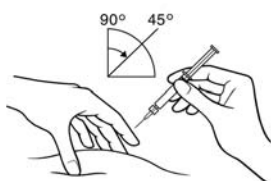
- Check you have the right dose, then remove the syringe from the EasyMIX adapter using a 'twist and pull' action.

You are now ready to attach the injection needle.

- Take the injection needle and, with its shield still in place, carefully screw it on to the syringe tip.

You are now ready to select and prepare your injection site. Your doctor or nurse will have already advised you where to inject. Sites for self-injection include the buttocks, thigh, abdomen or upper arm. The injection sites should be rotated.

- Wipe the chosen area with an alcohol swab. Remove the shield from the injection needle.
- Immediately inject the solution as follows: Firmly pinch the skin together and insert the needle at a 45° to 90° angle using a dart-like motion. Inject under the skin, as you were taught. Do not inject directly into a vein. Pull back the plunger very slightly. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject but withdraw the needle and repeat the injection procedure. Inject the solution by pushing gently on the plunger. Take as much time as you need to inject all the solution. Immediately withdraw the needle and clean the skin with an alcohol swab using a circular motion.



- Dispose of all used items: Once you have finished your injection, immediately discard all needles and empty glass containers in a sharps container. Any unused solution must be discarded.

#### **If you use more Raptiva than you should**

If you have injected more Raptiva than told by your doctor, please contact your doctor or pharmacist. It is recommended that you are monitored for any signs or symptoms of adverse effects and that you are given appropriate symptomatic treatment immediately.

#### **If you forget to use Raptiva**

Do not take a double dose to make up for a forgotten dose.

Please contact your doctor if you forget to take 2 or more doses of Raptiva.

#### **If you stop using Raptiva**

If you discontinue treatment with Raptiva without substitution treatment, your psoriasis may significantly worsen. (See “Take special care with Raptiva”)

In case re-treatment with Raptiva is needed you should follow the guidance of your doctor. Re-treatment may be associated with lower or inadequate response to Raptiva than in the earlier treatment periods. Therapy should be continued only when adequate response is observed. Your doctor will advise you what to do when insufficient response to treatment or worsening of your disease is observed. (See also under Take Special Care with Raptiva)

If you have any further questions on the use of the product, ask your doctor or pharmacist.

#### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Raptiva can cause side effects, although not everybody gets them.

The side effects in this section are given with an estimation of the frequency with which they may occur. For this purpose the following classification has been used:

- Very common: Side effects that may occur in more than 1 out of 10 patients;
- Common: Side effects that may occur in 1 to 10 out of 100 patients;
- Uncommon: Side effects that may occur in 1 to 10 out of 1,000 patients;
- Rare: Side effects that may occur in 1 to 10 out of 10,000 patients;
- Very rare: Side effects that may occur in less than 1 out of 10,000 patients;

Raptiva may cause mild to moderate flu-like symptoms including headache, chills, nausea, muscle aches and occasionally fever within 48 hours of an injection of Raptiva. These symptoms are very common and occur most often after the first two doses and decrease with continued use. If any of these symptoms are severe or persist, you should contact your doctor. In clinical trials, visible side effects at the injection site and injection site pain were uncommon.

Tell your doctor or go to the local casualty and stop using Raptiva immediately if you:

- Notice serious hypersensitivity or allergic reactions, such as anaphylaxis. Symptoms of an allergic reaction are common and generally include overall body itching, hives, skin flushing or rash. Anaphylaxis is a more serious allergic reaction that may involve dizziness, vomiting, low blood pressure, and difficulty with breathing. Prompt medical care is needed since serious allergic reactions may be potentially life-threatening.
- Notice symptoms of low blood platelet counts, such as easy bleeding from the gums, bruising or pinpoint red spots on the skin. These symptoms are uncommon.
- Notice signs of nerve disorder such as tingling or onset of weakness in legs or arms or new or sudden change in thinking, balance, strength, talking, walking or vision.
- Notice severe headache accompanied with nuchal rigidity. This may occur rarely in particular at the beginning of the treatment.
- Are diagnosed with cancer.
- Develop a diffuse skin rash or blisters in your oral cavity.

Tell your doctor and discuss with him your general health if you notice any of the following:

- Back pain, joints pain, headache, vomiting, weakness, fatigue or rash. These common side effects have not been clearly associated with Raptiva but have been observed when using it. Your doctor may want to examine you more closely and ask you to have blood tests.
- Fever or if you think that you have an infection. Raptiva acts on the immune system, which may potentially increase your risk of infectious diseases or may reactivate old infections. Infections are very common.
- A relapse or flare or strong worsening of psoriasis or red, inflamed psoriatic plaques, sometimes with swelling of your arms or legs or joint inflammation, especially after stopping Raptiva. These side effects are common.
- Shortness of breath or any persistent respiratory difficulties.
- Signs of facial paralysis usually on one side of the face (such as weakness of face muscles and dribbling) possibly preceded by pain in the ear area. Generally patients with facial paralysis recover within a few weeks without any specific treatment.

Certain laboratory tests may change, such as the number of white or red blood cells (including leukocytes and lymphocytes) as well as alkaline phosphatase and ALT values (blood laboratory values). These changes, which may be associated with the use of Raptiva, can usually only be detected with blood tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE RAPTIVA

Keep out of the reach and sight of children.

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

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

Do not use Raptiva after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Do not use if you notice that the solution is not clear or contains particles.

To maintain sterility, Raptiva must be used immediately after first opening and reconstitution.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Raptiva contains

- The active substance is efalizumab, each vial contains a deliverable dose of 125 mg efalizumab.
- The other ingredients are polysorbate 20, histidine, histidine hydrochloride monohydrate and sucrose.
- Each pre-filled syringe of solvent contains sufficient water for injections to make up the solution for injection.

### What Raptiva looks like and contents of the pack

Raptiva is presented as a powder and solvent for solution for injection. The powder is a white to off-white cake and the solvent is a colourless liquid. The product is supplied in packs of 1 vial of powder, 1 pre-filled syringe of solvent, 1 EasyMIX adapter for reconstitution, 1 needle for injection; in packs of 4 vials of powder, 4 pre-filled syringes of solvent, 4 EasyMIX adapters for reconstitution, 4 needles for injection and in packs of 12 vials of powder, 12 pre-filled syringes of solvent, 12 EasyMIX adapters for reconstitution and 12 needles for injection. Not all pack sizes may be available in each country.

### Marketing Authorisation Holder

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

### Manufacturer

Merck Serono S.p.A.  
Via Luigi Einaudi 11  
00012 Guidonia Montecelio/Rome  
Italy

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Puh/Tel: +358-9-8678 700

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This leaflet was last approved on