

RAPTIVA[®]
[efalizumab]

For injection, subcutaneous

WARNING:

RISK OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

- **RAPTIVA increases the risk for PML, a rapidly progressive viral infection of the central nervous system that has no known treatment and that leads to death or severe disability. The risk of PML may markedly increase with longer duration of RAPTIVA exposure. The time dependent threshold when the risk for PML increases is unknown (see WARNINGS).**
 - **Patients on RAPTIVA should be monitored frequently to ensure they are receiving significant clinical benefit, to ensure they understand the significance of the risk of PML, and for any sign or symptom that may be suggestive of PML (see WARNINGS).**
 - **RAPTIVA dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, brain magnetic resonance imaging (MRI) and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended (see WARNINGS).**

RISK OF SERIOUS INFECTIONS

- **Infections, including serious infections leading to hospitalizations or death, have been observed in patients treated with RAPTIVA (see WARNINGS and ADVERSE REACTIONS). These infections have included bacterial sepsis, viral meningitis, invasive fungal disease and other opportunistic infections. Patients should be educated about the symptoms of infection and be closely monitored for signs and symptoms of infection during and after treatment with RAPTIVA. If a patient develops a serious infection, RAPTIVA should be discontinued and appropriate therapy instituted.**

DESCRIPTION

RAPTIVA[®] (efalizumab) is an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody that binds to human CD11a. Efalizumab has a molecular weight of approximately 150 kilodaltons and is produced in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

RAPTIVA is supplied as a sterile, white to off-white, lyophilized powder in single-use glass vials for subcutaneous (SC) injection. Reconstitution of the single-use vial with 1.3 mL of the supplied sterile water for injection (non-USP) yields approximately 1.5 mL of solution to deliver 125 mg per 1.25 mL (100 mg/mL) of RAPTIVA. The sterile water for injection supplied does not comply with USP requirement for pH. After

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reconstitution, RAPTIVA is a clear to pale yellow solution with a pH of approximately 6.2. Each single-use vial of RAPTIVA contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochloride monohydrate, 4.3 mg of L-histidine and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 mL.

CLINICAL PHARMACOLOGY

Mechanism of Action

RAPTIVA binds to CD11a, the α subunit of leukocyte function antigen-1 (LFA-1), which is expressed on all leukocytes, and decreases cell surface expression of CD11a. RAPTIVA inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types. Interaction between LFA-1 and ICAM-1 contributes to the initiation and maintenance of multiple processes, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation including psoriatic skin. Lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 cell surface expression is upregulated on endothelium and keratinocytes. CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Therefore, the potential exists for RAPTIVA to affect the activation, adhesion, migration, and numbers of cells other than T lymphocytes.

Pharmacokinetics

In patients with moderate to severe plaque psoriasis, following an initial SC RAPTIVA dose of 0.7 mg/kg followed by 11 weekly SC doses of 1 mg/kg/wk, serum concentrations reached a steady-state at 4 weeks with a mean trough concentration of approximately 9 $\mu\text{g/mL}$ (n=26). After the last dose, the mean peak concentration was approximately 12 $\mu\text{g/mL}$ (n=25). Mean steady-state clearance was 24 mL/kg/day (range=5–76 mL/kg/day, n=25). Mean time to eliminate RAPTIVA after the last steady-state dose was 25 days (range=13–35 days, n=17). The mean estimated RAPTIVA SC bioavailability was 50%. In a population pharmacokinetic analysis of 1088 patients, body weight was found to be the most significant covariate affecting RAPTIVA clearance. In patients receiving weekly SC doses of 1 mg/kg, RAPTIVA exposure was similar across body weight quartiles. RAPTIVA clearance was not

significantly affected by gender or race. The pharmacokinetics of RAPTIVA in pediatric patients have not been studied. The effects of renal or hepatic impairment on the pharmacokinetics of RAPTIVA have not been studied.

Pharmacodynamics

At a dose of 1 mg/kg/wk SC, RAPTIVA reduced expression of CD11a on circulating T lymphocytes to approximately 15–25% of pre-dose values and reduced free CD11a binding sites to a mean of $\leq 5\%$ of pre-dose values. These pharmacodynamic effects were seen 1–2 days after the first dose, and were maintained between weekly 1 mg/kg SC doses. Following discontinuation of RAPTIVA, CD11a expression returned to a mean of 74% of baseline at 5 weeks and stayed at comparable levels at 8 and 13 weeks.

Following discontinuation of RAPTIVA, free CD11a binding sites returned to a mean of 86% of baseline at 8 weeks and stayed at comparable levels at 13 weeks. No assessments of CD11a expression or free CD11a binding sites were made after 13 weeks.

In clinical trials, RAPTIVA treatment resulted in a mean increase (relative to baseline) in white blood cell (WBC) count of 34%, a doubling of mean lymphocyte counts and an increase in eosinophil counts of 29% due to decreased leukocyte adhesion to blood vessel walls and decreased trafficking from the vascular compartment to tissues. At Day 56 of 1 mg/kg/wk RAPTIVA treatment, 32% (213/676) of patients had a shift in total WBC from low or normal baseline value to above normal, 46% (324/701) had a shift to above normal absolute lymphocyte counts, and 5% (35/675) had a shift to above normal eosinophil counts. Following discontinuation of RAPTIVA treatment, the abnormal elevated lymphocyte counts took approximately 8 weeks to normalize among patients who had above normal lymphocyte counts. Plasma samples collected after first administration of 0.3 mg/kg IV RAPTIVA indicate that at 2 hours TNF- α and IL-6 plasma levels were elevated 9- and 90-fold, respectively, compared with baseline. Plasma samples collected after first administration of 0.7 mg/kg SC RAPTIVA indicate that at 2 days, IL-6 levels were elevated (10 pg/mL as compared with 5 pg/mL at baseline), whereas TNF- α was not detectable. In RAPTIVA-treated patients the mean levels of C reactive protein increased from baseline by 67% and the mean levels of fibrinogen increased by 15%.

CLINICAL STUDIES

RAPTIVA was evaluated in four randomized, double-blind, placebo-controlled studies in adults with chronic (>6 months), stable, plaque psoriasis, who had a minimum body surface area involvement of 10% and who were candidates for, or had previously received systemic therapy or phototherapy. In these studies 54–70% of patients had previously received systemic therapy or phototherapy (PUVA) for psoriasis. Patients with clinically significant flares and patients with guttate, erythrodermic, or pustular psoriasis as the sole form of psoriasis were excluded from the studies. Patients were randomized to receive doses of 1 mg/kg or 2 mg/kg of RAPTIVA or placebo administered once a week for 12 weeks. Patients randomized to RAPTIVA received 0.7 mg/kg as the first dose prior to receiving the full assigned dose in subsequent weeks. During the studies, patients could receive concomitant low potency topical steroids. No other concomitant psoriasis therapies were allowed during treatment or the follow-up period.

Patients were evaluated using the Psoriasis Area and Severity Index (PASI) during the study. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of the psoriatic changes within the affected regions (erythema, infiltration/plaque thickness, and desquamation). Both treatment groups in all four studies had baseline median PASI scores of 17. Both treatment groups across all four studies had baseline median body surface area involvement ranging between 22–28%. Compared with placebo, more patients randomized to RAPTIVA had at least a 75% reduction from baseline PASI score (PASI-75) 1 week after the 12-week treatment period (Table 1). RAPTIVA 2 mg/kg was not superior to RAPTIVA 1 mg/kg.

Table 1
 Proportion of Patients with $\geq 75\%$ Improvement
 in PASI after 12 Weeks of Treatment (PASI-75)

	Placebo	RAPTIVA 1 mg/kg/wk	Difference (95%CI)
Study 1	4% n=187	27% ^a n=369	22% (16%, 29%)
Study 2	2% n=170	39% ^a n=162	37% (28%, 46%)
Study 3	5% n=122	22% ^a n=232	17% (9%, 27%)
Study 4	3% n=236	24% ^a n=450	21% (15%, 27%)

^a $p < 0.001$ for comparison of RAPTIVA group with placebo group using Fisher's exact test within each study.

All three components of the PASI (plaque induration, scaling, and erythema) contributed comparably to the improvement in PASI. Other clinical responses evaluated (Table 2) included the proportion of patients who achieved minimal or clear status by a static Physician Global Assessment (sPGA) and the proportion of patients with a reduction in PASI of at least 50% from baseline (PASI-50) 1 week following the 12-week treatment period. The sPGA is a 6 category scale ranging from “very severe” to “clear” indicating the physician’s overall assessment of the psoriasis severity focusing on plaque, scaling and erythema. Treatment success of minimal or clear consisted of none or slight elevation in plaque, none or minimal white color in scaling, and up to moderate definite red coloration in erythema. Across all four studies, the percentage of patients with baseline sPGA classifications of moderate was 48–56%, severe 33–43%, and 3–6% were classified as very severe.

Table 2
Percentage of Patients Responding after 12 Weeks of Treatment

Outcome Measurement	Study	Placebo	RAPTIVA 1 mg/kg/wk	Difference ^a (95% CI)
sPGA: Minimal or Clear	1	3%	26%	23% (16, 30)
	2	3%	32%	29% (21, 39)
	3	3%	19%	16% (8, 25)
	4	4%	20%	16% (11, 22)
>50% improvement in PASI (PASI-50)	1	14%	59%	45% (37, 53)
	2	15%	61%	46% (37, 56)
	3	16%	52%	36% (26, 47)
	4	14%	52%	38% (31, 45)

The number of patients in each study and treatment group is the same as listed in Table 1.

^a p < 0.001 for comparison of RAPTIVA group to placebo group using Fisher's exact test for all comparisons between groups.

In Study 1, 12% of RAPTIVA-treated patients achieved a PASI-50 at Week 4 compared with 5% for placebo. The median time to PASI-50 among PASI-75 achievers was approximately 6 weeks. Similar results were observed in Studies 2, 3, and 4.

In Study 3, sustained response to extended RAPTIVA treatment was evaluated. RAPTIVA-treated patients who achieved a PASI-75 response at Week 12 were re-randomized to receive RAPTIVA or placebo for a second contiguous 12-week treatment period. Sixty-one of 79 patients (77%) re-randomized to a second 12-week treatment period with RAPTIVA maintained PASI-75 response compared with 8 of 40 patients (20%) re-randomized to placebo. Sustained responses to RAPTIVA have also been observed in uncontrolled, open-label extension treatment trials when patients received RAPTIVA without interruption for 24 weeks.

In Study 2, response to intermittent RAPTIVA treatment was evaluated among patients who achieved PASI-75 response with 12 weeks of RAPTIVA treatment and were followed off-treatment until relapse of psoriasis (50% loss of treatment response). In patients who resumed RAPTIVA treatment upon relapse of psoriasis, 31% (17/55) re-established a PASI-75 response (compared with the initial baseline). After 12 weeks of treatment, the median duration of a PASI-75 response after RAPTIVA discontinuation was between 1 and 2 months.

The safety and efficacy of RAPTIVA therapy beyond 1 year have not been established.

INDICATIONS AND USAGE

RAPTIVA[®] (efalizumab) is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

RAPTIVA should not be administered to patients with known hypersensitivity to RAPTIVA or any of its components.

RAPTIVA should not be administered to patients who have been diagnosed with PML (see **BOXED WARNING** and **WARNINGS: Progressive Multifocal Leukoencephalopathy**).

WARNINGS

Progressive Multifocal Leukoencephalopathy (PML)

PML is a rapidly progressive infection of the central nervous system caused by the JC virus that leads to death or severe disability.

RAPTIVA increases the risk for PML and this risk may markedly increase with longer duration of RAPTIVA exposure. Post-marketing cases of PML have been reported with RAPTIVA used as monotherapy. Three reports of confirmed PML were associated with exposure for greater than 3 years. At the time of these 3 reports, it is estimated that approximately 46,000 patients had been exposed to RAPTIVA worldwide; however, relatively few patients had been exposed beyond 2 years. Approximately 14,000 patients have been exposed for greater than 1 year, 5,100 patients have been exposed for greater than 2 years and 1,900 patients have been exposed for greater than 3 years. The time dependent threshold when the risk for PML increases is unknown since additional cases may have been misdiagnosed and/or not reported.

The effect of intermittent use of RAPTIVA, or the concomitant or sequential use of other immunosuppressant drugs, on the risk of PML is not known (see **BOXED WARNING, CONTRAINDICATIONS**). There are no known screening tests or medical interventions that can reliably predict, prevent, or treat PML. Typical symptoms

associated with PML are diverse, progress over days to weeks, and may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and/or changes in thinking, memory, and orientation leading to confusion and personality changes.

Healthcare providers treating patients with RAPTIVA should consider PML in any patient with new-onset neurologic manifestations. Patients being treated with RAPTIVA should be instructed to immediately report to their healthcare provider any new neurological signs or symptoms that they or anyone close to them notices. RAPTIVA should be withheld immediately at the first sign or symptom suggestive of PML (see **WARNINGS: Psoriasis Worsening and Variants**). It is not known whether early detection of PML and discontinuation of RAPTIVA will mitigate risk of irreversible neurological damage and death associated with the disease. Consultation with a neurologist, brain MRI and cerebrospinal fluid analysis for JC viral DNA should be considered. Patients should be evaluated frequently to ensure they are receiving significant clinical benefit that justifies continued treatment in light of the risks, to ensure they understand the significance of the risk of PML, and for any sign or symptom that is suggestive of PML. Patients who discontinue RAPTIVA should continue to be carefully monitored for the onset of neurologic symptoms that may represent PML and for worsening of psoriasis (see **BOXED WARNING**).

Serious Infections

RAPTIVA is an immunosuppressive agent and has the potential to increase the risk of infection and reactivate latent, chronic infections. RAPTIVA should not be administered to patients with compromised immune systems or clinically important infections. Caution should be exercised when considering the use of RAPTIVA in patients with a chronic infection or history of recurrent infections. If a patient develops a serious infection, RAPTIVA should be discontinued. New infections developing during RAPTIVA treatment should be monitored closely. During the first 12 weeks of controlled trials, serious infections occurred in 7 of 1620 (0.4 %) RAPTIVA-treated patients compared with 1 of 715 (0.1%) placebo-treated patients (see **ADVERSE REACTIONS: Infections**). Serious infections requiring hospitalization included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis,

Legionnaire's disease, and vertebral osteomyelitis (note some patients had more than one infection).

In postmarketing experience, serious bacterial, viral, fungal, and opportunistic infections have occurred, including pneumonia, sepsis, meningitis, and encephalitis. Some of these infections have been fatal. Postmarketing reports include cytomegaloviral infections; blastomyces, cryptococcal and tuberculous pneumonia; serious herpes infection; severe pneumonia with neutropenia (ANC 60/mm³); sepsis with seeding of distant sites; necrotizing fasciitis; and worsening of infection (e.g. cellulitis, pneumonia) despite antimicrobial treatment (see **BOXED WARNING**).

Malignancies

The immunosuppression caused by RAPTIVA may have the potential to increase the risk of malignancy. The role of RAPTIVA in the development of malignancies is not known. Caution should be exercised when considering the use of RAPTIVA in patients at high risk for malignancy or with a history of malignancy. If a patient develops a malignancy, RAPTIVA should be discontinued (see **ADVERSE REACTIONS: Malignancies**).

Immunosuppression

RAPTIVA causes immunosuppression. The safety and efficacy of RAPTIVA in combination with other immunosuppressive agents or phototherapy have not been evaluated. Patients receiving other systemic immunosuppressive agents should not receive concurrent therapy with RAPTIVA because of the possibility of increased risk of infections and malignancies. RAPTIVA should not be administered to patients with compromised immune systems, for example, due to HIV infection or AIDS, leukemia, or lymphoma.

Immune-Mediated Thrombocytopenia

Platelet counts at or below 52,000 cells per μL were observed in 8 (0.3%) RAPTIVA-treated patients during clinical trials compared with none among the placebo-treated patients (see **ADVERSE REACTIONS: Immune-Mediated Thrombocytopenia**). Five of the 8 patients received a course of systemic steroids for thrombocytopenia. Thrombocytopenia resolved in the 7 patients receiving adequate follow-up (1 patient was lost to follow-up). Reports of severe thrombocytopenia have

also been received postmarketing. Physicians should follow patients closely for signs and symptoms of thrombocytopenia. Assessment of platelet counts is recommended during treatment with RAPTIVA (see **PRECAUTIONS: Laboratory Tests**) and RAPTIVA should be discontinued if thrombocytopenia develops.

Immune-Mediated Hemolytic Anemia

Reports of hemolytic anemia, some serious, diagnosed 4-6 months after the start of RAPTIVA treatment have been received. RAPTIVA should be discontinued if hemolytic anemia occurs.

Psoriasis Worsening and Variants

Worsening of psoriasis can occur during or after discontinuation of RAPTIVA. During clinical studies, 19 of 2589 (0.7%) of RAPTIVA-treated patients had serious worsening of psoriasis during treatment (n=5) or worsening past baseline after discontinuation of RAPTIVA (n=14) (see **ADVERSE REACTIONS: Adverse Events of Psoriasis**). In some patients these events took the form of psoriatic erythroderma, pustular psoriasis, or development of new plaque lesions. Some patients required hospitalization and alternative antipsoriatic therapy to manage the psoriasis worsening. Patients, including those not responding to RAPTIVA treatment, should be closely observed following discontinuation of RAPTIVA, and appropriate psoriasis treatment instituted as necessary.

Neurologic Events

One case of transverse myelitis was observed during the clinical development program (2762 RAPTIVA-treated patients); neurologic events, including cases of Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy, facial palsy, and transverse myelitis have been observed in patients receiving RAPTIVA in the postmarketing setting (see **ADVERSE REACTIONS: Postmarketing Experience**). Patients being treated with RAPTIVA should be instructed to immediately report any new neurological signs or symptoms to their physician. Prescribers should not use RAPTIVA in patients with significant existing or new onset nervous system adverse events. RAPTIVA should be discontinued in patients who develop PML

PRECAUTIONS

First Dose Reactions

First dose reactions including headache, fever, nausea, and vomiting are associated with RAPTIVA treatment and are dose-level related in incidence and severity (see **ADVERSE REACTIONS**). Therefore, a conditioning dose of 0.7 mg/kg is recommended to reduce the incidence and severity of reactions associated with initial dosing (see **DOSAGE AND ADMINISTRATION**). Cases of aseptic meningitis resulting in hospitalization have been observed in association with initial dosing (see **ADVERSE REACTIONS; Inflammatory/Immune-Mediated Reactions**).

Arthritis Events

Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing. These arthritis events began while on treatment or following discontinuation of RAPTIVA and were uncommonly associated with flare of psoriasis. Patients improved after discontinuation of RAPTIVA with or without anti-arthritis therapy.

Immunizations

Prior to initiating therapy with RAPTIVA, psoriatic patients should receive all immunizations appropriate for age as recommended by current immunization guidelines. Patients on treatment with RAPTIVA should not receive live (including live-attenuated) vaccines. Vaccinations that are not live, which are received during a course of RAPTIVA, may not elicit an immune response sufficient to prevent disease. Patients receiving RAPTIVA should be cautioned if household contacts receive live vaccines, because of the potential risk for shedding and transmission.

In a small clinical study with IV administered RAPTIVA, a single-dose of 0.3 mg/kg given before primary immunization with a neoantigen decreased the secondary immune response, and a dose of 1 mg/kg almost completely ablated it. A dose of 0.3 mg/kg IV has comparable pharmacodynamic effects to the recommended dose of 1 mg/kg SC. In chimpanzees exposed to RAPTIVA at > 10 times the clinical exposure level (based on mean peak plasma levels) antibody responses were decreased following immunization with tetanus toxoid compared with untreated control animals.

Information for Patients

Healthcare providers should counsel patients about the risks and benefits of RAPTIVA before an initial prescription, including the risks of PML and other serious infections. Prescribers should monitor patients frequently while on therapy to ensure significant clinical benefit that justifies continued treatment in light of the risks, to ensure they understand the significance of the risk of PML, to assess for any sign or symptom that is suggestive of PML, to assess for adverse events, and to continue patient education about the risks and benefits of RAPTIVA (see **BOXED WARNING, CONTRAINDICATIONS, WARNINGS: Progressive Multifocal Leukoencephalopathy**).

Patients should be instructed to:

- Read the Medication Guide before starting RAPTIVA and before each RAPTIVA injection. They should be encouraged to ask questions about what they have read.
- Have frequent follow-up with their health care provider while on therapy (see **BOXED WARNING, WARNINGS: Progressive Multifocal Leukoencephalopathy**).
- Report and seek immediate medical attention if they experience any new or worsening medical problems, such as an infection that does not go away, or if they or people close to them notice a new or sudden change in the patient's thinking; if they develop a new or sudden change in balance, strength, talking, walking, or vision; if they develop any of the signs and symptoms associated with severe thrombocytopenia (such as easy bleeding from the gums, bruising, or petechiae) or with severe hemolytic anemia (such as weakness, orthostatic light-headedness, hemoglobinuria or jaundice), or with worsening of psoriasis or arthritis (see **BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS**).

Patients should also be informed that RAPTIVA is an immunosuppressant, and should not be used with other systemic immunosuppressive therapies due to the potential for an increased risk of developing an infection (including PML) or a malignancy that could lead to hospitalization, disability, or death.

Patients should be advised to inform all of their healthcare providers that they are receiving RAPTIVA and to immediately call their physician's office if they develop any signs of, or receive a diagnosis of infection, including PML, or malignancy while undergoing treatment with RAPTIVA. Patients should also be informed that their physician may monitor platelet counts during therapy.

Female patients should also be advised to notify their physicians if they become pregnant while taking RAPTIVA (or within 6 weeks of discontinuing RAPTIVA) and be advised of the existence of and encouraged to enroll in the RAPTIVA Pregnancy Registry by calling 1-877-RAPTIVA (1-877-727-8482).

If a patient or caregiver is to administer RAPTIVA, he/she should be instructed regarding injection techniques and how to measure the correct dose to ensure proper administration of RAPTIVA. Patients should be also referred to the RAPTIVA Medication Guide. In addition, patients should have available materials for and be instructed in the proper disposal of needles and syringes to comply with state and local laws. Patients should also be cautioned against reuse of syringes and needles.

Laboratory Tests

Assessment of platelet counts is 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). Severe thrombocytopenia has been observed (see **WARNINGS, Immune-Mediated Thrombocytopenia**).

Drug Interactions

No formal drug interaction studies have been performed with RAPTIVA. RAPTIVA should not be used with other immunosuppressive drugs (see **WARNINGS: Immunosuppression**).

Live (including live-attenuated) vaccines should not be administered during RAPTIVA treatment (see **PRECAUTIONS: Immunizations**).

Drug/Laboratory Test Interactions

Increases in lymphocyte counts related to the pharmacologic mechanism of action are frequently observed during RAPTIVA treatment (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of RAPTIVA.

Subcutaneous injections of male and female mice with an anti-mouse CD11a antibody, a murine surrogate for efalizumab, at up to 30 times the equivalent of the 1 mg/kg clinical dose of RAPTIVA had no adverse effects on mating, fertility, or reproduction parameters. The clinical significance of this observation is uncertain.

Genotoxicity studies were not conducted.

Pregnancy (Category C)

Animal reproduction studies have not been conducted with RAPTIVA. It is also not known whether RAPTIVA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RAPTIVA should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study conducted in mice using an anti-mouse CD11a antibody at up to 30 times the equivalent of the recommended clinical dose of RAPTIVA, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when administered during organogenesis. No adverse effects on behavioral, reproductive, or growth parameters were observed in offspring of female mice subcutaneously treated with an anti-mouse CD11a antibody during gestation and lactation using doses 3- to 30-times the equivalent of the recommended clinical dose of RAPTIVA. At 11 weeks of age, the offspring of these females exhibited a significant reduction in their ability to mount an antibody response, which showed evidence of partial reversibility by 25 weeks of age. Animal studies, however, are not always predictive of human response, and there are no adequate and well-controlled studies in pregnant women.

Since the effects of RAPTIVA on pregnant women and fetal development, including immune system development are not known, healthcare providers are encouraged to enroll patients who become pregnant while taking RAPTIVA (or within 6 weeks of discontinuing RAPTIVA) in the RAPTIVA Pregnancy Registry by calling 1-877-RAPTIVA (1-877-727-8482).

Nursing Mothers

It is not known whether RAPTIVA is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of lactating mice exposed to anti-mouse CD11a antibody and the offspring of the exposed females exhibited significant reduction in antibody responses (see **PRECAUTIONS: Pregnancy**). Since maternal immunoglobulins are known to be present in the milk of lactating mothers, and animal data suggest the potential for adverse effects in nursing infants from RAPTIVA, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

Pediatric Use

FDA has not required pediatric studies in ages 0 to 17 because of the potential risk of non-recoverable suppression of humoral immunity with repeat dose administration of RAPTIVA in pediatric patients, based on data from juvenile animal studies.

An immunotoxicity study was conducted in juvenile mice dosed from 3 to 11 weeks of age (human age equivalent approximately 1-14 years) using an anti-mouse CD11a antibody. Immediately following 8 weekly doses at 3 to 30 times the human equivalent dose of RAPTIVA, the mice exhibited a significant reduction in the ability to mount a humoral antibody response consistent with the mechanism of action of blocking LFA-1/ICAM interactions. Complete reversibility of the treatment related suppression of humoral immunity was not achieved following a 13 week recovery period.

Geriatric Use

Of the 1620 patients who received RAPTIVA in controlled trials, 128 were ≥ 65 years of age, and 2 were ≥ 75 years of age. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is

not sufficient to determine whether they respond differently from younger patients. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the elderly. There have been postmarketing reports of PML occurring in elderly patients who received RAPTIVA for more than three years (see **BOXED WARNING, WARNINGS: Progressive Multifocal Leukoencephalopathy**).

ADVERSE REACTIONS

The most serious adverse reactions observed during treatment with RAPTIVA are serious infections, including PML, malignancies, thrombocytopenia, hemolytic anemia, arthritis events, psoriasis worsening and variants, and neurologic events (see **WARNINGS**).

The most common adverse reactions associated with RAPTIVA were a first dose reaction complex that included headache, chills, fever, nausea, and myalgia within two days following the first two injections. These reactions are dose-level related in incidence and severity and were largely mild to moderate in severity when a conditioning dose of 0.7 mg/kg was used as the first dose. In placebo-controlled trials, 29% of patients treated with RAPTIVA 1 mg/kg developed one or more of these symptoms following the first dose compared with 15% of patients receiving placebo. After the third dose, 4% and 3% of patients receiving RAPTIVA 1 mg/kg and placebo, respectively, experienced these symptoms. Less than 1% of patients discontinued RAPTIVA treatment because of these adverse events.

Other adverse events resulting in discontinuation of RAPTIVA treatment were psoriasis (0.6%), pain (0.4%), arthritis (0.4%), and arthralgia (0.3%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect RAPTIVA exposure for 2762 adult psoriasis patients (age range 18 to 75 years), including 2400 patients exposed for three months, 904 for six months, and 218 exposed for one year or more, in all controlled and uncontrolled studies. The median age of patients receiving RAPTIVA was 44 years, with 189 patients above the age of 65; 67% were men, and 89% were Caucasian. These data include patients treated at doses higher than the recommended dose of 1 mg/kg weekly.

Controlled clinical trials provide the most informative basis for estimating the frequency of RAPTIVA-related adverse drug reactions. Table 3 enumerates the adverse events occurring during controlled periods of the clinical trials where the frequency of the adverse events is at least 2% greater in the RAPTIVA-treated group than the placebo group.

Table 3
Adverse Events in Placebo Controlled Study Periods
Reported at a $\geq 2\%$ Higher Rate in the 1 mg/kg/wk
RAPTIVA Treatment than Placebo Groups

	Placebo (n=715)	RAPTIVA 1 mg/kg/wk (n=1213)
Headache	159 (22%)	391 (32%)
Infection ^a	188 (26%)	350 (29%)
Chills	32 (4%)	154 (13%)
Nausea	51 (7%)	128 (11%)
Pain	38 (5%)	122 (10%)
Myalgia	35 (5%)	102 (8%)
Flu Syndrome	29 (4%)	83 (7%)
Fever	24 (3%)	80 (7%)
Back pain	14 (2%)	50 (4%)
Acne	4 (1%)	45 (4%)

^a Includes diagnosed infections and other non-specific infections. Most common non-specific infection was upper respiratory infection.

Adverse events occurring at a rate between 1 and 2% greater in the RAPTIVA group compared with placebo were arthralgia, asthenia, peripheral edema, and psoriasis.

The following serious adverse reactions were observed in RAPTIVA-treated patients.

Infections

In the first 12 weeks of placebo-controlled studies, the proportion of patients with serious infection was 0.4% (7/1620) in the RAPTIVA-treated group (5 of these were hospitalized, 0.3%) and 0.1% (1/715) in the placebo group (see **WARNINGS: Serious Infections**). In the complete safety data from 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. Including controlled, uncontrolled, and follow-up study treatment periods there were 27 serious infections in 2475 RAPTIVA-treated patients. These infections included cellulitis, pneumonia, abscess, sepsis, sinusitis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, septic arthritis, and vertebral osteomyelitis. In controlled trials, the overall rate of infections in RAPTIVA-treated patients was 3% higher than in placebo-treated patients (Table 3).

In postmarketing experience, serious bacterial, viral, fungal, and opportunistic infections have occurred, including JC virus infection resulting in PML. Some of these infections have been fatal. Worsening of infection despite antimicrobial treatment has been observed (see **BOXED WARNING, CONTRAINDICATIONS, WARNINGS: Serious Infections, Progressive Multifocal Leukoencephalopathy**).

Malignancies

Among the 2762 psoriasis patients who received RAPTIVA at any dose (median duration 8 months), 31 patients were diagnosed with 37 malignancies (see **WARNINGS: Malignancies**). The overall incidence of malignancies of any kind was 1.8 per 100 patient-years for RAPTIVA-treated patients compared with 1.6 per 100 patient-years for placebo-treated patients. Malignancies observed in the RAPTIVA-treated patients included non-melanoma skin cancer, non-cutaneous solid tumors, Hodgkin's lymphoma and non-Hodgkin's lymphoma, and malignant melanoma. The incidence of non-cutaneous solid tumors (8 in 1790 patient-years) and malignant melanoma were within the range expected for the general population.

The majority of the malignancies were non-melanoma skin cancers; 26 cases (13 basal, 13 squamous) in 20 patients (0.7% of 2762 RAPTIVA-treated patients). The incidence was comparable for RAPTIVA-treated and placebo-treated patients. However, the size of the placebo group and duration of follow-up were limited and a difference in rates of non-melanoma skin cancers cannot be excluded.

Immune-Mediated Thrombocytopenia

In the combined safety database of 2762 RAPTIVA-treated patients, there were eight occurrences (0.3%) of thrombocytopenia of < 52,000 cells per μ L reported (see **WARNINGS: Immune-Mediated Thrombocytopenia**). Three of the eight patients were hospitalized for thrombocytopenia, including one patient with heavy uterine bleeding; all cases were consistent with an immune-mediated thrombocytopenia. Antiplatelet antibody was evaluated in one patient and was found to be positive. Each case resulted in discontinuation of RAPTIVA. 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 of the patients. Onset was more delayed in 3 patients, occurring as late as one year in 1 patient. In these cases, the platelet count nadirs occurred between 12 and 72 weeks after the first dose of RAPTIVA.

Immune-Mediated Hemolytic Anemia

Two reports of hemolytic anemia were observed in clinical trials. Additional cases were reported in the postmarketing setting. The anemia was diagnosed 4-6 months after the start of RAPTIVA and in two serious cases the hemoglobin level decreased to 6 and 7 g/dl. RAPTIVA treatment was discontinued, erythrocyte transfusions and other therapies were administered (see **WARNINGS: Immune-Mediated Hemolytic Anemia**).

Adverse Events of Psoriasis

In the combined safety database from all studies, serious psoriasis adverse events occurred in 19 RAPTIVA-treated patients (0.7%) including hospitalization in 17 patients (see **WARNINGS: Psoriasis Worsening/Variants**). Most of these events (14/19) occurred after discontinuation of study drug and occurred in both patients responding and not responding to RAPTIVA treatment. Serious adverse events of psoriasis included pustular, erythrodermic, and guttate subtypes. During the first 12 weeks of treatment within placebo-controlled studies, the rate of psoriasis adverse events (serious and non-serious) was 3.2% (52/1620) in the RAPTIVA-treated patients and 1.4% (10/715) in the placebo-treated patients.

Arthritis Events

Infrequent new onset or recurrent severe arthritis events, including psoriatic arthritis events, have been reported in clinical trials and postmarketing (see **PRECAUTIONS: Arthritis Events**).

Hypersensitivity Reactions

Symptoms associated with a hypersensitivity reaction (e.g., dyspnea, asthma, urticaria, angioedema, maculopapular rash) were evaluated by treatment group. In the first 12 weeks of the controlled clinical studies, the proportion of patients reporting at least one hypersensitivity reaction was 8% (95/1213) in the 1 mg/kg/wk group and 7% (49/715) of patients in the placebo group. Urticaria was observed in 1% of patients (16/1213) receiving RAPTIVA and 0.4% of patients (3/715) receiving placebo during the initial 12-week treatment period. Other observed adverse events in patients receiving RAPTIVA that may be indicative of hypersensitivity included: laryngospasm, angioedema, erythema multiforme, asthma, and allergic drug eruption. One patient was hospitalized with a serum sickness-like reaction.

Inflammatory/Immune-Mediated Reactions

In the entire RAPTIVA clinical development program of 2762 RAPTIVA-treated patients, inflammatory, potentially immune-mediated adverse events resulting in hospitalization included inflammatory arthritis (12 cases, 0.4% of patients) and interstitial pneumonitis (2 cases). One case each of the following serious adverse reactions was observed: transverse myelitis, bronchiolitis obliterans, aseptic meningitis, idiopathic hepatitis, sialadenitis, and sensorineural hearing loss. Myositis, eosinophilic pneumonitis, resolving after discontinuation of RAPTIVA have been reported postmarketing.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RAPTIVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: serious bacterial, fungal, viral and other opportunistic infections, including JC virus resulting in PML (see **BOXED WARNING, WARNINGS: Serious Infections, Progressive Multifocal Leukoencephalopathy**).

Malignancies: lymphoma

Skin: toxic epidermal necrolysis and photosensitivity reactions

Neurologic: Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy, transverse myelitis, and facial palsy (see **WARNINGS: Neurologic Events**).

Laboratory Values

In RAPTIVA-treated patients, a mean elevation in alkaline phosphatase (5 Units/L) was observed; 4% of RAPTIVA-treated patients experienced a shift to above normal values compared with 0.6% of placebo-treated patients. The clinical significance of this change is unknown. Higher numbers of RAPTIVA-treated patients experienced elevations above normal in two or more liver function tests than placebo (3.1% vs. 1.5%).

Other laboratory adverse reactions that were observed included thrombocytopenia (see **WARNINGS, and ADVERSE REACTIONS: Immune-Mediated Thrombocytopenia**), lymphocytosis (40%) (including three cases of transient atypical lymphocytosis), and leukocytosis (26%).

Immunogenicity

In patients evaluated for antibodies to RAPTIVA after RAPTIVA treatment ended, predominantly low-titer antibodies to RAPTIVA or other protein components of the RAPTIVA drug product were detected in 6.3% (67/1063) of patients. The long-term immunogenicity of RAPTIVA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to RAPTIVA in the ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RAPTIVA with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

Doses up to 4 mg/kg/wk SC for 10 weeks following a conditioning (0.7 mg/kg) first dose have been administered without an observed increase in acute toxicity. The maximum administered single dose was 10 mg/kg IV. This was administered to one patient, who subsequently was admitted to the hospital for severe vomiting. In case of overdose, it is recommended that the patient be monitored for 2448 hours for any acute signs or symptoms of adverse reactions or effects and appropriate treatment instituted.

DOSAGE AND ADMINISTRATION

The recommended dose of RAPTIVA (efalizumab) is a single 0.7 mg/kg SC conditioning dose followed by weekly SC doses of 1 mg/kg (maximum single dose not to exceed a total of 200 mg).

RAPTIVA is intended for use under the guidance and supervision of a physician. If it is determined to be appropriate, patients may self-inject RAPTIVA after proper training in the preparation and injection technique and with medical follow-up (see **PRECAUTIONS: Information for Patients**).

Preparation for Administration

RAPTIVA should be administered using the sterile, disposable syringe and needles provided (see **HOW SUPPLIED** section). Remove the cap from the pre-filled syringe containing sterile water for injection (non-USP) and attach the needle to the syringe. Remove the plastic cap protecting the rubber stopper of the RAPTIVA vial and wipe the top of the rubber stopper with one of the provided alcohol swabs. After cleaning with the alcohol swab, do not touch the top of the vial. To prepare the RAPTIVA solution, using the provided pre-filled diluent syringe slowly inject the 1.3 mL of sterile water for injection (non-USP) into the RAPTIVA vial. Swirl the vial with a GENTLE rotary motion to dissolve the product. DO NOT SHAKE. Shaking will cause foaming of the RAPTIVA solution. Generally, dissolution of RAPTIVA takes less than 5 minutes. RAPTIVA is provided as a single-use vial and contains no antibacterial preservatives. Reconstitute immediately before use and use only once. If the reconstituted RAPTIVA is not used immediately, store the RAPTIVA vial at room temperature and use within 8 hours. The reconstituted solution should be clear to pale yellow and free of particulates.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates or discolorations are noted, the product should not be used.

Insert the needle into the vial containing the RAPTIVA solution, invert the vial, and keeping the needle below the level of the liquid, withdraw the dose to be given into the syringe. Replace the needle on the syringe with a new needle.

No other medications should be added to solutions containing RAPTIVA, and RAPTIVA should not be reconstituted with other diluents.

Sites for injection include thigh, abdomen, buttocks, or upper arm. Injection sites should be rotated.

Following administration, discard any unused reconstituted RAPTIVA solution.

Stability and Storage

Do not use a vial beyond the expiration date stamped on the carton or vial label. RAPTIVA (lyophilized powder) must be refrigerated at 2–8°C (36–46°F). Protect the vial from exposure to light. Store in original carton until time of use.

HOW SUPPLIED

RAPTIVA (efalizumab) is supplied as a lyophilized, sterile powder to deliver 125 mg of efalizumab per single-use vial.

Each RAPTIVA carton contains four trays. Each tray contains one single-use vial designed to deliver 125 mg of efalizumab, one single-use prefilled diluent syringe containing 1.3 mL sterile water for injection (non-USP), two 25 gauge×5/8 inch needles, two alcohol prep pads, a package insert with an accompanying patient information insert. The NDC number for the four administration dose pack carton is 50242-058-04.

MEDICATION GUIDE
RAPTIVA[®] (Rap-TEE-vah)
(efalizumab)
for injection, subcutaneous

Read the Medication Guide that comes with RAPTIVA[®] (efalizumab) before you start using it and before each injection. There may be new information. This information does not take the place of talking with your doctor about your condition or your treatment with RAPTIVA. Ask your doctor if you have any questions about this Medication Guide or RAPTIVA.

What is the most important information I should know about RAPTIVA?

RAPTIVA has serious side effects that can lead to death:

- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a serious brain infection caused by a virus. PML results in death or severe disability. Using RAPTIVA will increase your risk for PML. Your risk of PML may rise even more the longer you use RAPTIVA. Some patients who took RAPTIVA for 3 years died from PML and patients on RAPTIVA for less time could develop PML. There is no way to know ahead of time who will get PML. There is no treatment or cure for PML, and it almost always causes death. People who do live with PML are severely disabled.

Symptoms of PML include a new or sudden change in:

- thinking
- balance
- strength
- talking
- walking
- vision

Call your doctor right away if you have any of these symptoms or if anyone close to you notices a new or sudden change in your thinking.

Taking RAPTIVA increases your chances of PML because RAPTIVA weakens the ability of your immune system to fight the virus that causes PML. Your chance of getting PML may even be higher if you are also being treated with other medications that can weaken your immune system. You can still get PML even if you use RAPTIVA alone.

- **Serious infections.** Some of these infections have led to hospitalization or death and have been caused by bacteria, fungi, and viruses.

Symptoms of a serious infection include:

- fever
- cough
- flu-like symptoms

- feeling especially tired
- chills
- muscle aches
- stiff neck

Before you start using RAPTIVA, tell your doctor if you have an infection. During your RAPTIVA treatment, tell your doctor right away if you get an infection. Do not use RAPTIVA if you have a serious infection.

Stopping treatment with RAPTIVA. Stopping RAPTIVA may lead to serious side effects, such as severe worsening of your psoriasis, that can lead to hospitalization. Tell your doctor if you want to stop using RAPTIVA so that you and your doctor can carefully plan how to change to another psoriasis medicine.

What is RAPTIVA?

RAPTIVA is a prescription medicine used to treat adults with the type of psoriasis that is not adequately treated with medicines that go on the skin.

RAPTIVA has not been studied in children under 18 years of age.

Who should not use RAPTIVA?

- Do not use RAPTIVA if you have ever had an allergic reaction to RAPTIVA.
- Do not use RAPTIVA if you have been diagnosed with PML.

What should I tell my doctor before using RAPTIVA?

- **Vaccinations.** Ask your doctor whether you need any vaccinations **before** you start using RAPTIVA. Some vaccinations should not be given or will not work while you use RAPTIVA. Talk to your doctor about whether anyone in your household needs a vaccination. Some types of vaccines can spread to people with weakened immune systems, causing serious problems.

Tell your doctor about all of your medical conditions, including:

- **If you have any infections or a weakened immune system.** See “What is the most important information I should know about RAPTIVA?”
- **If you have or have had cancer.**
- **If you are pregnant, planning to become pregnant, or become pregnant while using RAPTIVA.** It is not known if RAPTIVA can harm your unborn baby. If you become pregnant while taking RAPTIVA, call your doctor right away. You and your doctor will decide if RAPTIVA is right for you during pregnancy. If you use RAPTIVA when you are pregnant, call 1-877-RAPTIVA (1-877-727-8482) to be included in the RAPTIVA Pregnancy Registry. This registry collects information to help understand the effects of RAPTIVA during pregnancy.

- **Breast feeding.** It is not known if RAPTIVA passes into your milk. It may harm your baby. You will need to decide whether to use RAPTIVA or breast feed, but you should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. It is not known if RAPTIVA and other medicines affect each other.

Especially, tell your doctor if you use:

- **Medicines that weaken your immune system.** Ask your doctor or pharmacist if you are not sure.
- **Other medicines or treatments for your psoriasis.**

How should I use RAPTIVA?

See the **Instructions for Use** at the end of this Medication Guide for how to prepare and inject RAPTIVA. Ask your doctor or pharmacist if you have any questions about using RAPTIVA.

- **Use RAPTIVA exactly as prescribed by your doctor.** Tell your doctor if you want to stop using RAPTIVA so that they can plan for other psoriasis treatment. Your psoriasis can worsen to severe levels quickly when RAPTIVA is stopped.
- RAPTIVA is an injection (shot) that you give yourself once a week. Your dose of RAPTIVA is based on your body weight. Tell your doctor if your weight changes. Do not change your dose without talking to your doctor.
- RAPTIVA is injected under the skin of your upper leg (thigh), upper arm, abdomen, or buttocks once a week. Use a different skin injection site (rotate) each time you give yourself an injection.
- Use RAPTIVA the same day each week. If you miss your dose of RAPTIVA, call your doctor to find out when to take your next dose of RAPTIVA and what schedule to follow after that.
- If you take more than your regular dose of RAPTIVA, call your doctor right away.
- Do not take light treatments for your psoriasis (UVB, PUVA, phototherapy) unless directed by your doctor.

What are the possible side effects of RAPTIVA?

Serious side effects with RAPTIVA include:

- **Progressive Multifocal Leukoencephalopathy (PML).** See “What is the most important information I should know about RAPTIVA?”
- **Serious infections.** See “What is the most important information I should know about RAPTIVA?”

- **Nervous system disorders.** People who use RAPTIVA can have serious disorders that affect the brain and nervous system.

Symptoms of a nervous system disorder include:

- sudden numbness or tingling
 - weakness in your arms, legs, or face
 - new or sudden change in thinking, balance, strength, talking, walking, or vision
- **Worsening of psoriasis.** Some people have severe worsening or a new psoriasis rash while taking RAPTIVA or after stopping RAPTIVA. Tell your doctor right away if your psoriasis gets worse or if you see any new rashes during or after treatment with RAPTIVA.

Call your doctor right away if you have any of these symptoms.

- **Cancer.** RAPTIVA weakens your immune system. When your immune system is weakened, you may have a higher chance of getting new cancer or making your cancer worse.
- **Low platelet counts (thrombocytopenia).** Platelets are cells that help your blood clot. Low platelets give you a higher chance for bleeding. Call your doctor right away if you have bleeding including your gums, a red rash, or more bruises than usual. Your doctor may do blood tests to check your platelets while you take RAPTIVA.
- **Low blood counts (anemia).** Some people who use RAPTIVA develop very low red blood cell counts. Call your doctor right away if you are:
 - weak
 - dizzy
 - lightheaded
 - out of breath
 - your skin or eyes turn yellow
 - your urine turns red or dark
- **Arthritis.** Some people have worsening or new arthritis while taking RAPTIVA or after stopping RAPTIVA. Tell your doctor if you get redness, pain, swelling, or stiffness of your joints.

The most common side effects of RAPTIVA usually happen within the first 48 hours after your RAPTIVA injection. Common side effects include:

- headache
- chills
- fever
- nausea
- muscle aches

Call your doctor if you are not sure if these problems are from an infection. See “What is the most important information I should know about RAPTIVA?”

These are not all the side effects of RAPTIVA. Talk to your doctor for medical advice about any signs and symptoms that bother you. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RAPTIVA?

- Store RAPTIVA vials in the refrigerator at 36° to 46°F (2° to 8°C) until you are ready to prepare your injection.
- Do not freeze or store at room temperature.
- Once RAPTIVA has been mixed with sterile water, you should use it right away to inject yourself. If you are unable to inject the RAPTIVA after mixing, the mixture can stay at room temperature for up to 8 hours. Do not use RAPTIVA that was mixed for more than 8 hours.
- If you are traveling, be sure to store RAPTIVA at the right temperature. If you have any questions, ask your doctor or pharmacist.
- Store RAPTIVA vials away from light.
- Throw away RAPTIVA vials that are out of date. The expiration date is marked on each vial of RAPTIVA.

Keep RAPTIVA and all medicines out of the reach of children.

GENERAL INFORMATION ABOUT RAPTIVA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RAPTIVA for a condition for which it was not prescribed. Do not give RAPTIVA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about RAPTIVA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about RAPTIVA that is written for health professionals. For more information, you can also call 1-877-RAPTIVA (toll free).

What are the ingredients in RAPTIVA?

Active ingredient: efalizumab

Inactive ingredients: sucrose, L-histidine hydrochloride monohydrate, L-histidine, polysorbate 20, and sterile water for injection.

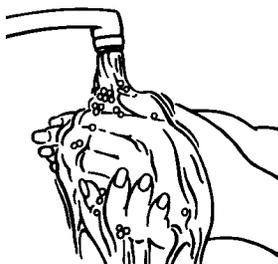
Instructions for use

How do I prepare and give a RAPTIVA injection?

If your dose is more than 1.25 mL, you will need to use 2 RAPTIVA blister trays, and you will give yourself 2 injections of RAPTIVA.

Setting up the Equipment

1. Take the RAPTIVA (efalizumab) blister tray out of the refrigerator, and place it on a flat, well-lit, clean work surface.
2. Wash your hands with soap and water before opening the blister tray.
3. Open the tray and lay out the contents. Allow the contents to come to room temperature.



As shown below, the tray contains:

- One RAPTIVA vial
- One 1.3-mL prefilled syringe of sterile water
- Two 25-gauge needles
- Two alcohol prep pads

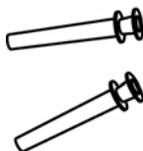
Contact your doctor or pharmacist if you are missing any of the items listed above.



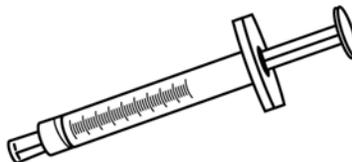
RAPTIVA
Vial



Alcohol Prep
Pads (2)



Needles (2)



Prefilled Syringe

4. Check the expiration date on the RAPTIVA vial label and prefilled syringe label. If the expiration date has passed, do not use the RAPTIVA vial or the prefilled syringe containing the sterile water. Contact your doctor.

5. Partially peel open the needle pack and place it on a clean surface. Be sure to grasp the needle by the plastic cover and avoid touching the end of the syringe and the needle.



6. Remove the plastic cap protecting the rubber stopper of the RAPTIVA vial. Open one alcohol prep pad package and wipe the rubber stopper with an alcohol prep pad. Do not touch the top of the vial after wiping.
7. Remove the cap covering the prefilled syringe tip. Remove one of the 25-gauge needles from its package by grasping the needle by the plastic cover and without touching the end of the needle. Carefully place the capped 25-gauge needle onto the syringe tip. Twist needle to secure.

Mixing RAPTIVA

1. Remove the needle cap. **Do not touch the needle.** Keep the RAPTIVA vial upright on a firm surface, and slowly puncture the rubber stopper with the needle. Slowly push down on the syringe plunger to inject all of the 1.3 mL of sterile water onto the side wall of the vial to cause less foaming. Some foaming may happen; this is normal.



2. With the needle and syringe still in the vial stopper, gently swirl the vial to mix. Wait 5 minutes for the medicine to completely dissolve. To avoid excess foaming, **do not shake the vial**. The RAPTIVA solution should be clear to pale yellow. **Do not use the solution if it is discolored or cloudy or if particles (solid matter) are in the solution.**



Preparing the RAPTIVA Dose for Injection

If you need more than one vial of RAPTIVA for the correct dose (dose amount is greater than 1.25 mL), repeat Steps 1-6 of this section using a second RAPTIVA blister tray, and divide your dose between two syringes.

1. Turn the vial upside down, keeping the needle in the vial. (The needle will now be pointing upward.) Make sure the tip of the needle is covered all the way by the medicine in the vial. Pull back the syringe slightly if necessary. This will make it easier to get the medicine into the syringe.
2. Pull back on the plunger to fill the syringe. Withdraw the correct dose of medicine by reading the numbers on the syringe. Remove the syringe from the vial.



3. Slide the needle into the cap on a flat surface to pick up the needle cap. To lower the chance of a needlestick injury, do not touch the cap until it covers the needle all the way. Push the cap all the way down over the needle

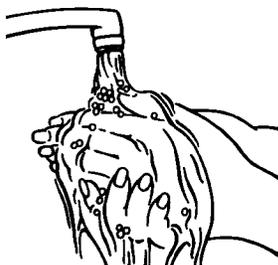


4. Hold the syringe upright and tap the side of the syringe to let air bubbles rise to the top. Gently push in the plunger of the syringe to push the air bubbles out.

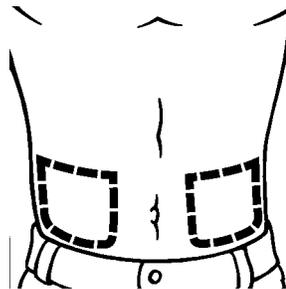
5. After removing the bubbles, recheck the dose of medicine in the syringe. If necessary, push the plunger again to remove any amount of medicine beyond the line that indicates your dose. Make sure you have the right dose as instructed by your doctor. Twist the capped needle off the syringe and discard it in a puncture-resistant container (see **DISPOSAL OF THE SYRINGE, NEEDLES, AND SUPPLIES**). **Never reuse a needle or syringe.**
6. Remove the other 25-gauge needle from its package by grasping **the needle by the plastic cover and** without **touching the end of the needle**. Carefully place the capped 25-gauge needle onto the syringe tip. Twist to secure. Put the syringe down while preparing your skin for injection.

Selecting and Preparing the Injection Site

1. Wash your hands well with soap and water.

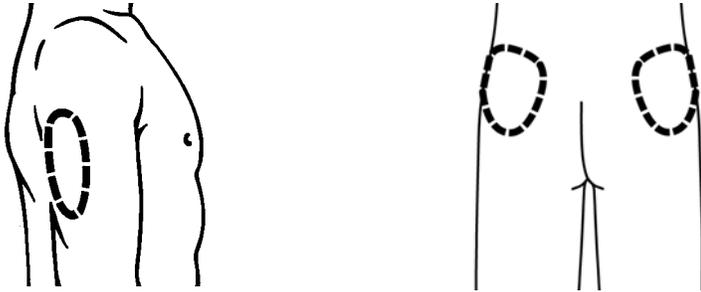


2. Choose an area of the body for the injection. Avoid, if possible, skin involved with psoriasis. Possible injection sites include the following:
 - Outer area of the upper legs (thighs)
 - Stomach area around the belly button

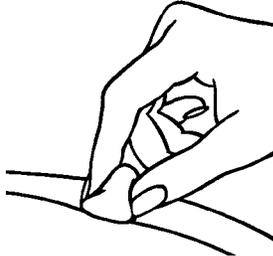


If someone else is giving you an injection, you can also use:

- Back of upper arms
- Buttocks



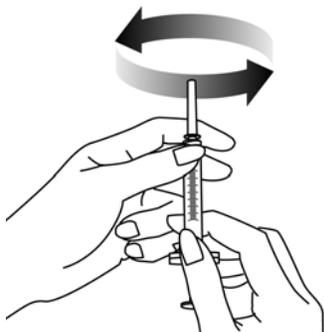
3. It is important to change (rotate) the injection site each time you take RAPTIVA to lower your chances of soreness and redness at the injection site. Changing the injection site will also improve absorption of the medication. Repeat injections given in the same area should be at least 1 inch apart. **Do not give an injection close to a vein that you can see under the surface of your skin.**
4. Wash the skin at the site of injection with soap and water. Let it air dry.
5. Cleanse the skin at the injection site with an alcohol prep pad using a circular motion. Let the area air dry all the way. **Do not touch this area again before giving the injection.**



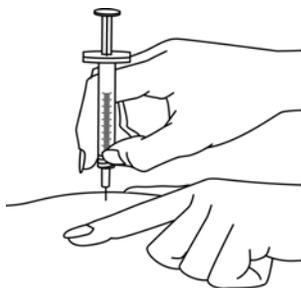
Giving the RAPTIVA Injection under the Skin

Your doctor will teach you how to inject RAPTIVA. Do not inject RAPTIVA unless you have been taught the right way to give the injection.

1. Hold the syringe and remove the needle cover. Twisting the needle cover while pulling will help in the removal. **Do not touch the needle or allow the needle to touch anything.**

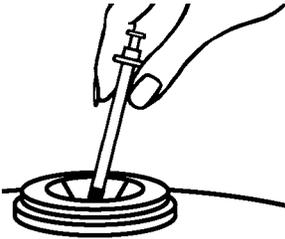


2. Hold the syringe in the hand you use to inject yourself. Use your other hand to pinch a patch of skin at the clean injection site. **Do not** lay the syringe down or allow the needle to touch anything.
3. Hold the syringe firmly between your thumb and fingers so that you have steady control. Insert the needle straight down at a 90-degree angle. This is important to make sure the medicine is injected into fatty tissue.



4. After the needle is inserted all the way into the skin, you can gently let go of the pinched skin. Be sure the needle stays in your skin. Slowly and smoothly push the plunger down into the syringe until it stops.

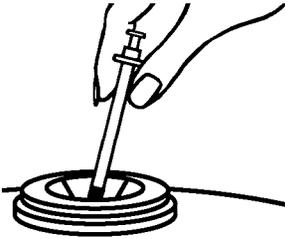
- When all of the medicine has been injected, remove the needle and do not re-cap it. Discard the used syringe with the attached needle into a puncture resistant container (see **DISPOSAL OF THE SYRINGE, NEEDLES, AND SUPPLIES**). **Never reuse a needle or syringe.** Press a dry, sterile gauze (not provided) over the injection site. Do not use the alcohol prep pad. A small bandage may be put over the injection site.



- If your dose amount is more than 1.25 mL, you will need to give a second injection. Choose the second injection site at least 1 inch from the first injection site.

DISPOSAL OF THE SYRINGE, NEEDLES, AND SUPPLIES

- As stated earlier, place the used syringe with the attached needle in a puncture-resistant container, like a sharps container. You can buy a sharps container at your local pharmacy.



- Talk to your doctor about how to properly dispose of a filled container of your used syringes and needles. There may be special local and state laws for disposing of used needles and syringes. **Do not throw the filled container in the household trash and do not recycle.**
- The needle cap, alcohol prep pads, and other used supplies can be thrown out with your regular trash.
- Always keep syringes, injection supplies, and disposal containers out of the reach of children.**
- Do not reuse these single-use syringes or needles.**

Rx Only

This Medication Guide has been approved by the U.S. Food and Drug Administration.

RAPTIVA® [efalizumab]

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