DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

NOV 14 2003

Our STN: BL 103764/5040

Novartis Pharmaceuticals Corporation
Attention: M. Daniel Gordin, Ph.D.
Director, Drug Regulatory Affairs (U.S.)
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gordin:

Your request to supplement your biologics license application for Basiliximab to revise the Clinical Studies section and the Malignancies subsection of the Adverse Reactions section of the package insert to include 5-year data has been approved.

This fulfills your commitment to submit final study reports on the long-term follow-up for protocols CHIB 352 and CHIB 201 as stated in commitment number 1 of the May 12, 1998 approval letter.

As FDA noted in its comments on Basiliximab's labeling, the labeling contains several references to Novartis's oral formulations of cyclosporine (Neoral) as "cyclosporine, USP (MODIFIED)." These references are not consistent with the change requested in FDA's June 14, 2000 letter (Our Ref. No. 99-2083), in which FDA stated: "As per the Agency's November 2, 1998 response to your citizen petitions and petitions for stay of action, and the responses there to, please revise all references to 'cyclosporine for microemulsion' to 'cyclosporine oral solution, USP (MODIFIED)'." FDA reiterated this instruction in its September 1, 2000 letter approving an earlier BLA supplement, which revised the Basiliximab package insert to include safety information regarding hypersensitivity reactions including anaphylaxis.

Nothing in today's supplemental approval should be construed as a concession on the appropriate established name(s) for the Neoral products, which is the subject of pending litigation, *Novartis Pharmaceuticals Corp. v. Thompson*, Civ. No. 99-323 (D.D.C.). Our approval of this Basiliximab BLA supplement does not reflect our concurrence with Novartis's references to cyclosporine in the Basiliximab labeling. FDA reserves the right to require changes in how the Basiliximab (Simulect) label refers to the cyclosporine products.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and

Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

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Marc K. Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

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[redacted]

STN 103764/5040
Approved 11/14/03

NOVARTIS

T2003-86
89007806

Simulect®

(basiliximab)

For Injection

Rx only

Prescribing Information

WARNING

Only physicians experienced in immunosuppression therapy and management of organ transplantation patients should prescribe Simulect® (basiliximab). The physician responsible for Simulect® administration should have complete information requisite for the follow-up of the patient. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources.

DESCRIPTION

Simulect® (basiliximab) is a chimeric (murine/human) monoclonal antibody ($IgG_{1\kappa}$), produced by recombinant DNA technology, that functions as an immunosuppressive agent, specifically binding to and blocking the interleukin-2 receptor α-chain (IL-2Rα, also known as CD25 antigen) on the surface of activated T-lymphocytes. Based on the amino acid sequence, the calculated molecular weight of the protein is 144 kilodaltons. It is a glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding the RFT5 antibody that binds selectively to the IL-2Rα.

The active ingredient, basiliximab, is water soluble. The drug product, Simulect®, is a sterile lyophilisate which is available in 6 mL colorless glass vials and is available in 10 mg and 20 mg strengths.

Each 10 mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 mg sodium chloride, 10 mg sucrose, 40 mg mannitol and 20 mg glycine, to be reconstituted in 2.5 mL of Sterile Water for Injection, USP. No preservatives are added.

Each 20 mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine, to be reconstituted in 5 mL of Sterile Water for Injection, USP. No preservatives are added.

CLINICAL PHARMACOLOGY

General

Mechanism of action: Basiliximab functions as an IL-2 receptor antagonist by binding with high affinity ($K_a = 1 \times 10^{10}\ M^{-1}$) to the alpha chain of the high affinity IL-2 receptor complex and inhibiting IL-2 binding. Basiliximab is specifically targeted against IL-2Rα, which is selectively expressed on the surface of activated T-lymphocytes. This specific high affinity binding of Simulect® to IL-2Rα competitively inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.

While in the circulation, Simulect® impairs the response of the immune system to antigenic challenges. Whether the ability to respond to repeated or ongoing challenges with those antigens returns to normal after Simulect® is cleared is unknown (see PRECAUTIONS).

Pharmacokinetics

Adults: Single-dose and multiple-dose pharmacokinetic studies have been conducted in patients undergoing first kidney transplantation. Cumulative doses ranged from 15 mg up to 150 mg. Peak mean ± SD serum concentration following intravenous infusion of 20 mg over 30 minutes is 7.1 ± 5.1 mg/L. There is a dose-proportional increase in C_{max} and AUC up to the highest tested single dose of 60 mg. The volume of distribution at steady state is 8.6 ± 4.1 L. The extent and degree of distribution to various body compartments have not been fully studied. The terminal half-life is 7.2 ± 3.2 days. Total body clearance is 41 ± 19 mL/h. No clinically relevant influence of body weight or gender on distribution volume or clearance has been observed in adult patients. Elimination half-life was not influenced by age (20-69 years), gender or race (see DOSAGE AND ADMINISTRATION).

Pediatric: The pharmacokinetics of Simulect® have been assessed in 39 pediatric patients undergoing renal transplantation. In infants and children (1-11 years of age, n=25), the distribution volume and clearance were reduced by about 50% compared to adult renal transplantation patients. The volume of distribution at steady state was 4.8 ± 2.1 L, half-life was 9.5 ± 4.5 days and clearance was 17 ± 6 mL/h. Disposition parameters were not influenced to a clinically relevant extent by age (1-11 years of age), body weight (9-37 kg) or body surface area (0.44-1.20 m^2) in this age group. In adolescents (12-16 years of age, n=14), disposition was similar to that in adult renal transplantation patients. The volume of distribution at steady state was 7.8 ± 5.1 L, half-life was 9.1 ± 3.9 days and clearance was 31 ± 19 mL/h (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics

Complete and consistent binding to IL-2Rα in adults is maintained as long as serum Simulect® levels exceed 0.2 μg/mL. As concentrations fall below this threshold, the IL-2Rα sites are no longer fully bound and the number of T-cells expressing unbound IL-2Rα returns to pretherapy values within 1-2 weeks. The relationship between serum concentration and receptor saturation was assessed in 13 pediatric patients and was similar to that characterized

in adult renal transplantation patients. *In vitro* studies using human tissues indicate that Simulect® binds only to lymphocytes.

The duration of clinically relevant IL-2 receptor blockade after the recommended course of Simulect® is not known. When basiliximab was added to a regimen of cyclosporine, USP (MODIFIED) and corticosteroids in adult patients, the duration of IL-2Rα saturation was 36 ± 14 days (mean ± SD), similar to that observed in pediatric patients (36 ± 14 days) (see DOSAGE AND ADMINISTRATION). When basiliximab was added to a triple therapy regimen consisting of cyclosporine, USP (MODIFIED), corticosteroids, and azathioprine in adults, the duration was 50 ± 20 days and when added to cyclosporine, USP (MODIFIED), corticosteroids, and mycophenolate mofetil in adults, the duration was 59 ± 17 days (see PRECAUTIONS-DRUG INTERACTIONS). No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by flow cytometry.

CLINICAL STUDIES

The safety and efficacy of Simulect® for the prophylaxis of acute organ rejection in adults following cadaveric- or living-donor renal transplantation were assessed in four randomized, double-blind, placebo-controlled clinical studies (1,184 patients). Of these four, two studies [Study 1 (EU/CAN) and Study 2 (US study)] compared two 20-mg doses of Simulect® with placebo, each administered intravenously as an infusion, as part of a standard immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids. The other two controlled studies compared two 20-mg doses of Simulect® with placebo, each administered intravenously as a bolus injection, as part of a standard triple-immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED), corticosteroids and either azathioprine or mycophenolate mofetil (Study 3 and Study 4, respectively). The first dose of Simulect® or placebo was administered within 2 hours prior to transplantation surgery (Day 0) and the second dose administered on Day 4 post-transplantation. The regimen of Simulect® was chosen to provide 30-45 days of IL-2Rα saturation.

729 patients were enrolled in the two studies using a dual maintenance immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids, of which 363 patients were treated with Simulect® and 358 patients were placebo-treated. Study 1 was conducted at 21 sites in Europe and Canada (EU/CAN Study); Study 2 was conducted at 21 sites in the USA (US Study). Patients 18-75 years of age undergoing first cadaveric (Study 1 and Study 2) or living-donor (Study 2 only) renal transplantation, with ≥ 1 HLA mismatch, were enrolled.[1,2]

The primary efficacy endpoint in both studies was the incidence of death, graft loss or an episode of acute rejection during the first 6 months post-transplantation. Secondary efficacy endpoints included the primary efficacy variable measured during the first 12 months post-transplantation, the incidence of biopsy-confirmed acute rejection during the first 6 and 12 months post-transplantation, and patient survival and graft survival, each measured at 12 months post-transplantation. Table 1 summarizes the results of these studies. Figure 1 displays the Kaplan-Meier estimates of the percentage of patients by treatment group experiencing the primary efficacy endpoint during the first 12 months post-transplantation for

Study 2. Patients in both studies receiving Simulect® experienced a significantly lower incidence of biopsy-confirmed rejection episodes at both 6 and 12 months post-transplantation. There was no difference in the rate of delayed graft function, patient survival, or graft survival between Simulect®-treated patients and placebo-treated patients in either study.

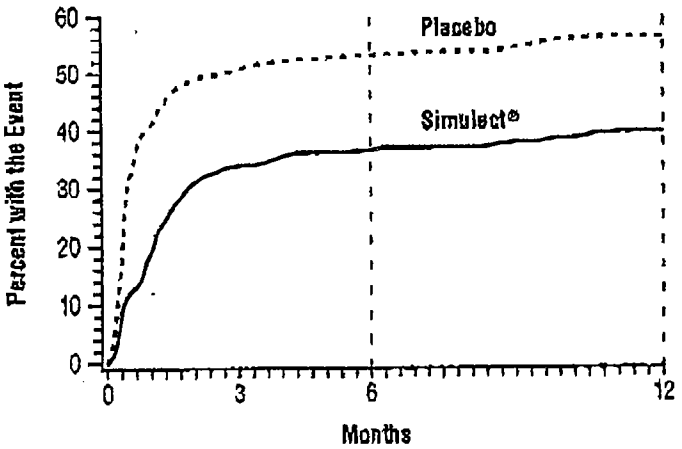
There was no evidence that the clinical benefit of Simulect® was limited to specific subpopulations based on age, gender, race, donor type (cadaveric or living donor allograft) or history of diabetes mellitus.

Table 1. Efficacy Parameters (Percentage of Patients)

	Dual-therapy Regimen (cyclosporine* and corticosteroids)					
	Study 1			Study 2		
	Placebo (N=185)	Simulect® (N=190)	p-value	Placebo (N=173)	Simulect® (N=173)	p-value
Primary endpoint						
Death, graft loss or acute rejection episode (0-6 months)	57%	42%	0.003	55%	38%	0.002
Secondary endpoints						
Death, graft loss or acute rejection episode (0-12 months)	60%	46%	0.007	58%	41%	0.001
Biopsy-confirmed rejection episode (0-6 months)	44%	30%	0.007	46%	33%	0.015
Biopsy-confirmed rejection episode (0-12 months)	46%	32%	0.005	49%	35%	0.009
Patient survival (12 months)	97%	95%	0.29	96%	97%	0.56
Patients with functioning graft (12 months)	87%	88%	0.70	93%	95%	0.50

* USP (MODIFIED)

Figure 1
Kaplan-Meier Estimate of the Percentage of Subjects with Death, Graft Loss or First Rejection Episode (Dual Therapy)
Month: 0-12



Two double-blind, randomized, placebo-controlled studies (Study 3 and Study 4) assessed the safety and efficacy of Simulect® for the prophylaxis of acute renal transplant rejection in adults when used in combination with a triple immunosuppressive regimen. In Study 3, 340 patients were concomitantly treated with cyclosporine, USP (MODIFIED), corticosteroids and azathioprine (AZA), of which 168 patients were treated with Simulect® and 172 patients were treated with placebo. In Study 4, 123 patients were concomitantly treated with cyclosporine, USP (MODIFIED), corticosteroids and mycophenolate mofetil (MMF), of which 59 patients were treated with Simulect® and 64 patients were treated with placebo. Patients 18-70 years of age undergoing first or second cadaveric or living donor (related or unrelated) renal transplantation were enrolled in both studies.

The results of Study 3 are shown in Table 2. These results are consistent with the findings from Study 1 and Study 2.

Table 2. Efficacy Parameters (Percentage of Patients)

Study 3: Triple-therapy Regimen (cyclosporine*, corticosteroids, and azathioprine)

	Placebo (N=172)	Simulect® (N=168)	p-value
Primary endpoint			
Acute rejection episode (0-6 months)	35%	21%	0.005
Secondary endpoints			
Death, graft loss or acute rejection episode (0-6 months)	40%	26%	0.008
Biopsy-confirmed rejection episode (0-6 months)	29%	18%	0.023
Patient survival (12 months)	97%	98%	1.000
Patients with functioning graft (12 months)	88%	90%	0.599

*USP (MODIFIED)

In Study 4, the percentage of patients experiencing biopsy-proven acute rejection by 6 months was 15% (9 of 59 patients) in the Simulect® group and 27% (17 of 64 patients) in the placebo group. Although numerically lower, the difference in acute rejection was not significant.

In a multicenter, randomized, double-blind, placebo-controlled trial of Simulect® for the prevention of allograft rejection in liver transplant recipients (n=381) receiving concomitant cyclosporine, USP (MODIFIED) and steroids, the incidence of the combined endpoint of death, graft loss, or first biopsy-confirmed rejection episode at either 6 or 12 months was similar between patients randomized to receive Simulect® and those randomized to receive placebo.

The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of a second renal allograft has not been demonstrated.

Long term Follow-up

Five year patient survival and graft survival data were provided by 71% and 58% of the original subjects of Study 1 and Study 2, respectively. Subjects in both studies continued to receive a dual-therapy regimen with cyclosporine, USP (MODIFIED) and corticosteroid. No difference was observed between groups in the 5-year graft survival in either Study 1 (91% Simulect group, 92% placebo group) or Study 2 (85% Simulect group, 86% placebo group). In Study 1, patient survival was lower in the Simulect-treated patients compared to the placebo-treated patients (142/163 (87%) versus 156/164 (95%), respectively). The cause of this difference in survival is unknown. The data do not indicate an increase in malignancy- or infection-related mortality. In Study 2, patient survival in the placebo group (90%) was the same compared to Simulect group (90%).

INDICATIONS AND USAGE

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids.

The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

CONTRAINDICATIONS

Simulect® is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation. See composition of Simulect® under DESCRIPTION.

WARNINGS. See Boxed WARNING.

General

Simulect® should be administered under qualified medical supervision. Patients should be informed of the potential benefits of therapy and the risks associated with administration of immunosuppressive therapy.

While neither the incidence of lymphoproliferative disorders nor opportunistic infections was higher in Simulect®-treated patients than in placebo-treated patients, patients on immunosuppressive therapy are at increased risk for developing these complications and should be monitored accordingly.

Hypersensitivity

Severe acute (onset within 24 hours) hypersensitivity reactions including anaphylaxis have been observed both on initial exposure to Simulect® and/or following re-exposure after several months. These reactions may include hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing. If a severe hypersensitivity reaction occurs, therapy with Simulect® should be permanently discontinued. Medications for the treatment of severe hypersensitivity reactions

including anaphylaxis should be available for immediate use. Patients previously administered Simulect® should only be re-exposed to a subsequent course of therapy with extreme caution. The potential risks of such re-administration, specifically those associated with immunosuppression, are not known.

PRECAUTIONS

General

It is not known whether Simulect® use will have a long-term effect on the ability of the immune system to respond to antigens first encountered during Simulect®-induced immunosuppression.

Immunogenicity

Of renal transplantation patients treated with Simulect® and tested for anti-idiotype antibodies, 4/339 developed an anti-idiotype antibody response, with no deleterious clinical effect upon the patient. In none of these cases was there evidence that the presence of anti-idiotype antibody accelerated Simulect® clearance or decreased the period of receptor saturation. In Study 2, the incidence of human anti-murine antibody (HAMA) in renal transplantation patients treated with Simulect® was 2/138 in patients not exposed to muromonab-CD3 and 4/34 in patients who subsequently received muromonab-CD3. The available clinical data on the use of muromonab-CD3 in patients previously treated with Simulect® suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Simulect® in an 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, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Simulect® with the incidence of antibodies to other products may be misleading.

Drug Interactions

No dose adjustment is necessary when Simulect® is added to triple-immunosuppression regimens including cyclosporine, corticosteroids, and either azathioprine or mycophenolate mofetil. Three clinical trials have investigated Simulect® use in combination with triple-therapy regimens. Pharmacokinetics were assessed in two of these trials. Total body clearance of Simulect® was reduced by an average 22% and 51% when azathioprine and mycophenolate mofetil, respectively, were added to a regimen consisting of cyclosporine, USP (MODIFIED) and corticosteroids. Nonetheless, the range of individual Simulect® clearance values in the presence of azathioprine (12-57 mL/h) or mycophenolate mofetil (7-54 mL/h) did not extend outside the range observed with dual therapy (10-78 mL/h). The following medications have been administered in clinical trials with Simulect® with no increase in

adverse reactions: ATG/ALG, azathioprine, corticosteroids, cyclosporine, mycophenolate mofetil, and muromonab-CD3.

Carcinogenesis/Mutagenesis/Impairment of Fertility

No mutagenic potential of Simulect® was observed in the *in vitro* assays with Salmonella (Ames) and V79 Chinese hamster cells. No long-term or fertility studies in laboratory animals have been performed to evaluate the potential of Simulect® to produce carcinogenicity or fertility impairment, respectively.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. No maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgus monkeys 100 days post coitum following dosing with basiliximab during the organogenesis period; blood levels in pregnant monkeys were 13-fold higher than those seen in human patients. Immunotoxicology studies have not been performed in the offspring. Because IgG molecules are known to cross the placental barrier, because the IL-2 receptor may play an important role in development of the immune system, and because animal reproduction studies are not always predictive of human response, Simulect® should only be used in pregnant women when the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should use effective contraception before beginning Simulect® therapy, during therapy, and for 4 months after completion of Simulect® therapy.

Nursing Mothers

It is not known whether Simulect® is excreted in human milk. Because many drugs including human antibodies are excreted in human milk, and because of the potential for adverse reactions, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

No randomized, placebo-controlled studies have been completed in pediatric patients. In a safety and pharmacokinetic study, 41 pediatric patients [1-11 years of age (n=27), 12-16 years of age (n=14), median age 8.1 years] were treated with Simulect® via intravenous bolus injection in addition to standard immunosuppressive agents including cyclosporine, USP (MODIFIED), corticosteroids, azathioprine, and mycophenolate mofetil. The acute rejection rate at six months was comparable to that in adults in the triple-therapy trials. The most frequently reported adverse events were hypertension, hypertrichosis, and rhinitis (49% each), urinary tract infections (46%), and fever (39%). Overall, the adverse event profile was consistent with general clinical experience in the pediatric renal transplantation population and with the profile in the controlled adult renal transplantation studies. The available pharmacokinetic data in children and adolescents are described in CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.

It is not known whether the immune response to vaccines, infection, and other antigenic stimuli administered or encountered during Simulect® therapy is impaired or whether such response will remain impaired after Simulect® therapy.

Geriatric Use

Controlled clinical studies of Simulect® have included a small number of patients 65 years and older (Simulect® 28; placebo 32). From the available data comparing Simulect® and placebo-treated patients, the adverse event profile in patients ≥ 65 years of age is not different from patients < 65 years of age and no age-related dosing adjustment is required. Caution must be used in giving immunosuppressive drugs to elderly patients.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The incidence of adverse events for Simulect® was determined in four randomized, double-blind, placebo-controlled clinical trials for the prevention of renal allograft rejection. Two of the studies (Study 1 and Study 2), used a dual maintenance immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED) and corticosteroids, whereas the other two studies (Study 3 and Study 4) used a triple-immunosuppressive regimen comprised of cyclosporine, USP (MODIFIED), corticosteroids, and either azathioprine or mycophenolate mofetil.

Simulect® did not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. Adverse events were reported by 96% of the patients in the placebo-treated group and 96% of the patients in the Simulect®-treated group. In the four placebo-controlled studies, the pattern of adverse events in 590 patients treated with the recommended dose of Simulect® was similar to that in 594 patients treated with placebo. Simulect® did not increase the incidence of serious adverse events observed compared with placebo.

The most frequently reported adverse events were gastrointestinal disorders, reported in 69% of Simulect®-treated patients and 67% of placebo-treated patients.

The incidence and types of adverse events were similar in Simulect®-treated and placebo-treated patients. The following adverse events occurred in ≥ 10% of Simulect®-treated patients: ***Gastrointestinal System:*** constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia; ***Body as a Whole-General:*** pain, peripheral edema, fever, viral infection; ***Metabolic and Nutritional:*** hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia; ***Urinary System:*** urinary tract infection; ***Respiratory System:*** dyspnea, upper respiratory tract infection; ***Skin and Appendages:*** surgical wound complications, acne; ***Cardiovascular Disorders-General:***

hypertension; ***Central and Peripheral Nervous System:*** headache, tremor; Psychiatric: insomnia; ***Red Blood Cell:*** anemia.

The following adverse events, not mentioned above, were reported with an incidence of ≥ 3% and < 10% in pooled analysis of patients treated with Simulect® in the four controlled clinical trials, or in an analysis of the two dual-therapy trials: ***Body as a Whole-General:*** accidental trauma, asthenia, chest pain, increased drug level, infection, face edema, fatigue, dependent edema, generalized edema, leg edema, malaise, rigors, sepsis; ***Cardiovascular:*** abnormal heart sounds, aggravated hypertension, angina pectoris, cardiac failure, chest pain, hypotension; ***Endocrine:*** increased glucocorticoids; ***Gastrointestinal:*** enlarged abdomen, esophagitis, flatulence, gastrointestinal disorder, gastroenteritis, GI hemorrhage, gum hyperplasia, melena, moniliasis, ulcerative stomatitis; ***Heart Rate and Rhythm:*** arrhythmia, atrial fibrillation, tachycardia; ***Metabolic and Nutritional:*** acidosis, dehydration, diabetes mellitus, fluid overload, hypercalcemia, hyperlipemia, hypertriglyceridemia, hypocalcemia, hypoglycemia, hypomagnesemia, hypoproteinemia, weight increase; ***Musculoskeletal:*** arthralgia, arthropathy, back pain, bone fracture, cramps, hernia, myalgia, leg pain; ***Nervous System:*** dizziness, neuropathy, paraesthesia, hypoesthesia; ***Platelet and Bleeding:*** hematoma, hemorrhage, purpura, thrombocytopenia, thrombosis; ***Psychiatric:*** agitation, anxiety, depression; ***Red Blood Cell:*** polycythemia; ***Reproductive Disorders, Male:*** genital edema, impotence; ***Respiratory:*** bronchitis, bronchospasm, abnormal chest sounds, coughing, pharyngitis, pneumonia, pulmonary disorder, pulmonary edema, rhinitis, sinusitis; ***Skin and Appendages:*** cyst, herpes simplex, herpes zoster, hypertrichosis, pruritus, rash, skin disorder, skin ulceration; ***Urinary:*** albuminuria, bladder disorder, dysuria, frequent micturition, hematuria, increased non-protein nitrogen, oliguria, abnormal renal function, renal tubular necrosis, surgery, ureteral disorder, urinary retention; ***Vascular Disorders:*** vascular disorder; ***Vision Disorders:*** cataract, conjunctivitis, abnormal vision; ***White Blood Cell:*** leucopenia. Among these events, leucopenia and hypertriglyceridemia occurred more frequently in the two triple-therapy studies using azathioprine and mycophenolate mofetil than in the dual-therapy studies.

Malignancies

The incidence of malignancies in the controlled clinical trials of renal transplant was not significantly different between groups at 1 year (9/590 Simulect-treated patients vs 12/594 placebo-treated patients) or among patients with 5-year follow-up from Studies 1 and 2 (21/295 Simulect-treated patients vs 21/291 placebo-treated patients). The incidence of lymphoproliferative disease was not significantly different between groups, and less than 1% in the Simulect-treated patients.

Infections

The overall incidence of cytomegalovirus infection was similar in Simulect®- and placebo-treated patients (15% vs. 17%) receiving a dual- or triple-immunosuppression regimen. However, in patients receiving a triple-immunosuppression regimen, the incidence of serious cytomegalovirus infection was higher in Simulect®-treated patients compared to placebo-treated patients (11% vs. 5%). The rates of infections, serious infections, and infectious

organisms were similar in the Simulect®- and placebo-treatment groups among dual- and triple-therapy treated patients.

Post-Marketing Experience

Severe acute hypersensitivity reactions including anaphylaxis characterized by hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, and/or sneezing, as well as capillary leak syndrome and cytokine release syndrome, have been reported during post-marketing experience with Simulect®.

OVERDOSAGE

A maximum tolerated dose of Simulect® has not been determined in patients. During the course of clinical studies, Simulect® has been administered to adult renal transplantation patients in single doses of up to 60 mg, or in divided doses over 3-5 days of up to 120 mg, without any associated serious adverse events. There has been one spontaneous report of a pediatric renal transplantation patient who received a single 20-mg dose (2.3 mg/kg) without adverse events.

DOSAGE AND ADMINISTRATION

Simulect® is used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids. Simulect® is for central or peripheral intravenous administration only. Reconstituted Simulect® should be given either as a bolus injection or diluted to a volume of 25 mL (10 mg) vial or 50 mL (20 mg) vial with normal saline or dextrose 5% and administered as an intravenous infusion over 20 to 30 minutes. Bolus administration may be associated with nausea, vomiting and local reactions, including pain.

Simulect® should only be administered once it has been determined that the patient will receive the graft and concomitant immunosuppression. Patients previously administered Simulect® should only be re-exposed to a subsequent course of therapy with extreme caution.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration. After reconstitution, Simulect® should be a clear-to-opalescent, colorless solution. If particulate matter is present or the solution is colored, do not use.

Care must be taken to assure sterility of the prepared solution because the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

It is recommended that after reconstitution, the solution should be used immediately. If not used immediately, it can be stored at 2°C to 8°C for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

No incompatibility between Simulect® and polyvinyl chloride bags or infusion sets has been observed. No data are available on the compatibility of Simulect® with other intravenous substances. Other drug substances should not be added or infused simultaneously through the same intravenous line.

Adults

In adult patients, the recommended regimen is two doses of 20 mg each. The first 20-mg dose should be given within 2 hours prior to transplantation surgery. The recommended second 20-mg dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to Simulect® or graft loss occur.

Pediatric

In pediatric patients weighing less than 35 kg, the recommended regimen is two doses of 10 mg each. In pediatric patients weighing 35 kg or more, the recommended regimen is two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. The recommended second dose should be given 4 days after transplantation. The second dose should be withheld if complications such as severe hypersensitivity reactions to Simulect® or graft loss occur.

Reconstitution of 10 mg Simulect® Vial

To prepare the reconstituted solution, add 2.5 mL of Sterile Water for Injection, USP, using aseptic technique, to the vial containing the Simulect® powder. Shake the vial gently to dissolve the powder.

The reconstituted solution is isotonic and may be given either as a bolus injection or diluted to a volume of 25 mL with normal saline or dextrose 5% for infusion. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.

Reconstitution of 20 mg Simulect® Vial

To prepare the reconstituted solution, add 5 mL of Sterile Water for Injection, USP, using aseptic technique, to the vial containing the Simulect® powder. Shake the vial gently to dissolve the powder.

The reconstituted solution is isotonic and may be given either as a bolus injection or diluted to a volume of 50 mL with normal saline or dextrose 5% for infusion. When mixing the solution, gently invert the bag in order to avoid foaming; DO NOT SHAKE.

HOW SUPPLIED

Simulect® (basiliximab) is supplied in a single-use glass vial.

Each carton contains one of the following

1 Simulect® 10 mg vial.....NDC 0078-0393-61
1 Simulect® 20 mg vial.....NDC 0078-0331-84

Store lyophilized Simulect® under refrigerated conditions (2°C to 8°C; 36°F to 46°F).

Do not use beyond the expiration date stamped on the vial.

REFERENCES

1. Kahan, B.D., Rajagopalan P.R. and Hall M., Transplantation, 67, 276-284 (1999).

2. Nashan, B., Moore R., Amlot P., Schmidt A.-G., Abeywickrama K. and Soulillou J.-P., Lancet 350, 1193-1198 (1997).

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936