NOVARTIS

Simulect®

(basiliximab)
For Injection
Rx only

30154901

SAMPLE

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. Each 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® (basiliximab) 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® were assessed in 12 pediatric renal transplantation patients, children (2-11 years of age, n=8) and adolescents (12-15 years of age, n=4). These data indicate that in children, the volume of distribution at steady state was 5.2 ± 2.8 L, half-life was 11.5 ± 6.3 days and clearance was 17 ± 6 mL/h. Distribution volume and clearance are reduced by about 50% compared to adult renal transplantation patients. Disposition parameters were not influenced to a clinically relevant extent by age, body weight (9-37 kg) or body surface area (0.44-1.20 m^2) in this age group. In adolescents, the volume of distribution at steady state was 10.1 ± 7.6 L, half-life was 7.2 ± 3.6 days and clearance was 45 ± 25 mL/h. Disposition in adolescents was similar to that in adult renal transplantation patients. *(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 two pediatric patients (2 and 12 years of age) and was similar to that characterized in adult renal transplantation patients. *In vitro* studies using human tissues indicate that Simulect® binds only to lymphocytes.

At the recommended dosing regimen, the mean ± SD duration of basiliximab saturation of IL-2Rα was 36 ± 14 days *(See DOSAGE AND ADMINISTRATION)*. The duration of clinically significant IL-2 receptor blockade after the recommended course of Simulect® is not known. No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by flow cytometry. Cytokine release syndrome has not been reported after Simulect® administration.

Clinical Studies

The safety and efficacy of Simulect® for the prophylaxis of acute organ rejection in adults following first cadaveric- or living-donor renal transplantation were assessed in two randomized, double-blind, placebo-controlled, multicenter trials. These studies compared two 20 mg doses of Simulect® with placebo when each was administered intravenously as part of a standard immunosuppressive regimen comprised of cyclosporine for microemulsion and corticosteroids, administered starting on Day 0, to prevent acute renal allograft rejection. 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, of which 363 Simulect®-treated patients and 358 placebo-treated patients underwent transplantation. One study was conducted at 21 sites in Europe and Canada (EU/CAN Study); the second was conducted at 21 sites in the USA (US Study). Patients 18-75 years of age undergoing first cadaveric (EU/CAN and US Studies) or living-donor (US only) renal transplantation, with ≥1 HLA mismatch, were enrolled.

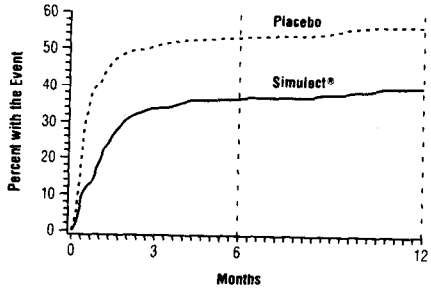
The primary efficacy endpoint in both studies was the incidence of death, graft loss or an episode of acute rejection during the first 6 months post-transplantation. Secondary efficacy endpoints included the primary efficacy variable measured during the first 12 months post-transplantation, the incidence 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 the US study. 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)

	EU/CAN Study			US Study		
	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

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



INDICATIONS AND USAGE
Simulect® (basiliximab) 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 and corticosteroids.

CONTRAINDICATIONS
Simulect® (basiliximab) 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® (basiliximab) 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. Anaphylactoid reactions following the administration of Simulect® have not been observed but can occur following the administration of proteins. Medications for the treatment of severe hypersensitivity reactions should be available for immediate use.

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.

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

Re-administration of Simulect® after an initial course of therapy has not been studied in humans. The potential risks of such re-administration, specifically those associated with immunosuppression and/or the occurrence of anaphylaxis/anaphylactoid reactions, are not known.

Immunogenicity
Of renal transplantation patients treated with Simulect® (basiliximab) and tested for anti-idiotype antibodies, 1/246 developed an anti-idiotype antibody response, with no deleterious clinical effect upon the patient. In the US Study, 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.

Drug Interactions
No formal drug-drug interaction studies have been conducted. The following medications have been administered in clinical trials with Simulect® (basiliximab) with no incremental increase in adverse reactions: ATG/ALG, azathioprine, corticosteroids, cyclosporine, mycophenolate mofetil, and muromonab-CD3.

Carcinogenesis, Mutagenesis and 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 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 2 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 adequate and well-controlled studies have been completed in pediatric patients. In an ongoing safety and pharmacokinetic study, pediatric patients [2-11 years of age (n=8), 12-15 years of age (n=4), median age 9.5 years] were treated with Simulect® via intravenous bolus injection in addition to standard immunosuppressive agents including cyclosporine, corticosteroids, azathioprine, and mycophenolate mofetil. Preliminary results indicate that 16.7% (2/12) of patients had experienced an acute rejection episode by 3 months post-transplantation. The most frequently reported adverse events were fever and urinary tract infections (41.7% each). 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® 15; placebo 19). 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
The incidence of adverse events for Simulect® (basiliximab) was determined in two randomized comparative double-blind trials for the prevention of renal allograft rejection. A total of 721 patients received renal allografts, of which 363 received Simulect® and 358 received placebo. All patients received concomitant cyclosporine for microemulsion and corticosteroids.

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 99% of the patients in the placebo-treated group and 99% of the patients in the Simulect®-treated group. 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 75% of Simulect®-treated patients and 73% 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, diarrhea, abdominal pain, vomiting, dyspepsia, moniliasis; ***Metabolic and Nutritional:*** hyperkalemia, hypokalemia, hyperglycemia, hyperuricemia, hypophosphatemia, hypocalcemia, weight increase, hypercholesterolemia, acidosis; ***Central and Peripheral Nervous System:*** headache, tremor, dizziness; ***Urinary System:*** dysuria, increased non-protein nitrogen, urinary tract infection; ***Body as a Whole-General:*** pain, peripheral edema, edema, fever, viral infection, leg edema, asthenia; ***Cardiovascular Disorders-General:*** hypertension; ***Respiratory System:*** dyspnea, upper respiratory tract infection, coughing, rhinitis, pharyngitis; ***Skin and Appendages:*** surgical wound complications, acne; ***Psychiatric:*** insomnia; ***Musculoskeletal System:*** leg pain, back pain; ***Red Blood Cell:*** anemia.

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

Incidence of Malignancies: The overall incidence of malignancies among all patients in the two 12-month controlled trials was not significantly different between the Simulect® and placebo treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 1 patient (0.3%) in the Simulect® group compared with 2 patients (0.6%) in the placebo group. Other malignancies were reported among 5 patients (1.4%) in the Simulect® group compared with 7 patients (1.9%) in patients treated with placebo.

Incidence of Infectious Episodes: Cytomegalovirus infection was reported in 14% of Simulect®-treated patients and 18% of placebo-treated patients. The rates of infections, serious infections, and infectious organisms were similar in the Simulect® and placebo treatment groups.

OVERDOSAGE

There have not been any reports of overdoses with Simulect® (basiliximab). A maximum tolerated dose has not been determined in patients. In clinical studies, Simulect® has been administered to renal transplantation patients in single doses of up to 60 mg without any associated serious adverse events.

DOSAGE AND ADMINISTRATION

Simulect® (basiliximab) is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids. *Simulect® is for central or peripheral intravenous* administration only. Reconstituted Simulect® (20 mg in 5 mL) should be diluted to a volume of 50 mL with normal saline or dextrose 5% and administered as an intravenous infusion over 20 to 30 minutes.

Adult: 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 second 20 mg dose should be given 4 days after transplantation.

Pediatric: For children and adolescents from 2 up to 15 years of age, the recommended regimen is two doses of 12 mg/m^2 each, up to a maximum of 20 mg/dose. The first dose should be given within 2 hours prior to transplantation surgery. The second dose should be given 4 days after transplantation.

RECONSTITUTION OF 20 mg Simulect® (basiliximab) VIAL

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

The reconstituted solution is isotonic and should be 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.

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.

HOW SUPPLIED

Simulect® (basiliximab) is supplied in a single use glass vial containing 20 mg of basiliximab. Each box contains 1 Simulect® 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.

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