PRODUCT MONOGRAPH

PrSIMULECT®

(basiliximab)

20 mg sterile lyophilized powder for injection/infusion

Immunosuppressant

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PrSIMULECT®

(basiliximab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
injection	20 mg sterile lyophilized powder	none

SIMULECT® IS A POTENT DRUG. THIS DRUG SHOULD ONLY BE USED BY PHYSICIANS EXPERIENCED IN IMMUNOSUPPRESSION THERAPY AND MANAGEMENT OF ORGAN TRANSPLANTATION PATIENTS IN A SETTING WHERE FULL RESUSCITATION FACILITIES ARE IMMEDIATELY AVAILABLE.

INDICATIONS AND CLINICAL USE

SIMULECT® (basiliximab) is indicated for the prophylaxis of acute organ rejection in *de novo* renal transplantation and is to be used concomitantly with NEORAL® (cyclosporine for microemulsion) and corticosteroid-based immunosuppression.

CONTRAINDICATIONS

SIMULECT® (basiliximab) is contraindicated in patients with known hypersensitivity to basiliximab, mouse cell proteins or any other component of the formulation. See PHARMACEUTICAL INFORMATION – Composition.

WARNINGS AND PRECAUTIONS

General

SIMULECT® (basiliximab) should be prescribed only by physicians who are experienced in the use of immunosuppressive therapy following organ transplantation.

Patients receiving SIMULECT® should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources including medications for the treatment of severe hypersensitivity reactions.

The addition of agents other than NEORAL® (cyclosporine for microemulsion) and corticosteroids to SIMULECT® therapy may increase the risk of overimmunosuppression.

Please note that following initiation of treatment with NEORAL®, due to the different bioavailabilities of the different oral cyclosporine formulations, patients should not be converted to any other oral formulation of cyclosporine without appropriate monitoring of cyclosporine blood concentrations, serum creatinine levels and blood pressure. This does not apply to the conversion between NEORAL® soft gelatine capsule and NEORAL® oral solution as these two dosage forms are bioequivalent.

It is therefore important that prescribers, pharmacists and patients be aware that substitution of NEORAL® with any other oral formulation of cyclosporine is not recommended as this may lead to alterations in cyclosporine blood concentrations. For this reason, it might be appropriate to prescribe by brand.

Carcinogenesis and Mutagenesis

Transplant patients receiving immunosuppressive regimens involving combinations with or without SIMULECT® are at increased risk of developing lymphoproliferative disorders (LPDs) (such as lymphoma) and opportunistic infections (such as cytomegalovirus, CMV). In clinical trials, the incidence of opportunistic infections was similar in patients using immunosuppressive regimens with or without SIMULECT®. In a pooled analysis of two five-year extension studies, no differences were found in the incidence of malignancies and LPDs between immunosuppressive regimens with or without SIMULECT®.

Immune

Severe acute (less than 24 hours) hypersensitivity reactions have been observed both on initial exposure to SIMULECT® and on reexposure to a subsequent course of therapy. These included anaphylactoid type reactions such as rash, urticaria, pruritis, sneezing, wheezing, hypotension, tachycardia, dyspnea, bronchospasm, pulmonary edema, cardiac failure, respiratory failure and capillary leak syndrome. If severe hypersensitivity occurs, therapy with SIMULECT® should be permanently discontinued and no further dose should be administered.

Therefore, physicians prescribing SIMULECT® for a second course of therapy should be fully aware of the risks of anaphylactic reaction and should exercise caution. There is accumulating evidence that

a subgroup of patients is at increased risk of developing hypersensitivity reactions. These are patients in whom, following the initial administration of SIMULECT®, the concomitant immunosuppression was discontinued prematurely, for example, due to abandoned transplantation or due to early loss of the graft. Acute hypersensitivity reactions were observed on re-administration of SIMULECT® for a subsequent transplantation in some of these patients.

Individual cases of suspected cytokine release syndrome (CRS) have been reported during post-marketing experience with SIMULECT® (see Post-Market Adverse Drug Reactions). Review of the clinical symptoms for each of the cases does not support the diagnosis of CRS. However, the contribution of SIMULECT® could not be excluded.

Vaccination

No data are available on either the effects of live and inactive vaccination or the transmission of infection by live vaccines in patients receiving SIMULECT®. Nevertheless, live vaccines are not recommended for immunosuppressed patients. Inactivated vaccines may be administered to immunosuppressed patients; however, response to the vaccine may depend on the degree of the immunosuppression.

Special Populations

Pregnant Women: There is no adequate information for use in pregnant women. SIMULECT® (basiliximab) should not be given to pregnant women except in cases where the potential benefit for the mother outweighs the potential risk for the fetus.

Nursing Women: There are no data in lactating women. Since basiliximab is an immunoglobulin G (IgG_{1k}) antibody, it may cross the human placenta and may be excreted in human milk. Women receiving SIMULECT® should not breast feed for 4 months following the last dose.

Pediatrics: No adequate and well-controlled studies have been completed in pediatric patients. Safety and efficacy in pediatric patients have not been established and pharmacokinetic data is very limited (See ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). No studies have been performed in neonates or children aged less than two years.

Geriatrics: Controlled clinical trials 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 initial age-related dosing adjustment is required. Caution must be used in giving immunosuppressive drugs to elderly patients.

Use in Women of Childbearing Potential: Women of childbearing potential should use effective contraception before beginning SIMULECT® therapy, during therapy and for 4 months after completion of SIMULECT® therapy.

Fertility: No human data on the effect of basiliximab on fertility are available. Formal studies of the potential effect of SIMULECT® on animal fertility have not been conducted (see TOXICOLOGY).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

SIMULECT® (basiliximab) does not appear to add to the background of adverse events seen in organ transplant patients as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. In two controlled, double-blind, multicenter trials, the pattern of adverse events in 363 SIMULECT®-treated patients was indistinguishable from that of 359 placebo-treated patients.

The cumulative incidence of adverse events which occurred in ≥ 6% in either treatment group during the first 12 months post-transplantation for the pooled studies is summarized in Table 1.

Serious adverse events occurred with similar incidence and profile in both the SIMULECT® and placebo treatment groups (SIMULECT® 59%, placebo 63% overall).

The rates of malignancies, reported infections, serious infections and infectious organisms were similar in the SIMULECT® and placebo treatment groups. No specific SIMULECT®-related risk was identified.

Incidence of death:
In a pooled analysis of two five-year extension studies, the incidence and cause of death remained similar in both treatment groups (SIMULECT® 15%, placebo 11%). The primary cause of death being cardiac-related disorders (SIMULECT® 5%, placebo 4%) such as cardiac failure and myocardial infarction.

Incidence of Malignant Neoplasms: The incidence of malignancies among the 722 patients in the two 12-month controlled trials was not significantly different between the SIMULECT® and placebo-treatment groups, and compared to the incidence reported in the literature for renal allograft recipients. 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. No differences were found in the incidence of malignancies and lymphoproliferative disease between SIMULECT® 7% (21/295) and placebo 7% (21/291) in a pooled analysis of two five-year extension studies.

Incidence of Infectious Episodes: Cytomegalovirus infection was reported in 14% of SIMULECT®-treated patients and 18% of placebo-treated patients. The rates of infections (SIMULECT® 81%,

placebo 81%), serious infections (SIMULECT® 27.5%, placebo 27.3%) and infectious organisms were similar in the SIMULECT® and placebo treatment groups.

Table 1 - Adverse Events in Controlled Clinical Trials (≥ 6%)

Organ System/Adverse Experience	SIMULECT® (N=363) %	PLACEBO (N=359) %
Body as a Whole		
Asthenia	35 (10%)	28 (8%)
Chest Pain	25 (7%)	27 (8%)
Drug Level Increased	21 (6%)	26 (7%)
Fatigue	30 (8%)	29 (8%)
Infection Viral	44 (12%)	54 (15%)
Edema	78 (21%)	71 (20%)
Edema Generalised	25 (7%)	24 (7%)
Edema - Legs	40 (11%)	29 (8%)
Edema - Peripheral	104 (29%)	109 (30%)
Pain	152 (42%)	141 (39%)
Pyrexia	73 (20%)	87 (24%)
Cardiovascular		
Hypertension	97 (27%)	93 (26%)
Hypotension	30 (8%)	38 (11%)
Nervous System		
Dizziness	40 (11%)	33 (9%)
Headache	87 (24%)	80 (22%)
Paraesthesia	27 (7%)	31 (9%)
Tremor	52 (14%)	66 (18%)
Gastro-Intestinal System		
Addomen Enlarged	28 (8%)	27 (8%)
Abdominal pain	76 (21%)	97 (27%)
Constipation	175 (48%)	177 (49%)
Diarrhea	75 (21%)	68 (19%)
Dyspepsia	50 (14%)	64 (18%)
Moniliasis	36 (10%)	29 (8%)
Nausea	123 (34%)	143 (40%)

Vomiting	73 (20%)	79 (22%)
Heart Rate and Rhythm Disorders		
Tachycardia	28 (8%)	21 (6%)
Metabolic and Nutritional		
Acidosis	37 (10%)	46 (13%)
Dehydration	22 (6%)	20 (6%)
Hypercholesterolemia	41 (11%)	38 (11%)
Hyperglycemia	58 (16%)	43 (12%)
Hyperkalemia	80 (22%)	85 (24%)
Hyperlipaemia	31 (9%)	25 (7%)
Hyperuricemia	49 (13%)	52 (14%)
Hypocalcemia	39 (11%)	41 (11%)
Hypokalemia	66 (18%)	85 (24%)
Hypomagnesemia	34 (9%)	43 (12%)
Hypophosphatemia	45 (12%)	46 (13%)
Weight Increase	40 (11%)	46 (13%)
Musculo-Skeletal		
Arthralgia	21 (6%)	23 (6%)
Back Pain	36 (10%)	48 (13%)
Cramps	33 (9%)	28 (8%)
Pain Leg(s)	46 (13%)	40 (11%)
Psychiatric		
Insomnia	86 (24%)	102 (28%)
Red Blood Cell		
Anemia	93 (26%)	101 (28%)
Polycythaemia	24 (7%)	16 (4%)
Respiratory System		
Chest Sounds Abnormal	29 (8%)	25 (7%)
Coughing	41 (11%)	37 (10%)
Dyspnea	59 (16%)	50 (14%)
Pharyngitis	35 (10%)	29 (8%)

Rhinitis	38 (10%)	39 (11%)
Sinusitis	26 (7%)	23 (6%)
Upper Respiratory Tract Infection	71 (20%)	64 (18%)
Skin and Appendages Disorders		
Acne	53 (15%)	56 (16%)
Herpes Simplex	30 (8%)	32 (9%)
Post-operative Wound Complication	58 (16%)	63 (18%)
Pruritus	29 (8%)	31 (9%)
Rash	24 (7%)	30 (8%)
Skin Disorder	29 (8%)	25 (7%)
Urinary System		
Bladder disorders	34 (9%)	38 (11%)
Dysuria	36 (10%)	30 (8%)
Hematuria	33 (9%)	41 (11%)
NPN increased	36 (10%)	23 (6%)
Oliguria	25 (7%)	25 (7%)
Surgery	21 (6%)	27 (8%)
Urinary tract infection	168 (46%)	166 (46%)

Post-Market Adverse Drug Reactions

The following adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntary from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Immune system disorders

Cytokine release syndrome has been reported.

Hypersensitivity/anaphylactoid reaction such as rash, urticaria, pruritus, sneezing, wheezing, bronchospasm, dyspnoea, pulmonary oedema, cardiac failure, hypotension, tachycardia, respiratory failure, capillary leak syndrome have also been reported (see WARNINGS AND PRECAUTIONS).

Some reports of anaphylaxis and other infusion-related adverse events suggest that patients receiving subsequent courses of therapy with SIMULECT® (for example, among those receiving a second transplant) are at higher risk of these events.

DRUG INTERACTIONS

Overview

Because SIMULECT® is an immunoglobulin, no metabolic interactions are to be expected. Therefore, no formal drug-drug interaction studies have been conducted.

In controlled clinical trials a limited number of patients, treated with the recommended doses of SIMULECT®, have also been administered azathioprine, mycophenolate mofetil, tacrolimus or antibody therapy such as OKT_3 or ATG/ALG with no increase in adverse events in SIMULECT® patients as compared to placebo patients.

Azathioprine and Mycophenolate Mofetil: During the first 3 months post-transplantation, 10.5% of patients in the SIMULECT® group and 21.7% of patients in the placebo group were treated with azathioprine or mycophenolate mofetil for at least one month. There was no increase in adverse events or infections in the SIMULECT® group compared to the placebo group, and no patients in the SIMULECT® group experienced lymphoma or any other malignancy during the first 12 months post-transplantation.

Antibody Therapy: During the first 3 months post-transplantation, 14% of patients in the SIMULECT® group and 27% of patients in the placebo group received augmented immunosuppression with antibody therapy (Orthoclone OKT_3 or ATG/ALG) with no increase in adverse events or infections in the SIMULECT® group compared to the placebo group. No patients in the SIMULECT® group who received antibody therapy experienced lymphoma or any other malignancy during the first 12 months post-transplantation.

Of 172 renal transplantation patients treated with SIMULECT® in one clinical trial, the incidence of human anti-murine antibody (HAMA) was 3.5% (6/172); since 4 of the 6 patients positive for HAMA also received Orthoclone OKT_3, the incidence may be as low as 1.2% (2/172). Analysis of rejection outcome in patients treated with Orthoclone OKT_3 demonstrates a lower rate of graft loss in the SIMULECT® (7/47 = 15%) than placebo-treated patients (16/71 = 23%), indicating the use of SIMULECT® has no deleterious effect upon the subsequent efficacy of Orthoclone OKT_3. The available clinical data on the use of Orthoclone OKT_3 in patients previously treated with SIMULECT® suggests that subsequent use of Orthoclone OKT_3 or other murine anti-lymphocyte antibody preparations is not precluded.

The use of SIMULECT® does not preclude subsequent treatment with murine anti-lymphocytic antibody preparations.

DOSAGE AND ADMINISTRATION

Reconstituted SIMULECT® (basiliximab) can be administered either as an intravenous infusion over 20 to 30 minutes or as a bolus injection.

Recommended Dose and Dosage Adjustment

The recommended total dose is 40 mg, given in 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.

Administration

Reconstitution:

Instructions for Use and Handling

Reconstitution Table			
Vial Size	**Diluent Volume to be added to Vial**	**Approximate available volume**	**Actual Concentration**
20 mg	5 ml	5 mL	4 mg/mL

To prepare the infusion/injection solution add 5 mL of Sterile Water for Injection to the vial containing the SIMULECT® lyophilized powder. *Care must be taken during reconstitution to maintain sterility because the formulation contains no antimicrobial preservatives.* Shake the vial gently to dissolve the powder. The sterile product is stable at 2-8^{0}C for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

OVERDOSAGE

In clinical studies SIMULECT® (basiliximab) has been administered to humans in single doses of up to 60 mg and multiple doses of up to 150 mg over 24 days with no untoward acute effects.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SIMULECT® (basiliximab) is a chimeric murine/human monoclonal antibody (IgG_{1k}) that is selectively directed against the interleukin-2 receptor alpha-chain (IL-2R alpha, also known as CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. SIMULECT® specifically binds to the CD25 antigen on activated T-lymphocytes expressing the high affinity interleukin-2 receptor and thereby prevents binding of interleukin-2, the signal for T-cell proliferation.

Complete and consistent blocking of the interleukin-2 receptor is maintained as long as serum basiliximab levels exceed 0.2 µg/mL. As concentration falls below this level, expression of the CD25 antigen returns to pretherapy values within 1-2 weeks. Cytokine release syndrome or

myelosuppression was not observed during SIMULECT® administration in the pivotal transplantation trials.

Pharmacokinetics

Table 2 Summary of basiliximab's Pharmacokinetic Parameters in patients undergoing kidney transplantation

	C_{max}	$t_{½}$ (h)	Clearance	Volume of distribution
Single dose mean	7.1 ± 5.1 mg/L	7.2 ±3.2 days	41 ± 19 ml/h	8.6 ± 4.1 L

Single-dose and multiple-dose pharmacokinetic studies have been conducted in patients undergoing kidney transplantation. Cumulative doses have ranged from 15 mg up to 150 mg.

Peak 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 has not been fully studied. *In vitro* studies using human tissues indicate that SIMULECT® binds only to lymphocytes and macrophages/monocytes. 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.

In a clinical trial with 23 adult liver transplant patients, the disposition of SIMULECT® was characterized by a steady-state distribution volume of 7.5 ± 2.5 L, half-life of 4.1 ± 2.1 days and clearance of 75 ± 24 mL/h. Contributing to clearance were drug loss via drained ascites fluid and post-operative bleeding. Offsetting the faster drug clearance was a lower receptor-saturating-concentration threshold of 0.1 µg/mL in this population. Hence, the duration of IL-2R alpha blockade at a given SIMULECT® dose level is similar to that seen in adult renal transplant patients.

Special Populations and Conditions

Pediatrics: Safety and efficacy in pediatric patients have not been established and pharmacokinetic data is very limited (See WARNINGS AND PRECAUTIONS). No data exist on the use of SIMULECT® (basiliximab) in neonates or infants aged less than 2 years. In one clinical study in 12 pediatric *de novo* renal transplant patients aged 2-11 years (n=8), 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.

Clearance and volume were not influenced by age (2- 11 years), body weight (9-37 kg) or body surface area (0.44-1.20 m^2) in this age group. The disposition of SIMULECT® in pediatric renal

transplant patients was characterized by an average 50% lower clearance compared to adult patients. In adolescents aged 12-15 (n=4), the volume of distribution at steady-state was 10.1 ± 7.6L, 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 transplant patients. The relationship between serum concentration and receptor saturation was assessed in two patients (2 and 12 years) and was similar to that characterized in adult renal transplant patients. No adequate and well-controlled studies have been completed in pediatric patients.

STORAGE AND STABILITY

Store in its original container at 2-8^{0}C. It is recommended that after reconstitution the colourless, clear to opalescent solution should be used immediately. If not used immediately, it is stable at 2-8^{0}C for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

Shipping and storage should be under refrigerated conditions (2-8^{0}C).

SPECIAL HANDLING INSTRUCTIONS

Instructions for Use and Handling

Reconstitution Table

Vial Size	Diluent Volume to be added to Vial	Approximate available volume	Actual Concentration
20 mg	5 ml	5 mL	4 mg/mL

To prepare the infusion/injection solution add 5 mL of Sterile Water for Injection to the vial containing the SIMULECT® lyophilized powder. *Care must be taken during reconstitution to maintain sterility because the formulation contains no antimicrobial preservatives.* Shake the vial gently to dissolve the powder. The sterile product is stable at 2-8^{0}C for 24 hours or at room temperature for 4 hours. Discard the reconstituted solution if not used within 24 hours.

The reconstituted solution is isotonic and may be given as a bolus injection or diluted to a volume of 50 mL or greater with normal saline or dextrose 5% for infusion.

Since no data are available on the compatibility of SIMULECT® with other intravenous substances, SIMULECT® should not be mixed with other medications/ substances and should always be given through a separate infusion line.

Compatibility with the following infusion sets has been verified:
Infusion Bag
- Baxter minibag NaC1 0.9%

Infusion Sets
- Luer Lock™, H. Noolens
- Sterile vented i.v. set, Abbott

- Infusion set, Codan
- Infusomat™, Braun
- Infusionsgerat R 87 plus, Ohmeda
- Lifecare 5000™ Plumset Microdrip, Abbott
- Vented basic set, Baxter
- Flashball device, Baxter
- Vented primary administration set, Imed

Compatibility with other commercial devices has not been tested.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SIMULECT® (basiliximab) is supplied in packages of one glass vial containing 20 mg sterile lyophilized powder for injection/infusion after reconstitution with 5.0 mL Sterile Water for Injection (not supplied).

Composition

One vial of SIMULECT® 20 mg contains 20 mg of basiliximab. The non-medicinal ingredients include 7.21 mg potassium dihydrogen phosphate, 0.99 mg disodium hydrogen phosphate, 1.61 mg sodium chloride, 20 mg sucrose, 40 mg glycine and 80 mg mannitol. No preservatives are included.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: basiliximab

Chemical name: chimeric murine/human monoclonal antibody (IgG_{1K})

Molecular formula and molecular mass: $C_{6400}H_{9888}N_{1696}O_{2006}S_{52}$; 144 355 Da

Physicochemical properties:	Physical Description:	white lyophilisate
	Solubility:	Water soluble
	pH value of reconstituted solution:	6.5

Description: Basiliximab is a glycoprotein obtained from the 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-2R.

CLINICAL TRIALS

The efficacy and safety of SIMULECT® (basiliximab) in prophylaxis of organ rejection in *de novo* renal transplantation has been demonstrated in placebo-controlled studies. Results from two pivotal 12-month multicentre studies (B201 and B352) comparing SIMULECT® with placebo show that SIMULECT®, used concomitantly with NEORAL® (cyclosporine for microemulsion) and corticosteroids, significantly reduces the incidence of acute rejection episodes (EU/CAN Study: 30% (SIMULECT®) vs. 44% (Placebo), p=0.007; U.S. Study: 33% (SIMULECT®) vs 46% (Placebo), p=0.015). Other expected renal transplantation events (acute tubular necrosis and cyclosporine toxicity) were observed at similar rates in the placebo and SIMULECT® groups (acute tubular necrosis: 18.7% (SIMULECT®) vs.18.4 (placebo), p=0.924; cyclosporine toxicity: 18.2% (SIMULECT®) vs. 15.9% (placebo), p=0.430.

Long Term Follow-up

Five-year patient survival and graft survival data were provided by 71% and 58% of the original patients of Study B201 and Study B352, respectively. Patients in both studies continued to receive a dual therapy regimen with NEORAL® (cyclosporine for microemulsion) and corticosteroid-based immunosuppression. No difference was observed between groups in the 5-year graft survival in

either Study B201 (91% SIMULECT® group, 92% placebo group) or Study B352 (85% SIMULECT® group, 86% placebo group). In Study B201, 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 B352, patient survival in the placebo group (90%) was the same compared to the SIMULECT® group (90%).

In a pooled analysis of two five-year open-label extension studies (586 patients total), the combined graft and patient survival rates were not statistically different for the SIMULECT® and placebo groups. Extension studies also showed that patients who experienced an acute rejection episode during the first year after transplantation experienced more graft losses and deaths over the five-year follow-up period than patients who had no rejection. These events were not influenced by SIMULECT®.

Of 270 patients treated with SIMULECT® and tested for anti-idiotype antibodies, only one developed an anti-idiotype antibody response.

Of 172 patients treated with SIMULECT® in one clinical study, the incidence of human anti-murine antibody (HAMA) was 3.5% (6/172); since 4 of the 6 patients positive for HAMA also received OKT3, the incidence may be as low as 1.2% (2/172).

DETAILED PHARMACOLOGY

Animal Pharmacokinetics

Basiliximab was evaluated for systemic exposure in 4-week toxicity studies in the rhesus monkey at doses of 0.5 to 5 mg/kg every 3-4 days and an embryo-fetal development study at 1 and 5 mg/kg doses administered every 4 days (Days 20-48 of pregnancy) in the cynomolgus monkey. In these studies, serum concentrations of basiliximab were measured after a single dose and after 3-4 weeks of multiple dosing.

Peak concentrations following a single 5 mg/kg dose in rhesus monkeys averaged 155 mg/mL (males) and 186 mg/mL (females), and multiple 5 mg/kg dosing yielded maximum concentrations of 463 mg/mL (males) and 295 mg/mL (females). Peak concentrations in pregnant cynomolgus monkeys following the same dose were somewhat lower, 77.1 mg/mL (single dose) and 130 mg/mL (multiple dose).

Exposure was proportional or nearly proportional to a single dose over the 0.5 to 5 mg/kg range. After multiple dosing, basiliximab exposure in several animals in each study was lower than that in the same animals following a single dose, especially in the low dose groups (0.5, 1.0, or 1.5 mg/kg). The reduced basiliximab exposure may be due to either the formation of anti-basiliximab antibodies or a high concentration of soluble Interleukin-2 receptor (sIL-2R) in some monkeys. The antibody and/or sIL-2R response was weak and had little, if any, effect at the higher doses studied. Multiple basiliximab dosing at 4.5 and 5 mg/kg doses yielded a modest accumulation of basiliximab, consistent with its 5-7 day half-life and the twice weekly dosing frequency.

TOXICOLOGY

General toxicology studies with basiliximab included: 4 week intravenous toxicity in rhesus monkey; 4 week intravenous toxicity in rhesus monkey with 8-week recovery; 39-week intravenous toxicity in rhesus monkey with 13-week recovery and local intravenous tolerance in the rabbit. These studies demonstrated that basiliximab was well tolerated in the rhesus monkey for 39 weeks (up to 24 mg/kg week) and it did not show any local intravenous irritation potential in the rabbit (up to 0.4% solution). In the 39-week study, the highest dose administered to rhesus monkey (24 mg/kg) resulted in approximately 1,000 times the systemic exposure (AUC) observed in renal transplant patients given the recommended clinical dose together with concomitant immunosuppressive therapy.

Table 2: Toxicology Studies

Species	Initial Group	Mode of Administration	Doses	Duration	Results
RhesusMonkey	12 M, 12 F	Intravenous Infusion	0,1,5 twice weekly (mg/kg)	4 weeks	well tolerated without incidence of toxicity
RhesusMonkey	20 M, 20 F	Intravenous injection	0, 0.5, 1.5, 4.5 every 4 days (mg/kg)	4 weeks; 8 weeks recovery	well tolerated without incidence of toxicity
RhesusMonkey	16 M, 16 F	Intravenous injection by slow bolus	0, 6, 12, 24 weekly (mg/kg)	39 weeks; 13 weeks recovery	well tolerated without incidence of toxicity
Rabbit	4 M, 5 F	Intravenous Infusion	0.0167%, 0.05% or 0.1%	Single dose, for 4 minutes at 0.5 mL/minute	no toxicity no local irritation
Rabbit	3 M, 3F	Intravenous Infusion (repeat)	0.13% or 0.4%	Single dose, for 4 minutes at 0.5 mL/minute	well tolerated up to 0.4%

Mutagenicity and Reproductive Toxicology

Basiliximab was evaluated for gene mutation test with Salmonella (Ames), chromosomal aberration test with V79 cells (Table 3) and intravenous embryo-fetal development in the cynomolgus monkey (Table 4). The embryo-fetal development study was conducted in cynomolgus monkeys. These studies demonstrated that basiliximab did not show any evidence of mutagenicity or chromosomal aberrations and did not produce maternal toxicity, embryotoxicity or teratogenicity in pregnant cynomolgus monkey (up to 5 mg/kg twice a week).

Table 3: Mutagenicity

Method	Strain	Mode of Administration	Doses	Results
Bacterial Mutagenicity Test	Salmonella typhimurium	in vitro test	8, 40, 200, 1000, 2000 µg/plate 312.5, 625, 1250, 2500, 5000 µg/plate	no mutagenic potential under these test conditions
	Salmonella typhimurium and E. Coli strains	in vitro test	312.5, 625, 1250, 2500, 5000 µg/plate	no mutagenic potential under these test conditions
Chromosome aberration test	Macaca mulatta	in vitro test	2240.7, 4090.9, 5000.0 µg/plate and 2924.0, 3823.6, 5000.0 µg/plate (without S9), 1833.3, 3347.2, 5000.0 µg/plate and 1833.3, 2738.6, 5000.0 µg/plate (with S9)	no clastogenic potential under these test conditions

Table 4: Reproductive Toxicity

Species	Mode of Administration	Doses	Duration	Results
Cynomolgus Monkey	Intravenous bolus injection twice weekly	1 and 5 mg/kg	Every 3-4 days from day 20-48 of gestation	no maternal toxicity , embryotoxicity or tetratogenicity

Formal non-clinical studies on the potential effects of basiliximab on fertility have not been conducted (see Special population: Fertility).

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PART III: CONSUMER INFORMATION

PrSIMULECT®
(basiliximab)

This leaflet is part III of a three-part "Product Monograph" published when SIMULECT® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SIMULECT®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Read all of this leaflet carefully before you are given this medicine.

- **Keep this leaflet. You may need to read it again.**
- **If you have further questions, please ask your doctor, nurse or pharmacist.**

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

What SIMULECT® is:

SIMULECT ® is an immunosuppressant.

What the medication is used for:

SIMULECT® is given to adults who are having a kidney transplant. It helps to prevent rejection of the transplanted kidney during the first 4 to 6 weeks after the transplant operation, which is the time when the body is most likely to try to reject the kidney. You will be given other medicines to help protect your new kidney during this time (for instance, cyclosporine for microemulsion), and you will need to continue taking some of these medicines every day after you leave the hospital. SIMULECT® is given to you only around the time of your transplant operation.

What it does:

SIMULECT® is a type of medicine known as an immunosuppressant. Immunosuppressants reduce the body's response to things that it recognises as "foreign", such as transplanted organs. SIMULECT® works to prevent your immune system from creating the specific cells that attack a transplant and lead to the body rejecting it. SIMULECT® binds to a certain type of white blood cell called a lymphocyte. These specific lymphocytes play a central role in the rejection reaction.

When it should not be used:

You should not be given SIMULECT®:

If you have had an allergic reaction to basiliximab, mouse cell proteins or to any of the other ingredients of SIMULECT® listed below under the heading "**What the medicinal and non-medicinal ingredients are".** Tell your doctor if you suspect you may have had an allergic reaction to any of these ingredients in the past.

Use in older people (aged 65 years and over)

SIMULECT® can be given to elderly people. Although experience with use of SIMULECT® in the elderly is limited, there is no evidence to suggest that any special precautions are needed when elderly people are treated.

Use in Pregnancy and breast-feeding

Tell your doctor before your transplant operation if you are pregnant or think that you may be pregnant. You should not be given SIMULECT® if you are pregnant unless the potential benefits are thought to be greater than the possible risks.

Tell your doctor if you are breast-feeding. basiliximab, the active ingredient of SIMULECT®, may pass into your milk and affect your baby. Do not breast-feed after having SIMULECT® or in the 4 months after the last dose.

Use in women of child-bearing potential

Use adequate contraception to prevent pregnancy and continue its use for an additional 4 months after the last dose of SIMULECT ®.

Use in Pediatric Patients

No adequate and well-controlled studies have been completed in pediatric patients. Safety and efficacy in pediatric patients have not been established and pharmacokinetic data is very limited. No studies have been performed in neonates or children aged less than two years.

Driving and using machines

SIMULECT ® is not expected to affect your ability to drive or use machines.

What the medicinal ingredient is:

The active ingredient of SIMULECT® is called

basiliximab.

What the nonmedicinal ingredients are:

Potassium dihydrogen phosphate, disodium phosphate anhydrous, sodium chloride, sucrose, mannitol, glycine, and sterile water (when prepared for use).

These are standard inactive ingredients that are needed for storing SIMULECT® and for preparing it for intravenous use.

What dosage forms it comes in:

SIMULECT ® is supplied in vials, which each contain 20 mg basiliximab.

WARNINGS AND PRECAUTIONS

Tell your doctor or nurse as soon as possible if you notice any unexpected symptoms while you are being given SIMULECT®, or for 4 months afterwards, even if you do not think that they are connected with the medicine (See Side Effects and What to do about them).

Take special care with SIMULECT®:

- If you have previously received a transplant that failed after only a short time or,
- If you have previously been in the operating theatre for a transplantation that in the end was not performed.

  In these situations, you may have received SIMULECT ®. Your doctor will check this for you and discuss with you the possibility of repeated treatment with SIMULECT ®.
- If you need to receive a vaccine, seek your doctor's advice first.

INTERACTIONS WITH THIS MEDICATION

- SIMULECT® should not change the way other medicines work, nor should other medicines change the way SIMULECT® works.
- Nonetheless, it is important that you tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dose of SIMULECT® given in each infusion or intravenous injection is 20 mg.

Normally, you will be given two doses of ~~Simulect~~ SIMULECT®. The first dose is given just before your transplant operation starts, and the second dose is given 4 days after the operation. A doctor or nurse will give the treatment, since SIMULECT® has to be injected into a vein. It can be either injected directly using a syringe, or given slowly as an infusion lasting 20-30 minutes.

If you have experienced a severe allergic reaction after the first dose of SIMULECT® or if you had complications after your surgery such as graft loss, the second dose of SIMULECT® should not be given to you.

Overdosage

If you are given more SIMULECT® than you should

An overdose of SIMULECT® should not cause immediate side effects, but it may lengthen the time during which the activity of the immune system is reduced. If you are given too much SIMULECT®, your doctor will watch for any consequences of this effect on your immune system and treat them if necessary.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SIMULECT® can have side effects, although not everybody gets them.

Sudden severe allergic reactions have been reported in patients treated with SIMULECT®. If you notice sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, fast heart beat, dizziness and light headedness, shortness of breath, sneezing, wheezing or trouble breathing, a severe decreased urine output, or anything new, such as fever and flu-like symptoms, tell your doctor or nurse immediately.

You will probably be taking several medicines in addition to SIMULECT®. You may get side effects from these or feel unwell after your transplant.

The most commonly reported side effects were constipation, nausea, diarrhoea, weight increase, headache, pain, swelling of hands, ankles or feet, high blood pressure, anaemia, changes in blood chemistry (potassium, cholesterol, phosphate, creatinine), surgical

wound complications, and different kinds of infections.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist right away**		**Stop taking drug and seek immediate emergency medical assistance**
		Only if severe	**In all cases**	
Common	constipation,	√		
	nausea,	√		
	diarrhea,	√		
	weight increase,	√		
	headache,	√		
	pain,	√		
	swelling of hands, ankles or feet,	√		
	high blood pressure,		√	
	anaemia, changes in blood chemistry (potassium, cholesterol, phosphate, creatinine),	√		
	surgical wound complications,	√		
	different kinds of infections,	√		
Uncommon	rash, itching or hives on the skin,	√		
	swelling of the face, lips, tongue or other parts of the body,		√	
	fast heart beat, dizziness and light headedness,	√		
	shortness of breath,		√	
	sneezing,	√		
	wheezing or trouble breathing,		√	
	a severe decreased urine output,		√	
	anything new, such as fever and flu-like symptoms	√		

This is not a complete list of side effects. For any unexpected effects while taking SIMULECT ®, contact your doctor or pharmacist.

HOW TO STORE IT

SIMULECT® should be stored under refrigerated conditions at 2-8 °C. The reconstituted solution can be kept at 2-8 °C for 24 hours or at room temperature for 4 hours, but for bacteriological reasons it should be used as soon as possible.

- Do not use after the expiry date shown on the box.
- Store in the original package.
- Do not use any SIMULECT® pack that is damaged or shows signs of tampering.
- Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- **Fax toll-free to 1-866-678-6789, or**
- **Mail to:** **Canada Vigilance Program**
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.Novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:

1-800-363-8883

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SIMULECT is a registered trademark.

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