NOVARTIS

Drug Regulatory Affairs

SIMULECT®

(basiliximab)

Powder and solvent for solution for infusion or injection

Basic Prescribing Information

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on this BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to characterisation of risks and benefits.

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1 Name of the medicinal product

SIMULECT®

2 Qualitative and quantitative composition

One vial of Simulect® 10 mg contains 10 mg basiliximab.

One vial of Simulect 20 mg contains 20 mg basiliximab.

An ampoule containing 5 mL water for injection is supplied for dissolution.

3 Pharmaceutical form

Glass vials containing 10 mg sterile freeze-dried powder of basiliximab for intravenous infusion or injection after reconstitution with 2.5 mL water for injection.

Glass vials containing 20 mg sterile freeze-dried powder of basiliximab for intravenous infusion or injection after reconstitution with 5 mL water for injection.

4 Clinical particulars

4.1 Therapeutic indications

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* renal transplantation in adult and paediatric patients. It is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

4.2 Posology and method of administration

Use in adults

Recommended dose

The standard 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. Simulect must not be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression. The second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld if severe hypersensitivity reactions to Simulect or graft loss occur (see section 4.4. Special warnings and special precautions for use).

Mode of administration

Reconstituted Simulect can be administered either as an intravenous infusion over 20-30 minutes or as a bolus injection.

For information on reconstituting Simulect, see section 6.6. Instructions for use and handling, and disposal (if appropriate).

Use in children and adolescents (1-17 years)

Recommended dose

In paediatric patients weighing less than 35 kg, the recommended total dose is 20 mg, given in two doses of 10 mg each. In paediatric patients weighing 35 kg or more, the recommended dose is the adult dose, i.e. a total dose of 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. Simulect must not be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression. The second dose should be given 4 days after transplantation. The second dose should be withheld if severe hypersensitivity reactions to Simulect or graft loss occur (see section 4.4. Special warnings and special precautions for use).

Use in the elderly (= 65 years)

There are limited data available on the use of Simulect in the elderly, but there is no evidence that elderly patients require a different dosage from younger adult patients.

Mode of administration

Reconstituted Simulect can be administered either as an intravenous infusion over 20-30 minutes or as a bolus injection.

For information on reconstituting Simulect, see section 6.6. Instructions for use and handling, and disposal (if appropriate).

4.3 Contraindications

Simulect is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation (see section 6.1. List of excipients).

4.4 Special warnings and special precautions for use

Simulect 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.

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 urticaria, pruritus, sneezing, hypotension, tachycardia, dyspnoea, bronchospasm, pulmonary oedema, and respiratory failure. These reactions have been reported rarely for patients receiving Simulect (< 1/1000 patients). If severe hypersensitivity occurs, therapy with Simulect should be permanently discontinued and no further dose should be administered. Caution should be exercised when patients previously given Simulect are re-exposed to a subsequent course of therapy with this medicine.

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 due, for example, to abandoned transplantation or early loss of the graft. Acute hypersensitivity reactions were observed on re-administration of Simulect for a subsequent transplantation in some of these patients.

Patients on immunosuppressive therapy following transplantation are at an increased risk of developing lymphoproliferative disorders (LPDs) and opportunistic infections. While Simulect is an immunosuppressive drug, to date no increase in LPDs or opportunistic infections has been observed in patients treated with Simulect. No differences were found in the incidence of malignancies and LPDs between Simulect and placebo in a pooled analysis of two five-year extension studies (see section 4.8. Undesirables effects).

4.5 Interaction with other medicinal products and other forms of interaction

Because Simulect is an immunoglobulin, no metabolic drug-drug interactions are to be expected.

In addition to ciclosporin for microemulsion, steroids, azathioprine and mycophenolate mofetil, other concomitant medications routinely administered in organ transplantation have been administered in clinical trials without any incremental adverse reactions. These concomitant medications include systemic antiviral, antibacterial and antimycotic medications, analgesics, antihypertensive medications such as beta-blocking agents or calcium channel blockers, and diuretics.

In the original phase 3 studies during the first 3 months post-transplantation, 14% of patients in the Simulect group and 27% of patients in the placebo group had an acute rejection episode treated with antibody therapy (OKT 3 or ATG/ALG), with no increase in adverse events or infections in the Simulect group as compared to placebo.

Three clinical trials have investigated Simulect use in combination with a triple therapy regimen which included either azathioprine or mycophenolate mofetil. The total body clearance of Simulect was reduced by an average 22% when azathioprine was added to a regimen consisting of ciclosporin for microemulsion and corticosteroids. The total body clearance of Simulect was reduced by an average 51% when mycophenolate mofetil was added to a regimen consisting of ciclosporin for microemulsion and corticosteroids. The use of Simulect in a triple therapy regimen including azathioprine or mycophenolate mofetil did not increase adverse events or infections in the Simulect group as compared to placebo (see section 4.8. "Undesirable effects").

Human antimurine antibody (HAMA) responses were reported in a clinical trial of 172 patients treated with Simulect, without predictive value for clinical tolerability. The incidence was 2/138 in patients not exposed to muromonab-CD3 and 4/34 in patients who received muromonab-CD3 concomitantly. The use of Simulect does not preclude subsequent treatment with murine antilymphocyte antibody preparations.

4.6 Use during pregnancy and lactation

No studies have been performed in pregnant or lactating women. Simulect should not be given to pregnant women except in cases where the potential benefit for the mother outweighs the potential risk for the fetus.

Women of child-bearing potential should use adequate contraception to prevent pregnancy and continue its use for an additional 4 months after the last dose of Simulect.

There is no animal or human data available concerning excretion of basiliximab into breast milk. However, since Simulect 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 breastfeed for 4 months following the last dose.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Simulect is not expected to affect the ability to drive or use machines.

4.8 Undesirable effects

Simulect has been tested in four randomised, double-blind, placebo-controlled studies in renal transplant recipients: in two studies patients were concomitantly treated with ciclosporin for microemulsion and corticosteroids (346 and 380 patients), in one study patients were concomitantly treated with ciclosporin for microemulsion, azathioprine and corticosteroids (340 patients), in one study patients were concomitantly treated with ciclosporin for microemulsion, mycophenolate mofetil and corticosteroids (123 patients).

Simulect has also been compared to a polyclonal anti-T-lymphocyte immunoglobulin preparation (ATG/ALG) in one active-controlled study in renal transplant recipients; all patients were concomitantly treated with ciclosporin for microemulsion, mycophenolate mofetil and corticosteroids (135 patients). Safety data in paediatric patients have been obtained from one open-label pharmacokinetic and pharmacodynamic study in renal transplant recipients (41 patients).

Incidence of Adverse Events: 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. In the four placebo-controlled trials, the pattern of adverse events in 590 patients treated with the recommended dose of Simulect was indistinguishable from that in 595 patients treated with placebo. Simulect did not increase the incidence of serious adverse events observed when compared to placebo. The overall incidence of treatment-related adverse events among all patients in the individual studies was not significantly different between the Simulect (7.1% - 40%) and the placebo (7.6% - 39%) treatment groups. In the active-controlled study, fewer Simulect (11.4%) than ATG/ALG (41.5%) patients experienced treatment-related adverse events.

Adult experience: The most commonly reported (> 20%) events following dual or triple therapy in both treatment groups (Simulect vs. Placebo or ATG/ALG) were constipation, urinary tract infection, pain, nausea, peripheral oedema, hypertension, anaemia, headache,

hyperkalaemia, hypercholesterolaemia, postoperative wound complication, weight increase, increase in blood creatinine, hypophosphataemia, diarrhoea, upper respiratory tract infection.

Paediatric experience: The most commonly reported (> 20%) events following dual therapy in both (< 35 kg vs. ≥ 35 kg weight) cohorts were urinary tract infection, hypertrichosis, rhinitis, pyrexia, hypertension, upper respiratory tract infection and viral infection, sepsis and constipation.

Incidence of Malignant Neoplasms: The overall incidence of malignancies among all patients in the individual studies was similar between the Simulect and the comparator treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 0.1% (1/701) of patients in the Simulect group compared with 0.3% (2/595) of placebo and 0% of ATG/ALG patients.

Other malignancies were reported among 1.0% (7/701) of patients in the Simulect group compared with 1.2% (7/595) of placebo and 4.6% (3/65) of ATG/ALG patients.

No differences were found in the incidence of malignancies and LPDs between Simulect 7% (21/295) and placebo 7% (21/291) in a pooled analysis of two five-years extension studies.

Incidence of Infectious Episodes: The overall incidence and profile of infectious episodes among dual and triple therapy patients was similar between the Simulect and the placebo treatment groups (Simulect = 75.9%, Placebo or ATG/ALG = 75.6%). The incidence of serious infections was similar in the Simulect and comparator groups (26.1% vs. 24.8%). The incidence of CMV-infections was similar in both groups (14.6% vs. 17.3%), following either dual or triple therapy regimen.

The incidence and causes of deaths following dual or triple therapy were similar in Simulect (2.9%) and placebo or ATG/ALG groups (2.6%), with the most common cause of deaths in both treatment groups being infections (Simulect = 1.3%, placebo or ATG/ALG = 1.4%). 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%).

Post-marketing adverse reactions

Immune system disorders	
Rare:	Hypersensitivity/anaphylactoid reaction such as rash, urticaria, sneezing, wheezing, bronchospasm, pulmonary oedema, cardiac failure, respiratory failure and capillary leak syndrome.
Very rare:	Cytokine release syndrome.

4.9 Overdose

In clinical studies Simulect 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.

In a 39-week study in rhesus monkeys followed by a 13-week recovery period, the no observable effect level was set at the highest dose level of 24 mg/kg week, leading to exposure values greater than 1,000-times the systemic exposure (AUC) in renal transplant

patients given the recommended clinical dose together with concomitant immunosuppressive therapy.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: specific immunosuppressant; ATC code: L04A A09.

Simulect is a murine/human chimeric monoclonal antibody ($IgG_{1\kappa}$) that is directed against the interleukin-2 receptor alpha-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. Simulect specifically binds with high affinity (K_D-value 0.1 nM) 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 micrograms/mL. As concentrations fall below this level, expression of the CD25 antigen returns to pretherapy values within 1-2 weeks. Simulect does not cause myelosuppression.

Clinical studies

The efficacy of Simulect in prophylaxis of organ rejection in *de novo* renal transplantation has been demonstrated in double-blind placebo-controlled studies. Results from two pivotal 12-month multicentre studies comparing Simulect with placebo show that Simulect, used concomitantly with ciclosporin for microemulsion and corticosteroids, significantly reduces the incidence of acute rejection episodes both within 6 (31% vs. 45%, $p < 0.001$) and 12 (33% vs. 48%, $p < 0.001$) months after transplantation. There was no significant difference between Simulect and placebo treated patients in graft survival after 6 and 12 months (at 12 months 32 graft losses on Simulect (9%) and 37 graft losses on placebo (10%)). The incidence of acute rejection episode was substantially lower in patients receiving Simulect and a triple drug immunosuppressive regimen.

Results from two multicentre double-blind studies comparing Simulect with placebo show that Simulect significantly reduces the incidence of acute rejection episodes within 6 months after transplantation when used concomitantly with ciclosporin for microemulsion, corticosteroids, and either azathioprine (21% vs. 35%, p=0.005 Fisher's exact) or mycophenolate mofetil (15% vs. 27%, p=0.046 K-M). Graft loss occurred in 6% of Simulect and 10% of placebo patients by 6 months. The adverse event profile remained comparable between treatment groups.

One 12-month active-controlled randomised open-label study compared Simulect used concomitantly with early ciclosporin for microemulsion to a polyclonal anti-T-lymphocyte immunoglobulin preparation (ATG/ALG) with delayed ciclosporin for microemulsion. Both groups received corticosteroids and mycophenolate mofetil. Biopsy proven rejection occurred in 19% of Simulect and 20% of ATG/ALG treated patients within 12 months post-transplant.

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.

Simulect was used concomitantly with ciclosporin for microemulsion and steroids in an uncontrolled study in paediatric *de novo* renal transplant recipients. Acute rejection occurred in 14.6% of patients by 6 months post-transplantation, and in 24.3% by 12 months. Overall the adverse event profile was consistent with general clinical experience in the paediatric renal transplantation population and with the profile in the controlled adult transplantation studies.

Of 339 renal transplant patients treated with Simulect and tested for anti-idiotype antibodies, 4 (1.2%) developed an anti-idiotype antibody response. In a clinical trial with 172 patients receiving Simulect, 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 received muromonab-CD3 concomitantly. 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.

5.2 Pharmacokinetic properties

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

Absorption

Peak serum concentration following intravenous infusion of 20 mg over 30 minutes is 7.1 ± 5.1 mg/L. There is a proportional increase in Cmax and AUC with dose up to the highest tested single dose of 60 mg.

Distribution

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. *In vitro* studies using human tissues indicate that Simulect binds only to lymphocytes and macrophages/monocytes.

Metabolism

Not applicable.

Elimination

The terminal half-life is 7.2 ± 3.2 days. Total body clearance is 41 ± 19 mL/h.

Characteristics in patients

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.

Disposition in adult liver transplant patients is characterised 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 micrograms/mL in this population. Hence, the duration of IL-2Ralpha blockade at a given Simulect dose level is similar to that seen in adult renal transplant patients.

Paediatrics

The pharmacokinetics of Simulect were assessed in 39 paediatric *de novo* renal transplantation patients. In infants and children (age 1–11 years, n=25), the steady-state distribution volume was 4.8±2.1 L, half-life was 9.5±4.5 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 (1–11 years), body weight (9–37 kg) or body surface area (0.44–1.20 m^2) in this age group. In adolescents (age 12–16 years, n=14), the steady-state distribution volume was 7.8±5.1 L, half-life was 9.1±3.9 days and clearance was 31±19 mL/h. Disposition in adolescents was similar to that in adult renal transplantation patients. The relationship between serum concentration and receptor saturation was assessed in 13 patients and was similar to that characterised in adult renal transplantation patients.

5.3 Preclinical safety data

No local irritation potential was observed in a sensitive rabbit model intravenously injected with up to 4 mg/mL of basiliximab.

No toxicity was observed when rhesus monkeys received intravenous doses of either up to 5 mg/kg basiliximab twice weekly for 4 weeks followed by an 8-week withdrawal period or 24 mg/kg basiliximab weekly for 39 weeks followed by a 13-week withdrawal period. The highest dose 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.

No maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgous monkeys 100 days *post coitum* following intravenous bolus injections of up to 5 mg/kg basiliximab administered twice weekly during the organogenesis period.

No mutagenic potential was observed *in vitro*.

6 Pharmaceutical particulars

6.1 List of excipients

A vial of Simulect contains, in addition to basiliximab, potassium dihydrogen phosphate, disodium phosphate, anhydrous, sodium chloride, sucrose, mannitol, and glycine. A solvent ampoule contains water for injection. No preservatives are included.

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf-life

Simulect has a shelf-life of 36 months when stored in its original container at 2-8°C. Once reconstituted, it may be stored at 2-8°C for 24 hours or at room temperature for 4 hours.

6.4 Special precautions for storage

Shipping and storage should be under refrigerated conditions (2-8°C).

6.5 Nature and content of container

Simulect powder

Simulect 10 mg

Nature of container: Colourless glass vial (6R), hydrolytic glass type I, according to Ph. Eur., grey fluor-resin coated butyl rubber stopper, held in place by a flanged aluminium band, light blue polypropylene flip-off cap.

Content: 10 mg drug substance.

Simulect 20 mg

Nature of container: Colourless glass vial (6R), hydrolytic glass type I, according to Ph. Eur., grey fluor-resin coated butyl rubber stopper, held in place by a flanged aluminium band, blue polypropylene flip-off cap.

Content: 20 mg drug substance.

Water for injection

Nature of container: Colourless glass ampoule, hydrolytic glass type I, according to Ph. Eur.

Content: 5 mL water for injection.

6.6. Instructions for use and handling, and disposal (if appropriate)

Simulect 10 mg

To prepare the infusion/injection solution, take 2.5 mL water for injection out of the accompanying 5 mL-ampoule aseptically and add this 2.5 mL of water for injection aseptically to the vial containing the Simulect powder. Shake the vial gently to dissolve the powder. Use the reconstituted colourless, clear to opalescent solution as soon as possible, but it may be stored at 2-8°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 25 mL or greater with normal saline or dextrose 5% for infusion.

Simulect 20 mg

To prepare the infusion/injection solution, add 5 mL of water for injection from the accompanying ampoule aseptically to the vial containing the Simulect powder. Shake the vial

gently to dissolve the powder. Use the reconstituted, colourless, clear to opalescent solution as soon as possible, but it may be stored at 2-8°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 NaCl 0.9%

Infusion sets

- Luer Lock™, H. Noolens
- Sterile vented i.v. set, Abbott
- Infusion set, Codan
- Infusomat™, Braun
- Infusionsgerät 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.