NOVARTIS

SIMULECT®

(basiliximab)

20 mg powder for solution for injection/infusion

Professional Information

Document status: Final

Release date: 02 May 2019

SCHEDULING STATUS: S4

PROPRIETARY NAME and dosage form:

SIMULECT® powder for solution for injection / infusion

COMPOSITION:

One vial contains 20 mg basiliximab (as protein).

The excipients include disodium hydrogen phosphate, anhydrous, glycine, mannitol, nitrogen, potassium dihydrogen phosphate, sodium chloride, sucrose.

Contains sugar (sucrose).

PHARMACOLOGICAL CLASSIFICATION:

A 34. Other

PHARMACOLOGICAL ACTION:

SIMULECT is a murine/human chimeric monoclonal antibody (IgG1κ) 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 in 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 death 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.

Pharmacokinetic properties:

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.

Absorption:

Peak serum concentration following intravenous infusion of 20 mg over 30 minutes is 7,1 $\pm$ 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 indicated that SIMULECT binds only to lymphocytes and macrophages/monocytes.

***Elimination*:**

The terminal half life is 7,2 ± 3,2 days. Total body clearance is 41 ± 19 ml/hr.

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/hr. 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 microgram/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.

***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.

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.

CONTRA-INDICATIONS:

Known hypersensitivity to basiliximab or any other component of the formulation.

WARNINGS and SPECIAL PRECAUTIONS:

Patients who are using anti-T-cell antibody infusions, can develop a characteristic set of clinical signs and symptoms that occurs as an immediate complication, more frequently with monoclonal or polyclonal lymphocyte-depleting antibodies. Anti-T-cell antibodies bind to the T-cell receptor, which leads to activation of the T-cells prior to their destruction. The cytokines released by the activated T-cells produce a type of systemic inflammatory response similar to that found in severe infection characterised by hypotension, pyrexia, and rigors. CRS can cause life-threatening pulmonary oedema with potential fatal outcome, especially if the patient is fluid overloaded.

General:

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.

Hypersensitivity reactions:

Severe acute (less than 24 hours) hypersensitivity reactions have been observed both on initial exposure to SIMULECT and on re-exposure to a subsequent course of therapy. These included anaphylactoid type reactions such as rash, urticaria, pruritus, sneezing, wheezing, hypotension,tachycardia, dyspnoea, bronchospasm, pulmonary oedema, 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. Caution should be exercised when patients previously given SIMULECT are re-exposed to a subsequent course of therapy with this medicine.

There is 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.

Neoplasms and infections:

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.

1. 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.

Effect on ability to drive and use machinery:

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.

Excipients:

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not be given SIMULECT.

INTERACTIONS:

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

Concomitant medications routinely administered in organ transplantation:

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 Side effects).

Human antimurine antibody (HAMA):

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.

PREGNANCY AND LACTATION:

Pregnancy

SIMULECT is contraindicated during pregnancy and lactation. Basiliximab has potentially hazardous pharmacological effects with respect to the course of gestation and the suckling neonate exposed to basiliximab in breast milk. This concern is based on basiliximab’s immunosuppressive action.

Women of Childbearing Potential

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

Lactation:

Since SIMULECT is an immunoglobulin G ($IgG_{1\kappa}$) 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 second dose.

DOSAGE AND DIRECTIONS FOR USE:

Use in Adults:

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 Warnings and Special Precautions).

Use in Children and adolescents (1-17 years):

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 Warnings and Special Precautions).

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 to 30 minutes or as a bolus injection.

Instructions for reconstitution:

To prepare the infusion/injection solution, add 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 (see Storage Instructions).

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 is 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

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.

SIDE 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

Adverse events reported in >20 % (very common) of adult patients following dual or triple therapy in both treatment groups (SIMULECT and Placebo or ATG/ALG)

System organ class	**Adverse events reported in** **> 20 % of adult patients following dual or triple therapy in both treatment groups (SIMULECT and Placebo or ATG/ALG)**
Gastrointestinal disorders	Nausea, diarrhoea, constipation
Infections and infestations	Upper respiratory tract infection, urinary tract infection
General disorders and administration site conditions	Pain, peripheral oedema
Vascular disorders	Hypertension
Blood and lymphatic system disorders	Anaemia
Nervous system disorders	Headache
Metabolism and nutrition disorders	Hyperkalaemia, hypophosphataemia, hypercholesterolaemia

Injury, poisoning and procedural complications	Postoperative wound complication
Investigations	Weight increase, increase in blood creatinine

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 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-year 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 such as cardiac failure and myocardial infarction (SIMULECT 5 %, placebo 4 %).

Listing of adverse reactions from post-marketing spontaneous reports

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

System organ class	Adverse reaction
Immune system disorders	hypersensitivity/anaphylactoid reaction such as rash, urticaria, pruritis, sneezing, wheezing, bronchospasm, dyspnoea, pulmonary oedema, cardiac failure, hypotension, tachycardia, respiratory failure, capillary leak syndrome, and cytokine release syndrome (CRS) (see Warnings and Special Precautions).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 1000-times the systemic exposure (AUC) in renal transplant patients given the recommended clinical dose together with concomitant immunosuppressive therapy.

IDENTIFICATION

Glass vial containing a white, sterile freeze-dried powder for intravenous injection or infusion after reconstitution. The reconstituted solution is a clear to opalescent colourless solution.

PRESENTATION

1 glass vial with blue flip-off cap containing 20 mg of drug substance.

STORAGE INSTRUCTIONS:

SIMULECT Vials

Store under refrigerated conditions (2 to 8 °C).

Do not freeze.

SIMULECT which has been reconstituted with sterile water for injection is stable at 2 to 8 °C for 24 hours or at room temperature (25 °C or below) for 4 hours.

Discard the reconstituted solution if not used within the specified time.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

32/30.4/0752

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT

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Manufacturers:

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