ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Simulect 20 mg powder and solvent for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20 mg basiliximab*.

One ml of the reconstituted solution contains 4 mg basiliximab.

* recombinant murine/human chimeric monoclonal antibody directed against the interleukin-2 receptor α-chain (CD25 antigen) produced in a mouse myeloma cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection or infusion

White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years) (see section 4.2). It is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, 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

Simulect should be prescribed only by physicians who are experienced in the use of immunosuppressive therapy following organ transplantation. Simulect should be administered under qualified medical supervision.

Simulect **must not** be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression.

Simulect is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression. It can be used in a ciclosporin for microemulsion- and corticosteroid-based triple immunosuppressive regimen including azathioprine or mycophenolate mofetil.

Posology

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. The second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld in the event of a severe hypersensitivity reaction to Simulect or post-operative complications such as graft loss (see section 4.4).

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. The second dose should be given 4 days after transplantation. The second dose should be withheld in the event of a severe hypersensitivity reaction to Simulect or post-operative complications such as graft loss (see section 4.4).

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.

Method of administration

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Immunosuppressive regimens involving combinations of medications increase the susceptibility to infection, including opportunistic infections, fatal infections and sepsis; the risk increased with total immunosuppressive load.

Simulect **must not** be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression.

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 a severe hypersensitivity reaction occurs, therapy with Simulect must be permanently discontinued and no further dose be administered. Caution should be exercised when patients previously given Simulect are re-exposed to a subsequent course of therapy with this medicinal product. There is accumulating evidence that a subgroup of patients is at an 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 basiliximab are at increased risk of developing lymphoproliferative disorders (LPDs) (such as lymphoma) and opportunistic infections (such as cytomegalovirus [CMV], BK virus). 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 combination of basiliximab (see section 4.8).

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. The use of live attenuated vaccines should therefore be avoided in patients treated with Simulect. Inactivated vaccines may be administered to immunosuppressed patients; however, response to the vaccine may depend on the degree of the immunosuppression, therefore vaccination during treatment with Simulect may be less effective.

Use in heart transplantation

The efficacy and safety of Simulect for the prophylaxis of acute rejection in recipients of solid organ allografts other than renal have not been demonstrated. In several small clinical trials in heart transplant recipients, serious cardiac adverse events such as cardiac arrest (2.2%), atrial flutter (1.9%) and palpitations (1.4%) have been reported more frequently with Simulect than with other induction agents.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

This medicinal product contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially ‘potassium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Because basiliximab 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.

Human antimurine antibody (HAMA) responses were reported in a clinical trial of 172 patients treated with basiliximab, without predictive value for clinical tolerability. The incidence was 2/138 in patients not exposed to muromonab-CD3 (OKT3) and 4/34 in patients who received muromonab-CD3 concomitantly. The use of basiliximab does not preclude subsequent treatment with murine antilymphocyte antibody preparations.

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

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

4.6 Fertility, pregnancy and lactation

Simulect is contraindicated in pregnancy and lactation (see section 4.3). Basiliximab has potentially hazardous immunosuppressive effects with respect to the course of gestation and the suckling neonate exposed to basiliximab in breast milk. Women of childbearing potential must use effective contraception during and up to 16 weeks after treatment.

There is no animal or human data available concerning excretion of basiliximab into breast milk. However, based on the IgG_1 nature of basiliximab, excretion into milk should be expected. Breast-feeding must therefore be avoided.

4.7 Effects on ability to drive and use machines

Simulect has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Basiliximab has been tested in four randomised, double-blind, placebo-controlled studies in renal transplant recipients as an induction agent in combination with the following immunosuppressive regimens: ciclosporin for microemulsion and corticosteroids in two studies (346 and 380 patients), ciclosporin for microemulsion, azathioprine and corticosteroids in one study (340 patients), and ciclosporin for microemulsion, mycophenolate mofetil and corticosteroids in another study (123 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: In the above four placebo-controlled trials, the pattern of adverse events in 590 patients treated with the recommended dose of basiliximab was comparable to that observed in 595 patients treated with placebo. The overall incidence of treatment-related adverse events among all patients in the individual studies was not significantly different between the basiliximab (7.1% - 40%) and the placebo (7.6% - 39%) treatment groups.

Adult patients

The most commonly reported (> 20%) events following dual or triple therapy in both treatment groups (basiliximab vs. placebo) 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 and upper respiratory tract infection.

Paediatric population

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, 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 basiliximab and the comparator treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 0.1% (1/701) of patients in the basiliximab group compared with 0.3% (2/595) of patients receiving placebo, both in combination with dual and triple immunosuppressive therapy. Other malignancies were reported among 1.0% (7/701) of patients in the basiliximab group compared with 1.2% (7/595) of placebo patients. In a pooled analysis of two five-year extension studies, the incidence of LPDs and cancer was found to be equal with basiliximab 7% (21/295) and placebo 7% (21/291) (see section 4.4).

Incidence of infectious episodes: The overall incidence and profile of viral, bacterial and fungal infections among patients treated with basiliximab or placebo in combination with dual and triple immunosuppressive therapy was comparable between the groups. The overall incidence of infections was 75.9% in the basiliximab group and 75.6% in the placebo group and the incidence of serious infections was 26.1% and 24.8%, respectively. The incidence of CMV infections was similar in both groups (14.6% vs. 17.3%), following either dual or triple therapy regimen (see section 4.4).

The incidence and causes of deaths following dual or triple therapy were similar in basiliximab (2.9%) and placebo groups (2.6%), with the most common cause of deaths in both treatment groups being infections (basiliximab = 1.3%, placebo = 1.4%). In a pooled analysis of two five-year extension studies the incidence and cause of death remained similar in both treatment groups, (basiliximab 15%, placebo 11%), the primary cause of death being cardiac-related disorders such as cardiac failure and myocardial infarction (basiliximab 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 class. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Immune system disorders
Hypersensitivity/anaphylactoid reactions such as rash, urticaria, pruritus, sneezing, wheezing, bronchospasm, dyspnoea, pulmonary oedema, cardiac failure, hypotension, tachycardia, respiratory failure, capillary leak syndrome (see section 4.4). Cytokine release syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies 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 acute undesirable effects.

For information on preclinical toxicology see section 5.3.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukin inhibitors, ATC code: L04AC02.

Mechanism of action

Basiliximab is a murine/human chimeric monoclonal antibody ($IgG_{1\kappa}$) that is directed against the interleukin-2 receptor α-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. Basiliximab 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 (IL-2R) and thereby prevents binding of interleukin-2, a critical signal for T-cell proliferation in the cellular immune response involved in allograft rejection. Complete and consistent blocking of the interleukin-2 receptor is maintained as long as serum basiliximab levels exceed 0.2 μg/ml (usually up to 4–6 weeks after administration). As concentrations fall below this level, expression of the CD25 antigen returns to pretherapy values within 1–2 weeks. Basiliximab does not cause myelosuppression.

Clinical efficacy and safety

The efficacy of basiliximab 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 (722 patients in total) comparing basiliximab with placebo show that basiliximab, 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 basiliximab and placebo-treated patients in graft survival after 6 and 12 months (at 12 months 32 graft losses on basiliximab (9%) and 37 graft losses on placebo (10%)). The incidence of acute rejection episode was substantially lower in patients receiving basiliximab and a triple drug immunosuppressive regimen.

Results from two multicentre double-blind studies comparing basiliximab with placebo (463 patients in total) show that basiliximab 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%) or mycophenolate mofetil (15% vs. 27%). Graft loss occurred in 6% of basiliximab-treated and 10% of placebo-treated patients by 6 months. The adverse event profile remained comparable between treatment groups.

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 basiliximab 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 basiliximab.

Paediatric population
The efficacy and safety of basiliximab were evaluated in two paediatric studies.

Basiliximab was used concomitantly with ciclosporin for microemulsion and steroids in an uncontrolled study in 41 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.

A 12-month, randomised, placebo-controlled, double-blind, multicentre study investigated basiliximab in combination with ciclosporin for microemulsion, mycophenolate mofetil and steroids in paediatric renal allograft recipients. The primary objective of the study was to demonstrate superiority of this combination versus treatment with ciclosporin for microemulsion, mycophenolate mofetil and steroids in the prevention of acute rejections. Of the 202 patients, 104 were randomised to basiliximab and 98 to placebo. The primary efficacy endpoint, time to first biopsy-proven acute rejection (BPAR) episode or treatment failure defined as graft loss, death or presumptive rejection within the first 6 months post transplantation, occurred in 16.7% of basiliximab-treated patients and 21.7% of placebo-treated patients. When borderline rejections were included in the primary efficacy endpoint, the rates were 26.0% and 23.9% respectively, with no statistically significant difference between the basiliximab- and placebo-treated groups (HR: 1.04, 90% CI: [0.64; 1.68]). The rates of BPAR were 9.4% in the basiliximab group and 17.4% in the placebo group (HR: 0.50, 90% CI: [0.25; 0.99]). When borderline rejections were included, the rates were 20.8% and 19.6% respectively (HR: 1.01, 90% CI: [0.59; 1.72]). The overall safety profiles were similar in both groups. The incidence rates of adverse events and the pattern of adverse events were comparable between the two treatment groups and to be expected for the treatment regimens and the underlying diseases.

Immunogenicity
Of 339 renal transplant patients treated with basiliximab and tested for anti-idiotype antibodies, 4 (1.2%) developed an anti-idiotype antibody response. In a clinical trial with 172 patients receiving basiliximab, the incidence of human antimurine antibody (HAMA) in renal transplantation patients treated with basiliximab 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 basiliximab suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.

5.2 Pharmacokinetic properties

Adults

Single-dose and multiple-dose pharmacokinetic studies have been conducted in adult patients undergoing kidney transplantation. Cumulative doses ranged from 20 mg up to 60 mg. 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 C_{max} and AUC from 20 mg to 60 mg, the range of single-dose administrations tested. The volume of distribution at steady state was 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 basiliximab binds only to activated lymphocytes and macrophages/monocytes. The terminal half-life was 7.2±3.2 days. Total body clearance was 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, gender, or race.

Paediatric population

The pharmacokinetics of basiliximab 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 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. In the 39-week study, the highest dose resulted in approximately 1,000 times the systemic exposure (AUC) observed in patients given the recommended clinical dose together with concomitant immunosuppressive therapy.

No maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgous monkeys following 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

Powder

Potassium dihydrogen phosphate
Disodium phosphate, anhydrous
Sodium chloride
Sucrose
Mannitol (E421)
Glycine

Solvent

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder: 3 years

Chemical and physical stability of the reconstituted solution is demonstrated for 24 hours at 2°C - 8°C or for 4 hours at room temperature (see section 6.6).

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C).

6.5 Nature and contents of container

Simulect powder

Colourless type I glass vial, grey fluor-resin coated butyl rubber stopper, held in place by a flanged aluminium band, blue polypropylene flip-off cap, containing 20 mg basiliximab as powder for solution for injection or infusion.

Solvent

Colourless glass ampoule, type I glass, containing 5 ml water for injections.

Simulect is also available in vials with 10 mg basiliximab.

6.6 Special precautions for disposal and other handling

Reconstitution

To prepare the solution for infusion or injection, add 5 ml of water for injections from the accompanying ampoule aseptically to the vial containing the Simulect powder. Shake the vial gently to dissolve the powder, avoiding foaming. It is recommended that after reconstitution the colourless, clear to opalescent solution should be used immediately. Reconstituted products should be inspected visually for particulate matter prior to administration. Do not use if foreign particles are present. After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or for 4 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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 50 mg/ml (5%) for infusion.

Since no data are available on the compatibility of Simulect with other medicinal products intended for intravenous administration, Simulect should not be mixed with other medicinal products and should always be given through a separate infusion line.

Compatibility with a number of infusion sets has been verified.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/084/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 October 1998
Date of latest renewal: 09 October 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Simulect 10 mg powder and solvent for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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4.1 Therapeutic indications

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years) (see section 4.2). It is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, 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

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Simulect **must not** be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression.

Simulect is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression. It can be used in a ciclosporin for microemulsion- and corticosteroid-based triple immunosuppressive regimen including azathioprine or mycophenolate mofetil.

Posology

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. The second dose should be given 4 days after transplantation. The second dose should be withheld in the event of a severe hypersensitivity reaction to Simulect or post-operative complications such as graft loss (see section 4.4).

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. The second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld in the event of a severe hypersensitivity reaction to Simulect or post-operative complications such as graft loss (see section 4.4).

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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 a severe hypersensitivity reaction occurs, therapy with Simulect must be permanently discontinued and no further dose be administered. Caution should be exercised when patients previously given Simulect are re-exposed to a subsequent course of therapy with this medicinal product. There is accumulating evidence that a subgroup of patients is at an 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.

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Simulect is contraindicated in pregnancy and lactation (see section 4.3). Basiliximab has potentially hazardous immunosuppressive effects with respect to the course of gestation and the suckling neonate exposed to basiliximab in breast milk. Women of childbearing potential must use effective contraception during and up to 16 weeks after treatment.

There is no animal or human data available concerning excretion of basiliximab into breast milk. However, based on the IgG_1 nature of basiliximab, excretion into milk should be expected. Breast-feeding must therefore be avoided.

4.7 Effects on ability to drive and use machines

Simulect has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Basiliximab has been tested in four randomised, double-blind, placebo-controlled studies in renal transplant recipients as an induction agent in combination with the following immunosuppressive regimens: ciclosporin for microemulsion and corticosteroids in two studies (346 and 380 patients), ciclosporin for microemulsion, azathioprine and corticosteroids in one study (340 patients), and ciclosporin for microemulsion, mycophenolate mofetil and corticosteroids in another study (123 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: In the above four placebo-controlled trials, the pattern of adverse events in 590 patients treated with the recommended dose of basiliximab was comparable to that observed in 595 patients treated with placebo. The overall incidence of treatment-related adverse events among all patients in the individual studies was not significantly different between the basiliximab (7.1% - 40%) and the placebo (7.6% - 39%) treatment groups.

Adult patients

The most commonly reported (> 20%) events following dual or triple therapy in both treatment groups (basiliximab vs. placebo) 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 and upper respiratory tract infection.

Paediatric population

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, 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 basiliximab and the comparator treatment groups. Overall, lymphoma/lymphoproliferative disease occurred in 0.1% (1/701) of patients in the basiliximab group compared with 0.3% (2/595) of patients receiving placebo, both in combination with dual and triple immunosuppressive therapy. Other malignancies were reported among 1.0% (7/701) of patients in the basiliximab group compared with 1.2% (7/595) of placebo patients. In a pooled analysis of two five-year extension studies, the incidence of LPDs and cancer was found to be equal with basiliximab 7% (21/295) and placebo 7% (21/291) (see section 4.4).

Incidence of infectious episodes: The overall incidence and profile of viral, bacterial and fungal infections among patients treated with basiliximab or placebo in combination with dual and triple immunosuppressive therapy was comparable between the groups. The overall incidence of infections was 75.9% in the basiliximab group and 75.6% in the placebo group and the incidence of serious infections was 26.1% and 24.8%, respectively. The incidence of CMV infections was similar in both groups (14.6% vs. 17.3%), following either dual or triple therapy regimen (see section 4.4).

The incidence and causes of deaths following dual or triple therapy were similar in basiliximab (2.9%) and placebo groups (2.6%), with the most common cause of deaths in both treatment groups being infections (basiliximab = 1.3%, placebo = 1.4%). In a pooled analysis of two five-year extension studies the incidence and cause of death remained similar in both treatment groups, (basiliximab 15%, placebo 11%), the primary cause of death being cardiac-related disorders such as cardiac failure and myocardial infarction (basiliximab 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 class. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Immune system disorders
Hypersensitivity/anaphylactoid reactions such as rash, urticaria, pruritus, sneezing, wheezing, bronchospasm, dyspnoea, pulmonary oedema, cardiac failure, hypotension, tachycardia, respiratory failure, capillary leak syndrome (see section 4.4). Cytokine release syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies 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 acute undesirable effects.

For information on preclinical toxicology see section 5.3.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukin inhibitors, ATC code: L04AC02.

Mechanism of action

Basiliximab is a murine/human chimeric monoclonal antibody ($IgG_{1\kappa}$) that is directed against the interleukin-2 receptor α-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. Basiliximab 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 (IL-2R) and thereby prevents binding of interleukin-2, a critical signal for T-cell proliferation in the cellular immune response involved in allograft rejection. Complete and consistent blocking of the interleukin-2 receptor is maintained as long as serum basiliximab levels exceed 0.2 μg/ml (usually up to 4–6 weeks after administration). As concentrations fall below this level, expression of the CD25 antigen returns to pretherapy values within 1–2 weeks. Basiliximab does not cause myelosuppression.

Clinical efficacy and safety

The efficacy of basiliximab 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 (722 patients in total) comparing basiliximab with placebo show that basiliximab, 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 basiliximab and placebo-treated patients in graft survival after 6 and 12 months (at 12 months 32 graft losses on basiliximab (9%) and 37 graft losses on placebo (10%)). The incidence of acute rejection episode was substantially lower in patients receiving basiliximab and a triple drug immunosuppressive regimen.

Results from two multicentre double-blind studies comparing basiliximab with placebo (463 patients in total) show that basiliximab 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%) or mycophenolate mofetil (15% vs. 27%). Graft loss occurred in 6% of basiliximab-treated and 10% of placebo-treated patients by 6 months. The adverse event profile remained comparable between treatment groups.

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 basiliximab 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 basiliximab.

Paediatric population
The efficacy and safety of basiliximab were evaluated in two paediatric studies.

Basiliximab was used concomitantly with ciclosporin for microemulsion and steroids in an uncontrolled study in 41 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.

A 12-month, randomised, placebo-controlled, double-blind, multicentre study investigated basiliximab in combination with ciclosporin for microemulsion, mycophenolate mofetil and steroids in paediatric renal allograft recipients. The primary objective of the study was to demonstrate superiority of this combination versus treatment with ciclosporin for microemulsion, mycophenolate mofetil and steroids in the prevention of acute rejections. Of the 202 patients, 104 were randomised to basiliximab and 98 to placebo. The primary efficacy endpoint, time to first biopsy-proven acute rejection (BPAR) episode or treatment failure defined as graft loss, death or presumptive rejection within the first 6 months post transplantation, occurred in 16.7% of basiliximab-treated patients and 21.7% of placebo-treated patients. When borderline rejections were included in the primary efficacy endpoint, the rates were 26.0% and 23.9% respectively, with no statistically significant difference between the basiliximab- and placebo-treated groups (HR: 1.04, 90% CI: [0.64; 1.68]). The rates of BPAR were 9.4% in the basiliximab group and 17.4% in the placebo group (HR: 0.50, 90% CI: [0.25; 0.99]). When borderline rejections were included, the rates were 20.8% and 19.6%, respectively (HR: 1.01, 90% CI: [0.59; 1.72]). The overall safety profiles were similar in both groups. The incidence rates of adverse events and the pattern of adverse events were comparable between the two treatment groups and to be expected for the treatment regimens and the underlying diseases.

Immunogenicity
Of 339 renal transplant patients treated with basiliximab and tested for anti-idiotype antibodies, 4 (1.2%) developed an anti-idiotype antibody response. In a clinical trial with 172 patients receiving basiliximab, the incidence of human antimurine antibody (HAMA) in renal transplantation patients treated with basiliximab 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 basiliximab suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.

5.2 Pharmacokinetic properties

Adults

Single-dose and multiple-dose pharmacokinetic studies have been conducted in adult patients undergoing kidney transplantation. Cumulative doses ranged from 20 mg up to 60 mg. 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 C_{max} and AUC from 20 mg to 60 mg, the range of single-dose administrations tested. The volume of distribution at steady state was 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 basiliximab binds only to activated lymphocytes and macrophages/monocytes. The terminal half-life was 7.2±3.2 days. Total body clearance was 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, gender, or race.

Paediatric population

The pharmacokinetics of basiliximab 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 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. In the 39-week study, the highest dose resulted in approximately 1,000 times the systemic exposure (AUC) observed in patients given the recommended clinical dose together with concomitant immunosuppressive therapy.

No maternal toxicity, embryotoxicity, or teratogenicity was observed in cynomolgous monkeys following 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

Powder

Potassium dihydrogen phosphate
Disodium phosphate, anhydrous
Sodium chloride
Sucrose
Mannitol (E421)
Glycine

Solvent

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder: 3 years

Chemical and physical stability of the reconstituted solution is demonstrated for 24 hours at 2°C - 8°C or for 4 hours at room temperature (see section 6.6).

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C).

6.5 Nature and contents of container

Simulect powder

Colourless type I glass vial, grey fluor-resin coated butyl rubber stopper, held in place by a flanged aluminium band, blue polypropylene flip-off cap, containing 10 mg basiliximab as powder for solution for injection or infusion.

Solvent

Colourless glass ampoule, type I glass, containing 5 ml water for injections.

Simulect is also available in vials with 20 mg basiliximab.

6.6 Special precautions for disposal and other handling

Reconstitution

To prepare the solution for infusion or injection, take 2.5 ml water for injections out of the accompanying 5 ml ampoule aseptically and add this 2.5 ml of water for injections aseptically to the vial containing the Simulect powder. Shake the vial gently to dissolve the powder, avoiding foaming. It is recommended that after reconstitution the colourless, clear to opalescent solution should be used immediately. Reconstituted products should be inspected visually for particulate matter prior to administration. Do not use if foreign particles are present. After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or for 4 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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 50 mg/ml (5%) for infusion.

Since no data are available on the compatibility of Simulect with other medicinal products intended for intravenous administration, Simulect should not be mixed with other medicinal products and should always be given through a separate infusion line.

Compatibility with a number of infusion sets has been verified.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/084/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 October 1998
Date of latest renewal: 09 October 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8 rue de l'Industrie
68330 Huningue
France

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Ronda de Santa Maria, 158
08210 Barberà del Vallès, Barcelona
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR 1 VIAL AND 1 AMPOULE AS UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Simulect 20 mg powder and solvent for solution for injection or infusion
basiliximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 20 mg of basiliximab.

3. LIST OF EXCIPIENTS

It also contains potassium dihydrogen phosphate; disodium phosphate, anhydrous; sodium chloride; sucrose; mannitol (E421); glycine.
The solvent ampoule contains 5 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection or infusion

1 vial with 20 mg powder
1 ampoule with 5 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after reconstitution (chemically and physically stable at 2°C - 8°C for 24 hours or at room temperature for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/084/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Please open here.

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simulect 20 mg powder for solution for injection/infusion
basiliximab
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Store in a refrigerator.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Simulect
Water for injections

2. METHOD OF ADMINISTRATION

See package leaflet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR 1 VIAL AND 1 AMPOULE AS UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Simulect 10 mg powder and solvent for solution for injection or infusion
basiliximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 10 mg of basiliximab.

3. LIST OF EXCIPIENTS

It also contains potassium dihydrogen phosphate; disodium phosphate, anhydrous; sodium chloride; sucrose; mannitol (E421); glycine.
The solvent ampoule contains 5 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection or infusion

1 vial with 10 mg powder
1 ampoule with 5 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after reconstitution (chemically and physically stable at 2°C - 8°C for 24 hours or at room temperature for 4 hours).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/084/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Please open here.

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Simulect 10 mg powder for solution for injection/infusion
basiliximab
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Store in a refrigerator.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Simulect
Water for injections

2. METHOD OF ADMINISTRATION

See package leaflet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Simulect 20 mg powder and solvent for solution for injection or infusion

basiliximab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Simulect is and what it is used for

Simulect belongs to a group of medicines called immunosuppressants. It is given in hospital to adults, adolescents and children who are having a kidney transplant. Immunosuppressants reduce the body's response to anything that it sees as "foreign" – which includes transplanted organs. The body's immune system thinks a transplanted organ is a foreign body and will try to reject it. Simulect works by stopping the immune cells that attack transplanted organs.

You will only be given two doses of Simulect. These will be given in hospital, around the time of your transplant operation. Simulect is given to stop your body from rejecting the new organ during the first 4 to 6 weeks after the transplant operation, when rejection is most likely. You will be given other medicines to help protect your new kidney during this time, such as ciclosporin and corticosteroids and after you leave hospital.

2. What you need to know before you are given Simulect

Follow your doctor's instructions carefully. If you are unsure about anything, ask your doctor, nurse or pharmacist.

You must not be given Simulect
- if you are allergic (hypersensitive) to basiliximab or any of the other ingredients of Simulect listed in section 6 under "What Simulect contains". Tell your doctor if you suspect you may have had an allergic reaction to any of these ingredients in the past.
- if you are pregnant or breast-feeding.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before you are given 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 this situation, 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 have a vaccination, seek your doctor's advice first.

Other medicines and Simulect
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

Older patients (aged 65 years and over)
Simulect can be given to older patients, but the information available is limited. Your doctor may discuss this with you before you are given Simulect.

Children and adolescents (aged 1 to 17 years)
Simulect can be given to children and adolescents. The dose for children who weigh less than 35 kg will be smaller than the dose usually given to adults.

Pregnancy and breast-feeding
It is very important to tell your doctor before your transplant if you are pregnant or you think that you may be pregnant. You must not be given Simulect if you are pregnant. You must use adequate contraception to prevent pregnancy during treatment and up to 4 months after receiving the last dose of Simulect. If you become pregnant during this time, despite the use of contraceptive measures, you should tell your doctor immediately.

You should also tell your doctor if you are breast-feeding. Simulect may harm your baby. You must not breast-feed after being given Simulect or up to 4 months after the second dose.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
There is no evidence to indicate that Simulect has an effect on your ability to drive a car or use machines.

Simulect contains sodium and potassium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially 'potassium-free'.

3. How Simulect is given

You will only be given Simulect if you are receiving a new kidney. Simulect is given twice, in hospital, either slowly through a needle in your vein as an infusion lasting 20–30 minutes or as an intravenous injection using a syringe.

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

The first dose is given just before the transplant operation, and the second dose 4 days after the operation.

Usual dose for adults
The usual dose for adults is 20 mg in each infusion or injection.

Usual dose for children and adolescents (aged 1 to 17 years)
- For children and adolescents who weigh 35 kg or more, the dose of Simulect given in each infusion or injection is 20 mg.
- For children and adolescents who weigh less than 35 kg, the dose of Simulect given in each infusion or injection is 10 mg.

If you are given too much Simulect
An overdose of Simulect is not likely to cause side effects straight away, but it may weaken your immune system for longer. Your doctor will watch out for any effects on your immune system and treat them if necessary.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse as soon as possible if you get any unexpected symptoms while you are being given Simulect, or during the 8 weeks afterwards, even if you do not think that they are related to the medicine.

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, light headedness, shortness of breath, sneezing, wheezing or trouble breathing, severely decreased urine output, or fever and flu-like symptoms, tell your doctor or nurse immediately.

In adults, 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 (e.g. potassium, cholesterol, phosphate, creatinine), surgical wound complications, and various kinds of infections.

In children, the most commonly reported side effects were constipation, excessive growth of normal hair, runny or blocked nose, fever, high blood pressure, and various kinds of infections.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Simulect

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

6. Contents of the pack and other information

What Simulect contains
- The active substance is basiliximab. Each vial contains 20 mg of basiliximab.
- The other ingredients are potassium dihydrogen phosphate; disodium phosphate, anhydrous; sodium chloride; sucrose; mannitol (E421); glycine.

What Simulect looks like and contents of the pack
Simulect comes as a white powder in a colourless glass vial containing 20 mg of basiliximab. It is supplied in a pack with a colourless glass ampoule containing 5 ml sterile water for injections. This solvent is used to dissolve the powder before it is given to you.

Simulect is also available in vials with 10 mg basiliximab.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

INSTRUCTIONS FOR RECONSTITUTION AND ADMINISTRATION

The following information is intended for healthcare professionals only:

Simulect must not be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression.

To prepare the solution for infusion or injection, add 5 ml water for injections from the accompanying ampoule to the vial containing the Simulect powder, using aseptic technique. Shake the vial gently to dissolve the powder, avoiding foaming. It is recommended that after reconstitution the colourless, clear to opalescent solution should be used immediately. Reconstituted products should be inspected visually for particulate matter prior to administration. Do not use if foreign particles are present. After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or for 4 hours at room temperature. Discard the reconstituted solution if not used within that time. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Reconstituted Simulect is administered as an intravenous infusion over 20 to 30 minutes or as a bolus injection. The reconstituted solution is isotonic. For infusion, the reconstituted solution should be diluted to a volume of 50 ml or greater with normal saline or dextrose 50 mg/ml (5%). The first dose should be given within 2 hours before transplantation surgery, and the second dose 4 days after transplantation. **The second dose should not be given if severe hypersensitivity reactions to Simulect or graft loss occur.**

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

Do not use after the expiry date stated on the pack.

Store in a refrigerator (2°C - 8°C).

Any unused product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Simulect 10 mg powder and solvent for solution for injection or infusion

basiliximab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Simulect is and what it is used for

Simulect belongs to a group of medicines called immunosuppressants. It is given in hospital to adults, adolescents and children who are having a kidney transplant. Immunosuppressants reduce the body's response to anything that it sees as "foreign" – which includes transplanted organs. The body's immune system thinks a transplanted organ is a foreign body and will try to reject it. Simulect works by stopping the immune cells that attack transplanted organs.

You will only be given two doses of Simulect. These will be given in hospital, around the time of your transplant operation. Simulect is given to stop your body from rejecting the new organ during the first 4 to 6 weeks after the transplant operation, when rejection is most likely. You will be given other medicines to help protect your new kidney during this time, such as ciclosporin and corticosteroids and after you leave hospital.

2. What you need to know before you are given Simulect

Follow your doctor's instructions carefully. If you are unsure about anything, ask your doctor, nurse or pharmacist.

You must not be given Simulect
- if you are allergic (hypersensitive) to basiliximab or any of the other ingredients of Simulect listed in section 6 under "What Simulect contains". Tell your doctor if you suspect you may have had an allergic reaction to any of these ingredients in the past.
- if you are pregnant or breast-feeding.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before you are given 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 this situation, 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 have a vaccination, seek your doctor's advice first.

Other medicines and Simulect
Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines.

Older patients (aged 65 years and over)
Simulect can be given to older patients, but the information available is limited. Your doctor may discuss this with you before you are given Simulect.

Children and adolescents (aged 1 to 17 years)
Simulect can be given to children and adolescents. The dose for children who weigh less than 35 kg will be smaller than the dose usually given to adults.

Pregnancy and breast-feeding
It is very important to tell your doctor before your transplant if you are pregnant or you think that you may be pregnant. You must not be given Simulect if you are pregnant. You must use adequate contraception to prevent pregnancy during treatment and up to 4 months after receiving the last dose of Simulect. If you become pregnant during this time, despite the use of contraceptive measures, you should tell your doctor immediately.

You should also tell your doctor if you are breast-feeding. Simulect may harm your baby. You must not breast-feed after being given Simulect or up to 4 months after the second dose.

Ask your doctor, nurse or pharmacist for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
There is no evidence to indicate that Simulect has an effect on your ability to drive a car or use machines.

Simulect contains sodium and potassium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially 'potassium-free'.

3. How Simulect is given

You will only be given Simulect if you are receiving a new kidney. Simulect is given twice, in hospital, either slowly through a needle in your vein as an infusion lasting 20–30 minutes or as an intravenous injection using a syringe.

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

The first dose is given just before the transplant operation, and the second dose 4 days after the operation.

Usual dose for children and adolescents (aged 1 to 17 years)
- For children and adolescents who weigh less than 35 kg, the dose of Simulect given in each infusion or injection is 10 mg.
- For children and adolescents who weigh 35 kg or more, the dose of Simulect given in each infusion or injection is 20 mg.

Usual dose for adults
The usual dose for adults is 20 mg in each infusion or injection.

If you are given too much Simulect
An overdose of Simulect is not likely to cause side effects straight away, but it may weaken your immune system for longer. Your doctor will watch out for any effects on your immune system and treat them if necessary.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse as soon as possible if you get any unexpected symptoms while you are being given Simulect, or during the 8 weeks afterwards, even if you do not think that they are related to the medicine.

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, light headedness, shortness of breath, sneezing, wheezing or trouble breathing, severely decreased urine output, or fever and flu-like symptoms, tell your doctor or nurse immediately.

In children, the most commonly reported side effects were constipation, excessive growth of normal hair, runny or blocked nose, fever, high blood pressure, and various kinds of infections.

In adults, 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 (e.g. potassium, cholesterol, phosphate, creatinine), surgical wound complications, and various kinds of infections.

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Simulect

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

6. Contents of the pack and other information

What Simulect contains
- The active substance is basiliximab. Each vial contains 10 mg of basiliximab.
- The other ingredients are potassium dihydrogen phosphate; disodium phosphate, anhydrous; sodium chloride; sucrose; mannitol (E421); glycine.

What Simulect looks like and contents of the pack
Simulect comes as a white powder in a colourless glass vial containing 10 mg of basiliximab. It is supplied in a pack with a colourless glass ampoule containing 5 ml sterile water for injections. 2.5 ml of the sterile water is used to dissolve the powder before it is given to you.

Simulect is also available in vials with 20 mg basiliximab.

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