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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

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8 MARKETING AUTHORISATION NUMBER(S)

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