מאי 2011

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Simulect 20 mg powder for solution for injection
סימולקט 20 מ"ג

התכשיר שבנדון רשום בישראל להתוויה הבאה:

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* renal transplantation in combination with cyclosporin and corticosteroid-based immunosuppression.

המרכיב הפעיל: Basiliximab 20 mg

במאי 2011 עודכן העלון לרופא של התכשיר כדלקמן (קו תחתי - תוספת טקסט, קו חוצה – מחיקת טקסט):

**1 Trade ~~N~~name ~~of the medicinal product~~**

SIMULECT®

**2 ~~Q~~ualitative ~~D~~description and ~~quantitative~~ composition**

One vial of Simulect 20 mg contains 20 mg basiliximab.

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

**~~3~~ Pharmaceutical form**

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

**Active substance**

Basiliximab.

***Excipients***

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

**~~4~~ ~~Clinical particulars~~**

***~~4.1~~3 ~~Therapeutic i~~Indications***

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* renal transplantation in combination with cyclosporin and corticosteroid-based immunosuppression.

***~~4.2~~ ~~Posology and method of~~Dosage and administration***

**Dosage**

**General target population:**

**~~Use in a~~Adults**

**~~Recommended dose~~**

The standard total dose is 40 mg, given in two doses of 20 mg each. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. Simulect must not be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression~~.~~. The second 20 mg dose should be given 4 days after transplantation. The second dose should be withheld if severe hypersensitivity reactions to Simulect or graft loss occur (see section ~~4.4.~~6 ~~Special w~~Warnings and ~~special~~ precautions ~~for use~~).

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~~**Mode of administration**~~

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

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

**Special populations:**

**~~Use in children and adolescents~~Paediatric patients (1-17 years)**

**~~Recommended dose~~**

In paediatric patients weighing less than 35 kg, the recommended total dose is 20 mg, given in two doses of 10 mg each. In paediatric patients weighing 35 kg or more, the recommended dose is the adult dose, i.e. a total dose of 40 mg, given in two doses of 20 mg each. The first dose should be given within 2 hours prior to transplantation surgery. Simulect must not be administered unless it is absolutely certain that the patient will receive the graft and concomitant immunosuppression. The second dose should be given 4 days after transplantation. The second dose should be withheld if severe hypersensitivity reactions to Simulect or graft loss occur (see section ~~4.4.~~6 ~~Special w~~Warnings and ~~special~~ precautions ~~for use~~).

**Use in the elderly Geriatric patients (≥ 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.

**Methode of administration**

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

For information on reconstituting Simulect, see section 14 Pharmaceutical information ~~6.6. Instructions for use and handling, and disposal (if appropriate~~).

***~~4.3~~5 Contraindications***

Simulect is contraindicated in patients with known hypersensitivity to basiliximab or any other component of the formulation (see section 2 Description and composition~~6.1. List of excipients~~).

***~~4.4~~6 ~~Special w~~Warnings and ~~special~~ precautions for use***

**General**

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

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

**Hypersensitivity reactions**

Severe acute (less than 24 hours) hypersensitivity reactions have been observed both on initial exposure to Simulect and on reexposure 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, ~~and~~ respiratory failure and capillary leak syndrome. ~~These reactions have been reported rarely for patients receiving Simulect (< 1/1000 patients).~~ If severe hypersensitivity occurs, therapy with Simulect should be permanently discontinued and no further dose should be administered. Caution should be exercised when patients previously given Simulect are re-exposed to a subsequent course of therapy with this medicine.

...

**Neoplasms and infections**

Transplant ~~P~~patients receiving ~~on~~ immunosuppressive regimens involving combinations with or without Simulect ~~therapy following transplantation~~ are at an increased risk of developing lymphoproliferative disorders (LPDs) (such as lymphoma) and opportunistic infections (such as cytomegalovirus (CMV). In clinical trials, ~~While Simulect is an immunosuppressive drug, to date no increase in LPDs or~~ the incidence of opportunistic infections ~~has been~~ was similar ~~observed~~ in patients ~~treated with Simulect~~using immunosuppressive regimens with or without Simulect. In a pooled analysis of two five-year extension studies, ~~N~~no differences were found in the incidence of

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malignancies and LPDs between ~~Simulect and placebo~~immunosuppressive regimens with or without Simulect ~~in a pooled analysis of two five-year extension studies~~ (see section ~~4.8.~~7 ~~Undesirables effects~~Adverse drug reactions).

**Vaccination**

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

***7 ~~4.8 Undesirable effects~~ Adverse drug reactions***

**Summary of the safety profile**

...

The incidence and causes of deaths following dual or triple therapy were similar in Simulect (2.9%) and placebo or ATG/ALG groups (2.6%), with the most common cause of deaths in both treatment groups being infections (Simulect = 1.3%, placebo or ATG/ALG = 1.4%). In a pooled analysis of two five-year extension studies the incidence and cause of death remained similar in both treatment groups (Simulect 15%, placebo 11%), the primary cause of death being cardiac-related disorders such as cardiac failure and myocardial infarction (Simulect 5%, placebo 4%).

**Listing of adverse drug reactions from ~~P~~post-marketing spontaneous reports~~adverse reactions~~**

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

**Immune system disorders**

~~Rare:~~ Hypersensitivity/anaphylactoid reaction such as rash, urticaria, pruritus, sneezing, wheezing, bronchospasm, dyspnoea, pulmonary oedema, cardiac failure, hypotension, tachycardia, respiratory failure, ~~and~~ capillary leak syndrome.

~~Very rare:~~ Cytokine release syndrome.

***~~8~~4.5 Interactions ~~with other medicinal products and other forms of interaction~~***

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

**Concomitant medications routinely administered in organ transplantation**

...

Three clinical trials have investigated Simulect use in combination with a triple therapy regimen which included either azathioprine or mycophenolate mofetil. The total body clearance of Simulect was reduced by an average 22% when azathioprine was added to a regimen consisting of ciclosporin for microemulsion and corticosteroids. The total body clearance of Simulect was reduced by an average 51% when mycophenolate mofetil was added to a regimen consisting of ciclosporin for microemulsion and corticosteroids. The use of Simulect in a triple therapy regimen including azathioprine or mycophenolate mofetil did not increase adverse events or infections in the Simulect group as compared to placebo (see section ~~4.8. "Undesirable effects~~7 Adverse drug reactions~~"~~).

**Human antimurine antibody (HAMA)**

...

***~~9~~4.6 ~~Use during p~~Pregnancy and ~~lactation~~breast-feeding***

**Pregnancy**

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

**Breast-feeding**

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

There is no animal or human data available concerning excretion of basiliximab into breast milk. However, since Simulect is an immunoglobulin G ($IgG_{1K}$) antibody, it may cross the human placenta and may be excreted in human milk.

Women receiving Simulect should not breastfeed for 4 months following the last dose.

**Women of childbearing potential**

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

~~***4.7 Effects on ability to drive and use machines***~~

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

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

~~***4.8 Undesirable effects***~~

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

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

~~**Incidence of Adverse Events:** Simulect did not appear to add to the background of adverse events seen in organ transplantation patients as a consequence of their underlying disease and the concurrent administration of immunosuppressants and other medications. In the four placebo-controlled trials, the pattern of adverse events in 590 patients treated with the recommended dose of Simulect was indistinguishable from that in 595 patients treated with placebo. Simulect did not increase the incidence of serious adverse events observed when compared to placebo. The overall incidence of treatment-related adverse events among all patients in the individual studies was not significantly different between the Simulect (7.1% - 40%) and the placebo (7.6% - 39%) treatment groups. In the active-controlled study, fewer Simulect (11.4%) than ATG/ALG (41.5%) patients experienced treatment-related adverse events.~~

~~**Adult experience:** The most commonly reported (> 20%) events following dual or triple therapy in both treatment groups (Simulect vs. Placebo or ATG/ALG) were constipation, urinary tract infection, pain, nausea, peripheral oedema, hypertension, anaemia, headache, hyperkalaemia, hypercholesterolaemia, postoperative wound complication, weight increase, increase in blood creatinine, hypophosphataemia, diarrhoea, upper respiratory tract infection.~~

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

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

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

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

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

~~The incidence and causes of deaths following dual or triple therapy were similar in Simulect (2.9%) and placebo or ATG/ALG groups (2.6%), with the most common cause of deaths in both treatment groups being infections (Simulect = 1.3%, placebo or ATG/ALG = 1.4%). In a pooled analysis of two five-year extension studies the incidence and cause of death remained similar in both treatment groups (Simulect 15%, placebo 11%), the primary cause of death being cardiac-related disorders (Simulect 5%, placebo 4%).~~

~~**Post-marketing adverse reactions**~~

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

### ~~*4.9*~~*10 Overdose*

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

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

~~5~~11 Clinical ~~P~~pharmacology~~ical properties~~

### ~~*5.1*~~ *Pharmacodynamic properties (PD)*

Pharmacotherapeutic group: ~~specific immunosuppressant~~Interleukin inhibitors; ATC code: L04A ~~A09~~C02.

...

~~**Clinical studies**~~

~~The efficacy of Simulect in prophylaxis of organ rejection in *de novo* renal transplantation has been demonstrated in double-blind placebo-controlled studies. Results from two pivotal 12-month multicentre studies comparing Simulect with placebo show that Simulect, used concomitantly with ciclosporin for microemulsion and corticosteroids, significantly reduces the incidence of acute rejection episodes both within 6 (31% vs. 45%, $p < 0.001$) and 12 (33% vs. 48%, $p < 0.001$) months after transplantation. There was no significant difference between Simulect and placebo-treated patients in~~

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~~graft survival after 6 and 12 months (at 12 months 32 graft losses on Simulect (9%) and 37 graft losses on placebo (10%)). The incidence of acute rejection episode was substantially lower in patients receiving Simulect and a triple drug immunosuppressive regimen.~~

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

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

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

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

~~Of 339 renal transplant patients treated with Simulect and tested for anti-idiotype antibodies, 4 (1.2%) developed an anti-idiotype antibody response. In a clinical trial with 172 patients receiving Simulect, the incidence of human anti-murine antibody (HAMA) in renal transplantation patients treated with Simulect was 2/138 in patients not exposed to muromonab-CD3 and 4/34 in patients who received muromonab-CD3 concomitantly. The available clinical data on the use of muromonab-CD3 in patients previously treated with Simulect suggest that subsequent use of muromonab-CD3 or other murine anti-lymphocytic antibody preparations is not precluded.~~

### ~~*5.2*~~ *Pharmacokinetic properties ~~(PK)~~*

## 12 Clinical studies

The efficacy of Simulect in prophylaxis of organ rejection in *de novo* renal transplantation has been demonstrated in double-blind placebo-controlled studies. Results from two pivotal 12-month multicentre studies comparing Simulect with placebo show that Simulect, used concomitantly with ciclosporin for microemulsion and corticosteroids, significantly reduces the incidence of acute rejection episodes both within 6 (31% vs. 45%, $p < 0.001$) and 12 (33% vs. 48%, $p < 0.001$) months after transplantation. ...

### ~~*5.313*~~ ~~*Preclinical*~~ *~~Non-clinical~~ safety data*

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

...

~~6~~14 Pharmaceutical ~~particulars~~information

### ~~*6.1 List of excipients*~~

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

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~~***6.2***~~ ***Incompatibilities***

No known incompatibilities.

~~***6.3 Shelf-life***~~

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

~~***6.4***~~ ***Special precautions for storage***

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

~~***6.5 Nature and content of container***~~

~~**Simulect powder**~~

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

~~Content: 20 mg drug substance.~~

~~**Water for injection**~~

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

~~Content: 5 mL water for injection.~~

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

...

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העלון לרופא נשלח למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על-ידי פניה לבעל הרישום.

בברכה,

מגר' נעמה אור
רוקחת ממונה

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