INSTRUCTION FOR USE

1. NAME OF THE MEDICINAL PRODUCT

ATG-Fresenius S 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the concentrate contains 20 mg anti-human T-lymphocyte immunoglobulin from rabbits. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and therapy of rejection crisis in organ and tissue transplantation.

4.2 Posology and method of administration

ATG-Fresenius S should be prescribed only by physicians who are experienced in the use of immunosuppressive therapies. ATG-Fresenius S must be administered under qualified medical supervision.

Recommended dose

The dose of ATG-Fresenius S is dependent on the indication. Dose recommendations are based on body weight.

Prevention of acute transplant rejection in patients receiving allogeneic solid organ transplants

The recommended dose range is 2 to 5 mg/kg/d ATG-Fresenius S. The most common doses are in the range of 3 to 4 mg/kg/d. Therapy should commence on the day of transplantation pre-, intra-, or immediately postoperatively. Depending on the patient's condition, selected daily dose and the concomitant immunosuppressive regimen, the recommended duration of therapy is in the range of 5 to 14 days.

Therapy of acute corticosteroid-resistant rejection after allogeneic solid organ transplantation

The recommended dose range is 3 to 5 mg/kg/d ATG-Fresenius S. The most common dosages are in the range of 3 to 4 mg/kg/d. Duration of therapy will vary according to the condition of the grafted organ and clinical response, usually between 5 to 14 days.

Method of administration

ATG-Fresenius S is a hypotonic concentrate for solution for infusion with pH 3.7 0.3 and is not for direct injection. It has to be diluted in sodium chloride 9 mg/ml (0.9%) solution before intravenous administration to the patient. Recommended dilution volume is 250 - 500 ml. The standard infusion time in solid organ transplantation is 4 hours. In case of intra-operative administration infusion time of 0.5 to 2 hours has been usually used.

During administration, the patient shall be closely monitored for symptoms of hypersensitivity or anaphylaxis. The first dose of ATG-Fresenius S should be administered at a reduced infusion rate for the first 30 minutes. If no symptoms of intolerance occur, the infusion rate may be increased. In case of
anaphylactic or anaphylactoid reactions, the responsible physician must be prepared to deal promptly with such an event and appropriate medical treatment has to be implemented.

Alternatively to infusion via central venous catheter, a peripheral large high flow vein can be chosen. The administration of methylprednisolone and/or antihistamines prior to infusion is recommended in order to improve systemic and local tolerance. Standard hygienic handlings of the injection site, reduction of the infusion speed and/or change of the venous access site are to be considered.

Sodium heparin must not be added to the ATG-Fresenius S infusion solution or administered via the same route.

ATG-Fresenius S should not be used if the solution is not clear to opalescent.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

ATG-Fresenius S is contraindicated in patients with bacterial, viral or mycotic and parasitic infections, which are not under adequate therapeutic control.

ATG-Fresenius S is contraindicated in with severe thrombocytopenia, i.e. less than 50,000 platelets/l because ATG-Fresenius S may enhance thrombocytopenia and thus increase the risk of hemorrhage.

ATG-Fresenius S is contraindicated in patients with malignant tumours except in cases where stem cell transplantation is performed as part of the treatment.

4.4 Special warnings and precautions for use

Patients receiving ATG-Fresenius S must be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources to provide emergency treatment if necessary. ATG-Fresenius S must be administered and monitored under qualified medical supervision.

Hypersensitivity reactions

Hypersensitivity reactions have been reported with the administration of ATG-Fresenius S. Before the first administration of ATG-Fresenius S, it is recommended to determine whether the patient has an anamnestic allergic predisposition, in particular to rabbit proteins. In case of re-exposition in form of re-therapy with ATG-Fresenius S or treatment with rabbit immunoglobulin preparations of other manufacturers, the risk of developing an anaphylactic reaction is increased due to a possible sensitisation during the former therapy.

Severe thrombocytopenia

Treatment with ATG-Fresenius S should be interrupted or stopped in solid organ transplant patients in whom severe thrombocytopenia develops (i.e. less than 50,000 platelets/l) as ATG-Fresenius S may enhance thrombocytopenia and thus increase the risk of hemorrhage. Clinical personnel should be prepared for appropriate emergency measures.

Hepatic disorders

ATG-Fresenius S has to be administered with special caution in patients with hepatic diseases. Pre-existing clotting disorders may aggravate. Careful monitoring of thrombocytes and coagulation parameters is recommended.

Cardiovascular disorders

ATG-Fresenius S has to be administered with special caution in patients with known or suspected cardiovascular disorders. In patients with hypotension or cardiac decompensation with orthostatic symptoms (e.g. unconsciousness, weakness, vomiting, nausea), slowing/interrupting the infusion should be considered.
Infections
Immunosuppressive therapy increases the risk for infections in general. ATG-Fresenius S treated patients have an increased risk for the development of bacterial, viral, mycotic, and/or parasitic infections. Adequate monitoring and treatment measures are indicated.

Vaccination
During treatment with ATG-Fresenius S, patients should be advised that non-live vaccinations might be less efficacious. Live-attenuated virus vaccination is contraindicated in immunosuppressed patients.

Warning on transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared by using human components include selection of donors, screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared by using human components are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken for ATG-Fresenius S are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hemolytic anemia).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Immunosuppressive medicinal products
In addition to ATG-Fresenius S, other concomitant immunosuppressive medicinal products are routinely administered. No direct interaction between ATG-Fresenius S and corticosteroids, purin antagonists, calcineurin inhibitors or mTOR inhibitors has been observed. However, the co-administration of these medicinal products may increase the risk of infection, thrombocytopenia, and anemia. Thus, patients receiving combined immunosuppressive therapies are to be monitored carefully and an adequate adaptation of the regimen is recommended.

Vaccination
For immunosuppressed patients live-attenuated virus vaccination is contraindicated. The antibody response to other vaccines may be diminished (see section 4.4).

4.6 Pregnancy and lactation

No animal data are available. Human clinical data on pregnant or breast-feeding women are not available. The potential risk for the fetus is unknown. Caution should be exercised when prescribing to pregnant women.

At least human immunoglobulin can potentially penetrate the placental barrier or be excreted into human breast milk. Therefore, the decision to treat pregnant or lactating women should be made by the treating physician and based on a risk/benefit evaluation.

No data on fertility are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

ATG-Fresenius S is an immunoglobulin product with immunosuppressive properties. Well-known class related adverse effects include cytokine-release related symptoms, hypersensitivity reactions such as anaphylaxis and other allergic phenomena, enhanced susceptibility to infections, and occurrence of malignancies.
The nature and frequency of adverse reactions described in this section were analysed in an integrated safety analysis on the basis of 6 clinical studies consisting of 242 patients in the indications prevention of rejection in patients receiving renal transplants (136 patients) and conditioning prior to allogeneic stem cell transplantation (106 patients). 94% of the patients analysed, experienced at least one adverse reaction. The pattern of adverse reactions reported reflects in parts common complications typically occurring after the respective procedures, renal transplantation (urinary tract infection, renal failure) and allogeneic stem cell transplantation (pancytopenia, mucosal inflammation).

In the table below, adverse reactions reported with ATG-Fresenius S are listed and classified according to frequency and System Organ Class. Frequency groupings are defined according to the following convention: very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

### Adverse reactions with ATG-Fresenius S

<table>
<thead>
<tr>
<th>Blood and lymphatic tissues disorders</th>
<th>Common</th>
<th>pancytopenia**, thrombocytopenia, anemia, leukopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncommon</td>
<td>polycythemia</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>tachycardia</td>
<td></td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>photophobia</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>vomiting, nausea, diarrhea, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>stomatitis</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>inguinal hernia*, reflux esophagitis, dyspepsia</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>asthenia, chest pain, hyperthermia, mucosal inflammation, peripheral edema</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>edema</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>hyperbilirubinemia</td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>anaphylactic shock**, anaphylactic reaction , hypersensitivity</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>CMV infection*, urinary tract infection*</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>bacterial sepsis**, pneumonia**, pyelonephritis*, herpes infection, Influenza, oral Candidiasis, bronchitis, rhinitis, sinusitis, nasopharyngitis, skin infection</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>catheter site infection, Epstein-Barr virus infection, gastrointestinal infection, erysipelas, wound infection</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>blood creatinine increased*, Cytomegalovirus antigen positive, C-reactive protein increased,</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>hepatic enzymes increased</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>fluid retention, hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>myalgia, arthralgia, back pain, musculoskeletal stiffness</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>lymphoproliferative disorder*</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>headache, tremor</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>paresthesia</td>
<td></td>
</tr>
</tbody>
</table>
Renal and urinary disorders

| Common | renal tubular necrosis*, hematuria |
| Uncommon | renal failure**, renal necrosis* |

Respiratory, thoracic and mediastinal disorders

| Very common | dyspnea |
| Common | cough, epistaxis |

Skin and subcutaneous tissue disorders

| Common | erythema, pruritus, rash |
| Uncommon | drug eruption |

Vascular disorders

| Very common | flushing |
| Common | hypotension*, venoocclusive disease, hypertension |
| Uncommon | shock**, lymphocele |

* serious reaction
** serious reaction, in single cases with fatal outcome

Adverse reactions of special interest

Cytokine release related symptoms

These reactions occur due to release of cytokines and include fever, chills, headache, nausea, vomiting, tachycardia, and circulatory changes. These reactions could be summarized under the clinical entity of cytokine release syndrome. They are frequently observed during or after the administration of ATG Fresenius S. Symptoms are usually well manageable. Prophylactic medication could be administered to alleviate these symptoms.

Hypersensitivity reactions

Reactions such as flushing, rash, erythema, edema, dyspnea with or without bronchospasm, and cough are commonly observed during and after the administration. These reactions usually respond to treatment well. The administration of appropriate prophylactic medication can ameliorate these symptoms. The occurrence of anaphylaxis/anaphylactic shock requires immediate termination of the infusion. Serum sickness, observed if ATG-Fresenius S is administered for long treatment duration and at lower dosage, is rarely severe and usually responds well to symptomatic treatment.

Hematological changes

Transient changes of thrombocyte and leukocyte counts, otherwise documented as thrombocytopenia and leukopenia are commonly observed after ATG-Fresenius S administration. Anemia is commonly observed after administration of ATG-Fresenius S.

Infections

The patients treated with immunosuppressive regimens have an increased susceptibility to infections. In the first year after solid organ transplantation, the majority of patients who received ATG-Fresenius S developed infections of bacterial, viral or mycotic origin. Urinary tract infection is a very common bacterial infection; very common viral infections are caused by CMV. Commonly reported infections include bacterial sepsis, bacterial pneumonia, pyelonephritis, herpetic viral infections, and oral candidiasis. EBV infections, CMV pneumonia and CMV gastroenteritis are uncommon viral infections. Systemic candidiasis is an uncommon fungal infection. The majority of infections are usually manageable with treatment. There were isolated reports of life-threatening or even fatal infections. Appropriate monitoring and prophylactic treatment can reduce the infection rate.

Malignancy

The incidence of malignancy occurring after ATG-Fresenius treatment is generally low across studies and publications and is comparable with the incidence observed with other combinations of immunosuppressive medications. Post-transplant lymphoproliferative disease was reported exclusively from patients who underwent allogeneic stem cell transplantation (1.7%).
Other medically important reactions

Rare cases (less than 1 in every 1000 patients) of hemolysis were reported in connection with ATG Fresenius S administration.

4.9 Overdose

In case of overdose, immediate use of broad spectrum antibiotics, antifungal and antiviral therapy is recommended. ATG-Fresenius S therapy must be discontinued and any other concurrent immunosuppressive treatment must be adjusted according to the hemogram (in particular, leukocytes and lymphocytes). The platelet count must be monitored closely and substitution therapy initiated as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: specific immunosuppressant, ATC code: L04AA04.

ATG-Fresenius S is a polyclonal anti-T-lymphocyte immunoglobulin derived from rabbits immunized with Jurkat cells, a lymphoblastoid cell line. The expression of T-cell markers on Jurkat cells is consistent with the effects of ATG-Fresenius S on lymphocytes. ATG-Fresenius S has been found to contain antibodies against further surface antigens of Jurkat cells.

Analysis of lymphocyte subsets in patients who received ATG-Fresenius S, showed a decrease in lymphocyte subsets carrying surface proteins, which are expressed by the Jurkat cell line.

ATG-Fresenius S is cytotoxic against human lymphocytes. Data show that activated lymphocytes are more susceptible.

ATG-Fresenius S did not activate T-cells (via CD3) or lymphocytes but inhibited activation of T-cells by an anti-CD3 antibody.

ATG-Fresenius S reduced migration of human melanoma cells by binding to adhesion molecules.

Anti-adhesive properties (anti-LFA-1 and anti-ICAM-1 activity) might explain why addition of ATG Fresenius S diminished the vascular resistance of kidney vessels and reduced lymphocyte retention in the kidney when porcine kidneys were perfused with human lymphocytes incubated with or without ATG Fresenius S.

ATG-Fresenius S prolonged skin graft survival in rhesus monkeys. Immunosuppression was evident in this model and leukopenia and lymphopenia were observed. In cynomolgus monkeys, ATG-Fresenius S had a beneficial effect on ischemia/reperfusion injury by inhibition of adhesion of lymphocytes and neutrophils.

In renal transplant patients under standard therapy with ATG-Fresenius S, leukocyte, and platelet counts decreased but returned to normal levels within 10 days after transplantation. Also counts of lymphocytes and lymphocyte subpopulations decreased significantly. A decrease in CD2, CD3, CD4 and CD8 count was observed. A return to levels within normal range was seen for CD8 but not for CD2, CD3 and CD4 in the first 20 post-operative days.

The effect of standard therapy with ATG-Fresenius S on lymphocyte subpopulations and a persistent reversal of the CD4/CD8 ratio for up to 66 months were reported in patients after kidney transplantation.

After a single high-dose of 9 mg/kg ATG-Fresenius S, TNF- and IL-10 increased, while IL12p40 slightly decreased and IL-12p70 was not stimulated.
5.2 Pharmacokinetic properties

ATG-Fresenius S is administered intravenously and is therefore 100 % bioavailable.

ATG-Fresenius S is subject to protein metabolism as are other bodily proteins.

The half-life of ATG-Fresenius S is approximately 14 days (in case of a dosage of 4 mg/kg/d over 7 days) and varies from 4 to 45 days depending on the dose and duration of administration.

Literature studies have shown that T-cell specific antibodies were eliminated faster than total rabbit IgG.

Pharmacokinetic data have been obtained from the toxicokinetic sections of the toxicology studies. ATG Fresenius S is absorbed rapidly and is eliminated slowly. Systemic exposure was proportionate at all dose levels, increased with repeated dosing, without gender differences. No drug-drug interactions with prednisolone were seen.

5.3 Preclinical safety data

In non-clinical toxicology studies ATG-Fresenius S was investigated in single dose studies in rabbits, cynomolgus monkeys and rhesus monkeys, and in repeat-dose studies in rhesus monkeys. ATG-Fresenius S was well tolerated. Some of the effects observed are due to the specific pharmacodynamic activity of ATG Fresenius S, which results in immunosuppression and pronounced decrease in lymphocyte count, particularly T-lymphocytes. At high doses (250 to 300 mg/kg), anaphylactic reactions have been observed in rhesus monkeys. Co-administration of prednisolone reduced the toxicity of ATG-Fresenius S. No serum sickness was observed and there was a marked improvement in the clinical signs compared to ATG-Fresenius S alone.

No effects on the CNS, cardiovascular or respiratory systems were observed in a safety pharmacology study in cats.

No genotoxic activity, no local irritation and no anti-glomerular basement membrane antibodies were observed. Carcinogenicity or reproductive toxicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Phosphoric acid (85%) (for pH adjustment)
Water for injections

6.2 Incompatibilities

ATG-Fresenius S concentrate for solution for infusion must not be mixed with glucose, blood, blood-derivatives, solutions containing lipids, and sodium heparin.

6.3 Shelf life

2 years

Opened vials should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

For instruction on preparation and administration of the medicinal product, see section 4.2.
6.5 Nature and contents of container

Pack with 1 or 10 vials containing 5 ml solution
Pack with 1 or 10 vials containing 10 ml solution

6.6 Special precaution for disposal

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

7. MANUFACTURER

Fresenius Biotech GmbH
Am Haag 6-7
D-82166 Graefelfing

8. REGISTRATION HOLDER

Cure Medical & Technical Supply
6, Hashiloach st., Petach – Tiqva 49514.

The format of this leaflet has been defined by the MOH and its content has been checked and approved on April 2012.