Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Anti-human T-lymphocyte immunoglobulin from rabbits

ATG-Fresenius Thymoglobuline

DE/W/0011/pdWS/001

Rapporteur:	Germany (PEI)
Finalisation procedure (day 120):	18 September 2014

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Anti-human T-lymphocyte immunoglobulin from rabbits
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	L04AA04
Pharmaceutical form(s) and strength(s):	Concentrate for solution for infusion (20 mg/ml) Powder for solution for infusion (5 mg/ml)

I. EXECUTIVE SUMMARY

Anti-human T-lymphocyte immunoglobulin from rabbits is marketed by two companies, however it is not clear if these products are comparable as regards efficacy and safety, in fact there are indications these two products have different PD because the source of the antigen to immunise rabbits is not identical. For the production of ATG-Fresenius rabbits are immunised with the Jurkat cell line, for Thymoglobuline human thymocytes derived from thymus tissue is used. Both products contain a mixture of polyclonal antibodies against a variety of antigens. The mechanism of action for both products is not fully understood. Interestingly the medical community appears to treat both products as equivalent even if different doses are recommended.

The indications for anti-human T-lymphocyte immunoglobulin from rabbits vary by country and may encompass the following:
- Prophylaxis of acute graft rejection in solid organ transplantation
- Treatment of acute graft rejection in solid organ transplantation
- Treatment of aplastic anemia
- Prophylaxis of acute and chronic graft versus host disease in hematopoetic stem cell transplantation

Anti-human T-lymphocyte immunoglobulin from rabbits has been marketed for over 3decades and there is a vast clinical experience with the compounds. However, given the complex nature of the diseases/conditions treated with anti-human T-lymphocyte immunoglobulin from rabbits, the not fully understood mode of action and the few properly conducted trials, especially in the paediatric population, make any conclusion vulnerable to criticism. The differences in the indication statement between countries may also be indicative of different views as regards the strength of evidence for certain indications.
The Rapporteur proposes to include statements on the use of the products in paediatrics indicating the limited evidence

SmPC and PL changes are proposed in sections 4.2, 4.8 and 5.1

Summary of outcome

☒ Paediatric information clarified: section(s) 4.2, 4.8, 5.1

II. RECOMMENDATION

Proposals for changes to section 4.2, 4.8 and 5.1 are made, please see section V.

III. INTRODUCTION

Two MAHs submitted 36 completed paediatric study(ies) for anti-human T-lymphocyte immunoglobulin from rabbits, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

Fresenius Biotech stated that the submitted paediatric study(ies) do not influence the benefit risk for anti-human T-lymphocyte immunoglobulin from rabbits and that there is no need for a consequential regulatory action.

Genzyme proposed the following regulatory action: amendment of section 4.2 of the SmPC as regards posology in paediatric patients:
"The posology in paediatrics (patients with an age below 18 years) is identical to the posology in adults".

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SmPC wording of section 4.2, 4.8 and related to the paediatric use of the medicinal product, and related PL wording

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

N/A

IV.2 Non-clinical aspects

1. Introduction

No non-clinical studies have been provided.

2. Non clinical study(ies)

No non-clinical studies have been provided.

3. Discussion on non clinical aspects

No non-clinical studies have been provided.

Rapporteur's Comment
Non-clinical studies covering specific paediatric aspects have not been submitted. Given the complex and not fully understood mode of action, the difficulty/impossibility with choosing a relevant animal model and the long clinical experience with these products this is considered acceptable.

IV.3 Clinical aspects

1. Introduction

The MAHs submitted publications for treatment with anti-human T-lymphocyte immunoglobulin from rabbits in different indications:

Publications submitted by Genzyme for Thymoglobulin (studies reporting only paediatric results highlighted in grey)

Author	Indication	Age
Khositseth et al. 2005	prevention of rejection in kidney tx	range 0.8-18
Oberholzer et al. 2005	prevention of rejection in kidney tx	mean 10.4
Khwaja et al. 2003	prevention of rejection in kidney tx	mean 0.78
Ault et al.2002	prevention of rejection in kidney tx	mean 10.1
Brophy et al.2001	prevention of rejection in kidney tx	mean 9.7
Bell et al.1997	prevention of rejection in kidney tx	mean 9.6
Pederson et al. 2007	prevention of rejection in kidney tx	mean 11
Birkeland et al. 1998	prevention of rejection in kidney tx	mean 39.5
Daoud et al. 1997	Treatment of rejection in kidney Tx	mean 34
Shah et al. 2006	Prevention of rejection in liver Tx	mean 7
Sindhi et al. 2002	Prevention of rejection in liver Tx	range 0.6-17
Pollock et al. 2007	Prevention of rejection in heart Tx	median 0.58
Holt et al. 2007	Prevention of rejection in heart Tx	mean 7.6
Filippo et al. 2003	Prevention of rejection in heart Tx	median 14.2
Parisi et al. 2003	Prevention of rejection in heart Tx	mean 7.8
Scheinberg et al. 2006	Treatment of aplastic anemia	mean 13
Di Bona et al. 1999	Treatment of aplastic anemia	median 18.5
Horn et al. 2006	Prevention of acute and chronic GvHD	mean 5.9
Lu et al. 2006	Prevention of acute and chronic GvHD	median 24
Deeg et al. 2006	Prevention of acute and chronic GvHD	median 50
Fang et al. 2005	Prevention of acute and chronic GvHD	median 8.3
Bacigalupo et al. 2005	Prevention of acute and chronic GvHD	mean 14
Seidel et al. 2005	Prevention of acute and chronic GvHD	median 3.4
Duval et al. 2002	Prevention of acute and chronic GvHD	mean 8.3
Dugan et al. 2002	Prevention of acute and chronic GvHD	median 32
Nachbaur et al. 2002	Prevention of acute and chronic GvHD	median 26
Remberger et al. 2002	Prevention of acute and chronic GvHD	median 27.5

Publications submitted by Fresenius for ATG-Fresenius

Author	Indication	Age
De Santo et al. 2004	Solid organ transplantation	13 to 53
Laufer et al, 1989	Solid organ transplantation	6 to 59
Neuhaus et al., 1993	Solid organ transplantation	16 to 65
Remberger et al., 1999	Stem cell transplantation	1 to 55
Remberger et al., 2000	Stem cell transplantation	< 18
Schleuning 2003	Stem cell transplantation	16 to 51
Sedláek 2006	Stem cell transplantation	0.3-20.5
Zander et al., 2003	Stem cell transplantation	6 to 58

Fresenius submitted a description for:

- AP-AA-11-GB; AP-AA-11-GB investigated single high-dose therapy in children (up to 18 years of age) undergoing heart, lung or combined heart-lung solid organ transplantation (SOT).

2. Clinical study(ies)

PUBLICATIONS SUBMITTED FOR THYMOGLOBULIN

Khositseth et al. Thymoglobulin versus ATGAM induction therapy in pediatric kidney transplant recipients: a single center report. Transplantation 2005;79:958

- **Description**
- **Methods**

  - **Objective(s)**
    To compare ATGAM (polyclonal horse anti-thymocyte immunoglobulin) to Thymoglobuline
  - **Study design**
    Retrospective cohort study
  - **Study population /Sample size**
    198 pediatric patients (<19 yrs)
  - **Treatments**
    ATGAM or Thymoglobulin 15 mg/kg total, Azathioprin or MMF, CsA
  - **Outcomes/endpoints**
    Acute rejection, graft survival, overall survival, EBV infection

- **Results**

  - **Recruitment/ Number analysed**
    127 on ATGAM (1992-1999), 71 on Thymoglobuline (1999-2002)
  - **Baseline data**
    Reasonably well balanced
  - **Efficacy results**
    No difference in graft or patient survival, decreased incidence of acute rejection with Thymoglobuline (50 vs 33%)

- **Safety results**
  Symptomatic EBV infection increased in Thymoglobuline (8% vs 3%)

Rapporteur's Comment
This is a retrospective trial comparing two different strategies for immunosuppression. Although acute rejections appear to be less common with Thymoglobuline overall outcome appears to be comparable. Results contribute to the understanding of safety and efficacy of Thymoglobuline. Any further conclusions are hampered by the methodology (retrospective cohort design, different time periods), foremost the change in medical practise over time that is most likely biasing the results.

Oberholzer et al. Early discontinuation of steroids is safe and effective in pediatric kidney transplant recipients. Pediatr Transplantation 2005; 9: 456-

Rapporteur's Comment
This is a retrospective trial comparing strategies of steroid withdrawal, Thymoglobuline was part of the initial immunosuppression in the majority of patients. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobuline.

Khwaja et al. Kidney transplants for children under 1 year of age – a single center experience. Pediatr Transplantation 2003;7:163-167

Rapporteur's Comment
This is a report about kidney transplantation in very young recipients, mostly from living related donors. Thymoglobulin (15 mg/kg total) was part of the initial immunosuppression in the majority of patients. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Ault et al. Short-term outcomes of Thymoglobulin induction in pediatric renal transplant recipients. Pediatr Nephrol 2002; 17:815-818

- **Description**
- **Methods**

  - **Objective(s)**
    Description of pediatric experience
  - **Study design**
    Retrospective analysis of cases
  - **Study population /Sample size**
    17
  - **Treatments**
    65 % cadaveric allograft, triple immunosuppression, tacrolimus 62%, CsA 38%, MMF, Thymoglobulin 6-9 mg/kg total
  - **Outcomes/endpoints**
    Acute rejections, EBV infection, CMV infection

- **Results**

- **Efficacy results**
  No acute rejections
- **Safety results**
  No symptomatic EBV disease

Rapporteur's Comment
The results from this case series compare favourably with historic controls as regards acute rejections. There are no safety concerns. Results may be confounded by change in practise from CsA to Tac and azathioprine to MMF, making any comparison to historic controls difficult to judge.

Brophy et al. Comparison of polyclonal induction agents in pediatric renal transplantation. Pediatr Transplantation 2001;5:174-178

- **Description**
- **Methods**

  - **Objective(s)**
    Comparison of Thymoglobulin to horse anti lymphoblast globulin (ALG)
  - **Study design**
    Case series
  - **Study population /Sample size**
    Thymoglobulin 8 paediatric patients, ALG 9 paediatric patients, ATG (ATGAM) 13 paediatric patients
  - **Treatments**
    Triple immunosuppression with CsA, Azathioprin for patients receiving ALG or ATG, MMF for patients on Thymoglobulin (10 mg/kg total)
  - **Outcomes/endpoints**
    CD3, CD4, CD8

- **Results**

  - **Efficacy results**
    Similar degree of T cell depletion with 5 day course of Thymoglobulin compared to 10 day course with ATG, ALG

  - **Safety results**
    Not reported

Rapporteur's Comment
Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Bell et al. Lymphocyte subsets during and after rabbit anti-thymocyte globulin induction in pediatric renal transplantation: sustained T cell depletion. Transplantation Proc 1997; 29: 6S-9S

- **Description**

- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective case series 1992-1996
  - **Study population /Sample size**
    20 paediatric patients
  - **Treatments**
    Azathioprine, CsA, Prednisone, Thymoglobulin (average 22 mg/kg total)

  - **Outcomes/endpoints**
    Rejection, safety

Results

- **Baseline data**
  11 living donor kidneys
- **Efficacy results**
  Profound lymphocyte depletion, "low rejection rate" of 35% in the first 6 months, 3 patients lost allograft
- **Safety results**
  One case of PTLD, one death

Rapporteur's Comment
This report, compared to later studies, nicely illustrates the improvement of results over time, not necessarily dependant on the method of immunosuppression: rejection rate is rather high by today's standard but considered low at the time of study. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Pedersen et al. Avoiding steroids in pediatric renal transplantation: long-term experience from a single center. Pediatric transplantation 2007;11:730

- **Description**
- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective case series 1995-2005
  - **Study population /Sample size**
    Thirty four grafts in 32 recipients
  - **Treatments**
    Induction with thymoglobulin, maintenance with calcineurin inhibitor and MMF
  - **Outcomes/endpoints**
    Graft survival, steroid use

- **Results**

  - **Baseline data**

Median age 11 (range 2-15)

- **Efficacy results**
  29% acute rejections during first year
- **Safety results**
  Three cases of PTLD, five cases of CMV disease

Rapporteur's Comment
Main focus of this report is the reduction of steroids for immunosuppression. Rate of PTLD and infectious complications appears rather high. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Birkeland SA. Steroid-free immunosuppression after kidney transplantation with antithymocyte globulin induction and cyclosporine and mycophenolate mofetil maintenance therapy. Transplantation 1998;66:1207-1210

- **Description**
- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective case series
  - **Study population /Sample size**
    68 transplants
  - **Treatments**
    Induction with Thymoglobulin, maintenance with CsA and MMF, no steroids
  - **Outcomes/endpoints**
    Survival, graft survival,

- **Results**

  - **Recruitment/ Number analysed**
    68
  - **Baseline data**
    Median age 38.5 yrs (range 8-67)
  - **Efficacy results**
    Ten acute rejections, 64 grafts surviving
  - **Safety results**
    No CMV disease

Rapporteur's Comment
Main focus of this report is the elimination of steroids for immunosuppression. Number of included children is unclear. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Daoud et al. The US compassionate experience with Thymoglobulin for the treatment of resistant acute rejection. Transplantation Proc 1997;29:18S-20S

- **Description**
- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective case series
  - **Study population /Sample size**
    Resistent acute rejection, 34 recipients
  - **Treatments**
    Thymoglobulin (6-22 mg/kg total) after various standard regimens had failed (steroids, ATGAM, OKT3, etc.)
  - **Outcomes/endpoints**
    Graft survival

- **Results**

  - **Recruitment/ Number analysed**
    Rescue rejection 26 pts, prophylaxis 8 pts
  - **Baseline data**
    Age range 1-74, no of children unclear
  - **Efficacy results**
    85% of rejections reversed
  - **Safety results**
    10% infectious complications (1 CMV case), one death from lymphoma in a patient that had also received ATGAM OKT3

Rapporteur's Comment
Thymoglobulin appears to be efficacious as rescue immunosuppression even when other regimen have failed. With the exception of one death that is confounded by multiple therapies safety appears unremarkable.

Shah et al. Induction immuosuppression with rabbit antithymocyte globulin in pediatric liver transplantation. Liver Transpl 2006;12:1210-1214

- **Description**
- **Methods**

  - **Objective(s)**
    Report of experience
  - **Study design**
    Retrospective case series
  - **Study population /Sample size**
    18 children
  - **Treatments**
    Thymoglobulin 6 mg/kg total, TAC, steroids

- **Outcomes/endpoints**
  Patient survival, graft survival

➢ **Results**

- **Recruitment/ Number analysed**

- **Baseline data**
  Median 3 yrs (range 5 mo to 14 yrs)
- **Efficacy results**
  Patient survival 89%, graft survival 89%, no biopsy confirmed rejection in first 2 months
- **Safety results**
  No PTLD, no CMV disease

Rapporteur's Comment
This case series is intended to show that Thymoglobulin does not carry an untoward risk for infectious complications. No control group is included, sample size is small, so any conclusions are error-prone.

Sindhi. Developing steroid-free, primary immuosuppression for pediatric liver transplantation with sirolimus and tacrolimus. American Society of Transplantation 2002, American Transplant Congress, Abstract 628

➢ **Description**
➢ **Methods**

- **Objective(s)**
  Development of steroid sparing immunosuppression
- **Study design**
  Cohort study
- **Study population /Sample size**
  6 patients on conventional immunosuppression, 9 patients on new regimen

- **Treatments**
  Comparison of conventional steroid therapy to induction therapy with Thymoglobulin (2 mg/kg total) and delayed introduction of sirolimus

- **Outcomes/endpoints**
  Steroid use, rejection,

➢ **Results**

- **Efficacy results**
  1/6 acute rejections in conventional group, 3/9 rejections in Thymoglobulin group
- **Safety results**
  1/9 PTLD in Thymoglobulin group

Rapporteur's Comment
Thymoglobuline (single dose) was used with the intent to develop a new immunosuppressive regimen, using no steroids and introducing sirolimus later. Therefore results do not contribute to the comparative understanding of safety and efficacy of Thymoglobulin.

Pollock-BarZiv Pediatric heart transplantation in human leukocyte antigen sensitized patients: evolving management and assessment of intermediate term outcomes in a high risk population. Circulation 2007;116:I172-I178

Rapporteur's Comment
This report describes the complex intervention in allo-sensitised patients to enable successful transplantation. Immunsuppression consisted of Thymoglobulin, TAC, steroids, MMF. Plasmapheresis and IVIG was used when there was a positive cross-match on day 1, rituximab was used for antibody-mediated rejection. Results do not contribute to the comparative understanding of safety and efficacy of Thymoglobulin.

Holt et al. Mortality and morbidity in pre-sensitized pediatric heart transplant recipients with a positive donor crossmatch utilizin peri-operative plasmapheresis and cytolytic therapy. J Heart Lung Transpl 2007;26:876-882

Rapporteur's Comment
This report describes the complex intervention in allo-sensitised patients to enable successful transplantation. Immunsuppression consisted of ATGAM (prior to 1998), Thymoglobulin (after 1998), Csa (1995-2000), TAC (from 2000), steroids, MMF. Plasmapheresis and Thymoglobulin was used when there was a positive cross-match postOP. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Di Fillippo et al. Rabbit antithymocyte globulin as induction immunotherapy in pediatric heart transplantation. Transplantation 2003;75:354

- **Description**
- **Methods**

  - **Objective(s)**
    Report of experience
  - **Study design**
    Retrospective cohort study 1984-2001
  - **Study population /Sample size**
    30 children
  - **Treatments**
    Thymoglobulin according to platelet count, CsA, azathioprin
  - **Outcomes/endpoints**
    Survival, Graft Survival

- **Results**

  - **Recruitment/ Number analysed**

30 children, only patients with Thymoglobulin therapy were evaluated (17 patients in the same center did not receive Thymoglobulin for induction)

- **Efficacy results**
  90% one-year survival, 50% rejection during first year
- **Safety results**
  One case of lymphoma at 5 months

Rapporteur's Comment
Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Parisi et al. Thymoglobuline use in pediatric heart transplantation. J Heart Lung Transplant 2003;22:591–593.

- **Description**
- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective
  - **Study population /Sample size**
    paediatric patients 31
  - **Treatments**
    age-dependent doses (1–1.5 mg/kg/day, between 0 and 1 year; 1.5–2 mg/kg/day from 1 year to 8 years; and 2.5 mg/kg/day >8 years). Duration of treatment was 1 to 7 days.
  - **Outcomes/endpoints**
    Rejection, graft survival, survival

- **Results**

  - **Recruitment/ Number analysed**

  - **Baseline data**

  - **Efficacy results**
    13 rejections were observed
  - **Safety results**
    One death (chronic rejection), one case of PTLD

Rapporteur's Comment
Authors claim that Thymoglobuline can be safely used if lymphocyte counts are kept at a certain threshold. There are no controls to further bolster this claim. Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin.

Scheinberg et al. Retreatment with rabbit anti-thymocyte globulin and ciclosporin for patients with relapsed or refractory severe aplastic anaemia. British J Haematol 2006;

- **Description**
- **Methods**

  - **Objective(s)**
    Description of experience
  - **Study design**
    Retrospective
  - **Study population /Sample size**
    43 patients that had relapsed on horse ATG or were refractory to horse ATG, including 6 children
  - **Treatments**
    3.5 mg/kg x 5 d (17.5 mg/kg total), CsA co-medication
  - **Outcomes/endpoints**
    Response

- **Results**

  - **Efficacy results**
    3 partial responders, 3 non-responders
  - **Safety results**
    No information

Rapporteur's Comment
Paediatric response rates appear to be similar to adult response rates in this difficult to treat patient population. No further information specific for the paediatric population can be extracted.

Di Bona et al. Rabbit antithymocyte globulin (r-ATG) plus cyclosporine and granulocyte colony stimulating factor is an effective treatment for aplastic anaemia patients unresponsive to a 1st course of intensive immunosuppressive therapy. British J Haematol 1999;

- **Description**
- **Methods**

  - **Objective(s)**
    Report experience
  - **Study design**
    Prospective, single arm
  - **Study population /Sample size**
    30 patients that had failed on horse ATG
  - **Treatments**
    Thymoglobulin 3.5. mg/kg x 5 days (17.5 mg/kg total), CsA co-medication, G-CSF
  - **Outcomes/endpoints**
    Response, remission, survival

- **Results**

  - **Baseline data**
    No information on number of included children
  - **Efficacy results**

Remission 77%, survival 93%

- **Safety results**
  One death due to sepsis

Rapporteur's Comment
Paediatric response rates are not reported, number of included children is unknown.

Horn et al. Reduced intensity conditioning using intravenous busulfan, fludarabine and rabbit ATG for children with nonmalignant disorders and CML. Bone Marrow Transplant 2006;37:263-269

- **Description**
- **Methods**

  - **Objective(s)**
    Evaluate a reduced intensity conditioning in children
  - **Study design**
    Prospective, single arm
  - **Study population /Sample size**
    19 children with MDS, CML, non-malignant disease
  - **Treatments**
    Conditioning with busulfan, fludarabine, ATG 8 mg/kg total, transplantation of bone marrow, PBSC or cord blood; GvHD prophylaxis CsA, MTX
  - **Outcomes/endpoints**
    Graft failure, survival

- **Results**

  - **Recruitment/ Number analysed**
    19 patients
  - **Baseline data**
    Median age 5 years
  - **Efficacy results**
    4/19 patients lost graft, 89% survival
  - **Safety results**
    4 cases of aGvHD, cGvHD in 3/15 patients, one death from CMV

Rapporteur's Comment
This study describes a very heterogeneous population treated with different sources of stem cells. The contribution of Thymoglobulin to overall success rates are difficult to judge based on the single arm study and the variety of treatments administered. The authors conclude that the regimen compares favourably with other published results, however the trial was terminated prematurely because the graft failure rate was considered unacceptably high.

Lu et al. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. Blood. 2006;107:3065-3073)

- **Description**
- **Methods**

  - **Objective(s)**
    Compare matched to mismatched stem cell transplantation
  - **Study design**
    Prospective (?) cohort study, non-randomised
  - **Study population /Sample size**
    293
  - **Treatments**
    Conditioning with busulfan, cyclophosphamide, cytarabine; mismatched patients received a doubled dose of cytarabine and ATG 2.5 mg/kg x 4 days (10 mg/kg total)
  - **Outcomes/endpoints**
    Acute GvHD, chronic GvHD, survival

- **Results**

  - **Recruitment/ Number analysed**

  - **Baseline data**
    Median age HLA identical sibling group 37, median age related mismatched group 24 years, HLA identical group 8 patients below 20 yrs, mismatched group 51 patients below 20 yrs
  - **Efficacy results**
    Acute GvHD 32% (HLA identical) vs 40% (mismatched), cGvHD risk similar, survival similar
  - **Safety results**
    CMV viremia is more common in mismatched group, haemorrhagic cystitis is more common in mismatched group

Rapporteur's Comment
This study compares to different populations, one of which receives ATG whereas the other one does not. Formally the effect of ATG is therefore hard to judge. However the mismatched cohort gives similar results in OS and GvHD when it is expected that it would perform worse. These results are therefore seen as encouraging. A few children were included, there is a rather pronounced imbalanced as regards the inclusion of children in the groups. There is no separate analysis for children.

Deeg et al. Reduced Incidence of Acute and Chronic Graftversus-Host Disease with the Addition of Thymoglobulin to a Targeted Busulfan/Cyclophosphamide Regimen. Biol Blood Marrow Transplant. 2006 May;12(5):573-84.

- **Description**
- **Methods**

  - **Objective(s)**
    To investigate effect of addition of Thymoglobulin to conditioning on GvHD in allogeneic hematopoetic stem cell transplantation for MDS, AML or other myeloproliferative disorders
  - **Study design**
    Prospective single arm
  - **Study population /Sample size**
    Mixed population of MDS and other myeloproliferative disorders; concurrent control of patients with good risk MDS
  - **Treatments**
    Conditioning regimen with busulfan, cyclophosphamide, Thymoglobulin dose escalation in cohorts depending on GvHD and EBV reactivation, starting dose: 4.5 mg/kg total (day -3, -2, -1); MTX, CsA for GvHD prophylaxis
  - **Outcomes/endpoints**
    GvHD, EBV reactivation, survival, infection

- **Results**

  - **Recruitment/ Number analysed**
    56 in Thymoglobulin cohort, 27 in concurrent control, 93 historical controls
  - **Baseline data**
    Age 9-63 years, number of children unknown, about half had a matched sibling transplant, the other half unrelated donor, 3 of these mismatched for one allele
  - **Efficacy results**
    15 patients received 4.5 mg/kg, 32 received 6 mg/kg, further escalation was stopped because 1 patients developed EBV reactivation. 50% developed acute GvHD, there was no difference in two dose groups; there was no difference in chronic GvHD rates in the two dose groups; cumulative disease recurrence 21% in the Thymoglobulin group, no disease recurrence in the concomitant control;
  - **Safety results**
    Two patients died (day 19 and day 22) in the Thymoglobulin cohort,

Rapporteur's Comment
This study again compares different populations, one of which received ATG whereas the other one does not. Formally the effect of ATG is therefore hard to judge. The authors conclude that further study is warranted because Thymoglobulin may be beneficial. A few children were included but there is no separate analysis for children.

Fang et al. Immunsuppressive treatment of aplastic anemia in chinese children with antithymocyte globulin and cyclosporine. Pediatr Hematol Oncol 2006; 23:45-50

- **Description**
- **Methods**

  - **Objective(s)**
    Report of experience
  - **Study design**
    Retrospective, 1993-2004
  - **Study population /Sample size**
    73 children, 51 children received one specific regimen of three available
  - **Treatments**
    Three cohort: 1) levamisole, stanozole, securinine (11 patients); 2) CsA (16 patients); 3) Thymoglobulin 2.5 mg/kg x 5 days, methylprednisolone, IVIG 1g/kg every 3-4 weeks (24 patients)
  - **Outcomes/endpoints**
    Response

- **Results**

  - **Recruitment/ Number analysed**
    See above
  - **Baseline data**
    Age 4-15 years, median 8.3 years
  - **Efficacy results**
    Total response rate 58%, highest response rate in thymoglobulin cohort
  - **Safety results**
    9 deaths, all in non-responders to treatment, 2 patients in the thymoglobulin group

Rapporteur's Comment
This retrospective study gives an indication that a therapy regimen containing Thymoglobulin is more efficient at achieving treatment response in children with aplastic anemia compared to other regimen. Since this is a retrospective study and the treatment decisions appear to influenced by time of diagnosis bias is likely.

Bacigalupo et al. Fludarabine, cyclophosphamide and anti-thymocyte globulin for alternative donor transplants in acquired severe aplastic anemia: a report from the EBMT-SAA Working Party. Bone Marrow Transplant 2005;36:947-950

- **Description**
- **Methods**

  - **Objective(s)**
    Description of new conditioning regimen
  - **Study design**
    Prospective, single arm, uncontrolled
  - **Study population /Sample size**
    Severe aplastic anemia that had failed on immunosuppressive therapy and required allogeneic transplantation

- **Treatments**
  Conditioning with fludarabine, cyclophosphamide, Thymoglobulin 3.75 mg/kg x 4 days, allogeneic bone marrow transplant; GvHD prophylaxis with MTX and CsA

- **Outcomes/endpoints**
  Engraftment, survival, AE

➢ **Results**

- **Recruitment/ Number analysed**
  38 patients
- **Baseline data**
  Median age 14 years,
- **Efficacy results**
  Acute GvHD in 11% of patients, chronic GvHD in 27% of patients, two year survival 73%, 19 patients < 14 years showed a trend to improved survival
- **Safety results**
  Causes of death were graft failure, EBV-related lymphoma (2 cases) and hemorrhage.

Rapporteur's Comment
This is a prospective study without control arm. Results for children are not reported separately. For these reasons relevance for the paediatric population is difficult to judge.

Seidel et al. In vitro and in vivo T-cell depletion with myeloablative or reduced-intensity conditioning in pediatric hematopoietic stem cell transplantation. Haematologica 2005; 90:1405-1414

➢ **Description**
➢ **Methods**

- **Objective(s)**
  Define effect of in vitro T cell depletion in addition to ATG
- **Study design**
  Retrospective analysis, 1994-2003
- **Study population /Sample size**
  134 allogeneic stem cell transplant at a single centre
- **Treatments**
  All patients received ATG prior to transplant, different conditioning regimens
- **Outcomes/endpoints**
  Survival

➢ **Results**

- **Recruitment/ Number analysed**

- **Baseline data**
  Median age 5.8 years,
- **Efficacy results**

Highest mortality in patients with myeloablative conditioning and T cell depleted graft. Acute and chronic GvHD with fatal outcome only occurred in patients with unselected grafts

- **Safety results**
  Highest rate of mortality from viral infection in patients with myeloablative conditioning and T cell depleted graft

Rapporteur's Comment
This study shows that combination of in vivo and in vitro T cell depletion is associated with increased transplant related mortality. All patients received ATG prior to transplantation, therefore the efficacy cannot be evaluated. Doses appeared to vary over time and are not reported. These results emphasise that benefit and risk of T cell depleting therapies have a very delicate balance and thus can assessed in a meaningful way only in randomised controlled trials.

Duval et al. Immune reconstitution after haematopoietic transplantation with two different doses of pre-graft antithymocyte globulin. Bone Marrow Transplant 2002; 30: 421-426

- **Description**
- **Methods**

  - **Objective(s)**
    Report experiences with two different doses of ATG
  - **Study design**
    Retrospective analysis, single center
  - **Study population /Sample size**
    Matched unrelated donor
  - **Treatments**
    ATG low dose (median 7.5 mg/kg, range 2.5 – 10.5), ATG high dose (median 15.5 mg/kg total, range 14.4 -19.4)
  - **Outcomes/endpoints**
    GvHD, infections, engraftment

- **Results**

  - **Recruitment/ Number analysed**
    31 patients, 16 low dose, 15 high dose
  - **Baseline data**
    Heterogenous with respect to underlying disease
  - **Efficacy results**
    Rate of acute and chronic GvHD higher in low dose group, immune reconstitution later in the high dose group, higher rate of infection in the high dose group
  - **Safety results**
    Transplant related mortality was numerically higher in the high dose group, disease free survival and survival were numerically lower, these results are not statistically significant.

Rapporteur's Comment
The higher dose appears to be associated with worse outcome, although these results are not statistically significant. No conclusion can be made on the effect per se.

Duggan et al. Unrelated donor BMT recipients given pretransplant low-dose antithymocyte globulin have outcomes equivalent to matched sibling BMT: a matched pair analysis. Bone Marrow Transplant 2002; 30-681-686

- **Description**
- **Methods**

  - **Objective(s)**
    Comparison of outcomes for MUD and MRD using different conditioning protocols
  - **Study design**
    Retrospective, matched pair analysis
  - **Study population /Sample size**
    57 MUD and 57 MRD
  - **Treatments**
    CsA and MTX for GvHD prophylaxis, ATG at a dose of 4.5 mg/kg total divided in 3 doses, children less than 30 kg received ATG 6 mg/kg total
  - **Outcomes/endpoints**
    Survival, GvHD, engraftment

- **Results**

  - **Recruitment/ Number analysed**
    57 patients in each group
  - **Baseline data**
    13 paediatric patients, no separate reporting of findings
  - **Efficacy results**
    For UD and RD BMT, respectively, incidence of acute GVHD grade II-IV was 19 ± 6% vs 36 ± 8%, grade III-IV 10 ± 6% vs 18 ± 7%, chronic GVHD 44 ± 8% vs 51 ± 8%, non-relapse mortality 15 ± 5% vs 8 ± 4% at 100 days, 28 ± 8% vs 36 ± 7% at 3 years. At 3 years, relapse was 45 ± 7 % vs 42 ± 7%, and disease-free survival 39 ± 7% vs 37 ± 7%. None of these differences are significant. Three-year overall survival was identical at 42 ± 7%.
  - **Safety results**
    No clear cut findings as regards infection or OS.

Rapporteur's Comment
The protocol for patients receiving an unrelated donor graft changed in 1995, from then all recipients were treated ATG pretransplant. Recipients of matched related donor graft also received ATG from Dec 1998, therefore patients were only included in the retrospective study if treated prior to that timepoint. Patients receiving an unrelated donor graft and thymoglobulin behaved similarly to patients receiving an matched related donor graft although they would be expected to perform worse. This could be taken as an indication that thymoglobulin lowers the risk associated with an unrelated donor graft. No specific paediatric information is available.

Nachbaur et al. In vivo T cell depletion with low-dose rabbit antithymocyte globulin results in low transplant-related mortality and low relapse incidence following unrelated hematopoietic stem cell transplantation. J Hemother Stem Cell Res 2002;11:731

- **Description**
- **Methods**

  - **Objective(s)**
    Evaluation of lower thymoglobulin dose for prevention of GvHD
  - **Study design**
    Single center, single arm, prospective
  - **Study population /Sample size**
    21 patients, various hematologic malignancies
  - **Treatments**
    Matched or mismatched unrelated donor graft (bone marrow or peripheral blood stem cells), Thymoglobulin 3.5 mg/kg or 5 mg/kg total
  - **Outcomes/endpoints**
    GvHD, survival, engraftment

- **Results**

  - **Recruitment/ Number analysed**
    21 total, 6 children
  - **Baseline data**
    No separate reporting of paediatric results
  - **Efficacy results**
    All patients engrafted, OS was 56%, acute GvHD II-IV 55%, acute GvHD II-IV 21%, chronic GvHD 29%, relapse rate 24%
  - **Safety results**
    5 deaths from infection, transplant related mortality 16% at day 100

Rapporteur's Comment
The authors conclude that the lower dose regimen may be associated with lower risk of complications (infection, relapse) but similar outcome as regards GvHD and transplant related mortality. The heterogeneous population/intervention make any interpretation difficult, paediatric data are not available.

Remberger et al. Association between pretransplant Thymoglobulin and reduced nonrelapse mortality rate after marrow transplantation from unrelated donors. Bone Marrow Transplant 2002;29:391-397

- **Description**
- **Methods**

  - **Objective(s)**
    Evaluate effect of Thymoglobulin on survival
  - **Study design**
    Retrospective, matches cohorts from two different centres

- **Study population /Sample size**
  52 patients from Huddinge Hospital, for each patient 2 matched patients from Fred Hutchinson Cancer Center, AML, ALL, CML, 16% children
- **Treatments**
  Thymoglobulin 10 mg/kg total, CsA and MTX for GvHD prophylaxis, bone marrow graft from unrelated donors
- **Outcomes/endpoints**
  Non-relapse mortality, disease free survival, overall survival

➢ **Results**

- **Recruitment/ Number analysed**
  See above
- **Baseline data**
  Reasonably well matched
- **Efficacy results**
  Non relapse mortality significantly lower in the Thymoglobulin group (hazard ratio 0.3) overall mortality significantly lower in the Thymoglobulin group (hazard ratio 0.5), relapse risk not different, relapse risk in CML in CP higher, GvHD risk probably lower in thymoglobulin group (data not directly comparable due to different scoring)
- **Safety results**
  No specific findings reported, higher rate of fatal pneumonia in thymoglobulin group

Rapporteur's Comment
The authors conclude that the Thymoglobulin is associated with decreased non relapse mortality in patients with leukaemia. Paediatric data are not reported separately. Although the cohorts appear well matched (age, diagnosis, stage of disease, CMV status, marrow cell dose) there are differences in the treatment protocol. The higher rate of relapse in patients with CML in chronic phase is mentioned as concern that may be related with the dose.

PUBLICATIONS SUBMITTED BY FRESENIUS

De Santo et al. Midterm results of a prospective randomised comparison of two different rabbit-antithymocyte globulin induction therapies after heart transplantation. Transplantation Proc 2004;36:631-637

Rapporteur's Comment
One of the few methodologically better studies actually comparing treatments within a trial, in this case Thymoglobulin to ATG-Fresenius. No differences in efficacy are evident, safety appears to be comparable although more CMV infections were observed in the Thymoglobulin group. Although some children were included no further information is extractable. Dose was 2.5 mg/kg x 7 days.

Laufer et al. Impact of low-dose steroids and prophylactic monoclonal versus polyclonal antibodies on acute rejection in cyclosporine and azathioprine immunosuppressed cardiac allografts. J Heart Transplant 1989;8:253-261

Rapporteur's Comment

Although some children were included no further information relevant for paediatrics is extractable. Dose 10 mg/kg x 7-10 days.

Neuhaus et al. Comparison of quadruple immunosuppression after liver transplantation with ATG or IL-2 receptor antibody. Transplantation 1993;55:1320-1327

Rapporteur's Comment
Anti-IL2 receptor therapy compares favourably to ATG-Fresenius. Although some children were included no further information relevant for paediatrics is extractable. Dose 5 mg/kg x 7 days.

Remberger et al. Polyclonal ATG as part of the preparative regimen for paediatric allogeneid stem cell transplantation. Second ATG-Fresenius Satellite Symposium

- **Description**
- **Methods**

  - **Objective(s)**
    Report of experience
  - **Study design**
    Retrospective cohort 1988-2000
  - **Study population /Sample size**
    65 children
  - **Treatments**
    Allogeneic stem cell transplantation, ATG used as part of the conditioning regimen. 40 cases with matched unrelated donor, 16 cases with HLA-identical sibling, one from a two antigen mismatched parent, eight from mismatched donor. PBSC in six cases, bone marrow in 59 cases.
    Conditioning with cyclophosphamide, some patient additionally received TBI/TLI, some where conditioned with busulfane/cyclophosphamide
    GvHD prophylaxis consisted of MTX/CsA, six patients received an in vitro T cell depleted graft. 20 patients received ATG-Fresenius, 45 were given Thymoglobulin, duration of treatment was variable.
    ATG-Fresenius dose median 4.9 mg/kg x 5 days.
  - **Outcomes/endpoints**
    Engraftment, AE,

- **Results**

  - **Efficacy results**
    Neutrophil engraftment was faster with Thymoglobulin (16 days vs. 19 days)
  - **Safety results**
    AE were more common with Thymoglobulin (73% vs 40%), chronic GvHD developed in 25% of patients

Rapporteur's Comment
Results do not contribute to the understanding of comparative safety and efficacy of Thymoglobulin or ATG-Fresenius, they merely document the use.

Remberger et al. Effect on cytokine release and graft-versus-host disease of different anti-T cell antibodies during conditioning for unrelated haematopoietic stem cell transplantation. Bone Marrow Transplant 1999;24:823-830

- **Description**
- **Methods**

  - **Objective(s)**
    Report of experience
  - **Study design**
    Retrospective analysis
  - **Study population /Sample size**
    145 patients receiving stem cell transplant from an unrelated donor.
  - **Treatments**

  - **Outcomes/endpoints**
    Survival, GvHD

- **Results**

  - **Recruitment/ Number analysed**

  - **Baseline data**
    Patients were treated according to pricing and availability. ATG-F was used in 26, Thymoglobuline in 61 patients and OKT-3 in 45 patients.
  - **Efficacy results**
    Lowest rate of acute GvHD in Thymoglobulin (12%) vs ATG-Fresenius (25%) vs. OKT3 (43%); highest relapse rate at 4 years with Thymoglobulin (49%), lowest with ATG-Fresenius (8%); overall survival at 4 years best with ATG-Fresenius (63%) vs Thymoglobulin (50%) vs. OKT3 (45%)
  - **Safety results**
    AE most common (also most severe) in OKT3 (90%) vs Thymoglobulin (78%) vs. ATG-Fresenius (38%)

Rapporteur's Comment
There are no data that would enable specific conclusion for the paediatric field. This study nicely highlights the difficulties in defining benefit of therapy in this patient population. Prevention of GvHD appears to be associated with higher relapse rate, the results for survival are inconclusive. OKT3 appears to be the worst substance in many aspects.

Schleuning et al. Dose-dependant effects of in vivo antithymocyte globulin during conditioning for allogeneic bone marrow transplantation from unrelated donors in patients with chronic phase CML. Bone Marrow Transplant 2003; 32:243-250

Rapporteur's Comment
This was a dose escalation trial. Acute GvHD was more frequent in patients with lower dose of ATG-Fresenius, however there was no difference in chronic GvHD. Overall survival was also best in those patients that had received > 60 mg/kg ATG-Fresenius. There are no separate data from pediatric patients that would enable specific conclusion for the paediatric field. In addition CML is rather rare in the paediatric population.

Sedlacek et al. Low mortality of children undergoing hematopoietic stem cell transplantation from 7 to 8/10 human leukocyte antigen allele-matched unrelated donors with the use of antithymocyte globulin. Bone Marrow Transplant 2006;745-750

- **Description**
- **Methods**

  - **Objective(s)**
    Report experience
  - **Study design**
    Retrospective, 2001-2005
  - **Study population /Sample size**
    88 paediatric patients, different diseases
  - **Treatments**
    Allogeneic stem cell transplantation (PBSC, bone marrow)
  - **Outcomes/endpoints**
    Survival, engraftment, GvHD

- **Results**

  - **Recruitment/ Number analysed**

  - **Baseline data**
    Diverse population, malignant and non-malignant disease. ATG-Fresenius total 40 mg/kg (range 30-60 mg/kg)
  - **Efficacy results**
    Acute GvHD in 65% of patients, chronic GvHD in 32% of patients, relapse in 22% of patients with malignant disease; overall survival not different in malignant vs. non-malignant disease, 13% transplant related mortality
  - **Safety results**
    PTLD in 5% of patients, one fatal CMV pneumonia

Rapporteur's Comment
As this is a non-comparative trial it is difficult to draw any firm conclusions. Transplantation appears possible with the used regime, cumulative dose is comparable to the dose used in adults. Whether a decrease in GvHD is offset by an increase in relapse and/or infectious complications cannot be answered using this design.

Zander et al. ATG as part of the conditioning regimen reduces transplant-related mortality (TRM) and improves overall survival after unrelated stem cell transplantation in patients with chronic myelogenous leukemia (CML). Bone Marrow Transplant 2003;32:355-361

- **Description**
- **Methods**

  - **Objective(s)**
    Comparison of different conditioning regimens
  - **Study design**
    Retrospective
  - **Study population /Sample size**
    333 CML patients in 7 centers
  - **Treatments**
    145 patients had received ATG-Fresenius at a dose of 40 mg/kg or higher, 188 received no ATG
  - **Outcomes/endpoints**
    Survival, engraftment, GvHD

- **Results**

  - **Recruitment/ Number analysed**
    145 patients had received ATG-Fresenius at a dose of 40 mg/kg or higher, 188 received no ATG
  - **Baseline data**
    Imbalance in stem cell source
  - **Efficacy results**
    Engraftment sooner with ATG-Fresenius, survival at 3 years 70% with ATG-Fresenius vs 57% in non-ATG group, EFS 58% vs 55%, acute GvHD 65% in ATG-Fresenius group vs. 77% in non-ATG group; chronic GvHD 44% in ATG group vs. 66% in non-ATG group,
  - **Safety results**
    Transplant related mortality higher in non-ATG group

Rapporteur's Comment
This retrospective analysis shows consistent advantage of therapy with ATG-Fresenius compared to no ATG as regards survival, acute GvHD and chronic GvHD. No specific conclusions for the paediatric field are possible as results are not reported separately. CML is rather rare in children.

Study AP-AA-11-GB

- **Description**
- **Methods**

  - **Objective(s)**
    The study was planned to be a prospective, active controlled, randomized, open-label, phase III, pilot study to evaluate the efficacy and safety of single high-dose ATG-Fresenius compared to standard Lymphoglobulin therapy in pediatric patients undergoing heart, lung, or combined heart-lung transplantation.
  - **Study population /Sample size**
    30 planned
  - **Treatments**
    ATG-Fresenius single 9 mg/kg bw IV dose intra-operatively, Lymphoglobulin 0.5 mL/kg bw/day after cross clamp release post transplantation (day 0); dose adjustment on days +1 and +2 according to T-cell count (administration scheduled for a total of three days)
  - **Outcomes/endpoints**
    Graft survival, patient survival, rejections, heart function, and heart-lung function

- **Results**

  - **Recruitment/ Number analysed**
    Sixteen patients were randomized to treatment and received study medication: nine patients (9/16, 56%) in the ATG-Fresenius group and seven patients (7/16, 44%) in the Lymphoglobulin group.
    A total of three patients (3/9, 33%) in the ATG-Fresenius group underwent combined heart-lung transplants, five (5/9, 56%) received a heart transplant and one (1/9, 11%) received a lung transplant. In the Lymphoglobulin group, one patient (1/7, 14%) received a combined heart-lung transplant, and six (6/7, 86%) received heart transplants.
  - **Baseline data**
    Reasonably balanced
  - **Efficacy results**
    Five patients in the ATG-Fresenius group died compared with one patient in the Lymphoglobulin group. None of the deaths appeared to be directly related to the administration of either of the immunoglobulin preparations.
  - **Safety results**
    In the ATG-Fresenius group, one patient experienced a cardiac arrest peri-operatively and died. The second patient died on oxygen awaiting a donor for re-transplantation. The third patient died following seizure with hypoxia and ventricular fibrillation following hospitalization on day 378 for lethargy, fevers, abdominal pain and vomiting followed by tonic seizure. The fourth patient died due to cardiac failure on day 315. Autopsy revealed chronic allograft rejection with arteriopathy. The fifth patient died on day 16 during acute rejection crisis. In the Lymphoglobulin group one patient died on day 630 due to consequences of severe coronary vasculopathy.

Rapporteur's Comment
This prospective trial was not finished and any analysis is difficult as data collection appears to be inconsistent. At least 3 of the 5 deaths in the ATG-Fresenius group appear to be caused by rejection i.e. insufficient efficacy. However in both groups rejection rate was 100%.

3. Overall conclusion

It should be noted first that although Thymoglobulin and ATG-Fresenius have the same ATC code they actually constitute two different drug products. Both products are a highly complex mixture of rabbit immunoglobulin that is raised against different antigens, human thymus tissue in the former and a human cell line in the latter product. Dosage recommendations are also different for both products, at least in the documents that are available to the Rapporteur. Neither company has provided all of the SmPCs that are approved in the different countries.

The submitted studies document the broad clinical experience with Thymoglobulin and ATG-Fresenius in paediatrics and their use in the medical community. There is no clear consensus evident as regards the dosing or the indications and use appears to be changing over time. This is most likely also evident in the different indications that were granted in different countries. It has to be seen in the context of the long history of the products which were approved a long time ago, and the difficult indications where both products are used. In the opinion of the Rapporteur the quality of the provided publications does prevent any further conclusions as most studies are non-controlled, the interventions are often multiple, doses vary, co-medications vary, changes in medical practise are evident over time and patient populations are not comparable over time. In those studies that contain a control group multiple confounding factors are present, most often different time periods where patients were treated with one or the other protocol, or different baseline characteristics as regards the underlying disease. Some studies involve adult patients and paediatric patients but do not differentiate in the analysis.

Genzyme Europe B.V. has provided a specific and detailed “Overview of Safety”, taking into account post-marketing observation and specific safety concerns taken from the published literature. This effort is acknowledged and could be helpful in at least describing safety in more precise terms.

The comments that have been received support the rapporteur’s assessment.

One of the goals of the paediatric worksharing is to provide an overview of study data concerning the use in children and to update the SPC with these data. No proposal to include the results of the studies in section 5.1 was made. The MAHs are requested to submit a text proposal for section 5.1 or justify the omission of such a proposal in order to facilitate the discussion.

Request for supplementary information

1) The MAHs are requested to provide SmPC from all countries where the product is approved, including paediatric relevant information

2) Fresenius Biotech GmbH is requested to provide an evaluation of safety based on post-marketing observation and specific safety concerns.

3) The MAHs are requested to submit a text proposal for section 5.1 or justify the omission of such a proposal in order to facilitate the discussion.

Assessment of responses to questions

1) Both MAHs have provided SmPC from the European countries where the respective product is approved. As expected the indications are varied from country to country but posology

recommendations are reasonably similar. Only few SmPCs contain information related to paediatric use, most of them are related to the posology section 4.2, one is related to section 4.8.

2) Fresenius has provided the requested safety analysis based on post-marketing observations and the analysis of specific concerns. The conclusion of the MAH is that the overall safety profile of ATG-Fresenius is similar in children and in adults. The Rapporteur agrees that based on the currently available information there is no qualitative difference in the safety profile. It may very well be that there is a quantitative difference, e.g. it is generally believed that complications caused by certain viruses (EBV, CMV, BKV) are more common and more severe in children than in adults. However, the safety database does not allow to make exact statements.
   Fresenius proposes to amend section 4.2 with the following statement: “The experience in paediatric patients is limited. Current experience shows that paediatric patients do not require a different dosage than adult patients.”
   Fresenius also proposes to amend section 4.8 with the following statement: “ATG-Fresenius is administered in relation to body weight. The experience in paediatric patients is limited. Current experience shows that the safety profile in paediatric patients does not differ from the adult populations.”
   The Rapporteur agrees on the Fresenius proposal for section 4.2 and 4.8 in principle but would recommend a wording in line with the QRD templates (see Section VIII) that could be used for both products.

3) Fresenius has provided a proposal for section 5.1 that describes the experience in paediatric kidney transplantation and in allogeneic stem cell transplantation in some detail. Given the varied indications in European countries and the quality of the clinical trial data the Rapporteur does not agree on this proposal.

   Genzyme proposes to include a more general statement that reflects on the widespread clinical use but also the limitations of the available data. This approach is agreed to in principle by the Rapporteur but would recommend a slightly more cautious wording that could be used for both medicinal products.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

It should be noted first that although Thymoglobulin and ATG-Fresenius have the same ATC code they actually constitute two different drug products. Both products are a highly complex mixture of rabbit immunoglobulin that is raised against different antigens, human thymus tissue in the former and a human cell line in the latter product. Dosage recommendations are also different for both products.

The submitted studies document the broad clinical experience with Thymoglobulin and ATG-Fresenius in paediatrics and their use in the medical community. There is no clear consensus evident as regards the dosing or the indications and use appears to be changing over time. This is most likely also evident in the different indications that were granted in different countries. It has to be seen in the context of the long history of the products which were approved a long time ago, and the difficult indications where both products are used. In the opinion of the Rapporteur the quality of the provided publications does prevent any further conclusions as most

studies are non-controlled, the interventions are often multiple, doses vary, co-medications vary, changes in medical practise are evident over time and patient populations are not comparable over time. In those studies that contain a control group multiple confounding factors are present, most often different time periods where patients were treated with one or the other protocol, or different baseline characteristics as regards the underlying disease. Some studies involve adult patients and paediatric patients but do not differentiate in the analysis.

In order to get better insight in the current information of SmPC in Europe the MAHs were requested to provide the documents and specifically provide information on the mentioning of paediatric information within the SmPC.

Both companies have provided satisfactory responses to the questions posed, even though the Rapporteur does not agree an all proposals for SmPC changes.

- **Recommendation**

The MAHs are recommended to include the following paediatric information in the SmPC.

Section 4.2 Posology
Paediatric Population
Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. Available information indicates that paediatric patients do not require a different dosage than adult patients.

Section 4.8 Undesirable Effects
Paediatric Population
Currently available data are limited. Available information indicates that the safety profile of <product name> in paediatric patients is not fundamentally different to that seen in adults.

Section 5.1
Paediatric population
Multiple reports regarding the use of <product name> in children have been published. These reports reflect the broad clinical experience with this product in paediatric patients and suggest that the safety and efficacy profiles in paediatric patients are not fundamentally different to that seen in adults.
However, there is no clear consensus with regards to the dosing in paediatrics. As in adults, the posology in paediatrics depends on the indication, the administration regimen, and the combination with other immunosuppressive agents. This should be considered by physicians before deciding on the appropriate dosage in paediatrics.

The MAHs are recommended to include paediatric information in the Package Leaflet (PL) corresponding to the SmPC changes.

Type IB variation to be requested from the MAH within 90 days.

VI. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s)
Neovii Biotech GmbH	AT	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	BE	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
C.A.Papaellinas & Co Ltd	CY	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	CZ	ATG-Fresenius S	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	DE	ATG-Fresenius S	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	EE	ATG-Fresenius S	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	ES	ATeGe-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	FR	Globulines Antilymphocytaires Fresenius 20 mg/ml	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Fresenius Medical Care Budapest	HU	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	IE	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s)
Neovii Biotech GmbH	IT	Immunoglobuline anti-linfociti T umani Fresenius	20 mg/ml	Concentrate for solution for infusion	Concentrate for solution for infusion
Neovii Biotech GmbH	LT	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	LV	ATG-Fresenius S	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Fresenius Kabi Nederland B.V.	NL	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	PL	ATG-Fresenius S	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Fresenius Medical Care Portugal	PT	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	RO	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	SE	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Neovii Biotech GmbH	SK	ATG-Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-human T-lymphocyte immunoglobulin from rabbits
Medias International	SL Slovenia	Anti-T-lymphocyte Immunoglobulin Fresenius	20 mg/ml	Concentrate for solution for infusion	Anti-T-Limfocitni Imunoglobulin Fresenius
Genzyme Europe B.V.	AT	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s)
Genzyme Europe B.V.	BG	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	BE	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	CZ	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	DE	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	DK	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	EE	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	EL	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	ES	Timoglobulina	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	FI	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	FR	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	HU	Thymoglobulin	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	IT	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	LT	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	LU	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	LV	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	NL	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form	Active Substance(s)
Genzyme Europe B.V.	NO	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	PL	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	PT	Timoglobulina	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	RO	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	SE	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin
Genzyme Europe B.V.	SK	Thymoglobuline	5 mg/ml	powder for solution for infusion	Rabbit anti-human thymocyte immunoglobulin