THYMoglobuline
(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021

UKPAR

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THYMOGLOBULINE

(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021

LAY SUMMARY

The MHRA today granted Genzyme Europe BV a Marketing Authorisation (licence) for the medicinal product Thymoglobuline (PL 12375/0021), which is an immunosuppressive agent. This medicine is prescription only and indicated for immunosuppression in solid organ transplantation. It is indicated for the prevention of graft rejection in renal transplantation, treatment of steroid resistant graft rejection in renal transplantation, and prevention of graft rejection in heart transplantation.

Organ transplantation has been an area of rapid development during more than four decades. Transplantation of human organs and tissues saves many lives and restores essential functions in circumstances when no medical alternative of comparable effectiveness exists. End-stage organ failure is a public health concern with few treatment alternatives, transplantation often being the best option for vital organs: kidney, liver, heart and lungs. The transplantation of solid organs, such as kidney and heart, is increasingly a regular component of health care in all countries and over 1 million people worldwide have undergone successful organ transplantation. Of the 70 000 or so solid organs transplanted annually world-wide, 50 000 are kidney replacements. In Europe, the annual transplantation rate is 15 000 kidneys and 2 000 hearts.

When an organ or tissue from one individual is transplanted into a genetically non-identical other individual, a series of cellular and molecular events are initiated. If no action is taken, this will result in rejection of the graft. The incidence of rejection depends on many internal factors and type of transplantation. The aim of immunosuppression in clinical practice is to control an undesirable immune response while avoiding, if possible, the complications of immunodeficiency. Improvements in immunosuppressant agents also reduce the need for living donors to be genetically related to the recipient. Immunosuppressant agents are used to prevent acute rejection episodes without adversely affecting the organs and also without overly immunosuppressing patients in the long term with the consequent increased risk of infections and malignancies.

The data presented to the MHRA demonstrated that Thymoglobuline is effective in immunosuppression in solid organ transplantation and there were no unexpected safety concerns. It was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
THYMOGLOBULINE

(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of clinical, pre-clinical and quality data, the UK granted a marketing authorisation for the medicinal product Thymoglobuline on 19th March 2008. The product is prescription only and indicated for immunosuppression in solid organ transplantation in the following instances:

- Prevention of graft rejection in renal transplantation
- Treatment of steroid resistant graft rejection in renal transplantation
- Prevention of graft rejection in heart transplantation.

This was a national bibliographic application for Thymoglobuline submitted under article 10(a)(ii) of Directive 2001/83/EC as amended, a product with well established use in the Community.

Thymoglobuline must always be used under strict medical supervision and prescribed by physicians with experience in using immunosuppressive agents. The posology depends on the indication, the administration regimen and the combination with other immunosuppressive agents.

Current immunosuppressive pharmacological therapies can be classified according to mechanism of action.

- Glucocorticosteroids (e.g., prednisolone)
- Immunophilin binding agents: calcineurin inhibitors (e.g., cyclosporine, tacrolimus) or mTOR inhibitors (e.g., sirolimus, everolimus)
- Inhibitors of de novo nucleotide synthesis: purine synthesis (e.g., mycophenolic acid, mizoribine), pyrimidine synthesis (e.g., leflunomide)
- Antimetabolites: (e.g., azathioprine)
- Antibodies: antibodies against immune proteins (e.g., polyclonal ALG, ATG, IL-2R targeted, anti-CD25 and anti-CD3 monoclonal), intravenous immunoglobulin (e.g., IVIG).

Thymoglobuline falls into the category of antibodies against immune proteins. The active ingredient of Thymoglobuline is a stabilised solution of purified rabbit immune globulins with immunosuppressive activity which recognises thymocytes and human peripheral blood lymphocytes. Immune globulin type is IgG.
QUALITY ASSESSMENT

INTRODUCTION
This is a National bibliographic application submitted under article 10(a)(ii) of Directive 2001/83/EC as amended, a product with well established use in the Community. The active ingredient of Thymoglobuline is a stabilised solution of purified rabbit immune globulins with immunosuppressive activity which recognises thymocytes and human peripheral blood lymphocytes. Immune globulin type is IgG. The proposed indication is for prophylaxis and/or treatment of rejection episodes in organ transplantation. Thymoglobuline is currently prescribed on a compassionate use basis (named patient basis) in the UK. However, in light of the continuing need for Thymoglobuline, the company has decided that they now wish to apply for a marketing authorisation in the UK.

ATC classification: L04AA04 (Immunosuppressive agents). The pharmaceutical form is Powder for solution for infusion and strength after reconstitution with water for injections is 5 mg/ml. The product is given by intravenous infusion.

BACKGROUND
Genzyme is seeking approval in accordance with 10a of 2001/83/EC, i.e. a "bibliographic application", as this best reflects the well-established use of the product. Thymoglobuline was first approved in 1984 in France. This product is currently authorised in 21 EU member states, with Sweden (2002) being the most recent, and 29 non-EU member states. Most of the clinical development was conducted in the late 1970s and early 1980s around the time of first EU approvals. There are differences in medical practice within Member States and this is, to a large extent reflected in different indications. Medical practice also varies in the selection of the population of patients to be treated. As a result, it would not be feasible to harmonise the use of the product in clinical practice. However, the proposed indications in this MAA encompass those approved in current national authorisations. The European Commission communicated the need for maintaining bibliographical national applications in 1998 at the end of the transition phase for the Mutual Recognition Procedure. This is reflected in their Communication, (1998/C 229/03). "In the case of a medicinal product with a well established use demonstrated in accordance with Article 4 (3) (8a) (ii) of 65/65/EEC, 'bibliographic application' (now Article 10a of 2001/83/EC), this well established use being based on data referring to an existing group of products with different SPCs in the Member States, national independent procedures could continue to be followed.". This explanation justifies the application for this product by the National, instead of the Mutual Recognition route.

The active ingredient is obtained by immunization of rabbits with human thymocytes and subsequent isolation and purification. This immunosuppressive product contains cytotoxic antibodies directed against a broad array of surface antigens expressed on T cells and adhesion molecules including CD2, CD3, CD4, CD8, CD11a, CD28, CD45, Human Leukocyte Antigen (HLA) Class I and HLA-DR subsets.

Possible mechanisms by which Thymoglobuline induces immunosuppression include: lymphocyte depletion from the circulation and modulation of T-cell activation, homing. Thymoglobuline is thought to induce T-cell depletion and modulation by a variety of methods, including receptor-mediated complement-dependent lysis, opsonization and
subsequent phagocytosis by macrophages, and immunomodulation leading to long-term depletion via antibody dependent cell mediated cytotoxicity (ADCC), and activation-induced and activation-associated apoptotic cell death.

**COMPOSITION**

**Composition**
Thymoglobuline is a freeze-dried powder consisting of rabbit anti-human thymocyte globulin (5mg/ml reconstituted), glycine, mannitol and sodium chloride. It is reconstituted with 5 ml of Water for Injections. The minimum and maximum lyophiliser load adequately cover the range of DP detailed under “Manufacturing Formula”.

**Container**
Drug Product is presented in 10 ml type I glass tubing vials. A representative Certificate of Analysis and list of specifications is provided for each component. Suppliers are audited.

**Development Pharmaceutics**

**Drug Substance**
As this application is based on the use of bibliographical data for efficacy and safety, the applicant has used this section to demonstrate that the product proposed is similar from a manufacturing perspective to the product described in the literature. The Drug Substance manufacturing process described in this application is identical to the manufacturing process approved by other EU countries with one exception: the number of cells used for the immunization of the rabbits. It was planned to submit the variation for immunization of rabbits with a decrease in the number of cells used for immunisation in all other EU customer countries in 2006. As of June 2007, this variation is approved in Austria, Estonia, Finland, France, Germany, Latvia, The Netherlands, Norway, Romania, Sweden and Norway (and USA). It is under review in 10 member states and 5 non-EU countries. It is not a reportable change in the remaining countries in which a licence is granted.

The reason for the decrease in the number of cells used for immunisation is an increase in demand for Thymoglobuline and the scarcity of thymocytes.

Data provided on DS remains valid for the bibliographic application.

**Drug Product**
The Thymoglobuline filling and lyophilization process has been transferred from the Sanofi-Aventis facility in France to the Genzyme facility in Ireland. Several differences in manufacturing equipment were noted. Critical parameters of protein concentration, monomer/dimer content, aggregates and residual water content pre and post lyophilisation are unaffected.

**Vial Capping**
A study report detailing the change in composition of the vial, and studies performed to assure the adequacy of the new vial is provided and is acceptable.

**Product Compatibility testing**
The suitability of the closure system was demonstrated.
The changes which have been introduced into the manufacture of drug product have been adequately justified, the development has been adequately documented and it would appear to be unlikely that they would adversely affect the quality or safety of the product. This is confirmed by demonstrating that product meets current specifications. In particular, it has been noted that no significant difference is noted in complement dependent activity, molecular size distribution or residual water content. Solubility has not been affected.

Overall, the applicant has demonstrated that the quality of DS and DP has not changed compared to product manufactured by the current process and facilities and the bibliographic application remains valid.

**METHOD OF PREPARATION**

**Manufacturing Sites**

GMP certificates from EU competent authorities (AFSSAPS, IMB,MHRA) are provided for the following sites: manufacture and control of Thymoglobuline drug substance and final bulk product, fill/finish, sterile filtration, labelling and packaging, finished product storage, QC testing and batch release.

The Finished Product has been manufactured at Sanofi-Aventis, France. To increase reliability it is proposed to manufacture the drug product at Genzyme Ireland Ltd, Ireland. There are no changes made to the Finished Product components or formulation. Batch release data from FP from Sanofi-Aventis, and several process validation lots from Genzyme Ireland Ltd have been provided and pass all batch release specifications.

**Manufacturing Formula**

This has been provided and is acceptable.

**Manufacturing Process**

Process Flow Diagrams have been provided and are acceptable.

**Active Ingredient**

**Preparation of Primary batches of Active Ingredient**

This has been adequately described and demonstrates the suitability of the process.

**Final Product**

**Shipping and Storage**

Details have been provided and are satisfactory.

**Component/Equipment Preparation**

Details of line clearance, cleaning and sterilisation are provided for the major items of equipment and are acceptable.

**Sterile Filtration and Filling**

Details of sterile filtration and filling have been provided and are satisfactory.
Lyophilization
The process of lyophilisation has been adequately described and is acceptable.

Capping
Details of capping of lyophilized vials are capped have been provided and are satisfactory. Incompletely sealed or uncapped vials are rejected. Capped vials are transported to a refrigerated holding room within an inspection area of the Fill/Finish facility.

Inspection
Product inspection is performed by trained operators.

Labelling and Packaging
Automatic labelling and packaging are performed in two facilities in the UK and Ireland. Descriptions of the processes have been given and are satisfactory. Checks are made to ensure correct labelling with product name, batch code, expiry date etc.

Overall the manufacturing process is adequately described and controlled. Details have been provided as requested. Transport has been successfully validated in study 02-0161. Study date is in 1995. A more recent study, W2-0436 (March 2007) successfully validated shipping in a refrigerated van by SMS Temp Critical within the range 2-8°C.

Process Validation
A number of process validation studies have been performed. These have been described for the manufacture of drug substance and manufacture of drug product and are satisfactory.

Validation of DS and DP is comprehensive and has demonstrated the suitability of the process.

CONTROL OF STARTING MATERIALS

ACTIVE SUBSTANCES

Immunogen
Thymoglobuline is prepared from rabbits which have been immunised with a thymocyte suspension.

The preparation of immunogen is adequately described validated and controlled.

Rabbit Sera
Rabbits of New-Zealand or California or hybrid strains thereof are used. Generally, procedures and controls are adequately described. Rabbit breeding and serum collection facilities have been named and procedures to ensure SPF status are adequately described.

Formaldehyde-treated Red Blood Cells
The red blood cells (pre-formaldehyde treatment) are supplied and tested by the American Red Cross. Certification covers testing for antibodies to HIV 1+2, antibodies to HTLV 1+2, antibodies to HCV, antibodies to HBe, antigen to HBs, syphilis and HCV (RNA) and HIV (RNA). Red Blood Cells are collected, stored and shipped in accordance with current US

Use of RBC which are collected, stored and shipped according to the relevant US legislation is acceptable. Since the USA is regarded as a low risk country for TSE infection, then RBC sourced from the US are preferable to EU sourced cells. The collection centres used by the ARC have been named and current certification from US and EU competent inspectors provided for these sites.

OTHER INGREDIENTS

The following chemical ingredients are to current EP and USP specifications: glycine, sodium chloride, D-mannitol, WFI.

The following chemical reagents are to current EP and USP specifications: hydrochloric acid, sodium hydroxide, disodium phosphate dihydrate, anhydrous sodium sulphate, Tween 80, formaldehyde, isopropyl alcohol, purified water. The applicant proposes including “Contains traces of Polysorbate 80 (Tween 80)” in SPC 6.1, and the PIL.

DEAE Cellufine A-500 (Millipore) is tested to in house specifications which are provided.

The applicant states that Thymoglobuline does not contain any ingredients or reagents of human or animal origin. Human RBC is considered separately.

The testing and specifications are acceptable.

PACKAGING MATERIAL (IMMEDIATE PACKAGING)

Details have been provided and are acceptable.

CONTROL TESTS ON INTERMEDIATE PRODUCTS

Specifications

Testing is performed on the Active Ingredient (AI) and on the Final Bulk Product (FBP). The tests used in the specifications are selected based on past experience and on compendial requirements.

The release specifications and the end of shelf life specifications for the Active Ingredient are identical to each other.

Comment

The RBC supplied by ARC are not specifically tested for resistant non-enveloped viruses. A specific assay for parvovirus B19 is included in batch release specifications, and the applicant should also introduce testing for HAV to provide additional assurance.

Insufficient assurance is provided about the freedom of this product from HAV and specific testing should be introduced as a batch release assay, as requested in the initial assessment.
Batch Analysis

Active Ingredient
AI batch release results are supplied and all results are within current specification and no trends are apparent.

Final Bulk Product
Data from consecutive FBP batches have been supplied. All results are within current specifications and no trends are apparent.

Final Product
Data from commercial batches which were manufactured at the Waterford fill/finish facility is provided. All results are within current specifications and no trends are apparent.

Data from consecutive batches of AI, FBP and FP has been provided and all data is within current specifications and no trends are apparent.

Assays and Assay Validation
Test methods for haemolysins titre, haemagglutinins titre, determination of pH, bacterial and fungal sterility and the test for pyrogens are performed according to European Pharmacopoeial monographs and so the methods or validations are not required.

Appearance
The test consists of a visual examination of the product and validation data is not required for this assay. Specification complies with PhEur <1928>.

Sufficient and satisfactory information is provided.

Determination of the lymphocytotoxic activity (LT 25%)
The validation as presented is adequate and demonstrates that the assay is under control.

Total Protein
Sufficient and satisfactory information is provided.

Residual Formaldehyde Content
The limit of formaldehyde is based on historical data and is at a safe level.

Gammaglobulin Purity
Gammaglobulin purity is tested by agarose gel electrophoresis. Sufficient and satisfactory information is provided.

Distribution of Molecular Size
Sufficient and satisfactory information is provided.

Mannitol Content
Mannitol content is tested by ion exchange chromatography, with refractive index detection. Sufficient and satisfactory information is provided.
Glycine Content
The specification is in compliance with the PhEur monograph <1928> and sufficient and satisfactory information is provided.

Chloride Content
Sufficient and satisfactory information has been provided.

Parvovirus B19
A SOP has been provided regarding detection of parvovirus B19. Development, validation and analysis are performed under GLP conditions. Sufficient and satisfactory information is provided.

CONTROL TESTS ON THE FINISHED MEDICINAL PRODUCT

SPECIFICATIONS AND ROUTINE TESTS

The release specifications and test methods have been provided and generally the requirements of the PhEur monograph 1928 are complied with.

Assay and Assay Validation
Test methods for identification A and B, determination of pH, osmolality, purity by SDS-PAGE, haemolysins titre, haemagglutinins titre, bacterial and fungal sterility test, and the test for pyrogens are performed according to the European Pharmacopoeia (EP) and so methods and validation are not required.

The assays for; appearance after reconstitution, determination of lymphocytotoxic activity LT 25%, Identification C), total protein content, mannitol, glycine, chloride content, distribution of molecular size and gammaglobulin purity (agarose gel electrophoresis) are identical to the drug substance assays. FBP and FP have identical composition and therefore, validation with FBP is relevant to FP. The remaining, FP specific assays are discussed below.

Appearance of freeze-dried product
The appearance is determined by a visual examination of the lyophilizate. Aspect and colour are recorded. SOP is supplied, validation is not required.

Sufficient and satisfactory information is provided.

Solubility
The product is reconstituted with 5 ml of Water For Injection (WFI). Time for complete dissolution is recorded. Validation is not required.

Sufficient and satisfactory information is provided.

Water
The principle of the method is the one described in the European Pharmacopoeia “Water: Micro Determination”. That is the Karl Fischer method. Specification is in compliance with PhEur 1928. Sufficient and satisfactory information is provided.
Thrombocyte antibodies
Specification is sufficient to satisfy the requirements of PhEur monograph 1928.

Sufficient and satisfactory information is provided.

LTIP50 (Experimental Test for Additional Studies)
Sufficient and satisfactory information is provided.

STABILITY

STABILITY TESTS ON ACTIVE SUBSTANCES
The stability test results for several batches of Active Ingredient (AI) remain within specifications after storage at 2-8 °C for up to 26 weeks. The applicant has committed to adjusting the current stability protocol to comply with PhEur monograph 1928. The protocol has been adjusted to comply with PhEur 1928. A copy of the protocol is provided.

STABILITY TESTS ON THE FINISHED MEDICINAL PRODUCT
Accelerated stability data to 6 months supports the stability of the product.

In-Use Stability Tests
A shelf-life of 36 months was accepted.

OTHER INFORMATION

Facilities and Equipment
Details of sub-contractors and external contract test laboratories have been provided.

The facilities and equipment have been adequately described, and appropriate and up to date GMP licenses have been provided by EU competent authorities. The status (GLP, GMP) of the contract facilities has been clarified and appropriate certification provided.

Pathogen Safety

Adventitious Bacteria and Fungi
The manufacturing process for the DS contains adequate steps to remove bacterial and fungal bioburden. Bioburden is controlled throughout the DS process. The Final Product is controlled for bacterial and fungal sterility and endotoxins (PhEur).
TSE Risk
The risk assessment made for thymus is accepted.

This product has been available since the early 1980’s and there appears to be no known association of this product with nvCJD. Therefore, the measures taken to ensure a positive risk assessment of this product regarding TSE infectivity are regarded as sufficient.

Adventitious Viruses

Selection and testing of the Materials of Biological Origin

**Rabbits:** The animals are kept in Specific Pathogen Free groups. The conditions of an SPF group including control of feedstuff and water, personnel, entry procedures, air quality, containment from other animals, cleaning, and removal of potentially sick animals have been described. A detailed discussion of pathogens of concern in rabbits has been provided. Serology testing is carried out on rabbit blood sample.

Measures in case of positive serology result, or clinical sign of disease are outlined, and include suspension of the use of the colony and quarantine or destruction of relevant sera. The facility, maintenance procedures, testing and measures in case of disease are adequate

In addition, justifications are provided for the safety of the product from the appropriate animal viruses.

**Human Thymus Fragments:** Thymus donors must be less than 14 years old and fit the selection criteria. They must also be low risk for CJD and other transmissible subacute spongiform encephalopathies. Blood samples from the donor are screened for a number of viruses using EU/US approved test kits.

**Human Red Blood Cells:** RBCs packs are supplied by American Red Cross (ARC) Blood Services. They are controlled in accordance with US regulations in force for blood collection. The contract specifications for supply of RBC have been provided in the application. Specifications include suitability of donors, storage, collection of blood, testing of blood, donor follow up, batch size, temperature, presentation, labelling, and shipment conditions. Each bag is tested with FDA approved tests and found negative for a number of viruses. Prior to use, the red blood cells are treated with formaldehyde to reduce risks of viral contamination.

Rabbit Serum: The rabbit serum is also tested for contaminating viruses.

**Viral Testing on the Active Ingredient and Final Bulk Product:** Parvovirus B19 testing is performed on Final Bulk Product (FBP) batches.

Inactivation and Removal Steps in the Downstream Process.

The viral clearance studies were performed in accordance with ICH guidance document Q5A “Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin” and CPMP/BWP/268/95 “Note for Guidance on Virus Validation Studies:
The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses”.

**Virus Inactivation during Pasteurisation**
The selected panel of viruses has been appropriately justified in terms of physicochemical properties, resistance to inactivation and actual/model pathogens.

**Viral Inactivation of Red Blood Cells before Use**
Validation of virus inactivation was performed on a scaled down model of the commercial process. Details are provided. The study was performed according to GLP and demonstrated that formaldehyde treatment of RBC causes a significant amount of inactivation of the enveloped and non-enveloped viruses tested. The viruses constitute a reasonable panel of actual and model viruses with differing physicochemical properties.

**Viral study of the regeneration of the DEAE resin**
A virus inactivation study has been performed on the cleaning procedure of the DEAE A500 Cellufine resin to demonstrate the efficiency of this procedure to inactivate or to remove virus bound onto the resin. This experiment indicates that the resin is effectively cleaned and sanitised (for viruses) by the commercial conditions.

Reference Standards
Description and qualification of reference standards is generally acceptable.

**DISCUSSION**
As would be expected for a product which has already been licensed in approximately 50 countries, the standard of this application was high, and no major objections have been raised on Quality issues.

Since this is a bibliographic application, it has been important for the applicant to establish that the product which is proposed in this MAA is the same as the product with which the non-clinical and clinical data has been generated. The drug substance manufacture is identical to the licensed product, but with the introduction of a variation to the number of thymocyte cells which are used during rabbit inoculation. A comparison of in-process control and batch release data demonstrate that this does not appear to make any identifiable difference to the potency or quality of the serum/product. The applicant wishes to use a different manufacturing site for the drug product which uses equipment from different vendors, and also a new step in the manufacturing process. Due to the nature of the operations it is unlikely that the changes would impact on the product. Consequently, it is accepted that this product is consistent with a bibliographic application.

**CONCLUSION**
Marketing authorisation for this product may be granted.
PRECLINICAL ASSESSMENT

INTRODUCTION

TYPE OF APPLICATION AND ASPECTS ON DEVELOPMENT
This application is made in accordance with Article 10 (1)(a) of Directive 2001/83/EC, as amended – an application for a product with well-established use in the Community. The product has been available in other European countries since it was first approved in 1984 in France. The indications sought are virtually identical to those for which it is approved in other EU countries and are the prevention and treatment of graft rejection in renal transplantation and prevention of graft rejection in heart transplantation.

The product contains polyclonal rabbit anti-human thymocyte immunoglobulin and is produced by immunisation of rabbits with human thymocytes and removal and separation of immunoglobulin from rabbit sera, with pasteurisation, filtration, sterilization and freeze drying to produce the finished dose form. Glycine, sodium chloride and mannitol are used as excipients and the product is reconstituted for use in sterile water for injections, diluted to the total infusion volume of 50 to 500 ml in 0.9% sodium chloride and infused intravenously with use of an in-line filter. Premedication with steroids and antihistamines to facilitate tolerability of the infusion is recommended in the SPC. Typically, the product will be administered every day for several days post-transplant.

The application was discussed in a meeting between the Applicant and the MHRA in July 2004 in which the Applicant sought advice from the MHRA on quality, preclinical and clinical data, as well as the route of submission. Concerning the standards of data in the preclinical section of the dossier, because many of the studies were conducted many years ago (in some cases, more than 25 years), study designs are not consistent with current practices, with the consequence that the preclinical module in the dossier cannot be structured as it would be for a new development programme. As examples, pharmacological effects are explored in combined studies that also determine pharmacokinetic endpoints; combined primary pharmacology and toxicology studies are reported and the quality of description of studies is generally not at current standards (e.g. lack of GLP, limited detail in experimental methods and results descriptions, no data for individual animals presented). The Applicant has been straightforward about these deficiencies and the MHRA advised that presentation of the preclinical and clinical experience with the product, with establishment of the comparability of the products used in these studies with the current commercial product, should constitute an acceptable data set. In the presentation of this Assessment Report, study results are described under the most relevant heading.

The non-clinical expert is an employee in the Applicant’s group of companies. The nonclinical overview is acceptable.

GLP ASPECTS
The status of many of the preclinical studies submitted is not described. Lack of compliance is assumed except where specifically described in this report. As the application is determined on the basis of well-established clinical use, the GLP status of the preclinical safety studies is not an issue.
PHARMACOLOGY

BRIEF SUMMARY
The primary pharmacological action of rabbit anti-human thymocyte immunoglobulin is depletion of T lymphocytes in blood and in lymphoid organs. This impairs the capacity of the immune system to mount responses to foreign tissues and is of value in the short term to prevent organ rejection in transplantation.

PHYSICAL CHEMISTRY
The structure is that of a polyclonal gamma immune globulin, with two heavy chains of approximately 450 amino acids and two light chains of 211 – 217 amino acids. The drug substance is a colourless or pale yellow liquid, clear or slightly opalescent, and its protein concentration is 2 – 7 g/l.

PRIMARY PHARMACODYNAMICS

Study to assess effect of heat treatment on pharmacodynamics of Thymoglobuline
A GLP-compliant study was reported in which effects of the pasteurisation step (heating at 56 - 60ºC for 10 hours) on in vitro activities of the product were assessed. In this study, comparative binding to human peripheral blood mononuclear cells, and to B and T cell lines, mitogenic activity on peripheral blood mononuclear cells, as measured by triated thymidine incorporation, and competitive binding inhibition of monoclonal antibodies to CD2, CD3, CD4, CD8, CD11a and CD18 was assessed. No significant differences were found between pasteurised and non-pasteurised product and comparability between the two was concluded.

Toxico-pharmacology study with non-heat-treated Thymoglobuline
The Applicant submitted work conducted with non-heat-treated Thymoglobuline in 1981 – 1983 and which was reported in 1991. The report summarises pharmaceutical, pharmacological and toxicological tests conducted. Pharmacological studies are described immediately below and toxicological studies are presented under the heading of Safety Pharmacology, in this Assessment Report. Details are extremely scant in some cases and the text of the report has been reproduced to indicate this.

PHARMACOLOGICAL STUDY

1. Material and methods
   1.1. in vitro test of lymphocytotoxicity
   1.2. in vivo test in monkeys

2. Results
   2.1. Lymphocytotoxicity
       2.1.1. Lymphocytes in M. cynomolgus
   2.2. Rejection of skin grafts in monkeys
In vitro test of cytotoxicity to human lymphocytes using blood from cynomolgus monkeys
Summary of method: Human peripheral blood lymphocytes were prepared in a suspension and one drop is added to three drops of antilymphocyte serum and one drop of rabbit complement. After incubation for 30 minutes at 37°C, 1 drop of Trypan blue is added for a further 10 minutes of incubation. Cell lysis is determined by counting 100 or 200 cells and cytotoxicity is calculated from these data.

Results: The entire section of the report is presented below. There is no narrative.

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<th>Lymphocytotoxicity</th>
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In vivo test in monkeys – rejection of skin grafts
Summary of method: Pharmacological proof of concept was sought by determining the effect of treatment to prolong skin allografts in two cynomolgus monkeys, each of whom had three skin grafts (2 from other monkeys and one allograft).

Results: The Applicant states that: ‘It was noted that in grailer animals, the graft survived longer than in controlled animals’ – these are the only words describing the results. The table below provides the data. Although not statistically robust, monkeys treated with three different lots of Thymoglobuline survived longer than control monkeys.
This report describes multiple experiments conducted over a three-year period (1998 – 2000) in cynomolgus monkeys into the mechanism of action of Thymoglobuline. The objective was to determine the effects of Thymoglobuline on heterotopic heart transplant or skin grafts in monkeys. For heart transplants, the duration of graft survival was recorded from the day of implantation to the last day when the heart was beating, as determined by palpation. For skin grafts, graft survival duration was assessed by the time elapsed between grafting to complete graft rejection, based on the presence of a scabby aspect, or brown colouring with loss of flexibility, or complete necrosis of the epidermis. It is not described as to whether blinded assessments were done, but two assessments were performed with a further check by the sponsoring company’s appointed veterinarian at unspecified key points. Monkeys were mismatched for major histocompatibility complex by serology.

Effects on red blood cells, platelets, neutrophils and lymphocytes were determined by blood cell counts. Immunohistochemical analysis of samples from lymph nodes, spleen and thymus was undertaken. These measures were supported by kinetic measurements of rabbit antilymphocyte globulin in monkey blood (quantified using an immunoenzymatic assay using goat anti-rabbit IgG). This method was also applied for determining anti-rabbit antibodies, except that peroxidase-conjugated goat anti-monkey IgG was used instead of anti-rabbit IgG.

Doses of Thymoglobuline of 1, 5 or 20 mg/kg were used, described as low dose (LOD), high dose (HID) and very high dose (VHID) as shown in Figure 1. Doses were selected on the basis of the human therapeutic dose of 1.5 mg/kg, with reference to a claim that ‘binding of Thymoglobuline to human lymphocytes is twice that to cynomolgus lymphocytes’ and to the consideration that, on a body surface area comparison, the surface area is greater in the...
monkey than in humans, on a weight-corrected basis, by a factor of 3 to 6. The Assessor’s calculations of these doses are:

doctor dose of 1.5 mg/kg in humans = 55 mg/m²
  “1 mg/kg in cynomolgus monkey = 12 mg/m² (LOD)
  “5 mg/kg in cynomolgus monkey = 60 mg/m² (HID)
  “20 mg/kg in cynomolgus monkey = 240 mg/m² (VHID)

Figure 1: Experimental schedule to study the effect of Thymoglobuline in skin grafts in cynomolgus monkeys

Table II: Thymoglobulin Dose Ranges

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cumulative dose per animal</th>
<th>Total cumulative dose* mg/kg/course</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOD 1 mg/kg/injection</td>
<td>8 mg/kg</td>
<td>5</td>
</tr>
<tr>
<td>HID 5 mg/kg/injection</td>
<td>40 mg/kg</td>
<td>25</td>
</tr>
<tr>
<td>VHID 20 mg/kg/injection</td>
<td>40 mg/kg</td>
<td>40</td>
</tr>
<tr>
<td>short VHID</td>
<td>100 mg/kg</td>
<td>100</td>
</tr>
<tr>
<td>long VHID</td>
<td>Day 6 = sacrifice</td>
<td></td>
</tr>
</tbody>
</table>

Results: There were no unexpected deaths in the study. Behavioural changes indicative of ‘a first infusion syndrome linked to cytokine release’ (prostration, vomiting) were observed. The graft survival data are presented below in Figure 2. Skin allografts had a median survival time of 9.25 days in control monkeys (black circles, left hand trace, A, left panel) whereas for LOD, HID and VHID groups, this figure was 13, 22 and 24 days respectively. Heart allograft median survival times were 8.5 days in control, 12.5 in LOD, and 17 in HID groups. The Applicant notes that the allograft survival was correlated with the magnitude of blood lymphopenia during the first week of treatment.
Figure 2: Graft survival and lymphocyte count data

Binding of rabbit anti-thymocyte globulin to human and monkey lymphocytes is shown in Figure 3, where the upper line is human and the lower is monkey. This is the evidence for comment above that ‘binding of Thymoglobulin to human lymphocytes is twice that to cynomolgus lymphocytes’.

Peripheral blood counts are presented in Figure 4. Of note is that treatment produced a transient dose-dependent lymphocytopenia (2d) with drops in each subset of lymphocyte analysed (2e, f, g, h, i). Neutrophils were also depleted with the very high dose (VHID) producing neutropenia (2c). Platelets were almost unaffected, except with VHID and red blood cells were unaffected, except by a possible effect which is attributable to blood withdrawal. The Applicant concluded that these results demonstrate that treatment resulted in a significant decrease in peripheral blood lymphocytes on a dose-dependent basis, without major depletion of other cell types, except for neutrophils and platelets in both VHID groups.

In lymphoid tissue, there was a dose-dependent T-cell depletion in lymph nodes and spleen (Figure 5a). Depletion of B cells and natural killer cells occurred only at high dose (Figure 5e, f). There was no effect on thymocytes (data not shown). There was a dose-dependent increase in the proportion of apoptotic lymphocytes (Figure 6). Additional testing also indicated an increase in double strand DNA breakages in lymph nodes and down-regulation of T cell surface antigens (data not shown here).
Figure 3: Binding of Thymoglobuline to human and monkey lymphocytes

![Graph showing binding of Thymoglobuline to lymphocytes](image1.png)

Fig 1. Binding of rATG to human and monkey lymphocytes. Increasing concentrations of rATG were incubated with Ficoll® isolated peripheral blood mononuclear cells from human (diamonds) and cynomolgus monkey (squares). Median of fluorescence intensities obtained by FACS® analysis are represented for each concentration of rATG. Lymphocytes were gated according to their size and granularity.

Figure 4: Peripheral blood counts in monkeys dosed with Thymoglobuline

![Graphs showing peripheral blood counts](image2.png)

Fig 2. Alterations of peripheral blood cell counts. Venous blood samples were collected at given time intervals in the different groups (controls: solid circles, LOD: open squares, HID: open diamonds, short VHID: closed triangles, long VHID: open triangles). The percentage of lymphocytes was determined by FACS® analysis after staining with CD2, CD3, CD4, CD8 and CD20 specific mAbs. All results are expressed in giga/liter as arithmetical mean within each group. Double asterisks indicates P < 0.001 and single asterisk signifies P < 0.05 (Scheffé test). Small asterisks refer to a significant difference between HID and control groups, big ones to a significant difference between LOD and control groups (controls, n=10; LOD, n=12; HID, n=15; sVHID, n=4; IVHID, n=3).
Kinetic results indicate that rabbit IgG concentration reached a maximum by day 6 then returned to undetectable amounts by day 13 (Figure 7). The Applicant attributes clearance of Thymoglobuline to ‘the immunization of the animals, as demonstrated by the presence of anti-rabbit IgG antibodies by day 8 in the sera of all treated animals’ and indicated by the (-) and (+) identifiers in the left half of Figure 7 panel a.
Figure 7: Kinetics of Thymoglobuline and anti-thymoglobuline antibodies in monkeys

Fig 3. (A) Evolution of free and cell bound antibodies in circulating blood. (a) The amount of total rabbit IgG was measured by ELISA. (b) The amount of specific antilymphocyte antibodies in monkeys sera was estimated by FACS® analysis using MedFls obtained with lymphocytes from untreated monkeys incubated with known quantities of ATG as a standard curve (controls, n=10, solid circles; LOD, n=12, open squares; HID, n=15, open diamonds; short VHID n=4, closed triangles).

Overall, from this study, the Applicant made the following conclusions:

(1) the mechanism of action of T cell depletion is apoptosis in peripheral lymphoid organs
(2) non-depleted T cells were coated by antithymocyte globulin and showed decreased T-cell surface antigens
(3) statistically significant dose-dependent survival of graft was shown
(4) lymphocyte depletion and graft survival were correlated and the depletion of lymphocytes seemed to be proportional to the dose of Thymoglobuline injected; however, the relative contribution of T cell depletion and functional impairment cannot be delineated.

The Applicant’s conclusions are substantiated by the data presented.

SECONDARY PHARMACODYNAMICS
Separate secondary pharmacodynamic studies were not reported. The Applicant refers to published literature on the effects of rabbit anti-human thymocyte immunoglobulin.

SAFETY PHARMACOLOGY

Pharmacotoxicological studies with non-heat-treated Thymoglobuline
The work described in this report was conducted with non-heat-treated Thymoglobuline in 1981 – 1983 and was reported in 1991. The report summarises pharmaceutical, pharmacological and toxicological tests conducted. Pharmacological studies are described immediately below and Toxicological studies summarised are then listed. The conclusion of the Applicant is presented thereafter.
Each of these studies is summarised below.

**Bacterial and fungal sterility test**
Summary of method: The presence of possible contaminant is tested by inoculation onto a variety of media and assessing growth of various bacterial or fungal organisms.

Results: No organisms ‘were shown up in the serum’. Purity was thus concluded.

**Research on cytotoxicity**
Summary of method: The existence of cytotoxic antibodies in the product is assessed by determining induction of fibroblast cell death by Thymoglobuline. The test uses MRC-5 or WI-38 cells.

Results: The absence of toxicity was shown.

Summary of method: A second test assesses the potential effect of Thymoglobuline on the granulomonocyte cell lineage, extracted from bone marrow and cultured. The source species is not specified.

Results: These are presented below.
2. On granulomonocyte strain cells:
(Cf. attachment II)
Lot SL81.1: no toxic or inhibiting effect
(attachment II.1)
Lot SL82.1: discreet inhibition at 500 g (attachment II.1)
Lot SL82.2: discreet inhibition (attachment II.2 and II.3)
Lot SL82.3: no toxic or inhibiting effect
(attachment II.4)

The tests as a whole are satisfactory.

Acute toxicity tests by intramuscular and intraperitoneal routes in mice, and by intramuscular and intravenous routes in rabbits
Summary of method: 5 male and 5 female mice of the Swiss strain are injected by these routes with a single injection of 0.5 ml of Thymoglobuline from Lot S 1136 (SL 81-1) (equivalent to 10% of a human dose) and mortality, behaviour and body weight are assessed over the subsequent 12 days with terminal autopsy examination. Twenty female albino rabbits are injected by these routes with a single injection of 5 ml of Thymoglobuline from Lot 1136 (SL 81-1) (equivalent to a full human dose) and mortality, behaviour and body weight are assessed over the subsequent 14 days with terminal autopsy examination.

Results: Treatment did not have any influence on the parameters under evaluation.

Administration every week for 12 weeks by intramuscular route in guinea pigs
Summary of method: 8 guinea pigs (sex described) are injected by the intramuscular route with a single injection of 2 ml of Thymoglobuline from Lot S 1136 (SL 81-1) (equivalent to 40% of a human dose) every week for 12 weeks and mortality, behaviour and body weight are
assessed over this period with terminal autopsy examination at an unspecified timepoint thereafter.

Results: No animal died in the study and local tolerance was ‘satisfactory’. The examinations made ‘make it possible to conclude the absence of conclusive traces of any toxic action of the sera tested’.

Administration every day for 5 days, then 3 days a week until rejection of the graft in monkeys, by the intramuscular route

Summary of method: 12 cynomolgus monkeys each undergo three skin grafts (2 from other monkeys and one autograft) and are given 5 ml of Thymoglobuline (the full human dose) by intramuscular injection every day for the first 5 days then 3 days a week until the graft is rejected. Clinical, behavioural, haematological and anatomopathological examinations are carried out.

Results: No animal died and no clinical or behavioural symptoms were observed throughout the study, with local tolerance also described as ‘satisfactory’. Haematological examination did not show any significant differences between controls and treated monkeys. On macroscopic examination, no lesions were observed with the exception of pulmonary emphysema which is ‘not imputable to treatment’. No differences in the structure of the lymphoid structures or organs were noted. The overall conclusion was that ‘ATG administered by intramuscular route into monkeys did not lead to any clinical, behavioural, haematological or biochemical modification, or any histological lesion the frequency of which was significant or could be imputable to treatment’.

Research for phenomena of hypersensitivity in guinea pigs

Statement of principle: 10 guinea pigs are injected with 0.2 ml of Thymoglobuline intradermally with a further 30 given similar injections of equine anti-lymphocyte globulin or physiological saline to act as controls. 21 days later, Thymoglobuline is given by intracardiac injection of half the 10 guinea pigs with controls treated by a parallel test using either equine anti-lymphocyte globulin or physiological saline. Immediate hypersensitivity is assessed over the 8 hours following injection. The other 5 guinea pigs are injected by the intradermal route and delayed hypersensitivity is assessed in the 72 hours after injection.

Results: Immediate hypersensitivity was confirmed in that in Thymoglobuline-primed guinea pigs, all died following intracardiac injection of Thymoglobuline, as did those primed with and given equine anti-lymphocyte globulin. There was specificity in this response as no deaths occurred in Thymoglobuline-primed guinea pigs injected with equine anti-lymphocyte globulin. No manifestation of delayed hypersensitivity was observed.

The Applicant’s comment on these data is copied below. This was written by an approved expert toxicologist and pharmacologist.

“GENERAL CONCLUSIONS

The toxico-pharmacological expertise of anti human thymocyte immunoglobulin, prepared in rabbits, (ATG), by the Institute Merieux has demonstrated that the product presents:
− absence of acute toxicity in mice and rabbits, and subacute toxicity in guinea pigs and monkeys, but it is however capable of prevoking a phenomenon of immediate hypersensitivity in guinea pigs, after a low dose priming injection and a high dose triggering injection by intracardiac or intravenous route (it may be noted that the
phenomenon does not appear when the animals are given high repeated doses of the product, if the subacute toxicity test on guinea pigs is considered;
– distinct activity and efficacy;

That, in consequence, this product indeed seems to present the safety and efficacy required (article 5-120-1 and article 601 of the Code de la Santé Publiqué) under the conditions of use, the diverse experiments and different animal species described above.

And that, as it satisfies the requirements, its use may be authorised in human medicine."

The paucity of description present in this report is reflected in the above summaries. The quality of the data and level of detail in description of methods and outcomes reflect standards from over 25 years ago when GLP was not in place. This is sufficient to conclude that no major hazard is identified. As current legislation requires, an expert summary of these data is presented and this specifically endorses human use of the product.

PHARMACODYNAMIC DRUG INTERACTIONS
There is a cross-reference in the relevant section of dossier for pharmacodynamic drug interactions to one report published in 2006\(^1\). This report describes the immunopharmacological actions of Thymoglobulin administered at different doses to cynomolgus monkeys receiving either skin allografts or heterotopic heart transplants. As such, this study is not a study of pharmacodynamic interactions, although the drug is used in a procedure resembling clinical use, and zolazepam and atropine are used. The study’s conclusion, however, that ‘ATG monotherapy in cynomolgus monkeys resulted in a dose-dependent T-cell depletion in peripheral blood and to a lesser extent in peripheral lymphoid tissues but not in the thymus’ clearly indicates that the intent of this study is not to assess pharmacodynamic interactions.

ASSESSOR’S OVERALL CONCLUSIONS ON PHARMACOLOGY
The mechanism for how depletion of lymphocytes is induced by Thymoglobulin is suggested to be related to induction in peripheral tissues of apoptosis of cells coated with the immunoglobulin. Similar cellular depletion occurs in immune tissues but the extent to which this contributes to the observed therapeutic effect is difficult to judge. The target epitope is unclear, but this may be because multiple epitopes may be involved in this polyclonal preparation. Thymoglobulin binds to CD4+ and CD8+ peripheral T cells.

The data indicate correlation between peripheral T cell depletion and graft survival in vivo in monkeys. No difference in immunological properties of Thymoglobulin was detected when a heat-treatment step was introduced to the manufacture, which was done to improve microbiological safety and consequently findings on non-heat-treated immunoglobulin may apply to the heat-treated product which is the subject of this application. Pharmacotoxicological tests in mice, guinea pigs, rabbits or monkeys did not identify unexpected toxicity.

PHARMACOKINETICS

ANALYTICAL METHODS
The Applicant describes that in nonclinical studies Thymoglobuline was quantified using immunological tests, including ELISA.

PHARMACOKINETIC STUDIES
Pharmacokinetics of Thymoglobuline, at one dose level of 20 mg/kg were described. Either heat-treated or non-heat-treated Thymoglobuline was given to male and female cynomolgus monkeys (n = 1 or 2) daily by intravenous administration for two weeks, followed by a four-week treatment free period. Blood samples were taken for toxicokinetic measures.

The results are depicted in Figure 8, where the filled-in black diamond represents data from monkeys treated with heat-treated Thymoglobuline, the same product as is the subject of this application. Kinetic parameters calculated from these data indicated that kinetics were not different between heat-treated and non-heat-treated Thymoglobuline. Serum half life was estimated at 30 days and mean maximal concentrations are reached by day 9 and peak at 988 ± 200 µg/ml. Antibodies to Thymoglobuline are detected and there is a clear correlation with their development and the reduction in Thymoglobuline concentration in plasma (Figure 9). From this study, the Applicant concluded that bioequivalence was shown between the heat-treated and non-heat-treated products.

Figure 8: Kinetics of Thymoglobuline in cynomolgus monkeys given daily injections

![Graph showing kinetics of Thymoglobuline](image)
No metabolism or excretion studies have been submitted. The Applicant states that in the light of long term human experience, animal studies are not considered necessary and that Thymoglobuline is expected to be cleared from the blood like other immunoglobulins. This is accepted.

ASSESSOR’S OVERALL CONCLUSIONS ON PHARMACOKINETICS
Further animal studies are unnecessary due to extent of clinical experience with the product.

TOXICOLOGY

BRIEF SUMMARY
The following studies have been reported:
- cross-reactivity study in human tissues
- single dose toxicity by the intravenous route in the mouse
- single dose toxicity by the intravenous route in the rat
- 2 week repeated dose toxicity by the intravenous route in the cynomolgus monkey
- local tolerance in the rabbit.

CROSS-REACTIVITY
A GLP-compliant study was conducted to assess cross-reactivity with human tissues of Thymoglobuline. The quality of the specimens used in the study was affirmed and its results are judged to be reliable. Tissue samples were obtained within 24 hours of death from one female and two male subjects, but cause of death was not reported. The study objective was to determine binding of Thymoglobuline to related or unrelated epitopes on cells from various human tissues (bone marrow, cerebrum, heart, ileum, jejenum, kidney, liver, lung, lymph node, skin, spleen and thymus).

Lymphocytes were intensively stained with Thymoglobuline and were the only cells stained in the tissue tested. Staining included the cytoplasm and the cell membrane, but not the cell nucleus. Negative (on-immune IgG) and positive (anti-collagen IV antibody) controls validated the findings of specificity of binding of Thymoglobuline to lymphocytes.
GENERAL TOXICITY

*Single intravenous dose in the mouse*
Thymoglobuline was administered by the intravenous route to 10 male and 10 female OF1 (Swiss) mice at one dose of 15 ml/kg and mice were monitored for a subsequent 14 day period and necropsied on Day 15. No deaths or abnormal signs were noted, either on clinical observations in the 14 days following injection or on macroscopic examination. This study was reported in April 1992: no statement of GLP compliance is made. Data on individual animals are not reported.

*Single intravenous dose in the rat*
Thymoglobuline was administered by the intravenous route to 10 male and 10 female Sprague Dawley rats at one dose of 15 ml/kg and mice were monitored for a subsequent 14 day period and necropsied on Day 15. No deaths or abnormal signs were noted, either on clinical observations in the 14 days following injection or on macroscopic examination. This study was reported in April 1992: no statement of GLP compliance is made. Data on individual animals are not reported.

These two single dose tests, which are reported together in one report, are not of an acceptable standard as no data on individual animals is presented. Although the Applicant has to submit the data that are available, the data presented in this report are not considered sufficiently reliable to be accepted for assessment.

REPEAT-DOSE TOXICITY

*2-week repeated intravenous dose toxicity study in the cynomolgus monkey*
Thymoglobuline, at one dose level of 20 mg/kg, was given to male and female cynomolgus monkeys (n = 1 or 2) daily by intravenous administration for two weeks, followed by a four-week treatment-free period. This study was conducted in compliance with GLP. These monkeys were wild-caught, but healthy at the start of dosing.

This test was conducted to compare the toxicity associated with heat-treated thymoglobuline with that associated with non-heat-treated thymoglobuline and was done to support a change in the production process to introduce the viral inactivation step of a 10 hour treatment at 60°C. As the product for which approval is sought is only the heat-treated product, this comparison is not of direct relevance to the present application; rather, the absolute toxicity of heat-treated Thymoglobuline is of interest. The dose was selected to be approximately three times the anticipated maximum therapeutic dose.

With reference to the objective of the study, there was no detectable difference in toxicity profile between heat-treated and non-heat-treated Thymoglobuline. These are called test article in further descriptions of this study.

Mortality was significant in this study: in total, 5 monkeys dosed with test article died or were killed due to moribund condition, of a total of 12 dosed with test article. These deaths occurred in the following time sequence: one female was killed moribund on day 9 and one male was found dead on day 13. Dosing stopped on day 14 and one male was killed moribund on day 18 and two females were killed moribund on day 21. All monkeys alive at this timepoint survived to the end of the four week treatment-free period.
Clinical signs in the monkeys that died or were moribund were generally representative of septicaemia, and reductions in food intake and body weight, with a short episode of hyperthermia followed by hypothermia, subdued behaviour and the presence of sores or abscesses. Haematological and histopathological changes were also indicative of septicaemia and infection, although blood samples for bacterial examination were only taken from two monkeys, in only one of whom only Staphylococcus aureus was isolated. There was a severe but reversible (in surviving monkeys) decrease in absolute and relative lymphocyte counts in all monkeys dosed with test article and in monkeys that died extremely low counts, as low as 2%, were noted (Table 1). Recovery to normal ranges took until day 43. Absolute neutrophil counts generally decreased from starting treatment until about day 29, when recovery began. Severe immune depression was expected as the pharmacological action of the test article and the Applicant attributes the deaths to this, combined with the variable health status of the wild-caught animals before start of treatment (although the Applicant also states that ‘animals were clinically in good health at the beginning of the treatment period’). The pathologist reported that ‘Septicaemia secondary to this immune suppression was the cause of moribund condition and unscheduled death’.

Table 1: Individual white blood cell and lymphocyte count data in monkeys

<table>
<thead>
<tr>
<th>DAY</th>
<th>Gp 1 (control)</th>
<th>Gp 2 (non-heat-treated Thymoglobuline, 20 mg/kg)</th>
<th>Gp 3 (heat-treated Thymoglobuline)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M 2571</td>
<td>M 2572</td>
<td>F 2573</td>
</tr>
<tr>
<td>&lt;4</td>
<td>WBC L (%)</td>
<td>14.8</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte L (%)</td>
<td>10.9</td>
<td>16.3</td>
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<tr>
<td>1</td>
<td>WBC L (%)</td>
<td>14.0</td>
<td>17.2</td>
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<tr>
<td></td>
<td>Lymphocyte L (%)</td>
<td>10.1</td>
<td>18.4</td>
</tr>
<tr>
<td>3</td>
<td>WBC L (%)</td>
<td>15.1</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte L (%)</td>
<td>15.1</td>
<td>21.9</td>
</tr>
<tr>
<td>5</td>
<td>WBC L (%)</td>
<td>15.0</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte L (%)</td>
<td>15.0</td>
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</tr>
<tr>
<td>9</td>
<td>WBC L (%)</td>
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<td>WBC L (%)</td>
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<td>Lymphocyte L (%)</td>
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<td>7.5</td>
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<td>24</td>
<td>WBC L (%)</td>
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</tr>
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<td></td>
<td>Lymphocyte L (%)</td>
<td>11.3</td>
<td>71</td>
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<td>36</td>
<td>WBC L (%)</td>
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</tr>
<tr>
<td></td>
<td>Lymphocyte L (%)</td>
<td>12.6</td>
<td>44</td>
</tr>
</tbody>
</table>

Gp 1 = control; Gp 2 = non-heat-treated Thymoglobuline, 20 mg/kg; Gp 3 = heat-treated Thymoglobuline.

Similar clinical signs, but of lesser intensity, were observed in surviving monkeys. In all monkeys given test article, decreases in red cell parameters (haemoglobin, red blood cell count, PCV) were observed, progressing throughout the treatment period, and tending to
reverse from day 20. Platelet counts showed a similar pattern. Reticulocyte counts showed an increase from day 3 in all groups, with monkeys given test article showing higher increases than those in the control group, and a slower recovery in the treatment-free period. White blood cell counts, which was described as the ‘main severe but reversible treatment-related observation’ are discussed above. Bone marrow smears showed a difference in the number of lymphocytes from monkeys killed at day 14 (‘very poor’) compared to smears from those killed after the 4 week treatment free period (‘normally rich’).

No noteworthy changes on ophthalmological examination, on blood pressure, electrocardiographic parameters or on urinary parameters (with the possible exception of some protein, glucose, blood, reducing substances, bacteria, yeasts and epithelial cells in urine. at Day 13 which occurred in one male monkey) were observed. Changes in clinical chemistry parameters were such as to be judged by the Applicant as being not directly related to the treatment, ‘considering the clinical behaviour of treated animals’. Notable changes were reversible increases in cholesterol and decreases in protein. No notable findings were evident on organ weight. No macroscopic changes were identified in monkeys killed at the end of the 4 week treatment-free period: macroscopic changes indicative of septicaemia or infection in multiple organs were observed in monkeys that died or were killed moribund on the study. Microscopic changes were seen, but were attributed to either direct or secondary effects consequent upon the pharmacological action (e.g. atrophy of lymph tissues) or were attributed to study procedures (e.g. thrombosis in lungs, phlebitis or thrombophlebitis) or associated stress. The Applicant made further comment on the instances of thromboemboli: the study was conducted in 1992 at which time a historical database was not available. In a further 11 studies conducted in 1992 and 1993, spontaneous thromboemboli formation was noted in one cynomolgus monkey, and the Applicant judges that the instances observed in this study is random and are probably consequences of the method of administration and likely to have been exacerbated by the concurrent condition of the monkeys.

The toxicity induced in this study, although perhaps unexpectedly severe, is in keeping with the expected pharmacological action to deplete lymphocytes. In extrapolating to clinical use, it is noted that the dose is three times higher than the expected maximal human dosage. 14 days is the maximum dosing period recommended in the SPC. Clinical monitoring of lymphocyte counts will protect patients from drastic effects and reduced dosage or stopping treatment are recommended in the presence of thrombocytopenia.

**GENOTOXICITY**
Genotoxicity studies have not been conducted with Thymoglobuline.

**CARCINOGENICITY**
Carcinogenicity studies have not been conducted with Thymoglobuline.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**
Studies to assess reproductive and developmental toxicity have not been conducted with Thymoglobuline.

**LOCAL TOLERANCE**
This study was conducted in compliance with GLP. Local tolerance was assessed in male New Zealand White rabbits after multiple intravenous and single perivenous injection with the schedule as shown in Table 2. The test article is 25 mg Thymoglobuline per vial, reconstituted in 5 ml of water for injection: excipients are mannitol (10 g/l), glycine (10 g/l),
sodium chloride (2 g/l) and Tween 80 (0.5 g/l) which is the same as the test article, but without gamma globulin.

By repeated intravenous injection, the test article produced transient slight erythema in one rabbit on day 6 and haemorrhagic infiltration in two rabbits for 1 or 2 days. The excipients produced a similar effect in one rabbit on days 5 and 6 and haemorrhagic infiltration was seen in two rabbits for either 3 or 6 days. By single perivenous injection, one rabbit dosed with test article developed a haematoma, and transient haemorrhagic infiltration was noted in two out of three rabbits. Administration of the excipient was associated with more severe irritation, producing haemorrhagic infiltration in 7 out of 12 rabbits, slight erythema in 5 rabbits for 1 to 5 days and haematoma in three rabbits. On microscopic examination, it was concluded that all injections were well tolerated and changes observed were at a low level and of the type expected with the route of administration.

Table 2: Schedule for local tolerance study in the rabbit

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Route of administration</th>
<th>Days of treatment</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left ear</td>
<td>Right ear</td>
<td></td>
<td>Killed on day 7</td>
</tr>
<tr>
<td>1</td>
<td>Control article</td>
<td>Excipient</td>
<td>Intravenous</td>
<td>Days 0, 1, 2, 3 and 4</td>
</tr>
<tr>
<td>2</td>
<td>Control article</td>
<td>Excipient</td>
<td>Perivenous</td>
<td>Day 4 only</td>
</tr>
<tr>
<td>3</td>
<td>Excipient</td>
<td>Test article</td>
<td>Intravenous</td>
<td>Days 0, 1, 2, 3 and 4</td>
</tr>
<tr>
<td>4</td>
<td>Excipient</td>
<td>Test article</td>
<td>Perivenous</td>
<td>Day 4 only</td>
</tr>
</tbody>
</table>

Table 2: Schedule for local tolerance study in the rabbit (continued)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose level</th>
<th>Dose concentration (mg/ml)</th>
<th>Volume administered</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left ear</td>
<td>Left ear</td>
<td>Right ear</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>5 mg/kg/day</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.45 mg</td>
<td>0</td>
</tr>
</tbody>
</table>

Control article was 0.9 % NaCl solution.

The clinical route of administration is intravenous infusion. No concerns are raised.
OTHER TOXICITY STUDIES
No other studies were reported.

ECOTOXICITY/ENVIRONMENTAL RISK ASSESSMENT
The Applicant affirms that no genetically modified organisms are present in the product and that the excipients of the product (mannitol, sodium chloride and glycine) are not novel and their use in this product does not significantly alter their concentration in the environment. As a protein, the product does not need to be supported by an environmental risk assessment, according to the relevant guideline (Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00). As a rabbit polyclonal antibody mixture, Thymoglobuline is expected to break down into constituent amino acids in vivo, with no attendant environmental hazard. The Applicant’s justification for the excipients is accepted.

ASSESSOR’S OVERALL CONCLUSIONS ON TOXICOLOGY
The conclusion on the clinical safety data presented for the product should supersede the findings from toxicity studies in animals. The toxicity detected in animals is consistent with supra-pharmacological actions.

ASSESSOR’S OVERALL CONCLUSIONS
The well-established use criteria for seeking approval of a marketing authorization for a medicinal product state that results of preclinical studies do not have to be submitted if the Applicant ‘ … can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety’. Consequently, consideration of efficacy and safety of this product should rely on clinical experience. The preclinical studies presented are supportive of the safety of the product, particularly the specificity shown in the cross-reactivity study in human tissues. The pharmacodynamic actions of Thymoglobuline were shown repeatedly in studies in cynomolgus monkeys and toxic effects seen can be attributed to actions to deplete lymphocytes.

There are no objections, on preclinical grounds, to the granting of a marketing authorisation.
CLINICAL ASSESSMENT

INTRODUCTION

This is a national marketing authorisation application (MAA) for Thymoglobuline according to Article 10 (1) (a) (ii) of Directive 2001/83/EC as amended – abridged applications (‘well established use’).

Thymoglobuline (anti-thymocyte globulin [rabbit], rATG) is a purified, pasteurized, gamma immune globulin obtained by sensitization of rabbits with human thymocyte suspensions derived from thymus fragments that are surgical waste during cardiac surgery in children. The manufacture of Thymoglobuline involves a series of intricate processes and quality assurance checks that are intended to reduce lot-to-lot variability. This consistency permits the administration of drug from different lots during a clinical course of treatment with Thymoglobuline.

It is classified as ATC class LO4AA04, anti-human thymocyte immunoglobulin.

Thymoglobuline is approved in Europe on a National Procedure basis. It is registered in a total of 55 countries. In France and most international markets, Thymoglobuline is indicated for prevention and treatment of solid organ transplant rejection, prevention of acute and chronic graft-versus-host disease following haematopoietic stem cell transplantation (HCT), treatment of steroid resistant, acute graft-versus-host disease and treatment of aplastic anaemia (AA). Thymoglobuline was first approved in France in April 1984 for the indications of prevention and treatment of rejection in kidney and heart transplantation, treatment of severe aplastic anaemia, and treatment of acute graft versus host disease, obtained on the basis of well established use of antithymocyte globulins (ATGs) in general. No traditional pivotal trials were performed or presented as part of the original MAA dossier. The active ingredient as well as the composition of the product has been used in the medical practice for more than 10 years in the European Union. This meets the criteria established to justify well established medicinal use.

Thymoglobuline was registered in the USA in 1998 for the indication of treatment of acute rejection in renal transplantation in conjunction with concomitant immunosuppression.

There has been no worldwide modification(s) of the license status of Thymoglobuline, for safety reasons, since it was first licensed.

This submission was supported by a single company sponsored prospective study for Thymoglobuline (Study 00PTF01) which was conducted in compliance with the requirements and principles of Good Clinical Practice (GCP). In 2003, the additional indication of prophylaxis of graft versus host disease (GvHD) was approved in France.

The indications for which marketing approval is sought in the UK are the prevention of graft rejection in renal and heart transplantation and the treatment of steroid resistant graft rejection in renal transplantation.
Proposed doses:
1. Prophylaxis of acute graft rejection – renal transplantation 1 – 1.5 mg/kg/day for 3 to 9 days in transplantation of the kidney, corresponding to a cumulative dose of 3 – 13.5 mg/kg
2. Treatment of steroid resistant graft rejection – renal transplantation 1.5 mg/kg/day for 7 to 14 days, corresponding to a cumulative dose of 10.5 – 21 mg/kg
3. Prophylaxis of acute graft rejection – heart transplantation 1 – 2.5 mg/kg/day for 3 to 5 days in transplantation of the heart, corresponding to a cumulative dose of 3 – 12.5 mg/kg

GCP aspects
N/A

Orphan Medicinal Products
N/A

CLINICAL PHARMACOLOGY

Very few studies describing the pharmacokinetics and pharmacodynamics of Thymoglobuline have been published in the literature. However, three studies with Thymoglobuline are presented to provide an overview of the PK and PD effects characterised for Thymoglobuline.

PHARMACOKINETICS

Introduction
Pharmacokinetics of total Thymoglobuline was presented by Bunn et al. (Bunn, 1996, Clin Nephrol) in eleven patients who had received renal transplants using an ELISA with a goat anti-rabbit immunoglobulin. Eleven patients received 14 courses of rabbit ATG supplied either by Fresenius (F-ATG) or Mérieux (M-ATG ie Thymoglobuline) as a daily infusion of 2-6 mg/kg body weight for a therapeutic course lasting 5-10 days. ATG was infused over 8 hours through a controlled-rate pump. In addition, patients received triple therapy immunosuppression with cyclosporine, prednisolone and azathioprine. The dose of ATG was adjusted according to the daily white cell count: ATG was not given if the count was less than 3.0 x 10^9/l and if stopped was restarted when the count was greater than 4.0 x 10^9/l.

The study concluded the following:

- Serum concentration of Thymoglobuline rises throughout the regime of daily infusions with a clear maximum level on the final day.
- Significant serum concentrations persist for at least 60 days.
- Elimination half life T1/2 : 14.3 – 38.1 days
- Estimated volume of distribution Vd: 0.07 – 0.13 l/kg – this indicates that Thymoglobuline remains within the plasma and extravascular fluid and does not enter the lipophilic compartments of the body.
- A second course of Thymoglobuline given to an individual patient appears to have a slower rate of elimination than the first course.

Guttman et al. published pharmacokinetics data from 30 patients receiving renal and cardiac transplantation in two different centres in France (Guttmann, 1997, Transplant Proc). Elimination half life at the beginning of the administration, 0-24 hours was 44.2 hours and after 10 days it was 13.8 days.
It was recognised that these figures of elimination reflected a large variation depending on individual patient fluctuations. Elimination of Thymoglobuline is proposed to be effected by its binding to T cells, which consequently apoptose. The early and sharp drop in T cells following Thymoglobuline administration explains the sharp drop in elimination and increase in elimination half-life. There is a distinction between the measurement of total Thymoglobuline and the concentrations of IgG with relevant anti-lymphocyte activity.

Regan et al. (Regan, 2001, *Transplant Immunol*) differentiate between active Thymoglobuline (approximately 7% when measured in *vitro*) and total Thymoglobuline. Serum levels in renal transplant patients undergoing acute rejection were measured. Total Thymoglobuline levels in the serum were fairly close correlated to the number of doses (days of treatment).

- Active Thymoglobuline levels revealed the same profiles as the total levels, although the dose response was not as striking as that seen for total Thymoglobuline levels.
- 0.8% active Thymoglobuline was the highest value seen in serum during treatment.
- By day 20 after treatment cessation, levels dropped to 0.1%, representing a drop in 90%. Thus residual total levels measured in the Regan and other studies are not representative of activity.
- By day 90, only 12% of patients had detectable active Thymoglobuline compared to 81% of patients with total Thymoglobuline. Thus, in the absence of further treatment, active Thymoglobuline is rapidly depleted from the circulation.

About 7% of the protein content of Thymoglobuline is specific for human T cells (“active” Thymoglobuline), the rest being rabbit IgG that is not directed against human epitopes (Regan, 2001, *Transplant Immunol*). Initial pharmacokinetic (PK) studies looked only at the kinetics of total Thymoglobuline. As this includes Thymoglobuline with no activity against human cells, and no binding, the half–life is long, and not of relevance to the clinical situation (Bunn, 1996, *Clin Nephol*).

**Half-life**

The half-life is dependent on whether total or active Thymoglobuline levels are measured. Active Thymoglobuline, which binds to its target cells, lymphocytes, is more rapidly eliminated. This binding (and elimination) depends on the number of available cells present. As the “non-active” Thymoglobuline, the majority of the rabbit immunoglobulin, is not bound, it stays in the circulation for a considerable time. This explains why the Bunn study (Bunn, 1996, *Clin Nephol*) had an estimated half-life of elimination (of total Thymoglobuline) of 30 days, as compared to Regan (Regan, 2001, *Transplant Immunol*; (in renal transplant patients) where the elimination half-life (of active Thymoglobuline) was estimated to be one to two weeks.

Regan further distinguished between the half-life immediately after the first administration (44.2 hours) and the later measurements of half-life, again showing that the elimination half-life will be a function of the numbers of lymphocytes present to which Thymoglobuline can bind (which is related to infusion number in the case of solid organ transplantation). Total Thymoglobuline remains detectable in 80% of patients at 2 months.

**Sensitisation against Thymoglobuline**

About 6% of patients have anti-rabbit antibodies prior to treatment (Regan, 2001, *Transplant Immunol*; Regan, 1999, *Transplant Immunol*). Significant immunisation against rabbit IgG is observed in about 40-70% of patients after treatment with Thymoglobuline. In most cases,
immunisation develops within the first 15 days of treatment initiation. Sensitisation peak is reached around day 30, and declines subsequently.

Patients with antibodies show a faster decline in total Thymoglobuline levels, but not in active Thymoglobuline levels. There seems to be no relation between antibody levels and efficacy.

Methods
In the Bunn’s study (Bunn, 1996, Clin Nephrol) eleven patients received 14 courses of ATG supplied either by Fresenius (F-ATG) or Merieux (M-ATG) as a daily infusion of 2-6 mg/kg body weight for a therapeutic course lasting 5-10 days.

• Pharmacokinetic data analysis
Pharmacokinetics of total Thymoglobuline was presented by Bunn et al. (Bunn, 1996, Clin Nephrol) in patients who had received renal transplants using an Enzyme-Linked Immunosorbent Assay (ELISA) with a goat anti-rabbit immunoglobulin.

• Statistical analysis
Bunn presented the half-life of ATG per ATG and patient. Data for the first four days of treatment were analysed with linear regression to obtain mean value for the apparent volume of distribution of ATG. The results of the study were compared with results obtained from literature. In Reagan’s study multiple regression was used to examine the influence of dose number and sensitization on both total and active Thymoglobuline levels.

• Absorption
Since this product is administered intravenously, this is not applicable.

• Bioavailability
Thymoglobuline is administered intravenously, and as per Applicant 100% bioavailability can be assumed. Therefore no bioavailability studies have been performed. This is acceptable.

• Distribution
Bunn estimated the volume of distribution to be around twice the plasma volume (Bunn, 1996, Clin Nephrol).

• Elimination
The Bunn study (Bunn, 1996, Clin Nephrol) had an estimated half-life of elimination (of total Thymoglobuline) of 30 days, as compared to Regan (Regan, 2001, Transplant Immunol; (in renal transplant patients) where the elimination half-life (of active Thymoglobuline) was estimated to be one to two weeks.

• Children
The pharmacokinetics results in paediatric patients are not presented. However, a study on long-term effects has identified that the age of the patient may affect CD4+ T cell regeneration with adult patients exhibiting a persistent CD4+ lymphopenia and paediatric patients exhibiting normal reconstitution of the CD4+ T cell population.

Conclusions on pharmacokinetics
Comprehensive data on Pharmacokinetics are presented by the Applicant. It is concluded that the pharmacokinetic publications presented are adequate.
PHARMACODYNAMICS

Introduction

Thymoglobuline is a pasteurised preparation of rabbit IgG from animals that have been immunised with human thymocytes. Different techniques with different limitations have been used to investigate the antibody specificities (Bonnefoy-Bernard, 1991, Transplantation). The antibody specificities which have been characterised recognise key molecules involved in the regulation of the immune system:

- CD3 and the T cell receptor (TCR)
- Co-receptors CD4 and CD8
- Co-activation or adhesion molecules and their ligands, such as CD2, CD45, and CD28 (expressed on T lymphocytes); CD80 (B7-1) or CD86 (B7-2) (expressed on antigen presenting cells); CD11a/CD18 (LFA-1) (expressed on all leukocytes); CD54 (ICAM-1) (expressed on many cell types, notably leukocytes and endothelial cells).
- Lymphocyte antigens, such as CD5, CD6 and CD7, the functions and importance of which are poorly understood

Mechanism of action

Treatment of Solid Organ Transplant

The mechanism of action of Thymoglobuline in the treatment of solid organ transplants is not fully understood. ATGs direct against human T-cells, cause human lymphocyte depletion either by complement-dependent lysis, or by opsonisation and subsequent destruction via reticulo-endothelial system. This anti-lymphocyte effect interrupts both the cell-mediated and humoral components of the immune response cascade.

The Applicant presents a number of key effects that have been characterised and described in the literature. Immediate, pronounced and prolonged T cell depletion, both in the peripheral blood, but also of lymph nodes and spleen, demonstrated in both Cynomolgus monkeys and in man (Camitta, 1976, Blood; Young, 1995, Lancet) is long-lasting, and some T cell subsets are still below normal levels one year after treatment (Mueller, 2003, Front Biosci; Camitta, 1976, Blood). One study, where patients were pre-treated with Thymoglobuline several days before receiving their transplant, showed similar T cell depletion of biopsies from lymph nodes (Starzl, 2003, Lancet). Fiorina’s study demonstrated apoptotic cells in renal biopsies following Thymoglobuline “induction” treatment (Fiorina, 2004, Transplant Int). Initial brief activation of T lymphocytes causing cytokine release, and, in vitro, proliferation of T cells has also been demonstrated (Remberger, 1999, Bone Marrow Transplant; Bonnefoy- Bernard, 1992, Cell Immunol; Guttmann 1997, Transplant Proc).

The cell surface antigens against which Thymoglobuline has activity can be grouped into the following categories:

- Adhesion molecules, both on lymphocytes and endothelium, e.g. CD11a (LFA-1), or CD50 (ICAM-3) required for migration of activated lymphocytes to the graft
- Co-stimulatory molecules, e.g. CD28; CD152, required for initiation of the immune response
- T cell receptor (TCR) or CD3
- Dendritic cell markers, e.g. CD1a, CD11a, CD86, CD32
- Epitopes which have as yet unknown functions
Brophy et al. report on the effect of Thymoglobuline on T cell populations using flow cytometry (Brophy, 2001, *Pediatr Transplantation*) in patients receiving prophylaxis for renal transplantation. Thymoglobuline effects a drop in CD3+, CD4+ and CD8+ T cells upon and throughout administration—see next figure. The effect and degree is similar to that seen in adults (Guttmann, 1997, *Transplant Proc*).

**Figure 1: T Cell Distribution in Paediatric Patients Receiving Thymoglobuline Following Transplantation**

In paediatric patients, a similar effect is seen, whereby Thymoglobuline administration effects a rapid depletion in CD2, CD3, CD4 and CD8 positive cells (Piaggio, 1998, *Eur J Haematol*). This drop is sustained for 2-3 weeks after completion.

**Relationship between plasma concentration and effect**
Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney-transplant recipients), serum total Thymoglobuline levels of between 10 and 40 Yg/mL were obtained. The trough rabbit IgG levels increased progressively reaching 60 to 170 Yg/mL at the end of an 11-day course treatment. An increase in total Thymoglobuline levels with increasing dose was observed. In contrast, active Thymoglobuline levels did not show a dose response, with peak levels around 0.8Yg/ml (Regan, 2001, *Transplant Immunol*). A gradual decline was subsequently observed following discontinuation of the Thymoglobuline treatment.

**Conclusions on pharmacodynamics**
The applicant has discussed pharmacodynamics adequately.
CLINICAL EFFICACY

Introduction
The studies presented in the dossier originate from a review of clinical studies reported in the literature.

Dose-response studies and main clinical studies

Dose response studies
Prophylaxis of Rejection in Renal Transplantation (PRRT)
As per applicant there has been a trend with time for lower doses of Thymoglobuline to be used by clinicians. There might be two main factors – the introduction of newer, more potent maintenance immunosuppressive agents to the market requiring a lesser amount of induction immunosuppression, and a better appreciation of longer term safety problems caused by the global immunosuppressive load, as patients have survived longer.

The average prescribed mean daily dose in all these studies was 1.5 mg/kg, given for a mean of 9.3 days, with a maximum cumulative dose ranging from 7.6 – 16.1 mg/kg. The recommended dose range, based on the analysis here, is 1-1.5 mg/kg/day, for a duration of 3 to 9 days (which gives a cumulative dose of 3 –13.5 mg/kg). The choice of total dose depends on the risk the individual patient has of rejection, as well as the type and dose of concomitant immunosuppression given.

The maximum cumulative dose of 13.5 mg/kg and the daily dose of 1-1.5 mg/kg/day are supported by the data provided.

Treatment of Rejection in Renal Transplantation (TRRT)
The dose recommendation for Thymoglobuline when used in the treatment of acute renal rejection was mainly derived from the US study carried out by Gaber (Gaber, 1998, Transplantation), which studied biopsy proven acute rejection (i.e. not the more severe steroid resistant acute rejections), and compared Thymoglobuline to Atgam. In this trial (Gaber, 1998, Transplantation) the mean Thymoglobuline dose given to patients was 1.4 mg/kg/day, over a mean of 10 days (range 3-14 days). Nine patients (11%) were treated for less than 7 days, in 4 cases because of successful reversal of rejection, in two cases because of graft loss, in another two because no response was seen and rescue therapy was required, and in one patient because of both response and adverse event requiring early discontinuation of therapy.

The same dose was employed in the Alamartine study in fewer patients (32) than the Gaber study (82). In this study (Alamartine, 1994, Transplant Proc) the prescribed duration of the dose was 10 days, equivalent to the mean duration of dose in the Gaber study.

As the severity of renal rejection is usually determined by biopsy, and the length of the course by response to treatment (which is usually rapid, sometimes within 48-72 hours); a range of between 7 – 14 days is recommended, at a dose of 1.5 mg/kg.

The daily dose of 1-1.5 mg/kg/day seems appropriate.
Prophylaxis of Rejection in Heart Transplantation (PRHT)

In the three controlled studies presented, the dose of Thymoglobuline was 2.5 mg/kg/day for 5 days (Zuckermann, 2000, *Transplantation*; De Santo, 2004, *Transplant Proc*; Schnetzler, 2002, *Transplant Int*) making a cumulative dose of 12.5 mg/kg.

Schnetzler *et al.* additionally monitored total lymphocyte count (TLC) in patients, but it was not necessary to increase the Thymoglobuline dose in this study as the TLC did not exceed 300/ mm$^3$. A dose of 2 mg/kg/day Thymoglobuline was administered over three days by Aziz’s group (Aziz, 2001, *J Heart Lung Transplant*), or at 1.5 mg/kg/day over 5-7 days (Cantarovich, 2004, *Transplantation*). Individual tailoring of the dose, either in terms of amount or frequency, is possible. Such tailoring may be on the basis of, for example, the results of blood cell counts, e.g. T cells (Koch, 2005, *J Heart Lung Transplant*) or the need to delay calcineurin inhibitors because of renal dysfunction.

The symptoms of cytokine release syndrome increase with increasing dose of Thymoglobuline, so it would be safer to divide the cumulative dose given in these studies (12.5 mg/kg) into smaller daily doses, leading to a dose recommendation of: “1 –2.5 mg/kg over 3 to 5 days, giving a cumulative dose of 3 – 12.5 mg/kg”.

The maximum cumulative dose of 12.5 mg/kg and the daily dose of 1-2.5 mg/kg/day are supported by the data provided.

MAIN STUDIES

Prophylaxis of Rejection in Renal Transplantation (PRRT)

A total of seven randomised controlled studies for Prophylaxis of Rejection in Renal Transplantation (PRRT) are presented, three of which compare Thymoglobuline plus triple therapy to triple therapy alone (placebo-controlled), with the remaining four comparing Thymoglobuline to other antibodies (ATG-Fresenius, Atgam, basiliximab and OKT3), all with triple therapy.


Randomised prospective studies – comparing to triple therapy alone

The study of Mourad *et al* (Mourad, 2001, *Transplantation*) was carried out in 15 French and Belgium centres with 309 patients randomised to receive either induction with Thymoglobuline (n=151) followed by initiation of tacrolimus on day 9, or immediate tacrolimus-based triple therapy (n=158). Results at 12 months showed less biopsy proven acute rejection in induction group patients; 15.2% versus 30.4% (p=0.001). The mean prescribed dose was 1.25 kg/mg/day for 10 days; the mean cumulative dose received was 10.25 mg/kg/patient. Patient and graft survival at 12 months were not significantly different in the two groups, being 97.4% versus 95.8% and 92.1% versus 91.1%, respectively.
Statistically significant differences between the treatment groups (induction vs. noninduction) were observed for “CMV infection” (32.5% vs. 19.0%, P=0.009), “leukopenia” (37.7% vs. 9.5%, P=0.001), “fever” (25.2% vs. 10.1%, P=0.001), “herpes simplex” (17.9% vs. 5.7%, P=0.001), and “thrombocytopenia” (11.3% vs. 3.2%, P=0.007).

Conclusion of the authors was that low incidences of acute rejection were found in both treatment arms. Induction treatment with ATG has the advantage of a lower incidence of acute rejection, but it significantly increases adverse events, particularly CMV infection.

The study reported by Charpentier et al., included three arms, the first comprising Thymoglobuline induction with a ciclosporin-based triple therapy (n=190), the second comprising Thymoglobuline induction with a tacrolimus-based triple therapy (n=190), with a control arm comprising patients receiving a tacrolimus-based triple therapy alone (n=188). Acute rejection rates after six months were significantly better in the Thymoglobuline/tacrolimus arm than the other two arms (p=0.004 when compared to the Thymoglobuline/ciclosporin arm, p=0.003 when compared to the triple therapy alone arm). No significant difference in graft survival was found between the arms after six months.

In the ATG groups, the incidences of leukopenia, thrombocytopenia, serum sickness, fever, and cytomegalovirus infection were significantly higher (P<0.05).

### Table 2: Frequency of acute rejection (Charpentier et al, 2003)

<table>
<thead>
<tr>
<th>Rejection type</th>
<th>Tac triple (n=185)</th>
<th>ATG-Tac (n=186)</th>
<th>ATG-CSA (n=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%)</td>
<td>Episodes</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>Clinical signs and symptoms</td>
<td>61 (33.0%)</td>
<td>83</td>
<td>68 (37.0%)</td>
</tr>
<tr>
<td>of acute rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute rejections confirmed</td>
<td>47 (25.4%)</td>
<td>60</td>
<td>28 (15.1%)</td>
</tr>
<tr>
<td>by biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>3 (1.6%)</td>
<td>3</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Corticosteroid-sensitive</td>
<td>36 (19.5%)</td>
<td>41</td>
<td>20 (10.8%)</td>
</tr>
<tr>
<td>Corticosteroid-resistant</td>
<td>13 (7.0%)</td>
<td>16</td>
<td>9 (4.8%)</td>
</tr>
</tbody>
</table>

* One patient could have had two types of rejection; therefore, the numbers of patients in the subcategories do not add up to the total.

1 Tac triple vs. ATG-Tac, P=0.003.
2 ATG-Tac vs. ATG-CSA, P=0.004.
3 Tac triple vs. ATG-Tac, P=0.004.
4 ATG-Tac vs. ATG-CSA, P=0.017.
5 Tac triple vs. ATG-Tac, P=0.039.
6 ATG-Tac vs. ATG-CSA, P=0.038.

**UKPAR – Thymoglobulin**

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The authors conclude that acute rejection was significantly lower in the ATG-Tac group compared with the ATG-CsA and Tac triple groups. Significantly more hematologic and infectious adverse events were observed in both ATG induction groups.

Randomised prospective studies – comparing to another antibody (polyclonal or monoclonal)

Thymoglobuline was compared with Atgam in the Hardinger study (Hardinger, 2004, Transplantation) in transplants conducted more recently during the period of 1996 to 1997. The rate of rejection seen in the Thymoglobuline arm was significantly lower than the Atgam arm, 8% compared with 34% after 5 years (p<0.01) and the number of steroid resistant rejections was lower in the Thymoglobuline group. Graft survival at 5 years was significantly higher in the Thymoglobuline arm (73%) than the Atgam arm (54%), p=0.046.
More recently, monoclonal antibodies have been developed to prevent rejection in solid organ transplant, namely basiliximab and dacluzimab, which block the interleukin-2 receptor chain on the surface of activate T lymphocytes. Older studies have compared Thymoglobuline to OKT3, which binds to the T cell receptor.

Two studies are presented which compare Thymoglobuline with basiliximab, both using ciclosporin as the calcineurin inhibition component of the triple therapy. Unsurprisingly, due to the different mechanisms of action of the two drugs, Thymoglobuline caused a noticeably greater degree of leucopenia. With regards to study endpoints, no significant differences in acute rejection rates or graft survival were reported (Lebranchu, 2002, *Am J Transplantation*; Mourad, 2004, *Transplantation*). In the Lebranchu study graft survival after 6 months was 100% and 94% in the Thymoglobuline and basiliximab arms of the study, respectively.

Table 6: Efficacy at month 12 (Mourad, 2004)

<table>
<thead>
<tr>
<th>Biopsy-confirmed acute rejection episode</th>
<th>Basiliximab (%)</th>
<th>Anti-thymocyte globulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy-confirmed acute rejection episode</td>
<td>5 (9.6)</td>
<td>5 (9.4)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>2 (3.9)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.9)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Treatment failure*</td>
<td>8 (15.4)</td>
<td>8 (15.1)</td>
</tr>
</tbody>
</table>

* Treatment failure is defined as any patient who experienced either acute rejection, graft loss, or death.
Table 7: Safety parameters (Mourad, 2004)

<table>
<thead>
<tr>
<th></th>
<th>Basiliximab (%)</th>
<th>Anti-thymocyte globulin (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>20 (38.5)</td>
<td>14 (26.4)</td>
<td>NS*</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>1 (1.9)</td>
<td>4 (7.6)</td>
<td>NS*</td>
</tr>
<tr>
<td>Infections</td>
<td>22 (42.3)</td>
<td>28 (53.0)</td>
<td>NS*</td>
</tr>
<tr>
<td>CMV infection(\d)</td>
<td>11 (21.2)</td>
<td>22 (41.5)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (19.2)</td>
<td>27 (51.0)</td>
<td>0.0007*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>16 (30.2)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Chi-square test.
\(\d\) Fisher’s exact test (conditions for chi-square test unfilled).
\(\d\) Defined as positive antigenemia coupled with symptoms or test results justifying treatment with intravenous ganciclovir.

Conclusions of the Mourad study were that both ATG and basiliximab, when used for IT in a sequential protocol, are equally effective in terms of graft and patient survival as well as at preventing acute rejection. However, basiliximab is associated with a lower incidence of certain key adverse events, namely CMV infection, leukopenia, and thrombocytopenia.

It is noted that the administration of ciclosporin was not comparable between the two treatment groups, which may account for differences in acute rejection, although these were not significant. This was rectified in the protocol executed by Mourad et al. (Mourad, 2004, Transplantation) whereby ciclosporin was not administered immediately to patients, but was delayed in both arms of the trial until after serum creatinine levels in patients had dropped below 200Ymol/L. Graft survival after one year for the Thymoglobuline arm was 96% compared to 94% in the basiliximab arm of the study.

In the Norrby trial, transplants were conducted in an earlier period, whereby 48 patients receiving Thymoglobuline were compared to 45 patients given ATG-Fresenius (Norrby, 1997, Transplant Proc). The mean prescribed dose of Thymoglobuline was 2.5 mg/kg/day over 4-7 days; the mean cumulative dose was 14.49 mg/kg. However, in the Norrby trial the rate of rejection was 67% and 58% (not significant) in Thymoglobuline and ATG Fresenius groups respectively, a figure much higher than in the other studies. These major differences in the rate of rejection were probably due to differences in the population inclusion criteria i.e. patients had a high risk of delayed graft function in the Norrby trial. Additionally patients were treated between 1989 and 1995, when rejection rates generally were higher than current rates.

Two studies in “sensitised” patients (patients at higher risk of acute rejection because of immunological sensitisation to alloantigens) have been published. Fukuuchi et al. published the results of a study comparing Thymoglobuline with OKT3 in the treatment of highly sensitised renal transplant recipients (Fukuuchi, 1996, Transplant Proc). In this study Thymoglobuline delayed the onset time of first rejection, but graft and patient survival rates between the two arms of the study were not significantly different. The authors noted that Thymoglobuline seems to have a more beneficial effect in older patients than OKT3, as five of the six patients who died in the OKT3 arm were over 50 years of age, despite the OKT3 population having a lower number of patients in this age range.

An older study in which patients received transplants from 1991 to 1995 was reported by Thibaudin et al. Forty-seven (47) sensitised patients receiving Thymoglobuline induction therapy with triple therapy were compared with 42 patients receiving triple therapy alone (Thibaudin, 1998, Nephrol Dial Transplant). Although rejection rates in this study were higher than those seen in the later studies, both because of the fact that patients were sensitised, and because of the era in which the study was performed, Thymoglobuline
administration yielded a significant reduction in the rate of acute rejection at 3 months (53% Thymoglobuline compared to 71% without Thymoglobuline, p=0.008).

Table 8: Frequency of biopsy-proven acute rejection episodes in patients grouped on the basis of the lowest PRA (Thibaudin, 1998)

<table>
<thead>
<tr>
<th>PRA</th>
<th>No. of patients</th>
<th>No ATG n=42</th>
<th>ATG n=47</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5%</td>
<td>89</td>
<td>(27/42) 64%</td>
<td>(18/47) 38%</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>63</td>
<td>(21/30) 70%</td>
<td>(12/33) 35%</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt; 40%</td>
<td>37</td>
<td>(12/16) 75%</td>
<td>(8/21) 38%</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt; 60%</td>
<td>26</td>
<td>(7/11) 64%</td>
<td>(5/15) 33%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 80%</td>
<td>17</td>
<td>(4/7) 57%</td>
<td>(4/10) 40%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion:
Thymoglobuline induction was beneficial in terms of preventing acute rejection, but it significantly increases adverse events, particularly CMV infection.

Treatment of Rejection in Renal Transplantation (TRRT)
Rejection is the main cause of graft failure, and if injury is sufficiently severe, the renal function may not recover. It is therefore important to diagnose and treat rejection episodes as soon as possible. Clinical features of acute rejection can be minimal, and may include features such as moderate fever, increasing serum creatinine levels, and more rarely, decrease in urine output and graft tenderness. Percutaneous biopsy of the transplanted kidney is therefore routinely carried out to diagnose rejection, and to distinguish rejection from other causes of allograft dysfunction. In many centres, episodes of acute rejection are treated with a short term "pulses" of high dose methylprednisolone. When the rejection episode is sensitive to high dose of corticosteroids, renal function improves within 48-96 hours. However, if there is no early regression of the event because rejection is resistant to corticosteroids, other options must be sought. The histological features may also influence the waiting period, for example because vascular rejection has a poorer prognosis many centres will consider the early use of anti-thymocyte antibodies in such cases. NICE has recently issued guidance (26 April 2006) on the use of immunosuppressive therapy for renal transplantation in children and adolescents. They comment “If acute rejection does not resolve after treatment with corticosteroids, it is defined as ‘corticosteroid-resistant acute rejection’. Corticosteroid-resistant acute rejection may be treated with the polyclonal antibodies ALG or ATG or the monoclonal antibody muromonab-CD3, or by switching the calcineurin inhibitor to high-dose tacrolimus”.

The proposed SmPC indication with the following dosage guide: “1.5 mg/kg/day for 7 to 14 days, corresponding to a cumulative dose of 10.5 – 21 mg/kg”

Four studies are presented to support the claim for treatment of rejection in renal transplantation. All four studies were comparator trials. All the patients in three of the four studies were diagnosed with steroid-resistant rejection; most of the patients in the Gaber study (Gaber, 1998, Transplantation) also had steroid-resistant rejections (72 of 82 patients). Otherwise, the patient population was predominantly male (where defined in the literature) with a mean age between 39 and 51 years.
Randomised prospective studies – comparing to another antibody (polyclonal or monoclonal)

Gaber (Gaber, 1998, *Transplantation*) published the results of a company sponsored study that was used for the registration of Thymoglobuline in the US and Canada. This study compared the efficacy of two polyclonal antibodies (Atgam and Thymoglobuline) in a randomised, prospective, comparative, multicentre trial conducted in the US, which included 163 renal transplant patients with steroid resistant or histologically severe rejections (Gaber, 1998, *Transplantation*; Woodle, 1999, *Graft*; Gaber, 1999, *Kidney International*), randomised to receive Thymoglobuline (1.5 mg/kg/day) or Atgam (15 mg/kg/day; the manufacturer’s recommended dose) for 7 to 14 days and were followed-up for 12 months post-therapy. Concurrent immunosuppression included steroids, azathioprine and cyclosporin. Inclusion criteria were age ≥ 18 years, recipients of a first or second renal transplant and biopsy proven rejection of Banff grade I-III (patients with Banff grade I were required to have exhibited corticosteroid resistance, defined as an increase of ≤ 10% in serum creatinine level despite 3 or more consecutive days treatment with intravenous methylprednisolone of at least 250 mg/day). The primary end point was return of the serum creatinine to, or below, baseline on 2 consecutive measurements. The secondary end points were graft survival and serum creatinine at day 30, and improvement in biopsy grade. The results showed that Thymoglobuline was statistically significantly superior to Atgam for the primary end point; in the Thymoglobuline group 88% of patients successfully responded to treatment compared with 76% of Atgam treated patients (p=0.027).

Thymoglobuline and Atgam gave equivalent results for all secondary end-points. Allograft survival rate at 30 days were 94% and 90% for Thymoglobuline and Atgam groups respectively. Median serum creatinine levels at 30 days were 177 and 168 Ymol/L in the Thymoglobuline and Atgam treatment groups respectively; recurrent rejection was significantly less frequent 90 days after the end of treatment in the Thymoglobuline group; 17% versus 36% (p=0.001) respectively; and 8% versus 20% (p=0.039) for biopsy proven rejection. Twelve months after completion of therapy there was no statistically significant difference between two groups in terms of overall allograft survival, but there was a tendency in favour of Thymoglobuline (83% versus 75%). In this trial the dose of Thymoglobuline used for treatment of rejection as stated in the protocol was 1.5 mg/kg/day for 7 to 14 days; thus with an imposed minimum duration of treatment of seven days. However, the number of days of treatment actually received was less than that stated in the protocol being between 3-14 days, 69.5% of patients receiving 10 infusions, and in 34% of patients the daily dose of Thymoglobuline was reduced.

T-cell subset counts (CD2, CD3, CD4, CD8) were performed in a subgroup of 26 patients (n=12 Thymoglobuline, n=14 Atgam). In Thymoglobuline patients a significantly greater degree of T-depletion, as well as more prolonged depletion of T cells occurred, in comparison with the Atgam group. In patients given Thymoglobuline, from day 6 until day 14, T cell subset counts were as follows: CD2 cells < 9 ± 10 /ml; CD3 cells < 23 ± 36 /ml; CD4 cells< 5 ± 7 /ml and CD8 cells < 7 ± 6 /ml.

Similar results were reported by Alamartine in a prospective, randomised study of 59 renal transplant recipients experiencing a first steroid-resistant acute rejection episode (Alamartine, 1994, *Transplant Proc*) showed similar efficacy. The doses used were 1.5 mg/kg/day of Thymoglobuline or 5mg/kg/day of OKT3 for 10 days. The graft and patient survival were similar in the two groups after one and two years of follow up. This study used
Thymoglobuline that was manufactured prior to the introduction of the pasteurisation step for viral clearance.

In a prospective, randomised study of 60 renal transplant recipients having a first steroid-resistant acute rejection episode (Mariat, 1998, *Transplant Int*), the doses used in this study comparing Thymoglobuline and OKT3 were approximately half of that recommended by the manufacturers at 0.75 mg/kg/day and 0.05 mg/kg/day for Thymoglobuline and OKT3 respectively, both given for ten days. Successful reversion of rejection was similar in the two groups. Three months after therapy, one allograft (3%) was lost in the Thymoglobuline group and three (10%) in the OKT3 group. At 12 months actuarial allograft survival was 89% and 81% for the Thymoglobuline and OKT3 groups respectively. At the end of the three year follow-up 87.5% and 79.3% of allografts were still functioning in the Thymoglobuline and OKT3 groups respectively. Three patients died in the Thymoglobuline group and one in the OKT3 group. The authors conclude that low doses of Thymoglobuline and low doses of OKT3 are equally effective in reversing steroid resistant acute rejection. Tolerance was better with Thymoglobuline, which also gave a potent and long-lasting immunodepression. The use of reduced doses of Thymoglobuline and OKT3 did not appear to lessen their efficacy.

The most recent study is reported by Midtvedt (Midtvedt, 2003, *Clin Transplant*) where patients were treated and followed up in the period of 1996 to 1999. As with the Mariat and Alamartine studies, Thymoglobuline was compared with OKT3, but doses were administered on the basis of daily T cell counts CD2+ cells by an immunomagnetic method). An initial dose of 2 mg/kg of Thymoglobuline was administered on day 1 and re-administered daily at 1 mg/kg only if and when the T cell count increased above 50 cells/ mm$^3$. A mean of 2.3 administrations of Thymoglobuline was given i.e. 3.3mg/kg total dose. Five mg OKT3 was administered on day 1, with a daily administration thereafter only if the T cell count increased to more than 50 cells/ mm$^3$.

Serum creatinine levels were comparable in the two groups at the control timepoints. After treatment, serum creatinine levels in the Thymoglobuline group dropped from 308 ± 125 Ymol/l to 254 ± 122 Ymol/l, reaching 169 ± 45 Ymol/l after 3 months. Similarly, levels in the OKT3 group were 330 ± 94 Ymol/l prior to treatment and dropped to 193 ± 106 Ymol/l after 3 months. Re-rejection in this study (44% of Thymoglobuline patients and 50% of OKT3 patients) was higher than in the other studies, due to the patients being sensitized.

During the first three months following anti-lymphocyte antibody treatment, a total of 25 patients developed CMV infection (11 in the OKT3 group and 14 in the ATG group, p ¼ NS)

### Table 9: Serum creatinine values$^a$

<table>
<thead>
<tr>
<th></th>
<th>ATG (n = 27)</th>
<th>OKT3 (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before rejection</td>
<td>157 ± 72</td>
<td>151 ± 88</td>
</tr>
<tr>
<td>Start antibody therapy</td>
<td>308 ± 125</td>
<td>330 ± 94</td>
</tr>
<tr>
<td>End antibody therapy</td>
<td>254 ± 122</td>
<td>246 ± 144</td>
</tr>
<tr>
<td>1 wk after end antibody therapy</td>
<td>215 ± 77 (n = 26)</td>
<td>224 ± 116 (n = 27)</td>
</tr>
<tr>
<td>3 months follow-up</td>
<td>169 ± 45 (n = 24)</td>
<td>193 ± 106 (n = 26)</td>
</tr>
<tr>
<td>12 months follow-up</td>
<td>166 ± 58 (n = 24)</td>
<td>163 ± 60 (n = 25)</td>
</tr>
<tr>
<td>32 months follow-up (range 18–40)</td>
<td>166 ± 55 (n = 22)</td>
<td>164 ± 57 (n = 23)</td>
</tr>
</tbody>
</table>

$^a$Serum creatinine (µmol/L) data are expressed as mean ± SD for each group.
Conclusion:
On the basis of the four studies presented, Thymoglobuline acts as an immunosuppression therapy, producing a greater and more long-lasting drop in T cell count than OKT3. In terms of efficacy, particularly the endpoints of serum creatinine levels and graft loss, Thymoglobuline is considered comparable to OKT3 and superior to Atgam.

Prophylaxis of Rejection in Heart Transplantation (PRHT)
Induction prophylaxis by antibodies has been widely used in heart transplantation for more than twenty years, initially with polyclonal antibodies, then with a switch to monoclonal antibodies (OKT3), and for the last ten years with a return to the use of polyclonal antibodies such as Thymoglobuline, following the report of Swinnen demonstrating the increased risk of post-transplantation lymphoproliferative disorder (PTLD) with the use of OKT3 (Swinnen, 1990, *N Engl J Med*). Following the registration of new drugs including tacrolimus, mycophenolate mofetil and microemulsion ciclosporin, Thymoglobuline still continued to be widely used as induction immunosuppression.

In heart transplantation induction, doses of Thymoglobuline are usually higher than in renal transplantation, but the courses are usually of a shorter duration (2 to 5 days in the SmPC in countries where approved). Calcineurin inhibitors (being potentially nephrotoxic) are usually introduced on the second or third post-operative day, when haemodynamic stability is attained and the renal function returns to a satisfactory level.

The applicant proposed for this indication the following dosage: “1 – 2.5 mg/kg/day for 3 to 5 days giving a cumulative dose of 3 – 12.5mg/kg”

There are fewer publications in the field of cardiac transplantation than in renal transplantation. There are a number of difficulties in carrying out studies in the field of cardiac transplantation, which include the small numbers of potential patients, the low event rates leading to the need for unachievable patient numbers in order to have sufficiently powered studies, and the lack of an appropriate endpoint (Hosenpud, 2005, *N Engl J Med*). In general, in publications in cardiac transplantation, courses of Thymoglobuline tend to be shorter than those in renal transplantation, being about 3-5 days long. Probably as a result of the shorter course of therapy, less efficacy monitoring seems to be carried out by cardiac transplantation units compared to renal transplantation units, as monitoring of T lymphocyte subsets has no value until 48 –72 hours after the first dose of Thymoglobuline.

Nine studies are presented. Key studies in support of the indication are the three comparator controlled studies (placebo-controlled studies were not identified) – (De Santo, 2004, *Transplant Pro*; Schnetzler 2002, *Transplant Int*; Zuckermann, 2000, *Transplantation*). The Zuckermann study was a retrospective study. These studies are supported by other retrospective studies, which either have a historical control (Cantarovich, 2004, *Transplantation*; Koch, 2005, *J Heart Lung Transplant*) or were uncontrolled. The uncontrolled studies are included as a review of different immunosuppression protocols or patient subpopulations, principally paediatric.

Randomised prospective studies – comparing to another antibody (polyclonal or monoclonal)
Two prospective randomised trials (De Santo, 2004, *Transplant Proc*; Schnetzler, 2002, *Transplant Int*) were performed which compared Thymoglobuline to ATG-Fresenius, another rATG.
These two studies demonstrated that Thymoglobuline remains efficacious in the recent heart transplantation setting, and remains comparable (no statistically significant difference) to ATG-Fresenius in the prophylaxis of rejection in heart transplantation.

In the De Santo’s study patients (n=40) received thymoglobulin at a daily dose of 2.5 mg/kg for the first five postoperative days, while group B ATG-fresenius, at 2.5 mg/kg/d for seven days. Conclusions of De Santo were that although thymoglobulin and ATG-fresenius showed equivalent efficacy for rejection prevention, they have different immunological properties. In particular, thymoglobulin seems to be associated with a significantly higher incidence of cytomegalovirus disease/reactivation.

Patient survival in the Schnetzler study after one year was 85% (22/26) in the Thymoglobuline arm and 88% (21/24) in the ATG-Fresenius arm, improving in the later De Santo study to 95% in both arms (19/20 for both arms).

Randomised prospective studies – no comparator
A controlled clinical study has been performed to compare ciclosporin and tacrolimus as part of the triple therapy used in conjunction with Thymoglobuline (Wang, 2004, Transplant Proc). This study involved 21 patients only, randomized into the two arms. All patients received Thymoglobuline induction therapy (2.5 mg/kg on the first day post-operative and 1.5 mg/kg/day for a further four days) and follow-up was performed after six months. At this time, patient survival was 100% in both groups, but differences were seen in the number of acute rejections, with more rejections seen in the ciclosporin group, 40% at 60% at three and six months, respectively, than in the tacrolimus group, 9% at both timepoints (p=0.15 and p=0.14 at three and six months respectively).

Aziz et al. studied 220 patients who received Thymoglobuline in induction at a mean dose of 2 mg/kg/day, over three days, giving a mean cumulative dose of 6 mg/kg/patients (Aziz, 2001, J Heart Lung Transplant). Concomitant treatment was triple therapy by ciclosporin, azathioprine and steroids. The median follow up was 87 months (over seven years), and the aim of the study was to compare the outcomes of patients whose primary pathology was ischaemic heart disease, with those with cardiomyopathy. The rate of rejection in the first six months was not statistically significantly different in the two groups, 1.7 and 1.4 episodes of rejection/patient occurring in each group respectively. Between month 6 and month 12 an additional 0.64 and 0.46 acute rejections/patient occurred, and 0.42 and 0.38 acute rejection/patient, between 12 and 24 months respectively in each group. Actuarial survival at 1, 5, and 10 years was 77%, 62%, and 39% for ischaemic heart disease patients compared with 85%, 82%, and 80% for patients with cardiomyopathy.

It was concluded that after heart transplantation, medium- and long-term outcome is significantly better for cardiomyopathy than for Ischemic heart disease recipients.

Retrospective studies – comparator another antibody (polyclonal or monoclonal)
In the earliest publication (Zuckermann, 2000, Transplantation), a retrospective analysis covering 1984 to 1996, Thymoglobuline was used at a mean dose of 2.5 mg/kg/day over seven days, giving a theoretical cumulative dose of 17.5 mg/kg/course. The aim was to compare Thymoglobuline (n=342) to ATG Fresenius (n=142). The freedom from rejection at five years was significantly better in the Thymoglobuline group at 72% vs. 42% in the ATG Fresenius group (p<0.01). One and five year survival was also significantly better in Thymoglobuline group (87% vs. 78% and 76% vs. 60% respectively). Viral infections
occurred more often in Thymoglobuline patients (53% vs 39%). Patients in the Thymoglobuline group were older, with more HLA mismatches and received hearts which had suffered longer cold ischaemia times, but were treated more recently than the ATG-Fresenius patients.

It should be recognised that the Zuckermann results are limited by two factors, firstly the age of the study, in a field where patient survival rates have noticeably improved, and secondly the differences in study population between the two arms.

Conclusion:

The limitation of the review is the number of the published clinical trials with Thymoglobuline in the prophylaxis of rejection in heart transplantation. It is acknowledged that there are a number of difficulties in carrying out studies in the field of cardiac transplantation. However, presented publications support the proposed indication.

CLINICAL STUDIES IN SPECIAL POPULATIONS

Sensitised allograft recipients

Two prospective studies have been carried out in immunologically sensitised patients (defined as patients who have a high panel reactive antibody (PRA) or who are receiving a second or higher transplant (Fukuuchi, 1996, *Transplant Proc*). In these patients the risk of acute rejection is consistently higher and the benefit of induction by ATGs is well recognised. The first study (Thibaudin, 1998, *Nephrol Dial Transplant*) compared outcomes with or without Thymoglobuline induction in a total of 89 patients (47 received Thymoglobuline). The mean prescribed dose of Thymoglobuline was 1.25 mg/kg/day over ten days, the mean dose received was 0.79 mg/kg/day and so the mean cumulative dose received was 7.9 mg/kg (as a result of adaptation of the initial dose following lymphocyte subset monitoring). The incidence of acute rejection was less in Thymoglobuline group; 53% versus 71% (p=0.008), for biopsy proven acute rejection the improvement in the Thymoglobuline group remained statistically significant (38% vs. 64%; p = 0.02). Graft survival at six and twelve months was not significantly different in the two groups, 81% and 76%, 94% and 89% in control and Thymoglobuline groups respectively. The authors concluded that Thymoglobuline induction was beneficial for all sensitised patients regardless of their level of sensitisation, with regard to acute rejection episodes, graft survival and graft function.

In the study of Fukuuchi *et al.* (Fukuuchi, 1996, *Transplant Proc*) 82 high risk patients (sensitised, retransplant or both) were randomised to receive either OKT3 (n=45) or Thymoglobuline (n=37). The prescribed Thymoglobuline dose was 75 mg/day over ten days, the cumulative dose was 750 mg/patient (average cumulative dose was 10.7 mg/kg - for a presumed mean patient weight of 70 kg). The mean time to first acute rejection was delayed in the Thymoglobuline group, being 96 days vs. 21 days in the OKT3 group (p=0.002). No significant difference in the incidence of rejection, or graft and patient survival was demonstrated.

A retrospective study comparing Thymoglobuline with basiliximab in sensitised patients (high responders) concluded that Thymoglobuline was the more effective treatment, although limited by the small population size (Knight, 2004, *Transplantation*).
Paediatric population

The immune response is very dependent upon age and the stage of maturation or involution of the thymus. It is usually considered that the immune response will be strong in a paediatric population and thus “stronger” immunosuppressive therapy is required (Bell, 1997, Transplant Proc) - indeed immunosuppression is often given over a longer duration.

• Prevention of Renal Transplant Rejection

Three studies in paediatric patients are presented in support of Thymoglobuline administration in the prevention of renal transplant rejection. The only controlled study is retrospective (Khositseth, 2005, Transplantation) based on the review of medical records at the University of Minnesota. Patients (n=220) were categorised according to the administration of Thymoglobuline (1.5 mg/kg/day over ten days) or Atgam (5 mg/kg/day over 14 days). Authors concluded that Thymoglobuline induction was associated with a decreased incidence of acute rejection and an increased incidence of EBV infection in paediatric kidney transplant recipients. EBV monitoring should be performed in EBV-naïve recipients receiving Thymoglobuline.

A review of the demographics reveals that the patient populations did not differ significantly other than the type of triple therapy (azathioprine vs. mycophenolate mofetil). As with the adult study (Hardinger, 2004, Transplantation), the rate of acute rejection was lower in the paediatric patients receiving Thymoglobuline (33% after three years compared with 50%, p=0.02), but with higher incidences of EBV infection (8% vs. 3%, p=0.002). CMV infection was comparable in the two arms, all patients having received viral prophylaxis (ganciclovir 5mg/kg ever 12 hours i.v. for 10 -14 days, followed by oral acyclovir 20 mg/kg/dose four times a day for 12 weeks.

The remaining two studies (Ault, 2002, Pediatr Nephrol; Khwaja, 2003, Pediatr Transplantation) are uncontrolled and retrospective, with small denominators, but there are few reported studies on the use of Thymoglobuline in paediatric patients. Ault et al. presented data from a prospective study in 17 paediatric patients, with ages ranging from 2 to 17 years (Ault, 2002, Pediatr Nephrol).

Eleven of the patients were Caucasian and six were African-American. Thymoglobuline was administered at 1.5 mg/kg/day intraoperatively and daily over the following 4-6 post-operative days, which is comparable to the adult dosages used and the proposed SmPC. According to the European Renal Association, the patient survival after one year is 98.3% (97.0 – 99.1%) and 98.6% (98.0 – 99.2%), (ERA-EDTA Registry 2003 Annual Report - p67, p71) for the cadaver donor and living donor first transplant patients, respectively, of the 1997-2001 cohort. The attained patient survival of 100% is comparable to the database results, bearing in mind the small number of patients.

A retrospective study in 46 infants is reported by Khwaja et al. (patients under one year of age). In this study, patients received Thymoglobuline as induction therapy at a dose of 1.5 mg/kg/day for ten days, beginning post-operatively on day 1. Standard triple therapy was additionally administered, with the exception of 13 patients who were treated in the pre-ciclosporin era, who thus received azathioprine and steroids only. After introduction of ciclosporin, patient survival was 100% (Khwaja, 2003, Pediatr Transplantation).

The ERA-EDTA does not report on incidence of rejection events. In the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) (Seikaly, 2001, Pediatr
transplant), the authors report that the results of acute graft rejection with Thymoglobuline (0% at six months and twelve months) are superior to results reported for the US population (23% at six months for patients receiving living donor allografts and 25% at six months for patients receiving cadaver allografts). These three studies presented (Khositseth, 2005, Transplantation; Ault, 2002, Pediatr Nephrol; Khwaja, 2003, Pediatr Transplantation) suggest that Thymoglobuline is effective in preventing rejection of renal transplants in paediatric (and infant) patients.

- **Treatment of Rejection in Renal Transplantation (TRRT)**
  The applicant has not presented studies for paediatrics in the TRRT. Mariat included also patients less that 40kg in the study

- **Prevention of Heart Transplant Rejection**
  Two of the studies to support the use of Thymoglobuline in paediatric patients in the prevention of heart transplant rejection are retrospective and uncontrolled and not directly comparable as they employed different dosing regimens for Thymoglobuline tailoring the dose according to baseline platelet counts or absolute lymphocyte counts (Di Filippo, 2003, Transplantation; Parisi, 2003, J Heart Lung Transplant). Patient survival rates were 80% (24/30) and 97% (30/31) for the two studies, but over a varying duration of follow-up. In support of using Thymoglobuline in the paediatric population, efficacy was achieved in these small patient groups, but the studies are possibly more interesting as long-term safety studies in children.

**Geriatric population**
A retrospective analysis by the EBMT demonstrated that ATG treatment in older patients is effective and maintains a positive benefit/risk balance, though greater care should be taken in its administration and in the monitoring of the patients. The response rate was not significantly different in 664 patients <60 and 127 patients >60 (Tichelli, 1999, Ann Int Med).

Renal dysfunction in the prophylaxis of Rejection in Heart Transplantation (PRHT)
The efficacy of Thymoglobuline-based prophylaxis in a subpopulation of heart transplantation patients with renal dysfunction was confirmed by Cantarovich et al. (Cantarovich, 2004, Transplantation). The study was designed to investigate the possibility of delaying cyclosporin’s (nephrotoxic) administration during the first two weeks of immunosuppression. Patient survival after one year in the control arm (historical control), representing a standard Thymoglobuline plus triple therapy was 88% (15/17). The results suggested that ATG-induction allows for a prolonged and safe delay in the initiation of cyclosporin in heart transplant patients with postoperative renal dysfunction.

**Conclusions on clinical efficacy**
The studies presented in the dossier originate from a review of clinical studies reported in the scientific literature.

A total of seven randomised controlled studies are presented in Prophylaxis of Rejection in Renal Transplantation, three of which compare Thymoglobuline plus triple therapy to triple therapy alone (placebo-controlled), with the remaining four comparing Thymoglobuline to other antibodies (ATG-Fresenius, Atgam, basiliximab and OKT3), all with triple therapy.

Four comparator studies supported the claim for treatment of rejection in renal transplantation. Three comparator controlled studies are presented to support the indication for the Prophylaxis of Rejection in Heart Transplantation. The limitation of the review is the
number of the published clinical trials with Thymoglobuline in the prophylaxis of rejection in heart transplantation is acknowledged due to number of difficulties in carrying out studies in the field of cardiac transplantation. However, presented publications support the proposed indication.

Proposed indications and doses are discussed adequately and the presented data support the indications.

CLINICAL SAFETY

Introduction
The Applicant has collected data from the following sources:
- A prospective Pharmacovigilance (PV) survey, 00PTF01
- Periodic Safety Update Reports (PSURs)
- Safety data included in the efficacy publications discussed in this submission
- Safety data from publications carried out to examine certain safety concerns of clinicians in the field.

Adverse events
A mild to moderate first dose effect linked to the release of inflammatory cytokines. To minimise first-dose effects, use of prophylactic agents, control of infusion rate and concentration of the diluted product is specified in the SmPC.

As per applicant cytopenias (mostly thrombocytopenia) occur because of the cross reactivity of Thymoglobuline with platelet antigens. Thrombocytopenia can be a particular management problem in patients at risk of thrombocytopenia for other reasons such as the diagnosis of aplastic anaemia, or the use of extra-corporeal circulation during heart transplantation. Platelet transfusions may be required to be given during the course of the treatment period with Thymoglobuline in these patients.

Immunisation of patients against rabbit antibodies which may theoretically result in three separate problems: inefficacy of the product; anaphylaxis (type I immune reaction); serum sickness (type III immune reaction) (Regan, 2001, Transplant Immunol).

Infections, in particular, CMV infection or reactivation, have been noted to be increased in patients treated with Thymoglobuline, such that concomitant prophylaxis or close monitoring with subsequent pre-emptive treatment with an antiviral medication is becoming more common for renal transplant patients. Other malignancies occur commonly in solid organ transplant patients being associated with the immunosuppression patients receive. Thymoglobuline, as part of an immunosuppressive regimen may contribute to an increased incidence of malignancy.

Patients in French Multi-centre Post-Marketing Surveillance observational study (00PTF01) were solid organ transplant recipients. During the study period, the 240 patients each received a total dose of approximately 138 grams of Thymoglobuline over a median duration of ten days. All patients were evaluated for safety results.

In total, 32 serious adverse events were reported in 32 patients. Of these, 22 episodes in 22 patients occurred in the first month, the others occurring later.
There were no cases of anaphylaxis during the period of administration of Thymoglobuline. Infusion related reactions occurred in over half of patients, but were usually mild and spontaneously recovered with no sequelae. There were no reports of local reactions such as thrombophlebitis or pain at the site of the infusion in those patients who were infused Thymoglobuline via peripheral vein (n=1) or arterio-venous fistula (n=67). There were no reports of respiratory symptoms.

Temporary treatment discontinuations as a result of monitoring of efficacy, biological abnormalities or clinical adverse events occurred in about one third of patients. Twelve patients switched from Thymoglobuline to Lymphoglobuline. In six of these, the reason for the switch was known, and was mostly rash and/or fever, and in two cases was due to serum sickness. In most of the remaining six patients, there was either neutropenia (<1.5 x 10^9/l) or thrombocytopenia (<80 x 10^9/l) noted on the switch day or preceding day, which was likely to be the cause of the switch. Four deaths occurred during the study.

The table below lists the number of patients suffering from adverse events associated with Thymoglobuline administration, and thought to be related to its use:

Table 10: Number of patients suffering from adverse events associated with Thymoglobuline administration

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Fever &gt;38.5°C</td>
<td>131 (55%)</td>
</tr>
<tr>
<td>Fever 2 consecutive days</td>
<td>39 (16%)</td>
</tr>
<tr>
<td>Rash</td>
<td>28 (12%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (11%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>21 (9%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18 (8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Trismus</td>
<td>3 (1%)</td>
</tr>
<tr>
<td><strong>Biological adverse events</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia &lt;80 x 10^9/L;</td>
<td>34 (14%)</td>
</tr>
<tr>
<td>Thrombocytopenia &lt;50 x 10^9/L;</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Neutropenia &lt;2.5 x 10^9/L;</td>
<td>121 (50%)</td>
</tr>
<tr>
<td>Neutropenia &lt;1.5 x 10^9/L;</td>
<td>32 (13%)</td>
</tr>
<tr>
<td>Neutropenia &lt;0.8 x 10^9/L;</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

All these adverse reactions were transient, resolved spontaneously and had no clinical consequences. These infusion associated reactions were listed in the CRF and investigators had to tick boxes if the event occurred. Any events which occurred which were not listed in the CRF could be added in another section. Fever (> 38.5°C once) was the commonest
adverse reaction, affecting 131 patients (55%); 39 patients (16%) having a fever which lasted two or more consecutive days.

Twenty-one patients (9%) were reported as suffering from shivering/chills. Patients suffering from fever secondary to infection or rejection for example are not included in these figures unless they occurred within the first 15 days.

The definition used to identify possible cases of serum sickness was the occurrence after day seven, of fever, with or without rash, together with one or more of the following: arthralgia, myalgia, pruritus, dysphagia, trismus (i.e. temporo-mandibular joint pain and stiffness). This definition of serum sickness was developed by a committee of investigators who discussed each case or potential case of serum sickness. Using this definition, a total of 18 patients (7.5%) were identified on median day 11 (range 10-14).

All patients identified as having serum sickness had fever and arthralgia, seven had a rash as well, seven had myalgia, five dysphagia, five pruritus, and three trismus. Serum complement was measured in 15/18 patients. Of these, 14 patients had lowered serum complement levels. Four patients discontinued Thymoglobuline as a result of having serum sickness, two switching to Lymphoglobuline.

For cutaneous events, twenty-eight patients (11%) suffered a rash while under treatment with Thymoglobuline, and 12 patients (5%) pruritus. Of these patients, 11 (4%) suffered simultaneous fever and rash.

Over half the patients (137 or 57%) were reported as having experienced no significant infection in the year following transplantation; 102 patients had at least one episode of infection. Only 10% of patients had more than one episode of significant infection.

Table 11: Overview of adverse events occurring over the year of follow-up (n=240)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>patients n (%)</th>
<th>episodes n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>4 (1.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Graft losses</td>
<td>8 (3.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Treated rejections</td>
<td>65 (27%)</td>
<td>90</td>
</tr>
<tr>
<td>Biopsy proven rejections</td>
<td>48 (20%)</td>
<td>69</td>
</tr>
<tr>
<td>Rejections during Thymoglobuline treatment</td>
<td>4** (1.7%)</td>
<td>5</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>57 (24%)</td>
<td>-</td>
</tr>
<tr>
<td>Malignancies</td>
<td>7 (2.9%)</td>
<td>8</td>
</tr>
</tbody>
</table>
Serum sickness is also recognised in the literature with a frequency of approximately 4 – 16% (Charpentier, 2003, Transplantation; Mourad 2001, Transplantation; Lebranchu, 2002, Am J Transplantation; Mariat, 1998, Transplant Int). The common frequency in the PV trial, serum sickness was spontaneously reported in only 53 patients over the six-year post-marketing period. However, based on the results of the PV study, serum sickness should be considered as common (>1/100, <1/10).

The table below examines the frequency of the broad categories of infection in the year of follow up.

**Table 12: Frequency of infection by type**

<table>
<thead>
<tr>
<th>Patients/episodes:</th>
<th>Bacterial</th>
<th>Viral (incl. CMV)</th>
<th>Fungal</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients affected</td>
<td>29</td>
<td>79</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Episodes</td>
<td>38</td>
<td>95</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

On the basis of the PV trial, first dose effects consisting of fever and/or rash should be considered as very common (>1/10), but are expected. Thus, there are few spontaneous reports received.

**Table 13: Comparison of other adverse events reported in the literature with the postmarketing study (OOPTF01)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>Thymol 48</td>
<td>Thymol 184</td>
<td>Thymol 151</td>
<td>Thymol 50</td>
<td>Thymol 31</td>
<td>Thymol 26</td>
<td>Thymol 71</td>
<td>Thymol 240</td>
</tr>
<tr>
<td>Test drug</td>
<td>Thymol 48</td>
<td>Thymol 184</td>
<td>Thymol 151</td>
<td>Thymol 50</td>
<td>Thymol 31</td>
<td>Thymol 26</td>
<td>Thymol 71</td>
<td>Thymol 240</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>1.5</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.0 to 1.5</td>
<td>25 to 75 mg/day</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>10 days</td>
<td>10 days</td>
<td>6 to 10 days</td>
<td>10 days</td>
<td>5 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>cutaneous events</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>(NR)</td>
<td>NR</td>
<td>NR</td>
<td>(NR)</td>
<td>NR</td>
</tr>
<tr>
<td>urological-skeletal</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>urinary</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>hypertensive</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>hypercalcemia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>myalgia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not recorded
## Table 13 (cont): Comparison of infections and malignancies reported in the literature with the postmarketing study (OOPTF01)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>48</td>
<td>186</td>
<td>184</td>
<td>111</td>
<td>50</td>
<td>31</td>
<td>26</td>
<td>71</td>
</tr>
<tr>
<td>Test drug</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>1.5</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.0 to 1.5</td>
<td>25 to 75 mg/day</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
<td>6 to 10 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infections</td>
<td>NR</td>
<td>126 (67.7%)</td>
<td>138 (75.0%)</td>
<td>NR</td>
<td>43 (86.0%)</td>
<td>31 (100%)</td>
<td>36 (70%)</td>
<td>NR</td>
</tr>
<tr>
<td>Virus infections</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CMV reactivation</td>
<td>6 (13%)</td>
<td>45 (24.2%)</td>
<td>52 (28.3%)</td>
<td>49 (32.5%)</td>
<td>19 (38.0%)</td>
<td>12 (38.7%)</td>
<td>5 (19.2%)</td>
<td>NR</td>
</tr>
<tr>
<td>Hepatitis B infection</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Other viral infections</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Non-tuberculosis</td>
<td>77 (41.4%)</td>
<td>76 (41.3%)</td>
<td>44 (23.9%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>other infections</td>
<td>51 (26.9%)</td>
<td>47 (31.1%)</td>
<td>11 (6.0%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PTLD</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>3 (6%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Deaths</td>
<td>7 (15%)</td>
<td>3 (1.6%)</td>
<td>5 (2.7%)</td>
<td>7 (3.6%)</td>
<td>0 (0.5%)</td>
<td>3 (9.7%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NR = not recorded</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Table 13 (cont): Comparison of immune mediated adverse events reported in the literature with the postmarketing study (OOPTF01)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>48</td>
<td>186</td>
<td>184</td>
<td>111</td>
<td>50</td>
<td>31</td>
<td>26</td>
<td>71</td>
</tr>
<tr>
<td>Test drug</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
<td>Thy</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>1.5</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
<td>1.0 to 1.5</td>
<td>25 to 75 mg/day</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
<td>6 to 10 days</td>
<td>10 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Short-term events reported</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bloo loss associated reactions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactions listed</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fever</td>
<td>33 (17.7%)</td>
<td>40 (21.7%)</td>
<td>38 (25.2%)</td>
<td>16 (33%)</td>
<td>2 (6.5%)</td>
<td>2 (6.5%)</td>
<td>131 (55%)</td>
<td>NR</td>
</tr>
<tr>
<td>Shocking</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nause</td>
<td>3 (6.0%)</td>
<td>2 (4.0%)</td>
<td>3 (8.7%)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>NR = not recorded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The applicant has presented adverse events according to the MedDRA system organ class. Adverse events from the French Multi-centre Post-marketing Surveillance Study are presented in section 4.8 of the SmPC.

**Serious adverse events and deaths**

During the Short term no anaphylactic reactions or severe side effects were recorded. Two non-responding patients died, both of sepsis, one month and one year after treatment, respectively.
Within the French post-marketing study (00PTF01), there were no deaths in the first month; however two deaths from infection occurred during the second month. At one year, four patients had died. A fifth patient died after the year of follow-up, but of an event which occurred during the year of follow up. Causality assessment was not provided by investigators.

In this study twenty serious adverse events occurred before day 30 and twelve serious adverse events (in 11 patients) were reported by the investigators as occurring after day 30. Most of these adverse events were infections.

In the post-marketing study 00PTF01 at one year, eight malignancies had been reported in seven patients. Two malignancies (0.8%), a Kaposi’s sarcoma which has since partially resolved and an Epstein-Barr virus-associated post-transplant lymphoproliferative disorder from which a full recovery was made following reduction in immunosuppressive treatment, could be considered related to immunosuppressive treatment; and additionally the two cases of carcinoma of the cervix could possibly be related since they may be related to papilloma virus infection. Of these seven patients who suffered from malignancies, one died, four were in remission at one year and two patients had persistent disease at the end of the study period.

Most malignancies reported over the six year period of post-marketing under consideration were lymphomas (PTLD):

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>9</td>
</tr>
<tr>
<td>2000</td>
<td>12</td>
</tr>
<tr>
<td>2001</td>
<td>61</td>
</tr>
<tr>
<td>2002</td>
<td>29</td>
</tr>
<tr>
<td>2003</td>
<td>5</td>
</tr>
<tr>
<td>2004</td>
<td>27</td>
</tr>
</tbody>
</table>

Over the six year period of post-marketing under consideration a total of 143 cases were seen, a frequency was lower than 1 %. Use of immunosuppressive agents, including Thymoglobuline, may increase the incidence of malignancies, lymphoma or post-transplant lymphoproliferative disease (PTLD).

The applicant should closely monitor the appearance of the malignancies in the next PSURs.

**Anaphylaxis**

Anaphylaxis was not recorded as an adverse event in the PV trial, nor in the literature articles presented in support of efficacy.

Looking at the PSURs, during the period 1999 – 2003, 66 cases of anaphylactoid reactions or allergic reactions were reported, although the number of anaphylactic events alone is not specified. In 2004, seven reports of type 1 allergic reactions were made; two fatal (estimated corresponding patient exposure was 15 534 patients). Fatal anaphylaxis is very rare. Thus anaphylactic disorders should be considered as rare (>1/10 000 and <1/1000).

**Laboratory findings**

Leukopenia is commonly reported with Thymoglobuline use, and is expected as the primary mechanism of action is lymphocyte depletion.

In the PV trial solid organ transplant recipients, 123 patients (44%) suffered from neutropenia (<2.5x10^9/L), 35 patients (14%) from thrombocytopenia (< 80x10^9/L), but only six patients (2%) from severe neutropenia (< 0.8 x10^9/L), and nine patients (3%) from severe thrombocytopenia (<50x10^9/L). Anaemia occurred in 50% of patients; a relation with
Thymoglobuline use is possible but is more likely to be caused by other co-morbid conditions of the graft recipient, i.e. renal failure and/or surgical procedures.

Both thrombocytopenia (approximately 7 – 11%) and anaemia (approximately 25 – 35%) are reported in the literature, but without details of severity. Thrombocytopenia and neutropenia are classically reported side-effects and are spontaneously reported. Thus haematological events mainly thrombocytopenia, neutropenia and anaemia should be considered as very common (>1/10) or common (>1/100, <1/10).

In the PSURs covering the six year period from 1999 to 2004, there were only nine spontaneous reports of elevated hepatic enzymes associated with the use of Thymoglobuline. Elevation of hepatic enzymes has been usually transitory.

**Infections**

Infections are often reported in detail in the literature references describing clinical trials with Thymoglobuline. Bacterial infections are seen in all trials. Virus infections, especially CMV, but also other herpes infections, are commonly reported. A significantly higher incidence of CMV reactivations was recorded in patients treated with Thymoglobuline (75%) compared to ATG-Fresenius (30%, p=0.028) and new infections due to CMV only occurred in the Thymoglobuline arm (20%, p=0.05) (De Santo, 2004, Transplant Proc).

Ault et al. report on the prevalence of CMV infection in paediatric patients receiving renal transplants and treated with Thymoglobuline. Seven of the 17 paediatric patients were CMV naïve and 4 of these patients received an allograft from a CMV-positive donor. At 12 months post-transplant, all of these patients had a positive CMV IgM or IgG titre, but did not display any symptoms of CMV infection. Thus as per applicant infectious events should be considered as very common (>1/10).

Most organ transplant recipients will have had a primary CMV infection prior to transplantation, and thus will be latently infected, and will be at significant risk of reactivation. If they get a primary infection it is more severe than in a person with a normal immune system. CMV infection is not transmitted to humans by animals and vice versa. (Loh, 2006, virology). CMV reactivation is related to the overall level of immunosuppression, and not to an immunosuppressive individual agent. Prophylaxis of CMV infection is generally effective.

Analysis of all identified RCTs published since 1996 with Thymoglobuline in one arm and a comparator arm with no polyclonal antibody or T cell depleting antibody shows no evidence that CMV reactivation rates are higher in patients treated with Thymoglobuline

Based on the above, the Applicant states that there is no true increase in CMV infections attributable to Thymoglobuline.

**Post-transplantation lymphoproliferative disorder (PTLD)**

EBV-associated PTLD is a well recognised complication of immunosuppressive therapy. The incidence of PTLD reported in studies after Thymoglobuline therapy is comparable to that reported with other immunosuppressive regimens, 1 – 2%.
Table 14: Frequencies of PTLD and de novo tumours as reported in the safety studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Cases</th>
<th>Frequency/time</th>
<th>Annual incidence</th>
<th>Neoplasms and time</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational study 00PTF01</td>
<td>Thymoglobulin induction</td>
<td>240</td>
<td>1</td>
<td>1 year</td>
<td>0.4%</td>
<td>PTLD</td>
<td>1 case of PTLD.</td>
</tr>
<tr>
<td>Observational study 00PTF01</td>
<td>Thymoglobulin induction</td>
<td>240</td>
<td>6</td>
<td>1 year</td>
<td>2.5%</td>
<td>&quot;De novo tumours&quot;</td>
<td>5 patients with 7 neoplasms, Not all de novo.</td>
</tr>
<tr>
<td>Cherikh, 2003, Transplantation</td>
<td>Polyclonal anti-lymphocyte induction</td>
<td>4343</td>
<td>35</td>
<td>0.81% 767 days</td>
<td>0.4%</td>
<td>PTLD</td>
<td>1/97-12/00</td>
</tr>
<tr>
<td>Cherikh, 2005, Transplantation</td>
<td>Anti-thymocyte globulin</td>
<td>2096</td>
<td>19</td>
<td>0.7% 4/88 to 12/02</td>
<td>0.2%</td>
<td>PTLD</td>
<td>Selected only patients with known EBV status.</td>
</tr>
<tr>
<td>Bustami, 2004, Am J Transplant</td>
<td>Rabbit anti-thymocyte globulin</td>
<td>2376*</td>
<td>22*</td>
<td>0.53% 5 yrs</td>
<td>0.2%</td>
<td>PTLD</td>
<td>*Estimated based on data from Table 6 of the publication.</td>
</tr>
<tr>
<td>Bustami, 2004, Am J Transplant</td>
<td>Rabbit anti-thymocyte globulin</td>
<td>1757</td>
<td>43*</td>
<td>2.5% 1/96 to 2/02</td>
<td>0.5%</td>
<td>De novo tumours</td>
<td>*Estimated based on data from Table 5 of the publication.</td>
</tr>
</tbody>
</table>

PTLD although rare by spontaneous reporting, the analyses by Bustami and Cherikh suggest that it is common (>1/100, <1/10).

As PTLD is a common adverse event it is mentioned in the SmPC.

**Immunological events**

It is expected that the introduction of a xeno-protein, such as Thymoglobuline, will induce an immune response, even in the immunosuppressed patient.

A study was conducted by Regan (Regan, 2001, Transplant Immunol) to quantify the degree of sensitization following Thymoglobuline therapy. An analysis of anti-rabbit Ig antibodies was as part of their study on pharmacokinetics. Serum samples were obtained from 80 Thymoglobuline- treated patients participating in a multicenter, double-blind randomized phase III trial designed to compare Atgam. Anti-Thymoglobuline antibodies were demonstrated to decrease both total and active Thymoglobuline concentrations. The percent of patients with anti-Thymoglobuline antibodies on days O-5, days 6-14, day 21, day 30 and day 90 were 6, 41, 68, 70 and 29%, respectively.
Figure 2: Anti-Thymoglobuline antibody response. Percent of patients with anti-Thymoglobuline antibodies as a function of days after initiation of Thymoglobulin treatment as determined by ELISA. Number of patients tested for days 0-5, 6-14, 21, 30 and 90 were 62, 68, 38, 43 and 28 respectively.

Safety in special populations
No clinical safety study has been conducted in special groups and situations.

No data is available on intrinsic ethnic factors and differing responses to treatment, or need for individualisation of treatment. The dose recommendations in infants, children, adolescents and the elderly are the same as in adults, based on data from published studies where the same doses as in adults were used.

No data is available on the influence of cultural habits and response to treatment. Given the nature of the product it is unlikely that these would have any effect on response to the product.

Pregnancy and lactation
Animal reproduction studies have not been conducted with Thymoglobuline. It is not known whether Thymoglobuline can cause foetal harm or can affect reproductive capacity. Thymoglobuline should be given to a pregnant woman only if clearly needed.

Thymoglobuline has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breastfeeding should be discontinued during Thymoglobuline therapy. Thymoglobuline has not been studied in labour or delivery.

Effects on ability to drive and use machines
Given the possible adverse events which can occur during the period of Thymoglobuline infusion, in particular cytokine release syndrome, it is recommended that patients should not drive or operate machinery.

SmPC text regarding the Pregnancy and lactation and Effects on ability to drive and use machines is acceptable.
Safety related to drug-drug interactions and other interactions
No drug interaction studies have been carried out. Interactions with food and drink are unlikely.

In the SPC the combinations to be taken into account are mentioned: Cyclosporin, tacrolimus, mycophenolate mofetil: risk of over-immunosuppression with a risk of lymphoproliferation. Live attenuated vaccines: risk of systemic infection which may potentially be fatal. This risk is enhanced in subjects who are immunocompromised due to the underlying disease (aplastic anaemia). Rabbit anti-human thymocyte globulin may induce formation of antibodies which react with other rabbit immunoglobulins. Rabbit anti-human thymocyte globulin may interfere with ELISA tests involving rabbit antibodies over a period of two months.

Discontinuation due to AES
No rebound or withdrawal effects have been described. As per Applicant there is no need for gradual withdrawal or reduction of the product before discontinuation.

Contraindications
Thymoglobuline is contraindicated in patients with: 1) Hypersensitivity to rabbit proteins or to any product excipients and 2) Acute infections, which would contraindicate any additional immunosuppression.

The Applicant has not presented any data about contraindications, but contraindications in the section 4.3 in the SmPC are acceptable.

Post marketing experience
Thymoglobuline currently has marketing authorisations or authorization for sales in over 50 countries worldwide, with varying indications. The current marketing authorisation in France has the widest set of indications; whereas the USA has one indication, treatment of rejection in renal transplantation. There is no ATG currently with marketing authorisation in the UK.

In 1984, Thymoglobuline was registered and marketed in France. In the 1992 pharmacovigilance study THP04492, 78% of patients had at least one symptom following use of Thymoglobuline. Adverse events can be grouped into various types:

- allergic: including anaphylaxis, serum sickness, rashes, fever
- haematological
- infections
- other

Between 1st January 2000 and 31st December 2004, 1,843,589 vials of Thymoglobuline, corresponding to approximately 56,813 patients treated, were distributed worldwide. Between 1st January 1999 and 31st December 2004, the PSURs contain a cumulative total of 642 adverse events reported worldwide and relating to Thymoglobuline use, 576 were serious adverse events and 66 were non-serious adverse events. Up to the present day, adverse events reported world-wide for Thymoglobuline are generally those expected for a polyclonal anti-thymocyte globulin and confirm the good tolerability and safety of Thymoglobuline. The types of adverse events reported are mostly explicable as a result of the known mechanisms of action of Thymoglobuline: for example, virally induced lymphoma being a complication of immunosuppression and infusion associated reactions being due to hypersensitivity or cytokine release.
Study 00PTF01 was a prospective study with Thymoglobuline for prophylaxis of rejection after kidney transplantation between 1997 and 1998. At one year, 65 out of 236 patients still alive (28%) have suffered at least one acute rejection. In the first 30 days there were 35 episodes of clinically diagnosed rejections in 34 patients, of which 21 episodes were biopsy confirmed.

There were 15 cases of histologically confirmed chronic rejection in the first 12 months. During the first year four patients died, giving the survival rate of 98% at one year. At one year 228 patients were alive and with a functional graft (four deaths and eight graft losses). At one year in those with functional graft (n=228) the median creatinine was 124 mmol/l and the median creatinine clearance at one year was 63 mls/min.

There were no deaths in the first month. The median day of death was day 71. None of the deaths were considered to be causally related to Thymoglobuline use.

During the PSUR period between 01 January 2005 and 31 December 2005 forty-five (45) cases with fatal outcomes were reported to Genzyme during. Of the forty-five (45) reported fatal cases, thirty-four were considered related.

The results of the study 00PTF01 show a similar profile and incidence of adverse events as documented by previous studies. Fever remains the commonest reported adverse event, with 55% of patients suffering from it. As the Applicant noted it is difficult to ascertain the relationship of Thymoglobuline to the reported adverse events, because Thymoglobuline is always given in combination with other immunosuppressant drugs, drugs used for prophylaxis of infection and other drugs.

**Proposals for post authorisation follow up (post marketing surveillance)**
The product is well-established and documented in the literature. So there are no proposals for post authorisation follow up.

**Overall conclusions on clinical safety**
Data from clinical trials, spontaneous adverse event reporting, active post-marketing surveys, and literature reports demonstrate a consistent safety profile of Thymoglobuline therapy, which has not changed in the 20 years or more that it has been marketed.

Most of the adverse effects are explained by the immunological properties of Thymoglobuline. A mild to moderate first dose effect linked to the release of inflammatory cytokines. To minimise first-dose effects, use of prophylactic agents, control of infusion rate and concentration of the diluted product is specified in the SmPC. Cytopenias (mostly thrombocytopenia) occurs because of the cross reactivity of Thymoglobuline with platelet antigens. Thrombocytopenia can be a particular management problem in aplastic anaemia, or in the use of extra-corporeal circulation during heart transplantation. Platelet transfusions may be required to be given during the course of the treatment period with Thymoglobuline in these patients.

Immunisation of patients against rabbit antibodies may theoretically result in three separate problems: inefficacy of the product; anaphylaxis (type I immune reaction); serum sickness (type III immune reaction) (Regan, 2001, Transplant Immunol).
Induction therapy may be the most significant risk factor for developing infection and especially CMV infection or disease in patients treated with Thymoglobuline. Concomitant prophylaxis or close monitoring with subsequent pre-emptive treatment with an antiviral medication is becoming more common for renal transplant patients.

Another concern regarding the use of prophylactic antibody therapy is that it may be associated with an increased risk of malignancy or lymphoproliferative disease. Malignancies occur commonly in solid organ transplant patients being associated with the immunosuppression patients receive. Thymoglobuline, as part of an immunosuppressive regimen may contribute to an increased incidence of malignancy.

Estimates of frequencies of adverse events are usually derived from company sponsored randomised controlled studies (RCTs), where there is adequate identification and recording of adverse events and their relationship to the study drug. Spontaneous reporting usually underreports adverse events, and causality may be inadequately assessed. For Thymoglobuline adequate company sponsored RCTs across the range of indications and populations are lacking.

The efficacy and safety results presented in this overview are adequately reflected in the proposed SmPC.

The application for granting of a marketing authorisation is approvable.

**Risk benefit conclusions**

Thymoglobuline has been demonstrated to be effective both in the treatment of steroid-resistant renal rejections and as first-line treatment of acute rejection.

The studies presented in the application support the indication for the prevention of rejection in heart transplantation. Independent of the duration of treatment, the cumulative dose is the key, when considering the efficacy and safety of Thymoglobuline induction therapy, because of the long pharmacokinetic and even longer pharmacodynamic duration of action.

Clinical data gathered prospectively by the multicentre group (Di Bona, 1999, Br J Haematol) showed that Thymoglobuline was safe, in the short and the long term, and effective in 30 patients who failed to respond to a first course of Lymphoglobuline, in combination with ciclosporin and G-CSF.

The difficulty with Thymoglobuline is in finding a dose which is still effective, but which does not cause adverse events due to this immune suppression, such as infections and malignancies induced by viral agents (in particular PTLD). The risk of these adverse events can be reduced, not only by reducing the dose of Thymoglobuline, but also by the use of antiviral prophylaxis.

The efficacy and safety of Thymoglobuline is demonstrated in the immunosuppression in solid organ transplantation, prevention and treatment of graft rejection in renal transplantation and prevention of graft rejection in heart transplantation.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Thymoglobuline are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The preclinical studies presented are supportive of the safety of the product, particularly the specificity shown in the cross-reactivity study in human tissues. The pharmacodynamic actions of Thymoglobuline were shown repeatedly in studies in cynomolgus monkeys and toxic effects seen can be attributed to actions to deplete lymphocytes.

There are no objections, on preclinical grounds, to the granting of a marketing authorisation.

CLINICAL

No new or unexpected safety concerns arose from this application. The efficacy and safety of Thymoglobuline for the indications sought is demonstrated.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new pre-clinical, quality or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.
THYMOGLOBULINE
(ANTI-THYMCYTE GLOBULIN [RABBIT], rATG)
PL 12375/0021

STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 13th August 2006.</td>
</tr>
<tr>
<td>2</td>
<td>The MHRA’s quality assessment of the submitted data was completed on 21st March 2007.</td>
</tr>
<tr>
<td>3</td>
<td>The MHRA’s clinical and pre-clinical assessment of the submitted data was completed on 22nd March 2007.</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment, a series of requests for supplementary information were sent to the applicant to which they provided further information to complete assessment of the product.</td>
</tr>
<tr>
<td>6</td>
<td>The MHRA completed its assessment of the application on 28th February 2008.</td>
</tr>
<tr>
<td>7</td>
<td>The application was determined on 19th March 2008.</td>
</tr>
</tbody>
</table>
THYMOGLOBULINE

(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>27/01/2012</td>
<td>Type IB mutual recognition variation</td>
<td>To update sections 4.4 (Special warnings) and 4.8 (Undesirable effects) of the SPC and PIL in line with the agreed CSP following the finalisation of the EU PSUR work-sharing procedure EE/H/PSUR/0008/001 on 14th September 2011.</td>
<td>Granted 28.04.12</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Thymoglobuline® 25 mg powder for solution for infusion ▼

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rabbit anti-human thymocyte immunoglobulin 25 mg per vial. 1 ml reconstituted solution contains 5 mg rabbit, anti-human thymocyte immunoglobulin.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Immunosuppression in solid organ transplantation
  - Prevention of graft rejection in renal transplantation
  - Treatment of steroid resistant graft rejection in renal transplantation
  - Prevention of graft rejection in heart transplantation.

4.2 Posology and method of administration

Thymoglobuline must always be used under strict medical supervision and prescribed by physicians with experience in using immunosuppressive agents.

Posology
The posology depends on the indication, the administration regimen and the combination with other immunosuppressive agents.

The following dosage may be used as a reference. Treatment can be discontinued without gradual tapering of the dose.

**Immunosuppression in solid organ transplantation**

*Prophylaxis of graft rejection*

1 to 1.5 mg/kg/day for 3 to 9 days after transplantation of a kidney, corresponding to a cumulative dose of 3 to 13.5 mg/kg.

1 to 2.5 mg/kg/day for 3 to 5 days after transplantation of a heart, corresponding to a cumulative dose of 3 to 12.5 mg/kg.

*Treatment of steroid resistant graft rejection:*

1.5 mg/kg/day for 7 to 14 days after transplantation of a kidney, corresponding to a cumulative dose of 10.5 to 21 mg/kg.

*Dose modifications*

For obese patients dosing should be based on ideal weight rather than actual weight.

*Paediatric and elderly patients*

The dosage recommendations in the paediatric population (infants, children and adolescents) and elderly patients are the same as for adults. There are no paediatric data for the treatment of graft rejection in renal transplantation.

*Renal and hepatic impairment*

In view of the PK and metabolism no dose adjustment is necessary in patients with hepatic and/or renal impairment.

*Method of administration*

Thymoglobuline is usually administered in the context of a therapeutic regimen combining multiple immunosuppressive agents.

It is recommended to administer pre-medication with intravenous corticosteroids and antihistamines prior to infusion of rabbit anti-human thymocyte globulin. Anti-pyretic agents (e.g. paracetamol) may also increase the tolerability of the initial infusion.

Rabbit anti-human thymocyte globulin is infused after dilution in isotonic 0.9 % sodium chloride or 5 % glucose solution. Inspect solution for particulate matter after
reconstitution. To avoid inadvertent administration of particulate matter from reconstitution, it is recommended that Thymoglobuline is administered through a 0.22 μm in-line filter.

Infuse slowly into a high-flow vein. Adjust the infusion rate so that the total duration of infusion is not less than 6 hours. See "Special warnings and precautions for use" and section 4.8 "Adverse Events" for advice about the management of any adverse events associated with infusion.

4.3 Contraindications

Thymoglobuline is contraindicated in patients with:

- Hypersensitivity to rabbit proteins or to any product excipients (see Section 6.1 "Excipients").
- Active acute or chronic infections, which would contraindicate any additional immunosuppression.

4.4 Special warnings and precautions for use

Warnings

Immune-mediated reactions

In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline and consist of anaphylaxis or severe cytokine release syndrome (CRS).

Very rarely, fatal anaphylaxis has been reported (See section 4.8 “Adverse Events”). If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Any further administration of Thymoglobuline to a patient who has a history of anaphylaxis to Thymoglobuline should only be undertaken after serious consideration.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS which is attributed to the release of cytokines by activated monocytes and lymphocytes. In rare instances, these reported reactions are associated with serious cardiorespiratory events and/or death. (See under "Precautions" and section 4.8 “Adverse Events”).

Infection

Thymoglobuline is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly CMV) and sepsis have been reported after Thymoglobuline
administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

Precautions

General

Appropriate dosing for Thymoglobuline is different from dosing for other antithymocyte globulin (ATG) products, as protein composition and concentrations vary depending on the source of ATG used. Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the ATG product being administered.

Thymoglobuline should be used under strict medical supervision in a hospital setting. Patients should be carefully monitored during the infusion. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of IARs. Additionally, reducing the infusion rate may minimize many of these adverse reactions. Premedication with antipyretics, corticosteroids, and/or antihistamines may decrease both the incidence and severity of these adverse reactions.

Rapid infusion rates have been associated with case reports consistent with cytokine release syndrome (CRS). In rare instances, severe CRS can be fatal.

Hematological Effects

Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leukopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline is being administered, the following dose reductions are suggested.

- A reduction in dosage must be considered if the platelet count is between 50,000 and 75,000 cells/mm³ or if the white cell count is between 2,000 and 3,000 cells/mm³;
- Stopping Thymoglobuline treatment should be considered if persistent and severe thrombocytopenia (<50,000 cells/mm³) occurs or leukopenia (<2,000 cells/mm³) develops.

White blood cell and platelet counts should be monitored during and after Thymoglobuline therapy. Patients with severe neutropenic aplastic anaemia require very careful monitoring, appropriate prophylaxis and treatment of fevers and infections as well as adequate platelet transfusion support.

Infection

Infections, reactivation of infection, and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Malignancy
Use of immunosuppressive agents, including Thymoglobuline, may increase the incidence of malignancies, lymphoma or post-transplant lymphoproliferative disease (PTLD) (See section 4.8 “Adverse Events”).

**Special Considerations for Thymoglobuline Infusion**

As with any infusion, reactions at the injection site can occur and may include pain, swelling, and erythema.

The recommended route of administration for Thymoglobulin is intravenous infusion using a high-flow vein; however, it may be administered through a peripheral vein. When Thymoglobulin is administered through a peripheral vein, concomitant use of heparin and hydrocortisone in an infusion solution of 0.9% sodium chloride may minimize the potential for superficial thrombophlebitis and deep vein thrombosis.

The combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended (See section 6.2 Incompatibilities).

**Immunisations**

The safety of immunisation with attenuated live vaccines following Thymoglobuline therapy has not been studied; therefore, immunisation with attenuated live vaccines is not recommended for patients who have recently received Thymoglobuline.

### 4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed.

Interactions with food and drink are unlikely.

Thymoglobuline has not been shown to interfere with any routine clinical laboratory tests which use immunoglobulins. However, Thymoglobuline can induce production of human anti-rabbit antibodies which may interfere with rabbit antibody-based immunoassays and with cross-match or panel-reactive antibody cytotoxicity assays. Thymoglobuline may interfere with ELISA tests.

See also section 6.2 (incompatibilities).

### 4.6 Pregnancy and lactation
Animal reproduction studies have not been conducted with Thymoglobuline. It is not known whether Thymoglobuline can cause foetal harm or can affect reproductive capacity. Thymoglobuline should be given to a pregnant woman only if clearly needed.

Thymoglobuline has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breast-feeding should be discontinued during Thymoglobuline therapy.

Thymoglobuline has not been studied in labour or delivery.

4.7 Effects on ability to drive and use machines

Given the possible adverse events which can occur during the period of Thymoglobuline infusion, in particular cytokine release syndrome, it is recommended that patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse events from French Multi-centre Post-marketing Surveillance Study
From June 1997 to March 1998, 18 French transplantation centres participated in the French Multicentre Post-marketing Surveillance Study-00PTF0.
A total of 240 patients participated in this prospective, single arm, observational cohort study. All patients received Thymoglobuline as prophylaxis of acute rejection for renal transplant.
The safety data in the table represent all adverse events reported in the study regardless of relationship to Thymoglobuline.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common¹: lymphopenia, neutropenia, thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common¹: Diarrhoea, dysphagia, nausea, vomiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administrative site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Fever</td>
</tr>
<tr>
<td>Common: Shivering</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Serum sickness</td>
</tr>
</tbody>
</table>

| Infections and infestations |
Very common: Infection
Musculoskeletal and connective tissue disorders
Common: Myalgia
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Common: Malignancy
Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea
Skin and subcutaneous tissue disorder
Common: Pruritus, rash
Vascular disorder
Common: Hypotension

* Common: (≥1/100 to <1/10)
** Very common (≥1/10)

Undesirable effects which have been discussed in other sections of this document are listed per clinical disorder below. Because these events are from post marketing surveillance, their true frequencies are not known.

**Infusion-Associated Reactions and Immune System Disorders**

Infusion-associated reactions (IAR) may occur following the administration of Thymoglobulin and may occur as soon as the first or second dose. Clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/ rigor, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, and/or headache. IARs with Thymoglobulin are usually mild and transient and are managed with reduced infusion rates and/or medications. Serious and in very rare instances, fatal anaphylactic reactions have been reported (See section 4.4 "Warnings"). These fatal reactions occurred in patients who did not receive adrenaline during the event.

IARs consistent with **Cytokine Release Syndrome** (CRS) have been reported. Severe and potentially life-threatening CRS is rarely reported. Post-marketing reports of severe Cytokine Release Syndrome have been associated with cardiorespiratory dysfunction (including hypotension, ARDS, pulmonary oedema, myocardial infarction, tachycardia, and/or death).

**Serum Sickness**

During post-marketing surveillance, reactions such as fever, rash, arthralgia, and/or myalgia, indicating possible serum sickness, have been reported. Serum sickness tends to occur 5 to 15 days after onset of Thymoglobulin therapy. Symptoms are usually self-limited or resolve rapidly with corticosteroid treatment.

**Adverse events due to immunosuppression**

Infections, reactivation of infection, and sepsis have been reported after Thymoglobulin administration in combination with multiple immunosuppressive
agents, Malignancies including but not limited to post-transplant lymphoproliferative disorder (PTLD) and other lymphomas as well as solid tumours have been reported (See section 4.4 “Precautions”).

These adverse events were always associated with a combination of multiple immunosuppressive agents.

4.9 Overdose

Inadvertent overdose may induce leucopenia (including lymphopenia and neutropenia) and thrombocytopenia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressive agents. ATC code: L04AA04

Rabbit anti-human thymocyte globulin is a selective immunosuppressive agent (mostly acting on T lymphocytes). Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by rabbit anti-human thymocyte globulin. This depletion is both peripheral and central: peripheral lymphocyte depletion can be detected as early as 24 hours after the first infusion. Lymphocyte counts start to rise as soon as Thymoglobulin is discontinued.

This lymphocyte depletion has been shown to occur in vitro by a number of different mechanisms (eg apoptosis, complement dependent lysis and antibody dependent cytotoxicity); the exact mechanisms which take place in vivo remain undetermined.

In addition to the T cell depletion, Thymoglobulin also has effects on dendritic cells (causing apoptosis), and on B cells. In vitro, Thymoglobulin does not activate B-cells. Antiproliferative activity against B-cells and certain lymphoblastoid cell lines has also been demonstrated in vitro. This effect may be partially protective against the development of PTLD.

Thymoglobulin also has activity against a number of cell surface epitopes (eg CD 3, CD7, CD8, CD19, CD20, CD32, CD28), binding to them and causing downmodulation. The epitopes targeted include those involved in the immune response, in apoptosis, and in signal transduction, and include both B and T cell epitopes. In particular, Thymoglobulin has activity against both leucocyte and endothelial cell adhesion molecules (eg CD11a, CD18, CD11b, CD44, CD54, LPAM 1) which in animal studies has been shown to reduce tethering of leucocytes to the endothelium. Effector cells are thus unable to migrate through the endothelium to the
graft. This effect may also, in theory, reduce ischaemia-reperfusion injury by allowing better flow through the microcirculation.

The combination of T cell depletion and downmodulation of adhesion molecules results in interference with multiple pathways by which rejection occurs.

The exact mechanism of action of ATGs in the treatment of aplastic anaemia is unknown. Aplastic anaemia is caused by an autoimmune process resulting in destruction of all lineages cells in the bone marrow, but sparing some CD34+ stem cells. If the autoimmune process can be halted, the stem cells can regenerate all three blood lineages. The mechanism of action of Thymoglobuline may be through depleting T cells and by preventing their activation as well as by eliminating clonal expansion of cytotoxic T cells in patients with AA; additionally by acting directly on haematopoietic progenitors and improving their proliferative capacity, which appears to be strongly impaired in AA patients. Thymoglobuline induces a significant release of haematopoietic growth factors, including granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin-3 (IL-3), and the supernatant of ATG-primed lymphocytes has been shown to promote the proliferation of progenitor colonies.

5.2 Pharmacokinetic properties

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney transplant recipients), total serum rabbit IgG levels of between 10 and 40 µg/ml are obtained. The serum levels decline steadily until the following infusion with an estimated elimination half-life of 2-3 days. There has been shown to be a relationship between dose given and total Thymoglobuline levels.

The trough rabbit IgG levels increase progressively reaching 20 to 170 µg/ml at the end of an 11-day course of treatment. A gradual decline is subsequently observed following discontinuation of treatment with rabbit anti-human thymocyte globulin. However, total rabbit IgG remains detectable in 81% of patients at 2 months. Active Thymoglobuline (that is IgG which is available to bind to human lymphocytes and which causes the desired immunological effects) has a less noticeable relationship with dose given, and disappears from the circulation faster, with only 12% of patients having detectable active Thymoglobuline levels at day 90.

Significant immunisation against rabbit IgG is observed in about 40% of patients. In most cases, immunisation develops within the first 15 days of treatment initiation. Patients presenting with immunisation show a faster decline in total but not active rabbit IgG levels.

5.3 Preclinical safety data

No mutagenicity, reproduction or genotoxicity studies have been conducted due to the nature and intended use of the product.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- glycine
- sodium chloride
- mannitol

Other components:
Thymoglobuline may also contain residues of polysorbate, from the manufacturing process.

6.2 Incompatibilities

Based on a single compatibility study (Trissel L.A., 2003, *Am J Health Syst Pharm*) the combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended.

In the absence of additional pharmaceutical incompatibility data, Thymoglobuline should not be mixed with other medicinal products in the same infusion.

6.3 Shelf life

3 years.

Immediate use after dilution is recommended in order to prevent microbial contamination.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.
6.4 Special precautions for storage

Store and transport refrigerated (at 2°C to 8°C).
Do not freeze.

During transport a temperature excursion up to 25°C for 3 days will not alter the product characteristics.
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type 1 glass) closed with a stopper (chlo-robutyl). Each pack contains one 10 ml vial.

6.6 Special precautions for disposal

Reconstitute the powder with 5 ml of sterile water for injections to obtain a solution containing 5 mg protein per ml. The solution is clear or slightly opalescent. Reconstituted product should be inspected visually for particulate matter and discoloration. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter is visible. If particulate matter persists, discard the vial. Immediate use of reconstituted product is recommended. Each vial is for single use only. Depending on the daily dose, reconstitution of several vials of Thymoglobuline powder might be needed. Determine the number of vials to be used and round up to the nearest vial. To avoid inadvertent administration of particulate matter from reconstitution, it is recommended that Thymoglobuline is administered through a 0.22 μm in-line filter.

The daily dose is diluted in an infusion solution (0.9% sodium chloride or 5% glucose solution) so as to obtain a total infusion volume of 50 to 500 ml (usually 50 ml / vial).

The product should be administered on the same day.

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

Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 12375/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2008

10 DATE OF REVISION OF THE TEXT
19/03/2008
Patient Information Leaflet
THYMoglobuline

(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021
PACKAGE LEAFLET: INFORMATION FOR THE USER

Thymoglobuline® 25 mg, powder for solution for infusion
Rabbit anti-human thymocyte immunoglobulin

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- This medicine will be given to you by a doctor or nurse in hospital.
- If you have any further questions, please ask your doctor or nurse.
- If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Thymoglobuline® is and what it is used for
2. Before you are given Thymoglobuline®
3. How Thymoglobuline® is given
4. Possible side effects
5. How to store Thymoglobuline®
6. Further information

1. WHAT THYMoglobuline® IS AND WHAT IT IS USED FOR

Thymoglobuline® belongs to a group of medicines called immunosuppressants (anti-rejection medicines). These medicines can help prevent the rejection of transplanted organs. They can also be used to treat other unwanted immune reactions.

Thymoglobuline® is made by injecting human thymus cells into rabbits. It contains immunoglobulins (antibodies) which attach to and destroy some of the cells of your immune system in your body. These cells play a role in the rejection of transplanted organs or carry out other unwanted immune reactions.

Kidney and Heart Transplantation

Thymoglobuline® is used in patients who have had a kidney or heart transplant, to prevent the rejection of a kidney or a heart transplant. It is also used to treat the rejection of a kidney transplant in patients who are resistant to treatment with corticosteroids. Thymoglobuline® is a type of drug known as an immunosuppressant (anti-rejection drug). When a patient receives an organ, the body’s natural defence system will try to get rid of it (reject it). Thymoglobuline® modifies the body’s defence mechanism and helps it accept the transplanted organ.

2. BEFORE YOU ARE GIVEN THYMoglobuline®

You should not be given Thymoglobuline®
- if you are allergic (hypersensitive) to anti-human thymocyte globulin, rabbit or any of the other ingredients of Thymoglobuline® (see Section 6).
- if you have a severe infection because Thymoglobuline® decreases your body’s ability to fight infections.

Take special care with Thymoglobuline®

Tell your doctor if:
- you have ever had an allergic reaction to animals or other medicines. Your doctor will monitor you closely and stop treatment if there are any signs of an allergic reaction to Thymoglobuline®
- you have any blood disorders, such as lower than normal platelets in your blood (thrombocytopenia) or lower than normal white cells in your blood (leucopenia). The dose you will be given will depend on the number of white blood cells or platelets in your blood which will be checked before, during, and after treatment.

Taking other medicines

Please tell your doctor if you are taking, or have recently taken any other medicines, including medicines taken without a prescription. It is especially important if you are taking:
- any other anti-rejection medicine (immunosuppressants), such as azathioprine or corticosteroids.

This is because, if the body’s defence system is reduced too much, severe infections may occur. It may also increase the risk of developing cancer in the future.

Vaccinations

Do not have any vaccination during or soon after treatment with Thymoglobuline®. Without first discussing it with your doctor, it may cause side effects or may not work because your immune system cannot respond to it.

Using Thymoglobuline® with food and drink

It is unlikely that eating and drinking will affect your medicine.

Pregnancy and breastfeeding

Please tell your doctor if you are or think that you may be pregnant. This is because Thymoglobuline® should not be given to pregnant women unless it is absolutely necessary as the effects are unknown.

Do not breastfeed while you are being given Thymoglobuline®. This is because it may get into your breast milk and may affect the baby.

Driving and using machines

Do not drive or operate machinery while being treated with Thymoglobuline®.

3. HOW THYMoglobuline® IS GIVEN

Your medicine will be given to you by a doctor or nurse in a hospital. Thymoglobuline® is given through a plastic tube (catheter) directly into your blood stream (intravenous infusion) over a period of at least 6 hours. The first dose may be given over a longer period of time.

The dose you will be given will depend on your weight (unless you are obese when it will depend on your ideal weight), which medical problem you are being treated for, and if you are being given any other medicines at the same time.

To prevent kidney rejection:
Between 1 and 1.5 mg of Thymoglobuline® for every kilogram of weight every day for 3 to 9 days.

To prevent heart rejection:
Between 1 and 2.5 mg of Thymoglobuline® for every kilogram of weight for 3 to 5 days.

To treat kidney rejection in patients resistant to corticosteroids:
1.5 mg of Thymoglobuline® for every kilogram of weight every day for 7 to 14 days.

There are no data available in children for rejection of kidney transplantation.

Your doctor or nurse will check you regularly while you receive your first dose because this is when you are more likely to get side effects. They will check for rashes, check your pulse, blood pressure and breathing. From time to time your doctor may also want to you to have a blood test to monitor your blood cell count. If your white blood cell count is low, your doctor may also administer other medicines to prevent or treat infections, if your platelet counts are low, your doctor may give you a platelet transfusion.

The dose of Thymoglobuline® may be changed by your doctor if you have any side effects.
The following information is intended for medical or healthcare professionals only:
Each vial of Thymoglobulin® is intended for single use only.
Depending on the daily dose, reconstitution of several vials of Thymoglobulin® powder might be needed. Determine the number of vials to be used and round up to the nearest vial.
Using aseptic technique, reconstitute the powder with 5 ml of sterile water for injections to obtain a solution containing 5 mg protein per ml. The solution should be clear or slightly opalescent. Reconstituted product should be inspected visually for particulate matter and discoloration. Do not use vials exhibiting particles or discoloration.
Immediate use of reconstituted product is recommended.
Preparation of Thymoglobulin® Infusion (Use Aseptic Technique)
Withdraw the required volume of the reconstituted solution from the Thymoglobulin® vials. Add the daily dose to an infusion solution (0.9% sodium chloride or 5% glucose solution) so as to obtain a total infusion
Other medicines your doctor may give you

Your doctor may give you some other medicines before, or at the same time as Thymoglobulin®. These medicines are used to prevent, or treat possible side effects and could include:

- Analgesics (like paracetamol) to reduce fever
- Corticosteroids (e.g. hydrocortisone) to prevent organ rejection and prevent side effects
- Antihistamines (e.g. cetirizine) to prevent an allergic response
- Heparin to reduce the risk of blood clots

If you are given more Thymoglobulin® than you should have

It is unlikely you will be given more Thymoglobulin® than you should as you will be closely checked by your doctor or nurse during your treatment. If this does happen you may get a lower than normal platelet cell count (thrombocytopenia) or lower than normal white cell count (leucopenia). This can cause fever, chills, sore throat, mouth ulcers and bleeding or bruising more easily than normal.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Thymoglobulin® can cause side effects, although not everybody gets them. Some side effects, such as fever, rash and headache, and others affecting your pulse rate, blood pressure and breathing, as well as some allergic reactions, are more likely to occur with your first or second dose of Thymoglobulin® than with later doses.

Tell your doctor immediately if you notice any of the following as these may be life threatening signs of an allergic reaction:

- A raised itchy rash
- Difficulty breathing
- Stomach pain
- Swelling of the face, tongue or throat

Sometimes, receiving a Thymoglobulin® infusion may cause the following additional side effects. You should tell your doctor as soon as possible if you have any of the following:

- Difficulty breathing, wheezing or coughing
- Feeling or being sick
- Dizzy or feeling faint
- Tiredness
- Joint pain
- Headache
- Bleeding or bruising more easily than normal
- Irregular or fast heartbeat
- Symptoms of infection such as fever, chills, sore throat, mouth ulcers

The side effects listed below were recorded during a clinical study. This does not necessarily mean that all were caused by Thymoglobulin®.

Very common (more than 1 in 10 patients) side effects include:

- Low white blood cell count; low platelet count
- Fever
- Infection

Common (up to 1 in 10 patients) include:

- Diarrhoea, difficulty swallowing, nausea, vomiting
- Shivering
- Serum sickness, which is an illness caused by antibodies against Thymoglobulin® causing rash, itching, joint pains, kidney problems and swollen lymph nodes which develop within 6-21 days. Serum sickness is usually mild and goes away without treatment or with a short course of corticosteroids
- Muscle pain
- Growth (including cancers and non-cancers)
- Shortness of breath
- Itchiness, rash
- Low blood pressure

These side effects may be mild and go away on treatment with other medicines. They may also be reduced by changing the dose of Thymoglobulin® or increasing the period of time over which it is given.

Sometimes the effects of Thymoglobulin® may not occur until months after it is used. These delayed effects may include an increased risk of infections and of certain types of cancer.

If you are receiving Thymoglobulin® with other medicines which suppress your immune system, you may be more susceptible to infections.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE THYMoglobulin®

Your medicine will be stored in a hospital by a doctor or nurse, out of the sight and reach of children.

The unopened vials of Thymoglobulin® will be stored in a refrigerator (2 – 8 °C).

The doctor or nurse will check that the product has not passed its expiry date before preparation.

6. FURTHER INFORMATION

Thymoglobulin® is a prescription only medicine (POM) and Thymoglobulin® contains

The active substance is: 25 mg of rabbit anti-human thymocyte immunoglobulin.

The other ingredients are: mannitol, glycerine, sodium chloride (salt). Thymoglobulin® may also contain residues of polysorbate from the manufacturing process.

What Thymoglobulin® looks like and contents of the pack

Thymoglobulin® is supplied in a glass vial containing a white powder. Before it is used it is mixed with 5 millilitres (ml) of sterile water to make a liquid. Each millilitre (ml) contains 5 mg of rabbit anti-human thymocyte immunoglobulin. This liquid is then mixed with a sodium chloride or glucose solution so that it can be given slowly (infused) into your bloodstream through a plastic tube (catheter) in a large vein.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

Genzyme Europe B.V.
Gouwense 10
1411 DD Naarden
The Netherlands
Tel: +31 35 699 1200
Fax: +31 35 699 1444

The product is manufactured by:

Genzyme Polyclonals S.A.S
1541 avenue Marcel Meritx
69260 Marcy l’Etoile
France
Tel: +33 4 37 28 16 60
Fax: +33 4 37 28 16 70

Local representative:

Genzyme Therapeutics Ltd
4620 Kingsgate
Cascade Way
Oxford Business Park South
Oxford OX4 2SU
United Kingdom
Tel: +44 1865 405 200
Fax: +44 1865 744 172

Marketing Authorisation number: PL 12375/0021

For any information about Thymoglobulin®, please contact the local representative or Marketing Authorisation Holder.

This leaflet was last approved in 03/2008

501781
volume of 50 to 500 ml (usually 50 ml/vial). The product should be administered on the same day. The use of a 0.22 μm in-line filter is recommended.

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

For additional information about the product, please consult the SmPC or contact the local representative.
Labelling
THYMOGLOBULINE

(ANTI-THYMOCYTE GLOBULIN [RABBIT], rATG)

PL 12375/0021
Thymoglobulin® 25 mg
Powder for solution for infusion
rabbit anti-human thyroglobulin
immunoglobulin
Intravenous use.
For reconstitution with 5 ml sterile Water for injection.
MAH: Genzyme Europe B.V.

PL: 12375/0021

UKPAR – Thymoglobulin
Annex 1

Our Reference: PL 12375/0021–0022
Product: PL 12375/0021 Thymoglobuline
Marketing Authorisation Holder: GENZYME EUROPE BV

Reason:
To update sections 4.4 (Special warnings) and 4.8 (Undesirable effects) of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) in line with the agreed Core Safety Profile (CSP) following the finalisation of the European Union Periodic Safety Update Reports (EU PSUR) work-sharing procedure EE/H/PSUR/0008/001 on 14th September 2011.

Linked / Related Variation(s) or Case(s):
NA

Supporting Evidence
The P-RMS (Member State responsible for the PSUR assessment report) final assessment report from procedure EE/H/PSUR/0008/001.

Evaluation
Updates were made to sections 4.4, 4.8, and 10 of the SmPC for Thymoglobuline 25 mg powder for solution for infusion.

Conclusion
The following text was accepted for sections 4.4, 4.8, and 10.

The PIL is acceptable.

4.4 Special warnings and precautions for use

Thymoglobuline should be used under strict medical supervision in a hospital setting. Thymoglobuline must only be administered according to the instructions of a physician with experience of immunosuppressive therapy in the transplant setting. Patients should be carefully monitored during the infusion. Particular attention must be paid to monitoring the patient for any symptoms of anaphylactic shock. Close monitoring of the patient must continue during the infusion and for a period of time following the end of the infusion until the patient is stable.

Prior to administration of Thymoglobuline it is advisable to determine whether the patient is allergic to rabbit proteins. Medical personnel and equipment, etc. must be readily at hand during the first days of therapy to provide emergency treatment if necessary.

Warnings

Immune-mediated reactions
In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline and consist of anaphylaxis or severe cytokine release syndrome (CRS).

Very rarely, fatal anaphylaxis has been reported (See section 4.8 “Adverse Events”). If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Equipment for emergency therapy for anaphylactic shock must be readily available.
Any further administration of Thymoglobuline to a patient who has a history of anaphylaxis to Thymoglobuline should only be undertaken after serious consideration.

Severe, acute infusion-associated reactions (IARs) are consistent with CRS which is attributed to the release of cytokines by activated monocytes and lymphocytes. In rare instances, these reported reactions are associated with serious cardiorespiratory events and/or death (See under “Precautions” and section 4.8 “Adverse Events”).

Infection
Thymoglobuline is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral and protozoal), reactivation of infection (particularly CMV) and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

Precautions
General
Appropriate dosing for Thymoglobuline is different from dosing for other anti-thymocyte globulin (ATG) products, as protein composition and concentrations vary depending on the source of ATG used. Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the ATG product being administered.

Thymoglobuline should be used under strict medical supervision in a hospital setting. Patients should be carefully monitored during the infusion and for a period of time following the end of the infusion until the patient is stable. Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of IARs. Additionally, reducing the infusion rate may minimize many of these adverse reactions. Premedication with antipyretics, corticosteroids, and/or antihistamines may decrease both the incidence and severity of these adverse reactions.

Rapid infusion rates have been associated with case reports consistent with cytokine release syndrome (CRS). In rare instances, severe CRS can be fatal.

Haematological Effects
Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leukopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline is being administered, the following dose reductions are suggested:

- A reduction in dosage must be considered if the platelet count is between 50,000 and 75,000 cells/mm$^3$ or if the white cell count is between 2,000 and 3,000 cells/mm$^3$;
- Stopping Thymoglobuline treatment should be considered if persistent and severe thrombocytopenia (<50,000 cells/mm$^3$) occurs or leukopenia (<2,000 cells/mm$^3$) develops.

White blood cell and platelet counts should be monitored during and after Thymoglobuline therapy. Patients with severe neutropenic aplastic anaemia require very careful monitoring, appropriate prophylaxis and treatment of fevers and infections as well as adequate platelet transfusion support.

Infection
Infections, reactivation of infection (particularly CMV), and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.
Malignancy
Use of immunosuppressive agents, including Thymoglobuline, may increase the incidence of malignancies, lymphoma or lymphoproliferative disorders (which may be virally mediated). These events have sometimes been associated with fatal outcomes (See section 4.8 “Adverse Events”).

Risk of Transmission of Infectious Agents
Human blood components (formaldehyde treated red blood cells), as well as thymus cells are used in the manufacturing process for Thymoglobuline. Standard measures to prevent infections resulting from the use of medicinal products prepared using human components include selection of donors, screening of individual donations for specific markers of infection and the inclusion of effective manufacturing steps for inactivation/removal of viruses. Despite this, when medicinal products prepared 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 Thymoglobuline are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses such as HAV and parvovirus B19.

It is strongly recommended that every time that Thymoglobuline is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Special Considerations for Thymoglobuline Infusion
As with any infusion, reactions at the injection site can occur and may include pain, swelling, and erythema.

The recommended route of administration for Thymoglobulin is intravenous infusion using a high-flow vein; however, it may be administered through a peripheral vein. When Thymoglobuline is administered through a peripheral vein, concomitant use of heparin and hydrocortisone in an infusion solution of 0.9% sodium chloride may minimize the potential for superficial thrombophlebitis and deep vein thrombosis.

The combination of Thymoglobuline, heparin and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended (See section 6.2 Incompatibilities).

Immunisations
The safety of immunisation with attenuated live vaccines following Thymoglobuline therapy has not been studied; therefore, immunisation with attenuated live vaccines is not recommended for patients who have recently received Thymoglobuline.

4.8 Undesirable effects

Adverse events from French Multi-centre Post-marketing Surveillance Study
From June 1997 to March 1998, 18 French transplantation centres participated in the French Multicentre Post-marketing Surveillance Study-00PTF0. A total of 240 patients participated in this prospective, single arm, observational cohort study. All patients received Thymoglobuline as prophylaxis of acute rejection for renal transplant.
The safety data in the table represent all adverse events reported in the study regardless of relationship to Thymoglobuline.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very common: lymphopenia, neutropenia, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: Diarrhoea, dysphagia, nausea, vomiting</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td></td>
</tr>
<tr>
<td>Very common: Fever</td>
<td></td>
</tr>
<tr>
<td>Common: Shivering</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Common: Serum sickness</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Very common: Infection</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Common: Myalgia</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
</tr>
<tr>
<td>Common: Malignancy</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Common: Dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
</tr>
<tr>
<td>Common: Pruritus, rash</td>
<td></td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>Common: Hypotension</td>
</tr>
</tbody>
</table>

* Common: (≥1/100 to <1/10)  
** Very common (≥1/10)

Undesirable effects which have been discussed in other sections of this document are listed per clinical disorder below. Because these events are from post marketing surveillance, their true frequencies are not known.

**Infusion-Associated Reactions and Immune System Disorders**

Infusion-associated reactions (IAR) may occur following the administration of Thymoglobuline and may occur as soon as the first or second dose. Clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnoea, nausea/vomiting, diarrhoea, hypotension or hypertension, malaise, rash, urticaria, and/or headache. IARs with Thymoglobuline are usually mild and transient and are managed with reduced infusion rates and/or medications. Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during Thymoglobuline administration. Serious and in very rare instances, fatal anaphylactic reactions have been reported (See section 4.4 “Warnings”). These fatal reactions occurred in patients who did not receive adrenaline during the event.

IARs consistent with **Cytokine Release Syndrome** (CRS) have been reported. Severe and potentially life-threatening CRS is rarely reported. Post-marketing reports of severe Cytokine Release Syndrome have been associated with cardiorespiratory dysfunction (including hypotension, ARDS, pulmonary oedema, myocardial infarction, tachycardia, and/or death).

**Serum Sickness**

During post-marketing surveillance, reactions such as fever, rash, urticaria, arthralgia, and/or myalgia, indicating possible serum sickness, have been reported. Serum sickness tends to
occur 5 to 15 days after onset of Thymoglobuline therapy. Symptoms are usually self-limited or resolve rapidly with corticosteroid treatment.

**Adverse events due to immunosuppression**

Infections, reactivation of infection, febrile neutropenia, and sepsis have been reported after Thymoglobuline administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal. Malignancies including, but not limited to lymphoproliferative disorders (LPD) and other lymphomas (which may be virally mediated) as well as solid tumours have been reported. These events have sometimes been associated with fatal outcome. (See section 4.4 “Precautions”). These adverse events were always associated with a combination of multiple immunosuppressive agents.

For safety relating to transmissible agents, see section 4.4 “Precautions”
Thymoglobuline 25 mg powder for solution for infusion

**WARNING**

- **Please use caution when administering Thymoglobuline to patients with a history of allergy to any component of the product.**
- **Thymoglobuline is contraindicated in patients with a history of anaphylactic or anaphylactoid reactions.**
- **Do not administer to patients with a history of a previous reaction to Thymoglobuline.**
- **Thymoglobuline is not recommended for use in patients with a history of a reaction to horse blood products, including anti-D antibodies.**

**INDICATIONS AND USAGE**

Thymoglobuline is used to treat patients with autoimmune hemolytic anemia (AIHA) and autoimmune thrombocytopenia (AITP). It is also indicated for the treatment of aplastic anemia and for the prevention of fraternal and allogeneic bone marrow transplantation.

**DOSAGE AND ADMINISTRATION**

- **Thymoglobuline is administered intravenously as a 50 mg/mL solution.**
- **The recommended dose for adults is 50 mg/kg body weight per day for 5 days.**
- **The dose should be given slowly over at least 1 hour.**

**ADVERSE REACTIONS**

Common side effects of Thymoglobuline include:
- **Fever**
- **Chills**
- **Headache**
- **Dizziness**
- **Fatigue**

**Precautions**

- **Thymoglobuline is not recommended for use in patients with a history of a reaction to horse blood products, including anti-D antibodies.**
- **Patients with a history of anaphylactic or anaphylactoid reactions should be monitored closely during administration.**

**CONTRAINDICATIONS**

Thymoglobuline is contraindicated in patients with a history of anaphylactic or anaphylactoid reactions.

**NOTICE**

- **Thymoglobuline is not recommended for use in patients with a history of a reaction to horse blood products, including anti-D antibodies.**
- **Patients with a history of anaphylactic or anaphylactoid reactions should be monitored closely during administration.**

**HOW SUPPLIED**

Thymoglobuline is supplied as a powder for solution in a vial for intravenous use.

**REFERENCES**

- **Thymoglobuline is not recommended for use in patients with a history of a reaction to horse blood products, including anti-D antibodies.**
- **Patients with a history of anaphylactic or anaphylactoid reactions should be monitored closely during administration.**

**NOTICE**

- **Thymoglobuline is not recommended for use in patients with a history of a reaction to horse blood products, including anti-D antibodies.**
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**HOW SUPPLIED**

Thymoglobuline is supplied as a powder for solution in a vial for intravenous use.
UKPAR Thymoglobuline .......................................................... PL 12375/0021–0022

The preserved state of Thymoglobuline® will be stored in a refrigerator (2–8°C).
The doctor or nurse will check that the product has not passed its expiry date before preparation.

6. FURTHER INFORMATION

Thymoglobuline® is a prescription only medicine (POM).

When Thymoglobuline® is supplied

The active ingredient is a 22 mg of rabbit antihuman thymocyte immunoglobulin. The product is supplied as 25 mg powder for solution for infusion.

When Thymoglobuline® looks like and comes from the pack

Thymoglobuline® is supplied in a vial with contents of 25 mg of product in the vial, and a protective cap over the vial. The vial contains 5 ml of diluent which has been pre-set to a concentration of 5 mg/ml of product. The solution should be added to the patient's solution containing 5 mg powder per ml. The solution should be deep or slightly opalescent. The refrigerated product should be inspected visually for particulate matter and discoloration. Do not use vials exhibiting particles or discoloration.

Immediate use of refrigerated product is recommended.

Preparation of Thymoglobuline® infusion (this Aseptic Technique) involves the required volume of the reconstituted solution from the Thymoglobuline® vial. Add the required dose of the solution into an infusion volume of 50 to 200 ml (suitable 10 ml/vial).

The product should be administered on the same day. The use of a 0.22 μm is not recommended.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:

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Avenue Industrieldheid

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The product is manufactured by:

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Tel: +61 2 9360 4111

Marketing Authorisation holder:

UK: M 1235/0933

Ireland: M 1231/0201

For any information about Thymoglobuline®, please contact the local representative or Marketing Authorisation Holder.

This leaflet has been approved in:

The following information is intended for medical or healthcare professionals only.

Each vial of Thymoglobuline® is intended for single use only.

It is strongly recommended that every time you receive a dose of Thymoglobuline, the expiry and batch number of the powder are recorded in order to maintain a record of the batches used.

Depending on the clinical dose or treatment plan of Thymoglobuline® the number of vials to be used during the preparation will determine the number of vials to be used and the number of doses to be prepared.

Thymoglobuline 25 mg powder for solution for infusion