Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products

BLA	103676/5143
Product	ATGAM® (lymphocyte immune globulin, anti-thymocyte globulin [equine]) Sterile Solution, 50 mg/mL
Sponsor	Pharmacia & Upjohn Company LLC (a Pfizer, Inc. Company)
Indication	Treatment of renal allograft rejection; Treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation
Date Received	February 24, 2023
Reviewer	Xiaofei Wang, PhD. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation General Medicine
RPM	Linda Le
Through	Larissa Lapteva, MD. Associate Director Division of Clinical Evaluation General Medicine

Table of Contents

1 EXECUTIVE SUMMARY

On February 24, 2023, Pharmacia & Upjohn Company LLC (a Pfizer, Inc. company) submitted a Prior Approval Supplement (PAS) – labeling supplement for pharmacokinetic (PK) data update for BLA 103676 ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) sterile solution for intravenous (IV) infusion.

ATGAM sterile solution contains lymphocyte immune globulin, anti-thymocyte globulin [equine]. It is the purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horse immunized with human thymus lymphocytes. ATGAM is approved for 1) treatment of renal allograft rejection; and 2) treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The approved dosing recommendations are 1) 10 to 15 mg/kg daily intravenously for 14 days; additional alternate day therapy up to a total of 21 doses may be given for treatment of renal transplant rejection; and 2) 10 to 20 mg/kg daily intravenously for 8 to 14 days; additional alternate day therapy up to a total of 21 doses may be given for treatment of aplastic anemia.

This labeling supplement includes proposed revisions to section 12.3 Pharmacokinetics to add PK information of ATGAM in Japanese adult patients with moderate or severe aplastic anemia in Specific Populations - Ethnicity part. The proposed labeling revision is based on results of a study in Japanese subjects with moderate to severe aplastic anemia (Japanese AA Study ATG-AA-1).

Based on review of the clinical pharmacology updates submitted in the supplement, the clinical pharmacology reviewer finds the proposed labeling revision is acceptable with some modifications.

2 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 103676 and finds it acceptable pending the following revisions shown below.

Reviewer's Comments to Applicant:

1. Per FDA Guidance for Industry – Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016), the CLINICAL PHARMACOLOGY section of the labeling must contain the following subsections:
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics

Please include subsection 12.2 Pharmacodynamics in the label.

The reviewer recommended changes are in red color.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

ATGAM is composed of antibodies that bind a wide variety of proteins on the surface of lymphocytes. In addition, ATGAM binds to granulocytes, platelets, bone marrow cells, and other cell types. The mechanism of ATGAM-induced immunosuppression has not been determined. Published data indicate that the primary mechanism is the depletion of circulating lymphocytes, with greatest effect on T lymphocytes. Lymphocyte depletion may be caused by complement dependent lysis and/or activation-induced apoptosis. In addition, immunosuppression may be mediated by the binding of antibodies to lymphocytes which results in partial activation and induction of T lymphocyte anergy.

The mechanism of ATGAM therapy for aplastic anemia is attributed to its immunosuppressive actions. In addition, ATGAM directly stimulates the growth of hematopoietic stem cells and release of hematopoietic growth factors such as interleukin-3 and granulocyte/macrophage colony stimulating factor.

12.3. Pharmacokinetics

Distribution

In a multicenter study, ATGAM pharmacokinetics were evaluated in 27 renal transplant patients. During infusion of 10 to 15 mg/kg/day, the mean peak value ~~(n=27 renal transplant patients)~~ was found to be 727 ± 310 µg/mL.

Metabolism and Elimination

The half-life of equine immunoglobulin after ATGAM infusion was found to be 5.7 ± 3.0 days in renal transplant patients (n=27). The range for half-life was 1.5 to 13 days.

~~Special~~Specific Populations

Ethnicity

ATGAM pharmacokinetics were evaluated in a study of 6 Japanese adult patients with moderate or severe aplastic anemia. When administered via intravenous infusion at a dose of 10 mg/kg/day (n=3) or 20 mg/kg/day (n=3) for 8 days, the mean concentration was 1180 ± 240 µg/mL and 2060 ± 340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

3 RECOMMENDATIONS

The supplemental BLA 103676 is acceptable from the clinical pharmacology perspective. The Division of Clinical Evaluation General Medicine finds the labeling changes in clinical pharmacology section proposed by the applicant to be acceptable with some modifications. Please refer to section 2 for details.

4 APPENDIX

In current submission, the Applicant proposed following revisions to section 12.3 Pharmacokinetics to add PK information of ATGAM in Japanese adult patients with moderate or severe aplastic anemia in Specific Populations - Ethnicity part.

ATGAM pharmacokinetics were evaluated in a study of 6 Japanese adult patients with moderate or severe aplastic anemia. When administered via intravenous infusion at a dose of 10 mg/kg/day (n=3) or 20 mg/kg/day (n=3) for 8 days, the mean concentration was 1180 ± 240 µg/mL and 2060 ± 340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

The proposed labeling revision is based on results of a study in Japanese patients with moderate to severe aplastic anemia (Japanese AA Study ATG-AA-1).

4.1 Japanese AA Study ATG-AA-1

Study Title: Study of U-ATG (ATGAM) in aplastic anemia patients to determine serum concentration of horse IgG

This study is to confirm the efficacy, safety, and the concentration of ATGAM in the patients with moderate or severe aplastic anemia. A total of 6 subjects were randomly assigned to two groups: 10 mg/kg/day group (n=3) and 20 mg/kg/day group (n=3). Subjects received ATGAM via intravenous infusion daily for 8 consecutive days.

For PK analysis, blood samples were collected at pre-dose, and at 1 and 24 hours after the completion of infusion on Day 1 (or immediately before infusion on Day 2), 24hours after the completion of infusion on Day 4 (or immediately before infusion on Day 5), 24 hours after the completion of infusion on Day 7 (or immediately before infusion on Day 8), 1 and 24 hours after the completion of infusion on Day 8, and 1 week, 2 weeks, and 1 month after the end of treatment. Serum horse IgG concentrations were measured using a validated (b) (4)
(b) (4)

PK analysis results showed that when administered via intravenous infusion at a dose of 10 mg/kg/day (n=3) or 20 mg/kg/day (n=3) for 8 days, the mean concentration was 1180 ± 240 µg/mL and 2060 ± 340 µg/mL, respectively at 1 hour after completion of infusion on Day 8. The apparent elimination half-life after the last dose varied from 1.3 to 6 days in these patients.

Reviewer's Comments:

Based on review of Applicant's submission, the proposed labeling updates for PK information of ATGAM® in Japanese patients with moderate to severe aplastic anemia are acceptable.