BLA Prior Approval Supplement Clinical Review Memorandum

Application Type	Prior Approval Supplement (PAS) Update of Prescribing Information (PI)
STN	BLA 103676/5137
CBER Received Date	October 31, 2022
PDUFA Goal Date	May 2, 2023
Division / Office	DCEGM/OTP
Priority Review (Yes/No)	No
Reviewer Name(s)	Shelby Elenburg, MD (GMB1)
Review Completion Date / Stamped Date	May 1, 2023
Supervisory Concurrence Branch Chief, GMB1 Acting Director, DCEGM	Elizabeth Hart, MD Branch Chief, GMB1/DCEGM/OTP Acting Division Director, DCEGM/OTP
Applicant	Pharmacia & Upjohn Company LLC (a Pfizer, Inc. Company)
Established Name	Lymphocyte Immune Globulin, Anti-thymocyte Globulin (Equine)
Trade Name	ATGAM
Pharmacologic Class	Immune globulin
Formulation(s), including Adjuvants, etc.	50 mg/mL lymphocyte immune globulin, anti-thymocyte globulin [equine] concentrate
Dosage Form(s) and Route(s) of Administration	solution for intravenous infusion
Dosing Regimen	Renal allograft rejection: 10 to 15 mg/kg daily IV for 14 days. Additional alternate-day therapy up to a total of 21 doses may be given. Aplastic anemia: 10 to 20 mg/kg daily IV for 8 to 14 days. Additional alternate-day therapy up to a total of 21 doses may be given.
Indication(s) and Intended Population(s)	Treatment of renal allograft rejection; Treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation
Orphan Designated (Yes/No)	No

Executive Summary:

ATGAM (Lymphocyte Immune Globulin, Anti-thymocyte Globulin (Equine)) is an immunoglobulin G (IgG) product that contains antibodies to various proteins expressed on the surface of lymphocytes and various other cell types. Though the exact mechanism of immunosuppression is unknown, published data indicate the greatest immunosuppressive effect of ATGAM is the depletion of T lymphocytes. ATGAM is used for the management of acute allograft rejection in renal transplant patients and in the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation. The product is administered via intravenous (IV) infusion.

Pfizer, Inc. submitted a Prior Approval Supplement (PAS) for ATGAM [Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine)] on October 31, 2022. The PAS was submitted with updated Prescribing Information in the Physician Labeling Rule (PLR) format.

The purpose of this prior approval supplement (PAS) is to provide the following revisions to the existing United States Prescribing Information (USPI) for ATGAM, based on the review of post-marketing safety data related to hypersensitivity and immune-mediated reactions, infections, and cytopenias and administration of the product in specific populations:

- Section 2 Dosage and Administration
- Section 5 Warnings and Precautions
- Section 6.2 Post-marketing Experience
- Section 8 Use in Specific Populations

The following additional subsection has been proposed for addition to the USPI:

- Section 12.6 Immunogenicity

In addition to the proposed changes from the Applicant, FDA requests modifications to various sections of the USPI to be consistent with current clinical practice and PLR formats. Administrative changes are requested for consistency and clarity.

Conclusion

The Applicant accepted FDA-recommended changes in the USPI, and the reviewer considers the revised PI to be acceptable. This reviewer recommends approval of the PAS, based on the final version of USPI received on May 1, 2023, under BLA 103676/5137.

Proposed Changes and Review of Post-marketing Data

I. Hypersensitivity and Immune-Mediated Reactions

The Applicant proposes to modify Section 5.1 Hypersensitivity to include symptoms of immune-mediated reactions and add an additional warning about cytokine release syndrome (CRS), as follows:

"…and associated symptoms such as rash, arthralgia, pyrexia, chills, and pain have been reported.

Based on the mechanism of action of ATGAM, there is a potential risk of cytokine release syndrome, which can be fatal."

The Applicant cites published literature for cases of CRS reported in studies of similar anti-thymocyte globulin products, and symptoms of CRS and other immune-mediated or infusion-associated reactions in post-marketing studies of anti-thymocyte globulin products.

Reviewer Comment:

This reviewer does not agree with the proposed changes as phrased, because the noted associated symptoms are nonspecific and therefore not informative, and the discussion of cytokine release syndrome is insufficient. Additionally, the existing USPI language regarding anaphylaxis, infusion related-reactions, and serum sickness is inaccurate and insufficient to inform providers and patients of potential risks of ATGAM. The discussion of anaphylaxis, in particular, is misleading and minimizes the potentially fatal risk of anaphylaxis. Updates to existing sections and creation of new sections specific to each type of reaction are requested of the applicant, including symptomatology, monitoring and management of reactions.

Along with these updates, the existing Box Warning for Anaphylaxis contains misleading information, as the risk of anaphylaxis could be construed as theoretical and the risk is minimized by phrasing regarding processing of ATGAM to reduce risk of anaphylaxis despite the mechanisms of anaphylaxis not being fully understood.

Original:

WARNING: ANAPHYLAXIS

ATGAM can cause anaphylaxis when injected intravenously. Although ATGAM is processed to reduce the level of antibodies that will react to non-T cells, physicians should be prepared for the potential risk of anaphylaxis and monitor patients for signs and symptoms during infusion .

The following revision is requested:

WARNING: ANAPHYLAXIS

Anaphylaxis has been reported with the use of ATGAM. ATGAM can cause potentially life-threatening anaphylaxis when injected intravenously. Monitor patients for signs and symptoms of anaphylaxis during infusion and for at least 24 hours after infusion *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Additional changes proposed by the Applicant include the addition of language related to (b) (4)

The Applicant concludes that these additions to the USPI may be informative to providers.

Reviewer Comment:
This reviewer does not agree with the proposed additions. No new data is provided to support the changes, and the changes are prescriptive and consistent with practice of medicine. These additions should be removed.

The Applicant proposes the addition of (b) (4)

Reviewer Comment:
This reviewer disagrees with this addition. No new data is provided, and addition is based on information gathered from (b) (4) *assays that are not validated. The relevance of* (b) (4) (b) (4) *is unknown. This section is not informative and should be removed.*

II. Infections

The Applicant proposes updates to *Section 5.3 Infection* to address the risks of infection due to the immunosuppressive effects of ATGAM and concomitant immunosuppressants, including different types of infections. These updates are based on the totality of safety data from sponsored pivotal studies of ATGAM and post-marketing data, including post-marketing studies and cases reported in the safety database. Among 2830 cases of adverse event cases reported to the safety database for equine anti-thymocyte globulin (through April 30, 2022), 697 (25%) contained a total of 995 infection- related events, 376 (38%) of which had fatal outcomes. The Applicant provided a table of the most frequently reported (≥1%) infection-related events, and proposed the following addition to the USPI to encompass the most frequently-reported events in the totality of data:

"5.3 Infection
Due to the nature of the immunosuppressive effects of ATGAM, opportunistic infections (bacterial and fungal) are very common. Sepsis has also been reported. There is an increased risk of viral reactivation (e.g., cytomegalovirus [CMV] infection, Epstein-Barr virus [EBV] infection, herpes simplex virus [HSV]). Monitor patients carefully for concurrent infection. Some physicians have found that it may be possible to reduce this risk by decreasing the dosage of other immunosuppressive agents which might be administered concomitantly with ATGAM.

In common with products derived from, or purified with human blood components, the possibility of transmission of some infectious diseases should be borne in mind."

The Applicant concluded that a specific focus on the frequent occurrence of sepsis and viral infections/viral reactivation, particularly in the Herpesviridae family, were informative to safety monitoring of patients following ATGAM administration.

Reviewer Comment:
This reviewer agrees with additional language regarding risks of infection with ATGAM, with the following caveats:

- *The phrasing regarding types of opportunistic infections should include viral infections in*

additional to bacterial and fungal infections. Not all viral infections are related to viral reactivation.

- *The discussion about reducing risk of infection by decreasing doses of other immunosuppressive agents administered concomitantly with ATGAM is prescriptive and consistent with practice of medicine, and is not informative. This sentence should be removed.*
- *The separate phrase about risk of transmission of infectious disease from human blood products is redundant with Section 5.4 Transmissible Infectious Agents, and thus should be removed.*

The Applicant proposes changes to *Section 6.2 Post-Marketing Experience* to add, "sepsis," Epstein-Barr virus infection," and "Cytomegalovirus infection" to "Infections and infestations" to point out infections seen in a higher frequency in the totality of the safety data.

Reviewer Comment:

This reviewer agrees with additional language regarding risks of specific infectious events related to ATGAM administration; however, the Applicant should either add additional specific infections seen at similar frequencies to sepsis, EBV, and CMV in the Safety Database (including specific fungal infections) or remove the specific references to EBV and CMV.

The Applicant proposes revision of *Section 5.4 Immunizations*, citing changes in clinical practice and recommendations since the initial approval of the product. The following original language has been deleted:

> "Do not administer live vaccines to patients about to receive, receiving, or after treatment with ATGAM. Concomitant administration of ATGAM with live virus vaccines carries a potential of uncontrolled viral replication in the immunosuppressed patient. There is insufficient information to fully define the extent of the risk, or the period of time during which the risk exists. If administered, live viruses may interfere with ATGAM treatment."

And replaced with the following:

> *"The safety and effectiveness of immunization with vaccines and treatment with ATGAM have not been studied. Vaccination is not recommended in conjunction with ATGAM therapy as the effectiveness of the vaccines could be reduced. The prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to immunosuppressive therapy."*

The Applicant concludes that, "[t]he proposed changes are intended to provide more contemporary guidance, reflective of current medical practice and developments in types of vaccine used today. The safety and effectiveness of immunization with live attenuated viral vaccines in conjunction with eATG therapy has not been studied. Vaccination is not recommended in conjunction with eATG therapy, as the effectiveness of the vaccines could be reduced. Therefore, the prescribing information for the respective vaccine should be consulted to determine the appropriate interval for vaccination in relation to IST.

Reviewer Comment:
This reviewer does not agree with removal of language regarding risks of live/live attenuated vaccines. The Applicant has provided no new data to support changes, and the provided rationale still discusses risk of live vaccines, despite removal of the emphasis on, "live" in the newly proposed USPI language. The original language should be retained.

III. Cytopenias

The applicant proposes the addition of Section 5.5 Thrombocytopenia and Neutropenia to add the following:

> *"Treatment with ATGAM may exacerbate thrombocytopenia and neutropenia. Consider discontinuing therapy if severe and unremitting thrombocytopenia or leukopenia occurs."*

The Applicant indicates that the immunosuppressive effects of ATGAM may exacerbate thrombocytopenia in aplastic anemia patients due its effect on stem cells, but no further rationale is provided.

Reviewer Comment:
This reviewer agrees with addition of Section 5.5 Thrombocytopenia and Neutropenia to inform the risks of cytopenias related to ATGAM treatment and address management considerations. However:

- *the current USPI refers to thrombocytopenia and possible need for prophylactic platelet therapy in patients with aplastic anemia in Section 2.1 Dosage and Administration. This information should is not appropriate in Section 2.1 and should be moved to Section 5.5. Additionally, as thrombocytopenia is a possible adverse effect of ATGAM regardless of underlying indication, reference to aplastic anemia should be removed, as should reference to "prophylactic" administration of platelets, as cases of thrombocytopenia occurring following treatment with ATGAM may also necessitate management with platelet transfusions.*
- *the reference to "neutropenia" in the subheading and "leukopenia" in the text is confusing. Leukopenia is expected with ATGAM therapy, so this likely is a typo. The Applicant should be consistent with, "neutropenia" throughout the USPI.*

IV. Use in Specific Populations

The Applicant proposes to modify *Section 2.1 Dose* to specifically address the dosage for elderly or geriatric populations (65 years of age and older) to add the following clause for the aplastic anemia indication:

> "[…]
> *Geriatric population (≥65 years of age)*
> […]
> *Aplastic Anemia (Moderate to Severe): Clinical experience of elderly patients has not identified differences in responses between the elderly and younger patients. Therefore, no dose adjustment is recommended for elderly patients."*

Although no clinical studies have focused specifically on safety or efficacy of ATGAM in elderly populations, the Applicant proposes these changes based on the review of data for elderly patients

treated in the sponsored pivotal studies, as well as a review of the literature, that suggests no differences in responses between elderly and younger adult subjects. No new data is provided.

> ***Reviewer Comment:***
> *This reviewer disagrees with the Applicant's proposal to add reference to dosage in elderly populations to Section 2.1. The reference to a specific population is not appropriate in Section 2, and the addition is in contradiction to Section 8.5 Geriatric Use, which states, "[t]he dose for an elderly patient should be selected with caution, starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy in this age group." No new data was submitted to support the safety of standard doses of ATGAM in elderly populations, and therefore I disagree that "no dose adjustment is recommended for elderly patients."*

The Applicant proposes changes to *Section 8.1 Pregnancy* to include standard language regarding estimated background risk of birth defects and miscarriage in the United States. The Applicant proposes changes to *Section 8.3 Females and Males of Reproductive Potential* to add the following language to take a conservative approach to contraception with a recommended duration of contraception based on 5 times the maximum half-life of ATGAM:

> *"Contraception*
> *It is not known if ATGAM can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with ATGAM and for up to 10 weeks after cessation of therapy."*

> ***Reviewer Comment:***
> *This reviewer agrees with the proposed changes to Section 8.1 and 8.3, with the exception that contraception should also apply to male partners of females of reproductive potential, and the words "up to" should be removed due to potential confusion regarding the reccommended duration of contraception following ATGAM treatment.*