Clinical Memorandum

DATE:	September 25, 2023
FROM:	Prateek Shukla, MD Clinical Reviewer General Medicine Branch 1 (GMB1) Division of Clinical Evaluation General Medicine (DCEGM) Office of Therapeutic Products (OTP)
THROUGH:	Elizabeth Hart, MD Branch Chief CBER/OTP/DCEGM/GMB1
THROUGH:	Tejashri Purohit-Sheth, MD Division Director CBER/OTP/DCEGM
SUBJECT:	Update of Prescribing Information (PI)
PRODUCT:	GLASSIA, Alpha-1 Proteinase Inhibitor (Human)
APPLICANT:	Takeda Pharmaceuticals U.S.A, Inc
BLA:	125325/584
RECOMMENDATION:	Approval

Executive Summary:

Glassia [Alpha1-Proteinase Inhibitor (Human)] is a liquid preparation of purified alpha-1-proteinase inhibitor, also known as alpha-1-antitrypsin derived from human plasma. It is indicated for chronic augmentation and maintenance therapy in individuals with clinically evident emphysema due to severe hereditary deficiency of alpha-1-proteinase inhibitor. The product is administered via intravenous (IV) infusion and was approved in July 2010.

At the time of approval, the Applicant was required to conduct a post-marketing requirement (PMR) study related to identification of unexpected serious risk from adverse events relating to

the presence of visible protein aggregates in the product. The study was also to include viral nucleic acid testing (NAT) and testing for anti-Alpha1-PI antibodies using an appropriately validated assay. Additionally, the Applicant agreed to conduct a post-marketing commitment (PMC) clinical trial as a sub-study of the PMR described above. The primary endpoint for this study was to evaluate both antigenic and functional Alpha 1-PI levels in Epithelial Lining Fluid after 10-12 weeks of augmentation therapy with GLASSIA.

On January 12, 2023, FDA confirmed that PMR #1 and PMC #3 for Glassia have been fulfilled by Study 471101 (STN BL 125325/514). Takeda submitted this Labeling Prior Approval Supplement (PAS) to provide the following revisions to the existing United States Prescribing Information (USPI) for GLASSIA with data supported by the primary objectives from Study 471101:

- Updated Indications and Usage
- Updated to include immunogenicity data from Study 471101
- Updated to include findings from Epithelial Lining Fluid sub-study of Study 471101

After interactive review and labeling negotiations, the sponsor also amended the USPI to include the following:

- Updated tables to make labeling submission 508 compliant

Review of proposed changes

I. Update Indications and Usage
   - *Highlights of Prescribing Information:* included reference to increased functional lung epithelial lining fluid levels of $Alpha_1$-PI under Indications and Usage.

   Reviewer Comment:
   The applicant initially proposed adding the results of their Epithelial Lining Fluid sub-study demonstrating an increase in functional lung epithelial lining fluid levels of $Alpha_1$-PI to their Indications and Usage statement. During review of this PAS, it was noted that the Indications and Usage statement included both the indication and mechanism of action for this product. Following interactive review, the applicant agreed to move the mechanism of action statement related to antigenic and functional levels of $Alpha_1$-PI to Section 12: Clinical Pharmacology in order to conform with the format for an indication statement per labeling guidance and to be consistent with other similar products in this product class. The indication and limitations of use for GLASSIA previously included the USPI remain the same.

   Agreed upon Indications and Usage –
   GLASSIA is an Alpha1-Proteinase Inhibitor (Human), indicated for chronic augmentation and maintenance therapy in individuals with clinically evident emphysema due to severe hereditary deficiency of Alpha1-PI, also known as alpha1-antitrypsin (AAT) deficiency.

   Mechanism of Action added to Section 12 –
   GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) levels of Alpha1-PI in both the serum and the lung epithelial lining fluid (ELF) [see Clinical Studies (14)].

II. Updated to include immunogenicity data from PMR study

- *Section 6.1 Clinical Trials Experience:* Included immunogenicity data and a statement of immunogenicity impact on safety, as observed from GLASSIA Study 471101 as follows:

  Immunogenicity was further evaluated in the multicenter study (post-licensure) in subjects with Alpha1-PI deficiency. Of the 34 subjects studied, 2 (6%) developed neutralizing anti-Alpha1-PI antibodies. There was no association between patients with Alpha1-PI antibodies and immune-mediated treatment emergent adverse reactions or associated decrease in plasma Alpha1-PI levels.

Reviewer Comment:
The reviewer agrees with the proposed inclusion of immunogenicity data and amended specific details and verbiage for clarity during interactive review.

III. Updated to include findings from Epithelial Lining Fluid sub-study

- *Section 14 Clinical Studies:* Included findings from a PMC study evaluating antigenic and functional Alpha$_1$-PI levels in epithelial lining fluid following GLASSIA therapy in subjects with emphysema due to congenital A1PI deficiency as follows:

  The safety, immunogenicity, and effects on the Alpha1-PI levels in epithelial lining fluid (ELF) following GLASSIA therapy were evaluated in a multicenter study (post-licensure) of 34 subjects with emphysema due to congenital A1PI deficiency. Subjects received GLASSIA at a dosage of 60 mg/kg for 25 weeks. Sixteen subjects underwent bronchoalveolar lavage (BAL) at baseline and at Weeks 12-14. GLASSIA augmentation therapy resulted in a statistically significant increase in antigenic Alpha1-PI levels in ELF (median change=0.5 µM; geometric mean ratio=5.4, p<0.001; Table 6). Functional Alpha1-PI levels in ELF also showed a statistically significant increase in response to GLASSIA (median change=0.3 µM, geometric mean ratio=2.3, p<0.001; Table 6).

- *Section 14 Clinical Studies:* Included Table 6 (Summary and Analysis of Change from Baseline in Antigenic and Functional Alpha$_1$-PI Levels in the Epithelial Lining Fluid):

Table 6: Summary and Analysis of Change from Baseline in Antigenic and Functional Alpha1-PI Levels in the Epithelial Lining Fluid

Alpha$_1$-PI Levels (n = 16)	**Geometric Mean Baseline BAL (µM)**	**Geometric Mean On-Treatment BAL (µM) (Weeks 12-14)**	**Geometric Mean Ratio (p-value)**
Antigenic Alpha$_1$-PI Levels	0.1	0.6	5.4 (<0.001)
Functional Alpha$_1$-PI Levels	0.2	0.5	2.3 (<0.001)

Reviewer Comment:
This reviewer agrees with the proposed changes following interactive review in which the proposed inclusions were edited for content and clarity. Note that at the time of the original approval, the agreed upon endpoint for this PMC was the following: The primary endpoint for this study will be both antigenic and functional Alpha1-PI levels in Epithelial Lining Fluid after 10-12 weeks of treatment.

Review of additional label changes made with this supplement

IV. Updated tables 1, 2 and 3 to make labeling submission 508 compliant
- *Section 6.1 Clinical Trials Experience, Table 1:* filled empty header cell
- *Section 6.1 Clinical Trials Experience, Table 2:* filled empty header cell, renamed *adverse events* to *adverse reactions* to be consistent with FDA labeling guidance, and formatted table for readability
- *Section 6.1 Clinical Trials Experience:* filled empty header cell, added "nasopharyngitis" which was erroneously omitted from prior labeling

Reviewer Comment:
This reviewer agrees with the proposed changes as listed.

Conclusion:
The applicant accepted FDA-recommended changes in the USPI, and this reviewer considers the revised PI to be acceptable. This reviewer recommends approval of the PAS, based on the final version of USPI received on September 18, 2023, under Amendment 3 of BLA 125325/584.