PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

GLASSIA®

Alpha-1 Proteinase Inhibitor (Human) Injection

Solution - For Intravenous Use Only

1000 mg / 50 mL Vial

Takeda Canada Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

GLASSIA (alpha-1 proteinase inhibitor [human] injection) is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of Alpha1-PI, also known as alpha1-antitrypsin deficiency (AATD). GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels.

Limitations of Use:

- The effect of augmentation therapy with GLASSIA on pulmonary exacerbations and on the progression of emphysema in alpha1-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established.

1.1 Pediatrics

Pediatrics (<18 years): No pediatric studies have been performed to assess efficacy and safety of GLASSIA; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): In clinical trials, 11 subjects of 65 years of age or older received GLASSIA. This number of subjects was not sufficient to determine whether they respond differently from younger subjects.

2 CONTRAINDICATIONS

GLASSIA is contraindicated in:

- immunoglobulin A (IgA) deficient patients with antibodies against IgA.
- individuals with a history of anaphylaxis or other severe systemic reaction to Alpha1-PI products.
- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The recommended dose of GLASSIA is 60 mg/kg body weight of GLASSIA once weekly by intravenous infusion. Dose ranging studies using efficacy endpoints have not been performed.

GLASSIA may be given at a rate not to exceed 0.2 mL/kg/min and is determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg at a rate of 0.2 mL/kg/min will take approximately 15 minutes to infuse.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of GLASSIA is 60 mg/kg body weight of GLASSIA once weekly by intravenous infusion.

The carton and label on each vial of GLASSIA show the actual amount of functionally active Alpha1-PI in milligrams.

4.3 Administration

For intravenous infusion only.

GLASSIA should be administered by a healthcare professional or self-administered by the patient/caregiver after appropriate training.

First infusions should be administered under the supervision of a healthcare professional experienced in the use of human alpha1-proteinase inhibitor or in the treatment of alpha1-proteinase inhibitor deficiency. Subsequent infusions can be administered by a caregiver or by the patient if appropriate training is provided and the use is reviewed at regular intervals. The decision of whether a patient is suitable for home-treatment/self-administration is made by the treating doctor. There are limited data regarding the use of this medicinal product in home-treatment/self-administration. Potential risks associated with home-treatment/self-administration are related to the administration itself as well as to the handling of adverse drug reactions, particularly hypersensitivity.

1. Always use aseptic technique.
2. Inspect the vial of GLASSIA for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should be clear and colorless to yellow-green.
3. Administer GLASSIA alone. Do not mix with other agents or diluting solutions except when using the intravenous pooling infusion bag.
4. When infusing directly from the vials, use a vented spike (not supplied). If the contents of vials have been pooled to a sterile intravenous container, use an appropriate intravenous administration set.
5. Always use a 5 micron in-line filter (not supplied) during infusion.
6. Administer GLASSIA within 3 hours of entering the vials to avoid the potential ill effect of any inadvertent microbial contamination.
7. Administer GLASSIA at room temperature through an appropriate intravenous administration set at a rate not to exceed 0.2 mL/kg body weight per minute, and as determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg at a rate of 0.2 mL/kg/min will take approximately 15 minutes to infuse.
8. Monitor the infusion rate closely during administration and observe the patient for signs of infusion related reactions. If infusion related adverse reactions occur, reduce the rate or

interrupt the infusion as appropriate until the symptoms subside. Resume the infusion at a rate tolerated by the patient, except in the case of severe reaction [see Warnings and Precautions (7)].
9. Record patient and product batch number information (see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).
10. Following administration, discard all open vials, unused solution, vented spike and administration equipment in an appropriate manner, as per local requirements.

4.4 Missed Dose

Patients can proceed with their next scheduled dose immediately and continue at regular intervals, unless otherwise advised by their doctor or healthcare professionals.

5 OVERDOSAGE

To date, there have been no reported cases of suspected overdose for GLASSIA. No data are available in regard to overdosage in humans.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

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

Table 1: Dosage Forms, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution/2% A1-PI/ 0.02M Monobasic Sodium Phosphate Dihydrate/ 0.7 % Sodium Chloride/ 50 mL Water for Injection.	Sodium chloride, sodium phosphate, water for injection

Packaging: The drug product (50 mL) is contained in a glass vial, which consists of clear, colorless, Type I borosilicate glass and is sealed with chlorobutyl rubber stopper and a flip aluminium cap.

7 WARNINGS AND PRECAUTIONS

General

Because this product is made from human plasma, it may carry a risk of transmitting infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmitting an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process. Despite these measures, such products may still potentially transmit human pathogenic agents.

All infections possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Takeda Canada Inc. at 1-800-268-2772.

No seroconversions for hepatitis B or C (HBV or HCV) or human immunodeficiency virus (HIV) were reported with the use of GLASSIA during the clinical trials.

Hypersensitivity Reactions

GLASSIA may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing severe hypersensitivity and anaphylactic reactions. Monitor vital signs continuously and observe the patient carefully throughout the infusion. Discontinue the infusion if hypersensitivity symptoms occur and administer appropriate emergency treatment. Epinephrine and/or other appropriate supportive therapy should be available for the treatment of any acute anaphylactic or anaphylactoid reaction.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with GLASSIA. It is also not known whether GLASSIA can cause fetal harm when administered to pregnant women or can affect reproductive capacity.

GLASSIA should be given to a pregnant woman only if clearly needed.

7.1.2 Breast-feeding

There is no information regarding the presence of GLASSIA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GLASSIA and any potential adverse effects on the breastfed infant from GLASSIA.

7.1.3 Pediatrics

Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

In clinical trials, 11 subjects of 65 years of age or older received GLASSIA. This number of subjects was not sufficient to determine whether they respond differently from younger subjects. Dosing for geriatric patients should be appropriate to their overall situation.

Safety and effectiveness in patients over 65 years of age have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The serious adverse reaction observed during clinical trials with GLASSIA was exacerbation of chronic obstructive pulmonary disease (COPD).

The most common adverse reactions (>0.5% of infusions) in clinical trials were headache and upper respiratory infection.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of GLASSIA was evaluated in a randomized, double-blind, active-control trial (API-002) and an open-label, non-parallel, dose-escalation trial (API-001), in 67 subjects with pre-augmentation therapy serum Alpha1-PI levels less than 11 microM. In the open label, non-parallel, dose-escalation trial, 18 subjects received a single infusion of GLASSIA at dosages of 30, 60 or 120 mg/kg (n = 6 per dose). In the randomized, double-blind, active-control trial, 50 subjects received weekly infusions of GLASSIA or the comparator Alpha1-PI product at a dosage of 60 mg/kg for a total of 12 weeks after which all subjects remaining in the trial were treated for another 12 weeks with GLASSIA only. During the first 12 weeks of the trial, 33 subjects were treated with GLASSIA and 17 subjects were treated with comparator product, representing 66% and 34%of trial participants, respectively. Overall, 17 subjects received 12 doses and 32 subjects received 22 - 24 doses of GLASSIA during the trial. One subject randomized to the comparator Alpha1-PI product did not receive any treatment with GLASSIA during the last 12 weeks of the trial. 22 subjects in the GLASSIA treatment arm and 15 subjects in the comparator arm experienced adverse reactions during the initial 12 weeks (double-blind portion) of the trial. Table 2 compares the adverse reactions reported in >5% of subjects during the initial 12 weeks in subjects treated with GLASSIA with reactions in the concurrent comparator group. Table 3 shows the adverse reactions reported in >5 % of subjects receiving GLASSIA for the entire 24-week treatment period.

Table 2: Adverse Reactions Occurring in > 5% of Subjects During the First 12 Weeks of Treatment

	GLASSIA (n=33)	Comparator (n=17)
Adverse Event (AE)	No. of subjects with adverse reactions[1] (AR) (percentage of all subjects)	No. of subjects with adverse reactions[1] (AR) (percentage of all subjects)
Cough	3 (9.1%)	4 (23.5%)
Headache	3 (9.1%)	3 (17.6%)
Sinusitis	3 (9.1%)	1 (5.9%)
Upper respiratory tract infection	3 (9.1%)	0 (0%)
Chest discomfort	2 (6.1%)	0 (0%)
Dizziness	2 (6.1%)	0 (0%)
Hepatic enzyme increased	2 (6.1%)	0 (0%)

[1] An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began on the same day or within 3 days following the Glassia infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to Glassia administration, or (c) an adverse event for which causality assessment was missing or indeterminate.
Sinusitis was classified into either System Organ Class (SOC) 'Infections and Infestations' or 'Respiratory Thoracic and Mediastinal Disorders'. In Table 2, Sinusitis occurrences of both SOCs are counted.

Table 3: Adverse Reactions Occurring in > 5% of Subjects treated with GLASSIA for 24 Weeks

Adverse Event	GLASSIA (n=49)
Adverse Event (AE)	No. of subjects with adverse reactions[1] (AR) (percentage of all subjects)
Upper respiratory tract infection	8 (16.3%)
Headache	5 (10.2%)
Nasopharyngitis	5 (10.2%)
Cough	4 (8.2%)
Pharyngolaryngeal pain	4 (8.2%)
Rash	4 (8.2%)
Sinusitis	4 (8.2%)
Abdominal pain	3 (6.1%)
Dizziness	3 (6.1%)
Nausea	3 (6.1%)

[1] An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began on the same day or within 3 days following the Glassia infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to Glassia administration, or (c) an adverse event for which causality assessment was missing or indeterminate.
Rate by subject = total number of subjects experiencing the ADR divided by total number of subjects (N) and multiplied by 100.
Both Sinusitis and Nasopharyngitis were classified into either System Organ Class (SOC) Infections and Infestations or Respiratory Thoracic and Mediastinal disorders. In Table 3, Sinusitis and Nasopharyngitis, occurrences of both SOCs are counted.

Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

During the 12-week double blind portion of the randomized, active comparator trial, 4 subjects (12%) had exacerbations of chronic obstructive pulmonary disease (COPD) during GLASSIA treatment and 5 subjects (29%) had exacerbations of COPD during comparator treatment. In the 12-week open-label treatment period with GLASSIA, 14 subjects (29%) had exacerbations.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to GLASSIA with the incidence of antibodies to other products may be misleading.

In the double blind, randomized, active comparator trial of GLASSIA, low level anti-GLASSIA antibodies were detected in one subject (out of 50 subjects) at one time point (Week 12) and returned to negative at the end of the study (Week 24) despite continuous exposure to GLASSIA. No immune system adverse reactions were reported.

8.3 Less Common Clinical Trial Adverse Reactions

The following related adverse reactions have also occurred in subjects treated with GLASSIA:

General disorders and administration site conditions: Influenza like illness, lethargy

Immune system disorders: Urticaria

Investigations: Platelet count decreased

Musculoskeletal and connective tissue disorders: Joint swelling

Nervous system disorders: Headache NOS

Skin and subcutaneous tissue disorders: Pruritus

Vascular disorders: Hypertension

8.4 Postmarketing Adverse Reactions

The following adverse reactions have been identified during post-approval use of GLASSIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea

Gastrointestinal Disorders: Nausea

General Disorders and Administration Site Conditions: Fatigue

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Interactions with other drugs have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

GLASSIA administration is intended to inhibit serine proteases such as neutrophil elastase (NE) in the lung. In the healthy lung, NE is produced by activated neutrophils during inflammation (respiratory infection, smoking) and can be regulated by the inhibitory action of alpha-1 PI. Uninhibited activity of NE results in a protease-protease inhibitor imbalance and can destroy the alveolar wall, resulting in conditions like chronic obstructive lung disease or emphysema which is observed in Alpha-1 PI deficiency. Alpha1-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and alveolar levels of Alpha1-PI. Individuals with severe Alpha-1 PI deficiency have little protection against NE released during inflammation which can lead to progressive, moderate-to-severe chronic obstructive lung disease (emphysema) that eventually manifests with clinical symptoms in the third to fourth decades of life.

Smoking is an important risk factor for the development of emphysema including in patients with Alpha1-PI deficiency. Because emphysema affects many, but not all individuals with the more severe genetic variants of Alpha1-PI deficiency (AAT deficiency), augmentation therapy with Alpha1-Proteinase Inhibitor (Human) is indicated only in patients with severe Alpha1-PI deficiency who have clinically evident emphysema.

10.2 Pharmacodynamics

Administration of GLASSIA to patients with Alpha1-PI deficiency augments the level of circulating levels of the deficient protein following intravenous administration. Normal individuals have levels of Alpha1-PI greater than 22 microM.

The clinical efficacy of GLASSIA in influencing the course of pulmonary emphysema or the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated in randomized, controlled clinical trials.

The clinical benefit of the increased circulating levels of Alpha1-PI at the recommended dose has not been established for A1PI augmentation therapy.

10.3 Pharmacokinetics

A prospective, open-label, uncontrolled multicenter pharmacokinetic trial was conducted in 7 females and 11 males with congenital Alpha1-PI deficiency, ranging in age from 40 to 69 years. Subjects received a single dose of GLASSIA either 30 mg/kg, 60 mg/kg or 120 mg/kg (n=6 per dose level). Blood samples for pharmacokinetic assessment were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days and at 7 days post-dose.

The mean results for pharmacokinetic parameters are shown in Table 4. The pharmacokinetics of GLASSIA were linear over the dose range of 30-120 mg/kg.

Table 4: Pharmacokinetic Parameters (Mean and %CV) for Functional Alpha1-PI

Dose (mg/kg)	$AUC_{0\text{-}inf}$ (h• microM)	CL (L/day)	Vd,ss (L)
30	1194 ± 18.94	0.88 ± 14.69	3.64 ± 8.58
60	2544 ± 14.65	0.71 ± 11.83	3.20 ± 9.62
120	5438 ± 17.35	0.74 ± 16.61	3.57 ± 14.13

11 STORAGE, STABILITY AND DISPOSAL

Each carton of GLASSIA contains a single use vial containing approximately 1 gram of functional Alpha1-PI in 50 mL of solution.

Store GLASSIA at 2°C to 8°C (36°F to 46°F). Do not freeze.

Product may be stored at room temperatures not exceeding 25°C (77°F) for up to one month. Once removed from refrigeration use within one month.

Keep vial in carton until required for use.

Do not use after the expiration date printed on the label. GLASSIA contains no preservatives and no latex.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Alpha 1-Proteinase Inhibitor

Chemical name: Human Alpha-1Proteinase Inhibitor

Alpha-1-Proteinase inhibitor human

Molecular formula and molecular mass: 51-54 kDa

Structural formula: This drug substance has one Cysteine residue at position 232, which was found to be covalently linked to a free single Cysteine by a disulfide bridge. Drug substance has three Nglycosylation sites at Asn-46, Asn-83 and Asn-247, equipped with either diantennary or triantennary N-glycans.

Physicochemical properties:

Attribute	Description
Composition	A single-chain, 394 amino acid glycoprotein containing one cysteine residue covalently linked to free single Cysteine by a disulfide bridge, has three N-glycosylation sites equipped with either diantennary or triantennary N-glycans.
Theoretical Extinction Coefficient or Absorptivity (280 nm)	0.46 $(mg/mL)^{-1}cm^{-1}$
Mass	51-54 kDa
Glycosylation	Three N-glycosylation sites are attached to asparagine residues at positions 46, 83, and 247. The N-glycans are either diantennary or triantennary. Sialic acid residues on the N-glycans give A1PI a high negative charge. In an electric field, multiple isoforms of A1PI are separated mainly due to the different numbers of sialic acids residues on the N-glycans. (*Kolarich* et al, 2006).

Product Characteristics
The drug product is a ready-to-use sterile solution for intravenous infusion. The solution is clear, ranging from colorless to yellow-green and may contain a few protein particles. The drug product contains 2% solution of active A1PI in 20 mM sodium dihydrogen phosphate buffer containing 0.7% sodium chloride.

Viral Inactivation

Individual plasma units used for production of GLASSIA are tested using FDA- licensed serological assays for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as by FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is also tested by in-process NAT procedures for parvovirus B19 and the limit for B19 DNA in the manufacturing pool is set not to exceed 10^4 IU per mL.

To reduce the risk of viral transmission, the manufacturing process for GLASSIA includes two steps specifically designed to remove or inactivate viruses. The first of these is nanofiltration (NF) through a 15 nm filter which can remove both enveloped and non–enveloped viral agents and the second is solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TNBP) and Polysorbate 80 (Tween 80) which inactivates enveloped viral agents such as HIV, HBV and HCV.

The effectiveness of the S/D treatment and nanofiltration procedures for reducing virus content has been assessed using a series of viruses with a range of physico-chemical characteristics. In addition, Fractionation II+III and PEG precipitation further contribute to virus clearance. The results of the viral challenge studies are summarized in Table 5.

Table 5: Log10 Virus Reduction during Manufacture of GLASSIA

Process Step	Enveloped Viruses				Non-enveloped Viruses		
	HIV-1	PRV	BVDV	WNV	HAV	PPV	B19V
Fractionation II + III	4.6	2.1	1.4	ND	1.4	ND	2.3
PEG precipitation	ND	ND	ND	ND	ND	4.35	ND
Nanofiltration	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.04	ND
S/D treatment	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A	N/A
Overall Reduction Factor	> 16.6	> 13.8	> 12.8	> 6.3	> 6.4	8.4	2.3

HIV-1 Human immunodeficiency virus Type 1, WNV West Nile virus, PRV Pseudorabies virus, HAV Hepatitis A virus, BVDV Bovine viral diarrhea virus, PPV Porcine parvovirus, B19V Parvovirus B19

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6: Summary of patient demographics for clinical trials in AATD

Study #	Trial design	Dosage, route of administration and duration	Number of treated subjects (n)	Mean age (Range)	Sex
API-002	Randomized, double-blind, two-arm, multi-center study with a partial cross-over	60 mg/kg body weight for 12 weeks with either GLASSIA or comparator followed by another 12 weeks of GLASSIA only	50	GLASSIA: 55 years (42 – 72 years) Comparator: 56 years (42 - 74 years)	25 Male 25 Female

API-002

A randomized, double-blind trial with a partial cross-over was conducted to compare GLASSIA to a comparator product in 50 Alpha1-PI-deficient subjects. The trial objectives were to demonstrate that the mean trough levels (average of Weeks 7-12) of antigenic and/or functional Alpha1-PI in GLASSIA were not inferior to those of the control product and to determine whether GLASSIA maintained antigenic and/or functional plasma levels of at least 11 microM (57 mg/dL).

For inclusion in the trial, subjects were required to have lung disease related to Alpha1-PI deficiency and 'at-risk' alleles associated with Alpha1-PI plasma levels < 11 microM. Subjects already receiving Alpha1-PI therapy were required to undergo a 5-week wash-out period of exogenous Alpha1-PI prior to dosing.

Fifty subjects received either GLASSIA (33 subjects) or the comparator product (17 subjects) at a dose of 60 mg/kg intravenously per week for 12 consecutive weeks. From Week 13 to Week 24 subjects received open-label weekly infusions of GLASSIA at a dose of 60 mg/kg.

14.2 Study Results

API-002

Trough levels of functional and antigenic Alpha1-PI were measured prior to treatment, at baseline and throughout the trial until Week 24. The serum Alpha1-PI trough levels rose substantially in all subjects by Week 2 and remained stable during Weeks 7 to 12. GLASSIA was shown to be non-inferior to the comparator product.

The lower bounds of the 95% confidence intervals for the difference in means (GLASSIA minus Comparator) were greater than – 3 microM for both antigenic and functional A1PI levels thereby demonstrating the non-inferiority of GLASSIA to comparator. See results in Table 7.

Table 7: Circulating Trough Levels of Antigenic and Functional API (Average of Weeks 7-12) (ITT Population) (Study API-002)

	Antigenic API (microM)		Functional API (microM)	
Statistic	GLASSIA	Comparator	GLASSIA	Comparator
N	33	16	33	16
Mean (SD)	14.7 (1.9)	13.1 (2.5)	12.0 (1.9)	11.4 (2.6)
Median (Range)	14.7 (11.6, 18.5)	12.6 (10.4, 19.2)	11.9 (8.2, 16.9)	11.2 (7.7, 18.0)
95% CI*	0.26, 2.90		-0.61, 1.94	

*The confidence interval (CI) was derived from a t-test stratified by center for the difference GLASSIA - Comparator.
*Non-inferiority was defined as the lower bound of 95%CI for the difference in means between Week 7 and Week 12 (GLASSIA minus Comparator) being greater than -3 µM .

All subjects receiving GLASSIA had mean serum trough antigenic Alpha1-PI levels greater than 11 microM during Weeks 7-12. Ten of 33 subjects (30.3%) receiving GLASSIA had mean trough functional Alpha1-PI levels below 11 microM.

A subset of subjects (n = 7 receiving GLASSIA) underwent broncho-alveolar lavage (BAL) and were shown to have increased levels of antigenic Alpha1-PI in the epithelial lining fluid at Week 10-12 over levels found at baseline.

The clinical efficacy of GLASSIA in influencing the course of pulmonary emphysema or the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated in randomized, controlled clinical trials.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The thrombogenic potential of GLASSIA was assessed after a single IV administration at 200 mg/kg rabbits. GLASSIA was shown not to be thrombogenic in this study.

The acute toxicity of GLASSIA was evaluated in rats and rabbits. A single IV administration of 60 and 640-650 mg/kg and 60 and 600 mg/kg GLASSIA in the rats and rabbits, respectively, resulted in no overt toxicity.

Repeat-dose toxicity of GLASSIA was assessed in rabbits when administered IV daily for 5-days at 300 mg/kg. Overall, five once daily administrations of 300 mg/kg GLASSIA were well tolerated in rabbits. Any potential test article changes were minor in nature and/or of unknown significance and resolved by the end of the 14-day recovery period. No overt toxicity was observed.

Repeat-dose toxicity of GLASSIA was also assessed in Sprague-Dawley rats when administered IV every alternate day for 19 days at a dose of 612 mg/kg. The No-observed-adverse-effect-level was set at 612 mg/kg, which was the highest dose tested and the maximum feasible dose in rats.

No specific local tolerance studies were conducted with GLASSIA, but local tolerance was assessed within the repeat-toxicity studies where intravenous injection of GLASSIA was well-tolerated locally.

A neoantigenicity study was performed in rabbits to assess whether the inclusion of viral removal/inactivation steps in the manufacturing of GLASSIA resulted in protein structural changes and novel epitope presentation. After immunization of rabbits for 25 weeks, blood samples were collected for detection of neoantigenicity. The results indicate that the viral inactivation step in the manufacturing process does not result in neoantigenic changes to GLASSIA.

Carcinogenicity, Mutagenesis, Reproductive Toxicology

Studies with GLASSIA to evaluate carcinogenesis, mutagenesis, or reproductive toxicology have not been conducted.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

GLASSIA®
Alpha-1 Proteinase Inhibitor (Human) Injection
1000 mg / 50 mL Vial

Read this carefully before you start taking **GLASSIA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about GLASSIA.

What is GLASSIA used for?

GLASSIA is a liquid medicine containing human Alpha1-Proteinase Inhibitor (Alpha1-PI) also known as alpha1-antitrypsin (AAT), which is purified from human blood. The main purpose of infusing GLASSIA is to increase the levels of the AAT protein in your blood and lungs. AAT protein protects the lung tissue by blocking certain enzyme-caused damage. Such damage can lead to severe lung disease, such as emphysema.

Limitations of Use:

- The effects of increasing the AAT protein levels with GLASSIA on worsening pulmonary function and progression of emphysema have not been proven in clinical trials.
- The long-term effects of AAT replacement and maintenance therapy with GLASSIA have not been studied.
- GLASSIA is not intended as a therapy in individuals with lung disease other than severe Alpha1 –PI deficiency.

How does GLASSIA work?

This medicine contains the active substance human alpha1-proteinase inhibitor, which is a normal component of the blood and is found in the lung. There, its main function is to protect the lung tissue by limiting the action of a certain enzyme, called neutrophil elastase. Neutrophil elastase can cause damage if its action is not controlled (for example, in case you have an alpha1- proteinase inhibitor deficiency).

What are the ingredients in GLASSIA?

Medicinal ingredients: Alpha$_1$-Proteinase Inhibitor (Human) (A_1-PI)
Non-medicinal ingredients: 0.02M Sodium Phosphate, 0.7% Sodium Chloride, Water for Injection

GLASSIA comes in the following dosage forms:

GLASSIA is supplied in a single-use vial containing approximately 1000 mg of functionally active A1-PI (in 50 mL).

Do not use GLASSIA if:

- you are allergic to alpha1-proteinase inhibitor or to any ingredient in the formulation or component of the container
- your body does not make enough immunoglobulin A (IgA), which could cause you to have an allergic reaction to blood products that contain IgA

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GLASSIA. Talk about any health conditions or problems you may have, including if you:

- You have a history of allergic or other adverse reactions to human alpha1-proteinase inhibitor. Your doctor will inform you about signs of allergic reactions (for example chills, flushing, faster heartbeat, fall in blood pressure, light-headedness, rash, hives, itching, difficulty in breathing or swallowing as well as swelling of your hands, face, or mouth).
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or healthcare professional for advice before taking this medicine.
    - However, as there is no information available regarding the safety of GLASSIA use during pregnancy, if you are pregnant, this medicine should only be given to you with caution.
    - It is unknown whether GLASSIA passes into human milk. If you are breast-feeding, your doctor will discuss with you the risks and benefits of taking this medicine.
    - There are no data concerning the effect on fertility.

Other warnings you should know about:
GLASSIA like other products made from human plasma, part of our blood, may contain viruses or other agents (e.g., the vCJD agent) that can cause infection and illness. However, the processes used to make GLASSIA are specifically designed with the ability to destroy or remove certain viruses if they are present. You should discuss the risks and benefits of this product with your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take GLASSIA:

First infusions should be administered under the supervision of a healthcare professional experienced in the use of human alpha1-proteinase inhibitor or in the treatment of alpha1-proteinase inhibitor deficiency. Subsequent infusions can be administered by a caregiver or by the patient if appropriate training is provided and the use is reviewed at regular intervals. The decision of whether a patient is suitable for home-treatment/self-administration is made by the treating doctor. There are limited data regarding the use of this medicinal product in home-treatment/self-administration. Potential risks associated with home-treatment/self-administration are related to the administration itself as well as to the handling of adverse drug reactions, particularly hypersensitivity.

Do not attempt to do an infusion to yourself unless you or your caregiver have been taught how by your healthcare professional.

Always follow the specific instructions given by your healthcare professional. The steps listed below are general guidelines for using GLASSIA. If you are unsure of the procedures, call your healthcare professional before using.

Prepare a clean flat surface and gather all the materials you will need for the infusion. Check the expiration date and let the vial of GLASSIA warm up to room temperature. Do not apply heat,

place in hot water, or microwave. Wash your hands and put on clean exam gloves. If you are infusing yourself at home, the use of gloves is optional.

1. **Check the vial(s) of GLASSIA**:

- Do not use if the protective cap is missing or broken.
- Look at the color: it should be clear and colorless to yellow-green. Do not use if the solution is cloudy.
- It may contain a few (protein) particles.
- Do not shake the vial(s).

2. **Gather all supplies**

- Gather all supplies: vial(s) of GLASSIA as prescribed and infusion supplies: tourniquet, alcohol swabs, intravenous needle set, vented transfer device(s), 5 micron in-line filter (not provided) and 60 mL sterile syringe(s), sterile in-line needle (not provided), sterile intravenous infusion container (bag) (if necessary), administration infusion set, extension set (if necessary), bandage, tape, sterile gauze, sharps container, IV pole or hook, clean gloves (if necessary) and infusion log.
- If your doctor has prescribed epinephrine pen and/or other supportive care for certain severe allergic symptoms, keep it close at hand during your infusion. Carefully follow your doctor's instructions and training if you have to administer the prescribed medicine for a severe allergic reaction.
- Wash your hands and allow them to dry.
- Apply gloves as directed by your healthcare professional. Open supplies as shown by your healthcare professional.

3. **Prepare the vial(s) for infusion as directed by your healthcare professional:**

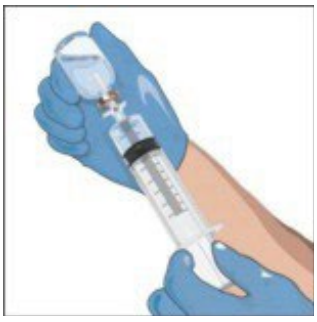
- Remove the protective cap from the vial.

- Wipe the stoppers of each vial that you will need for your dose with a sterile alcohol swab and allow the stopper to dry.

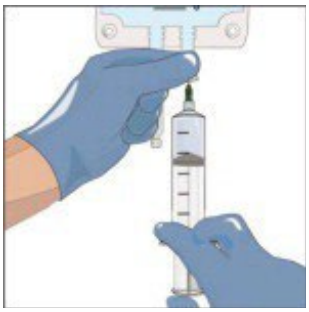
- As directed by your healthcare professional, you may infuse directly from the vial or pool the recommended number of vials of GLASSIA into an empty, sterile container (bag) for intravenous infusion. Use the product within 3 hours of entering the vial(s) or pooling into a sterile container (bag).

If you are pooling into a sterile container (bag):

- Attach a vented spike to a sterile syringe.
- Insert the vented spike into the center of the GLASSIA vial.
- Turn the vial upside down and pull back on the plunger to pull the GLASSIA solution into the syringe(s).



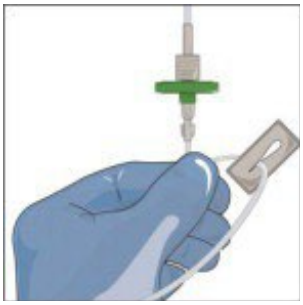
- Remove the syringe from the vented spike.
- Point the syringe tip up and gently push the plunger of the syringe to remove the air. Attach a an in-line needle (not provided) to the filled syringe.
- Wipe the injection port on the empty sterile container (bag) with an alcohol swab.
- Remove protective cover of needle and insert the needle into the injection port and fill the empty bag.



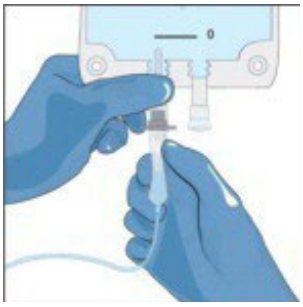
- Repeat these steps, if using multiple vials to achieve the desired dose as directed by your healthcare professional, using a new in-line needle with each vial.

4. Prepare the infusion set:

- Close the roller clamp on the IV infusion set.
- Attach an in-line 5 micron filter to the end of the IV infusion set. Attach an extension set (if necessary).



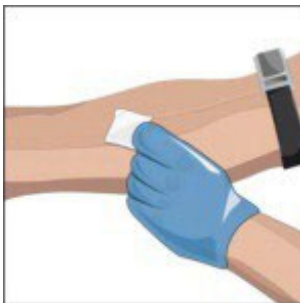
- Remove cap from the IV infusion set spike and insert spike into the infusion port on the bag containing GLASSIA.



- Hang the pooling bag from an IV pole or hook.
- Squeeze the drip chamber until it is half-full and fill the IV infusion set as directed by your healthcare professional.

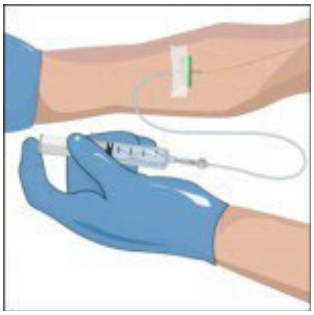
5. Prepare the infusion site(s):

- Select an infusion site as directed by your healthcare professional. Rotate infusion sites as directed.
- Apply a tourniquet and get the injection site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider) and wait for the skin to dry.



6. Insert and secure the intravenous needle set as directed by your healthcare professional.

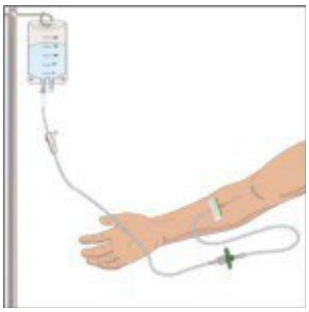
- Release the tourniquet and flush the intravenous needle set (butterfly) with normal saline to check needle placement is correct. If not successful repeat steps as directed by your healthcare professional.



- Remove the saline flush syringe and attach the IV infusion set filled with GLASSIA solution.

7. Follow your healthcare professional's instructions for infusing GLASSIA:

- Open the roller clamp and administer GLASSIA solution at room temperature at a rate as directed by your healthcare professional. The maximum recommended infusion rate for GLASSIA is 0.2 milliliter per kilogram body weight per minute which will take approximately 15 minutes to infuse.



- Check infusion site occasionally throughout the infusion.
- When the infusion is complete, take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes and then apply a sterile bandage.
- Do not recap the intravenous needle set. Place the needle in a hard-walled sharps container for proper disposal. Do not dispose of these supplies in ordinary household trash.

8. **Record the infusion:**

- Write down the product lot number and expiration date in your treatment record/infusion log. Write down the date, time (start and end), dose, site(s) of infusion (to assist in rotating sites) and any reactions after each infusion. Report all reactions to your healthcare professional.
- Throw away all open vials, and any unused solution into a sharps container, as recommended by your healthcare professional.

Usual dose:
Your doctor will determine the amount of GLASSIA that is right for you, and when your treatments should be given.

Overdose:

No cases of suspected overdose have been reported.

If you think you have taken too much GLASSIA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Proceed with your next dose immediately and continue at regular intervals as advised by your doctor or healthcare professional.
Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using GLASSIA?

- A possible side effect to GLASSIA is worsening or flare-up of your chronic obstructive pulmonary disease (COPD) in which your breathing gets worse than usual.
- The most common side effects are headache and upper respiratory tract infections. Other possible side effects of GLASSIA include: cough, sinus infection, chest discomfort, dizziness, increased liver enzymes, shortness of breath, nausea, and fatigue.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Serious allergic reaction (hives, swelling in the mouth or throat, itching, chest tightness, trouble breathing, wheezing, fainting or dizziness)		√	√

These are not all the possible side effects you may feel when taking GLASSIA. If you experience any side effects not listed here, contact your healthcare professional.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store GLASSIA in the refrigerator (2°C to 8°C). Do not freeze.
- You can store GLASSIA at room temperature (up to 25°C) for up to one month. You must use GLASSIA within one month once you remove it from the refrigerator. Do not return GLASSIA to the refrigerator once the product has been stored at room temperature.
- Keep the GLASSIA vial in the box until you are ready to administer the product.

- Check the expiration date on the carton and vial label. Do not use GLASSIA after the expiration date.

Keep out of reach and sight of children.

If you want more information about GLASSIA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website https://www.takeda.com/en-ca. or by calling 1-800-268-2772.

This leaflet was prepared by Takeda Canada Inc.
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