GLASSIA®

FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

GLASSIA®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alpha-1-antitrypsin (AAT) 1 g/50 ml

Excipient with known effect:

Sodium Content : This medicinal product contains about 200mg sodium per bottle of 50 ml, equivalent to 10 % of the WHO recommended maximum daily intake of 2 g sodium for adult.

For the full list of excipients, see section 14.

3. PHARMACEUTICAL FORM

Solution for infusion

4. INDICATIONS AND USAGE

Alpha$_1$-Proteinase Inhibitor (Human), GLASSIA is indicated for chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha$_1$-proteinase inhibitor (Alpha$_1$-PI), also known as alpha$_1$-antitrypsin (AAT) deficiency and clinical evidence of emphysema.

- The effect of augmentation therapy with GLASSIA or any Alpha$_1$-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha$_1$-PI deficiency has not been conclusively 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 Alpha$_1$-PI deficiency has not been established.

5 DOSAGE AND ADMINISTRATION

For intravenous use only.

5.1 Dosage

- Administer 60 mg/kg body weight of GLASSIA once weekly by intravenous infusion.

- Dose ranging studies using efficacy endpoints have not been performed.

5.2 Preparation

1. Use aseptic technique.
2. Allow the product to reach room temperature prior to infusing and administer within three hours of entering the vials.
3. Inspect the vial of GLASSIA. The solution should be clear and colorless to yellow-green and may contain a few protein particles. Discard if the product is cloudy.
4. The product is suitable for infusion directly from the vial or pooled into an empty sterile container for intravenous infusion.
5. Use a vented spike (not supplied) to withdraw the solution from the vial.
6. Then use a needle (not supplied) to transfer the solution into the intravenous infusion container.
7. If using multiple vials to achieve the desired dose, pool Glassia into the infusion container by repeating Steps 5 and 6 with a new vented spike and transfer needle for each vial.

5.3 Administration

For intravenous infusion only.

1. Use aseptic technique.
2. Inspect parenteral products visually for particulate matter and discoloration prior to administration whenever solution and container permit.
3. Administer GLASSIA alone. Do not mix with other agents or diluting solutions.
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 an in-line filter of 1.2 or 5 micron (not supplied) during infusion.
6. Administer GLASSIA within three 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* (8.1)].
9. Following administration, discard all open vials, unused solution and administration equipment.

6 DOSAGE FORMS AND STRENGTHS

GLASSIA is available as a single-use vial containing approximately 1 gram of functional $Alpha_1$-PI in 50 mL of ready to use solution.

7 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 $Alpha_1$-PI products.
- Hypersensitivity to the active substance or to any of the excipients listed in section **14**.

8 WARNINGS AND PRECAUTIONS

8.1 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. Have epinephrine and/or other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

8.2 Transmissible Infectious Agents

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.

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

9 ADVERSE REACTIONS

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.

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety profile of GLASSIA was evaluated in a randomized, double-blind, active-control trial and an open-label, non-parallel, dose-escalation trial, in 65 subjects with pre-augmentation therapy serum Alpha$_1$-PI levels less than 11 microM. In the randomized, double-blind, active-control trial, 50 subjects received weekly infusions of GLASSIA or the comparator Alpha$_1$-PI product, Prolastin, at a dosage of 60 mg/kg for a total of 12 doses after which all subjects remaining in the trial were treated for another 12 weeks with GLASSIA only. Overall, 17 subjects received 12 doses and 32 subjects received 22 – 24 doses of GLASSIA during the trial. (One subject randomized to the comparator Alpha$_1$-PI product did not receive any treatment with GLASSIA during the last 12 weeks of the trial). 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. The population treated in the two trials was 40-74 years old, 54% male, 100% Caucasian.

Tables 1 and 2 compare the adverse reactions reported during the initial 12 weeks (double-blind portion) of the randomized, active comparator trial in all subjects treated with GLASSIA with reactions in the concurrent Prolastin control group. Table 3 compares the frequency of adverse reactions as a percentage of all infusions for GLASSIA and Prolastin-treated subjects over the entire trial period.

Table 1: Number of Subjects/Infusions/Adverse Reactions[1] Occurring during the First 12 Weeks of Treatment

	GLASSIA	**Prolastin**
No. of subjects treated	33	17
No. of infusions	393	190
No. of subjects with serious adverse reactions (%)[1]	1 (3%)	1 (6%)
No. of subjects experiencing an adverse reaction[1] (%)	22 (67%)	15 (88%)
No. of adverse reactions[1]	47	39

[1] An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began within 72 hours following the end of product infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to product administration, or (c) an adverse event for which causality assessment was missing or indeterminate.

Table 2: Adverse Reactions[1] Occurring in > 5% of Subjects during the First 12 Weeks of Treatment

	GLASSIA No. of subjects: 33	**Prolastin** No. of subjects: 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%)	4 (24%)
Upper respiratory tract infection	3 (9%)	0 (0%)
Headache	3 (9%)	3 (18%)
Sinusitis	2 (6%)	1 (6%)
Chest discomfort	2 (6%)	0 (0%)
Dizziness	2 (6%)	0 (0%)
Hepatic enzyme increased	2 (6%)	0 (0%)

[1] An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began within 72 hours following the end of product infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to product administration, or (c) an adverse event for which causality assessment was missing or indeterminate.

Table 3: Adverse Reactions[1] Frequency as a % of all Infusions (> 0.5%)

	GLASSIA[a] No. of infusions: 960	**Prolastin[b]** No. of infusions: 190
Adverse Event (AE)	No. of adverse reactions[1] (AR) (percentage of all infusions)	No. of adverse reactions[1] (AR) (percentage of all infusions)
Upper respiratory tract infection	8 (0.8%)	0 (0.0%)
Headache	6 (0.6%)	3 (1.6%)

[1] An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began within 72 hours following the end of product infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to product administration, or (c) an adverse event for which causality assessment was missing or indeterminate.
[a] Throughout entire 24-week double-blind plus open-label trial period
[b] Throughout initial 12-week double-blind period

Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

During the 12-week double blind portion of the randomized, active comparator trial, 4 subjects (12%) had a total of 7 exacerbations of chronic obstructive pulmonary disease (COPD) during GLASSIA treatment and 5 subjects (29%) had a total of 6 exacerbations of COPD during Prolastin treatment. Seventeen additional exacerbations in 14 subjects (28%) occurred during the 12-week open-label treatment period with GLASSIA. The overall rate of pulmonary exacerbations during treatment with either product was 1.3 exacerbations per subject per year.

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 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.

9.2 Postmarketing Experience

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

Additionally, you should also report to Kamada LTD to email address:
pharmacovigilance@kamada.com

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There is no data with GLASSIA use in pregnant women to inform a drug-associated risk. 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.

10.2 Lactation

Risk Summary

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.

10.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

10.4 Geriatric Use

Clinical trials of GLASSIA included 11 subjects of 65 years of age or older. This number of subjects was not sufficient to determine whether they respond differently from younger subjects. As for all patients, 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.

11 DESCRIPTION

GLASSIA is a sterile, ready to use, liquid preparation of purified human alpha$_1$-proteinase inhibitor (Alpha$_1$-PI), also known as alpha$_1$-antitrypsin (AAT). The solution contains 2% active Alpha$_1$-PI in a phosphate-buffered saline solution. The specific activity of GLASSIA is $\geq$ 0.7 mg functional Alpha$_1$-PI per mg of total protein. Not less than 90% of the Alpha$_1$-PI in GLASSIA is of the monomeric form as measured by size-exclusion chromatography.

GLASSIA is prepared from human plasma by a modified version of the cold ethanol fractionation process and the Alpha$_1$-PI is then purified using chromatographic methods.

Individual plasma units used for production of GLASSIA are tested using 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 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. The results of the viral challenge studies are summarized in Table 4.

Table 4: Log_{10} Virus Reduction during Manufacture of GLASSIA

Process Step	Enveloped Viruses				Non-enveloped Viruses	
	HIV-1	PRV	BVDV	WNV	HAV	PPV
Nanofiltration	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.04
S/D treatment	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A
Global Reduction Factor	> 12.00	> 11.71	> 11.35	> 6.32	> 4.99	4.04

N/A – Not Applicable. The S/D treatment is not relevant for non-enveloped viruses.
ND – Not Done

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GLASSIA administration is intended to inhibit serine proteases such as neutrophil elastase (NE), which is capable of degrading protein components of the alveolar walls and which is chronically present in the lung.

$Alpha_1$-PI deficiency is a chronic, autosomal, co-dominant hereditary disorder characterized by reduced levels of $Alpha_1$-PI in the blood and lungs. Smoking is an important risk factor for the development of emphysema in patients with $Alpha_1$-PI deficiency. Because emphysema affects many, but not all individuals with the more severe genetic variants of $Alpha_1$-PI deficiency (AAT deficiency), augmentation therapy with $Alpha_1$-Proteinase Inhibitor (Human) is indicated only in patients with severe $Alpha_1$-PI deficiency who have clinically evident emphysema.

A large number of phenotypic variants of $Alpha_1$-PI deficiency exist, not all of which are associated with the clinical disease. Approximately 95% of identified $Alpha_1$-PI deficient individuals have the PiZZ variant, typically characterized by $Alpha_1$-PI serum levels < 35% of normal. Individuals with the Pi(null)(null) variant have no $Alpha_1$-PI protein in their serum. Individuals with the lack of, or low, endogenous serum levels of $Alpha_1$-PI, i.e., below 11 μM, manifest a significantly increased risk for development of emphysema above the general population background risk. In addition, PiSZ individuals, whose serum $Alpha_1$-PI levels range from approximately 9 to 23 μM are considered to have moderately increased risk for developing emphysema, regardless of whether their serum $Alpha_1$-PI levels are above or below 11 μM.

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with $Alpha_1$-PI deficiency. However, the efficacy of augmentation therapy in affecting the progression of emphysema has not been demonstrated in randomized, controlled clinical trials. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease

inhibitors. Whether augmentation therapy with GLASSIA or any Alpha$_1$-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been conclusively demonstrated in adequately powered, randomized controlled clinical trials. Although the maintenance of blood serum levels of Alpha$_1$-PI (antigenically measured) above 11 μM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection, this has not been proven. Individuals with severe Alpha$_1$-PI deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with Alpha$_1$-PI above 11 μM have emphysema attributed to Alpha$_1$-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of Alpha$_1$-PI during augmentation therapy.

12.2 Pharmacodynamics

Administration of GLASSIA to patients with Alpha$_1$-PI deficiency augments the level of the deficient protein. Normal individuals have levels of Alpha$_1$-PI greater than 22 μM. The clinical benefit of the increased blood levels of Alpha$_1$-PI at the recommended dose has not been established.

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.

12.3 Pharmacokinetics

A prospective, open-label, uncontrolled multicenter pharmacokinetic trial was conducted in 7 females and 11 males with congenital Alpha$_1$-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. Blood samples for pharmacokinetic study 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 7 days.

The mean results for pharmacokinetic parameters in the 60 mg/kg dosage group are shown in Table 5. The pharmacokinetics of GLASSIA were linear over the dose range of 30-120 mg/kg.

Table 5: Pharmacokinetic Parameters for Functional Alpha$_1$-PI (Dosage 60 mg/kg; n=6)

Pharmacokinetic Parameter	60 mg/kg Dose Group
Terminal Half-Life (h) *	111 ± 33
Area under the curve$_{(0\text{-}168\ h)}$ (mg·h/mL)	89 ± 10
Clearance (mL/h/kg)	0.68 ± 0.1
Volume of Distribution (L)	3.2 ± 0.3

*Any assessment of the clinical relevance of half-life in this trial should be viewed with caution, due to the short duration of blood sampling.

13 CLINICAL STUDIES

A randomized, double-blind trial with a partial cross-over was conducted to compare GLASSIA to a commercially available preparation of Alpha$_1$-PI (Prolastin) in 50 Alpha$_1$-PI-deficient subjects. The trial objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional Alpha$_1$-PI in GLASSIA were not inferior to those of the control product, to determine whether GLASSIA maintained antigenic and/or functional plasma levels of at least 11 microM (57 mg/dL) and to compare Alpha$_1$-PI trough levels (antigenic and functional) over 6 infusions.

For inclusion in the trial, subjects were required to have lung disease related to Alpha$_1$-PI deficiency and 'at-risk' alleles associated with Alpha$_1$-PI plasma levels < 11 microM. Subjects already receiving Alpha$_1$-PI therapy were required to undergo a 5-week wash-out period of exogenous Alpha$_1$-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 all subjects received open-label weekly infusions of GLASSIA at a dose of 60 mg/kg.

Trough levels of functional and antigenic Alpha$_1$-PI were measured prior to treatment, at baseline and throughout the trial until Week 24. The median trough Alpha$_1$-PI values for Weeks 7-12 for subjects receiving GLASSIA were 14.5 microM (range: 11.6 to 18.5 microM) for antigenic and 11.8 microM (range: 8.2 to 16.9 microM) for functional Alpha$_1$-PI. Eleven of 33 subjects (33.3%) receiving GLASSIA had mean steady-state functional Alpha$_1$-PI levels below 11 microM. GLASSIA was shown to be non-inferior to the comparator product.

Serum Alpha$_1$-PI trough levels rose substantially in all subjects by Week 2 and were comparatively stable during Weeks 7 to 12. All subjects receiving GLASSIA had mean serum trough antigenic Alpha$_1$-PI levels greater than 11 microM during Weeks 7-12.

A subset of subjects in both treatment groups (n = 7 for subjects receiving GLASSIA) underwent broncho-alveolar lavage (BAL) and were shown to have increased levels of antigenic Alpha$_1$-PI and Alpha$_1$-PI–- neutrophil elastase complexes in the epithelial lining fluid at Week 10-12 over levels found at baseline, demonstrating the ability of the product to reach the lung.

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.

A prospective, randomized, double-blind, active-controlled, crossover trial was conducted in thirty healthy adult subjects (23 [77%] male and 7 [23%] female; median age of 24 years [range: 19 to 61 years]), each receiving 2 infusions of GLASSIA at a dosage of 60 mg/kg. The objective of the trial was to assess the safety and tolerability of GLASSIA at an intravenous infusion rate of 0.2 mL/kg/min. On Day 1, 15 subjects received GLASSIA at 0.04 mL/kg/min with a simultaneous administration of placebo (2.5% human albumin in normal saline, for the

purpose of masking infusion) at 0.2 mL/kg/min (Cohort 1), and 15 subjects received GLASSIA at 0.2 mL/kg/min with a simultaneous administration of placebo at 0.04 mL/kg/min (Cohort 2). Two weeks later (Day 15), the 15 subjects in Cohort 1 received the second infusion of GLASSIA at 0.2 mL/kg/min with a simultaneous administration of placebo at 0.04 mL/kg/min, and the 15 subjects in Cohort 2 received GLASSIA at 0.04 mL/kg/min with a simultaneous administration of placebo at 0.2 mL/kg/min. Neither efficacy nor exposure (antigenic or functional AAT) was measured in this trial.

14 HOW SUPPLIED/STORAGE AND HANDLING

Each carton of GLASSIA contains a single use vial containing approximately 1 gram of functional Alpha$_1$-PI in 50 mL of solution.

Storage and Handling

- Store GLASSIA at 2°C to 8°C. Do not freeze.
- Product may be stored at room temperatures not exceeding 25°C for up to one month.
- Do not refrigerate once at room temperature.
- Once removed from refrigeration use within one month.
- Keep vial in carton until required for use.
- Do not use after the expiration date.
- The expiry date of the product is indicated on the packaging materials.
- GLASSIA contains no preservatives and no latex.

Excipients:

Sodium phosphate, sodium chloride, water for injection.

Manufactured by: Kamada Ltd.,Beit Kama ,Israel

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