

# NEW ZEALAND DATA SHEET

## 1 GLASSIA (20mg/mL) solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Alpha<sub>1</sub>-Proteinase Inhibitor (Human).

The solution contains 20mg/mL (1000mg in 50mL vial) active Alpha1-PI in a phosphate-buffered saline solution.

For the full list of excipients, see section 6.1.

### *Biological*

GLASSIA is prepared from human plasma obtained from US-licensed plasma collection centers by a modified version of the cold ethanol fractionation process and the Alpha1-PI is then purified using chromatographic methods.

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 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 10,000IU per mL. Nucleic Acid Testing (NAT) for hepatitis A virus (HAV) nucleic acid is also performed on each manufacturing pool used to manufacture the finished product, GLASSIA. 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 the following table.

<i>Log<sub>10</sub>Virus Reduction during manufacture of GLASSIA</i>						
<i>Process Step</i>	<i>Enveloped Viruses</i>				<i>Non-Enveloped Viruses</i>	
	<i>HIV-1</i>	<i>PRV</i>	<i>BVDV</i>	<i>WNV</i>	<i>HAV</i>	<i>PPV</i>
<i>Nanofiltration</i>	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.04
<i>S/D treatment</i>	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A
<i>Global Reduction Factor</i>	> 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  
PRV Pseudorabies virus  
BVDV Bovine viral diarrhoea virus  
WNV West Nile virus  
HAV Hepatitis A virus  
PPV Porcine parvovirus

## 3 PHARMACEUTICAL FORM

Solution for injection.

GLASSIA is a sterile, ready to use, liquid preparation of purified human alpha1-proteinase inhibitor (Alpha1-PI), also known as alpha1-antitrypsin (AAT).

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The solution contains 20mg/mL (1000mg in 50mL vial) active Alpha1-PI in a phosphate-buffered saline solution.

The specific activity of GLASSIA is  $\geq 0.7$ mg functional Alpha1-PI per mg of total protein. Not less than 90% of the Alpha1-PI in GLASSIA is of the monomeric form as measured by size-exclusion chromatography.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Alpha-1-Proteinase Inhibitor (Human), GLASSIA is indicated for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of alpha1-proteinase inhibitor (Alpha1-PI), also known as alpha1-antitrypsin (AAT) deficiency.

- The effect of augmentation therapy with GLASSIA or any Alpha1-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha1-PI 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.

### 4.2 Dose and method of administration

#### For Intravenous Use Only.

Use aseptic technique for all preparation and administration steps.

Administer GLASSIA alone; do not mix with other agents or diluting solutions.

Administer product brought to room temperature within three hours of entering the vials.

#### *Dose/Treatment of congenital alpha1-proteinase inhibitor deficiency*

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

The solution contains 20mg/mL (1000mg in 50mL vial) active Alpha1-PI in a phosphate-buffered saline solution.

#### *Preparation*

1. Inspect the vial of GLASSIA. The solution should be clear and colourless to yellow-green and may contain a few protein particles. Do not use if the product is cloudy. Infusion can be made directly from the vial or, alternatively, vials may be pooled into an empty, sterile container for intravenous infusion using the supplied filter needle. In the latter case, use a vented filter spike (not supplied) to withdraw the material from the vial and then use the supplied 5 micron filter needle to transfer the product into the intravenous infusion container.
2. Administer intravenously to the patient as described in section 4.2.

#### *Method of administration*

1. Inspect parenteral products visually for particulate matter and discoloration prior to administration whenever solution and container permit.
2. When infusing directly from the vials, use a vented filter spike (not supplied). If the contents of vials have been pooled into a sterile intravenous container, use an appropriate intravenous administration set.
3. Always use a 5 micron in-line filter (not supplied) during infusion.

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4. Administer GLASSIA within three hours of entering the vials to avoid the potential ill effect of any inadvertent microbial contamination.
5. Administer GLASSIA at room temperature through an appropriate intravenous administration set at a rate not greater than 0.04mL/kg body weight per minute. The recommended dosage of 60mg/kg takes approximately 60-80 minutes to infuse.
6. 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 until the symptoms subside. You may then resume the infusion at a rate tolerated by the patient.
7. Following administration, discard all open vials, unused solution and administration equipment.

### *Paediatric*

The safety and efficacy of GLASSIA in paediatric patients have not been established.

### *Elderly*

Clinical studies 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.

### *Patient counselling information*

Inform patients of the early signs of hypersensitivity reactions, including hives, generalized urticaria, chest tightness, dyspnoea, wheezing, faintness, hypotension, and anaphylaxis. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

Inform patients that GLASSIA is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk of GLASSIA transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing, see section 2. Symptoms of a possible virus infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhoea, or, in the case of hepatitis, jaundice.

Inform patients that administration of GLASSIA has been demonstrated to raise the plasma level of Alpha1-PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

### **4.3 Contraindications**

GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA.

GLASSIA is contraindicated in individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha1-PI products or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### *Hypersensitivity to IgA*

GLASSIA may contain trace amounts of IgA. Patients with selective or severe IgA deficiency and with known antibodies to IgA, have a greater risk of developing severe hypersensitivity and anaphylactic reactions. Monitor vital signs continuously and observe the patient carefully throughout the infusion.

**IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, DISCONTINUE THE INFUSION IMMEDIATELY.**

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

## *Transmissible infectious agents*

Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. 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 (see section 5.1 for description of viral reduction measures). Despite these measures, such products may still potentially transmit human pathogenic agents. There is also the possibility that unknown infectious agents may be present in such products.

The physician should weigh the risks and benefits of the use of this product and discuss the risks and benefits with the patient.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Shire.

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 studies.

## **4.5 Interaction with other medicines and other forms of interaction**

No interactions with other medicinal products are known.

## **4.6 Fertility, pregnancy and lactation**

### *Fertility*

Long-term studies in animals to evaluate impairment of fertility have not been conducted.

### *Pregnancy*

Pregnancy Category C. Animal reproduction studies have not been conducted with GLASSIA. It is also not known whether GLASSIA can cause foetal harm when administered to pregnant women or can affect reproductive capacity. GLASSIA should be given to a pregnant woman only if clearly needed.

### *Lactation*

It is not known whether Alpha1-PI is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when GLASSIA is administered to a nursing woman.

## **4.7 Effects on ability to drive and use machines**

No effects on the ability to drive and use machines have been observed.

## **4.8 Undesirable effects**

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

The most common medicine-related adverse reactions considered by the investigator to be at least possibly related to GLASSIA administration observed at a rate of > 5% in subjects receiving GLASSIA were headache and dizziness.

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### *Clinical studies experience*

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

A total of 65 subjects have received treatment with intravenous GLASSIA in two clinical studies, both performed in the US. Three subjects participated in both studies. However, because of the large temporal difference between studies (> 5 years) and major difference in study designs, each study was analysed separately without excluding these three subjects who participated in both trials from either study analysis. Thus, safety and efficacy of GLASSIA are reported on all 18 subjects in a Phase I study and all 50 subjects who received GLASSIA in a Phase II/III study, for a total of 68 subjects, representing 65 unique subjects.

In an open label, Phase I non-parallel, dose-escalation study, 18 subjects received a single infusion of GLASSIA at dosages of 30, 60 or 120mg/kg.

In a randomized, Phase II/III double-blind, active-control study, 50 subjects were scheduled to receive weekly infusions of GLASSIA or the comparator Alpha1-PI product, Prolastin, at a dosage of 60mg/kg for a total of 12 doses after which all subjects remaining in the study were treated for another 12 weeks with GLASSIA only. Overall, 17 subjects received 12 doses and 21 subjects received 24 doses of GLASSIA during the study. Eleven subjects received either 22 or 23 doses and one subject did not receive any treatment with GLASSIA during the last 12 weeks of the study.

The population treated with GLASSIA in these two studies was 40 - 74 years old, 54% male, 100% Caucasian and had congenital Alpha1-PI deficiency with clinical evidence of emphysema.

The following table compares the adverse reactions reported during the initial 12 weeks (double-blind portion) of the Phase II/III study occurring in all subjects treated with GLASSIA with reactions in the concurrent Prolastin control group.

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<i>Number of subjects/infusions/adverse reactions<sup>1</sup> occurring during the first 12 weeks of treatment</i>		
	<i>GLASSIA</i>	<i>Prolastin</i>
<i>No. of subjects treated</i>	33	17
<i>No. of infusions</i>	393	190
<i>No. of subjects with related adverse reactions according to investigator causality assessment (%)</i>	6 (18%)	6 (35%)
<i>No. of subjects with serious adverse reactions</i>	1 (3%)	1 (6%)
<i>No. of subjects experiencing an adverse reaction<sup>1</sup> (%)</i>	22 (67%)	15 (88%)
<i>No. of adverse reactions<sup>1</sup> (% of all adverse events)</i>	47 (67%)	39 (85%)
<i>No. of infusions associated with adverse reactions<sup>1</sup> occurring within 72 hours of infusion, (% of infusions)</i>	40 (10%)	35 (18%)

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.

<i>Adverse reactions<sup>1</sup> occurring in &gt; 5% of subjects during the first 12 weeks of treatment</i>		
	<i>GLASSIA No. of subjects: 33</i>	<i>Prolastin No. of subjects: 17</i>
<i>Adverse Event (AE)</i>	No. of subjects with Adverse Reactions <sup>1</sup> (AR) (percentage of all subjects)	No. of subjects with Adverse Reactions <sup>1</sup> (AR) (percentage of all subjects)
<i>Cough</i>	3 (9%)	4 (24%)
<i>Upper respiratory tract infection</i>	3 (9%)	0 (0%)
<i>Headache</i>	3 (9%)	3 (18%)
<i>Sinusitis</i>	2 (6%)	1 (6%)
<i>Chest discomfort</i>	2 (6%)	0 (0%)
<i>Dizziness</i>	2 (6%)	0 (0%)
<i>Hepatic enzyme increased</i>	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.

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<i>Adverse Reactions<sup>1</sup> Frequency as a % of all Infusions (&gt; 0.5%)</i>		
	<i>GLASSIA<sup>a</sup> No. of infusions: 960</i>	<i>Prolastin<sup>b</sup> No. of infusions: 190</i>
<i>Adverse Event (AE)</i>	No. of adverse reactions <sup>1</sup> (AR) (percentage of all infusions)	No. of adverse reactions <sup>1</sup> (AR) (percentage of all infusions)
<i>Upper respiratory tract infection</i>	8 (0.8%)	0 (0.0%)
<i>Headache</i>	6 (0.6%)	3 (1.6%)
<p>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.</p> <p>a Throughout entire 24-week double-blind plus open-label trial period.</p> <p>b Throughout initial 12-week double-blind period.</p>		

During the 12-week double blind portion of the Phase II/III 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.

Most adverse reactions were mild to moderate in severity, although two episodes of headache were severe. One subject experienced a treatment emergent serious adverse reaction (infective exacerbation of COPD), considered possibly related to treatment with GLASSIA due to its temporal association.

Out of 68 subjects treated with GLASSIA during clinical studies, 14 (21%) experienced  $\geq$  one adverse events that were assessed by the investigator as possibly or probably related to treatment, see the following table. A total of 3 subjects (approximately 5%) receiving GLASSIA reported urticaria, irrespective of the investigator's opinion of cause.

<i>Adverse reactions (no. of subjects: 68<sup>a</sup>: combined data from single-dose PK study and 24-week clinical study)</i>	
<i>Adverse Reaction (AR)<sup>b,c</sup></i>	<i>No. of subjects experiencing a related reaction according to investigator causality assessment (percentage of all subjects)</i>
<i>Any event</i>	14 (21%)
<i>Headache</i>	4 (6%)
<i>Dizziness</i>	2 (3%)
<i>Dysgeusia, Influenza-like illness, Lethargy, Pyrexia, Decreased platelet count, Joint swelling, Erythema marginatum, Pruritus, Rash, Urticaria, Hypertension.</i>	1 (1.5%)
<p>*a Three (3) subjects participated in both the single-dose PK study and the 24-week trial, such that 65 unique subjects were administered GLASSIA.</p> <p>b Adverse event assessed related or possibly related to GLASSIA.</p> <p>c Additional adverse reactions classified as unrelated by the investigator but temporally related to administration of GLASSIA might have been causally related to GLASSIA administration.</p>	

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Testing for viral markers for HBV, HCV, HIV-1 and HIV-2 showed no seroconversions during either study.

## *Post-marketing experience*

The following reactions have been identified during post-marketing use of GLASSIA in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to GLASSIA, or a combination of these factors, include: Headache, Dyspnoea, Fatigue and Nausea.

## *Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 Overdose**

No symptoms of overdose have been reported.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or the Poison Information Centre on 131126 in Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Blood and blood forming organs, antihemorrhagics, antifibrinolytics, proteinase inhibitors; ATC Code: B02AB.

#### *Mechanism of action*

Alpha1-PI deficiency is a chronic, autosomal, co-dominant hereditary disorder characterized by reduced levels of Alpha1-PI in the blood and lungs (1, 2). Smoking is an important risk factor for the development of emphysema in patients with Alpha1-PI deficiency (3). 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.

A large number of phenotypic variants of Alpha1-PI deficiency exist, not all of which are associated with the clinical disease. Approximately 95% of identified Alpha1-PI deficient individuals have the PiZZ variant, typically characterized by Alpha1-PI serum levels < 35% of normal. Individuals with the Pi(null)(null) variant have no Alpha1-PI protein in their serum (2, 3). Individuals with the lack of, or low, endogenous serum levels of Alpha1-PI, i.e., below 11 $\mu$ M, manifest a significantly increased risk for development of emphysema above the general population background risk (4, 5). In addition, PiSZ individuals, whose serum Alpha1-PI levels range from approximately 9 to 23 $\mu$ M are considered to have moderately increased risk for developing emphysema, regardless of whether their serum Alpha1-PI levels are above or below 11 $\mu$ M (6).

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with Alpha1-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 Alpha1-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been demonstrated in adequately powered,



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randomized controlled clinical trials. Although the maintenance of blood serum levels of Alpha1-PI (antigenically measured) above 11µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection, this has not been proven. Individuals with severe Alpha1-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 Alpha1-PI above 11µM have emphysema attributed to Alpha1-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of Alpha1-PI during augmentation therapy.

### *Pharmacodynamic effects*

Administration of GLASSIA to patients with Alpha1-PI deficiency augments the level of the deficient protein. Normal individuals have levels of Alpha1-PI greater than 22µM. The clinical benefit of the increased blood levels of Alpha1-PI at the recommended dose has not been established.

GLASSIA has been given provisional consent under Section 23 (s23) of the Medicines Act 1981. This means that further evidence on this medicine is awaited or that there are specific conditions of use.

### 5.2 Pharmacokinetic properties

A prospective, open-label, uncontrolled multicenter pharmacokinetic study was conducted in 7 females and 11 males with Alpha1-PI deficiency, ranging in age from 40 to 69 years. Subjects with congenital Alpha1-PI deficiency received a single dose of GLASSIA either 30mg/kg, 60mg/kg or 120mg/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 60mg/kg dosage group are shown in the following table. The pharmacokinetics of GLASSIA were linear over the dose range of 30 - 120mg/kg.

<i>Pharmacokinetic parameters for functional alpha1-PI (dosage 60mg/kg; n = 6)</i>	
<i>Pharmacokinetic Parameter</i>	<i>60mg/kg Dose Group</i>
<i>Terminal Half-Life (h) *</i>	111 ± 33
<i>Area under the curve<sub>(0-618h)</sub> (mg·h/mL)</i>	89 ± 10
<i>Clearance (mL/h/kg)</i>	0.68 ± 0.10
<i>Volume of Distribution (L)</i>	3.2 ± 0.3
*a	Three (3) subjects participated in both the single-dose PK study and the 24-week trial, such that 65 unique subjects were administered GLASSIA.
b	Adverse event assessed related or possibly related to GLASSIA.
c	Additional adverse reactions classified as unrelated by the investigator but temporally related to administration of GLASSIA might have been causally related to GLASSIA administration.
*	Any assessment of the clinical relevance of half-life in this study should be viewed with caution, due to the short duration of blood sampling.

### *Clinical studies*

A Phase II/III randomized, double-blind study with a partial cross-over was conducted to compare GLASSIA to a commercially available preparation of Alpha1-PI (Prolastin) in 50 Alpha1-PI-deficient subjects. The study objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional Alpha1-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 11µM (57mg/dL) and to compare Alpha1-PI trough levels (antigenic and functional) over 6 infusions.

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For inclusion in the study, subjects were required to have lung disease related to Alpha1-PI deficiency and 'at-risk' alleles associated with Alpha1-PI plasma levels < 11µM. 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 60mg/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 60mg/kg.

Trough levels of functional and antigenic Alpha1-PI were measured prior to treatment, at baseline and throughout the study until Week 24. The median trough Alpha1-PI values for Weeks 7 - 12 for subjects receiving GLASSIA were 14.5µM (range: 11.6 to 18.5µM) for antigenic and 11.8µM (range: 8.2 to 16.9µM) for functional Alpha1-PI. Eleven of 33 subjects (33.3%) receiving GLASSIA had mean steady-state functional Alpha1-PI levels below 11µM. GLASSIA was shown to be non-inferior to the comparator product.

Serum Alpha1-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 Alpha1-PI levels greater than 11µM 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 Alpha1-PI and Alpha1-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. An additional study is planned to evaluate changes in functional Alpha1-PI levels in epithelial lining fluid following administration of GLASSIA and a control Alpha1-PI product.

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.

### 5.3 Preclinical safety data

No toxicological effects due to the solvent detergent reagents, TNBP and Tween 80, used in the virus inactivation procedure are expected since the residual levels are less than 5 and 20ppm, respectively.

#### *Carcinogenesis, mutagenesis, impairment of fertility*

Long-term studies in animals to evaluate carcinogenesis, mutagenesis or impairment of fertility have not been conducted.

#### *Animal toxicology and/or pharmacology*

GLASSIA was evaluated in two single dose general toxicology studies in Sprague-Dawley rats and New Zealand White rabbits and one repeated dose study in New Zealand White rabbits.

In single dose studies, one intravenous dose of 0, 60 and 600mg/kg (rabbits) or 640mg/kg (rats) was administered and the animals were observed for 14 days. There were no changes in body weight, clinical chemistry, haematology and gross pathology that could be attributed to GLASSIA administration.

In the repeated dose study, New Zealand White rabbits received 300mg/kg GLASSIA once daily for 5 consecutive days. Animals were monitored for changes in clinical signs, body weight, clinical chemistry, haematology, necropsy and histopathology on day 1 or 14 after the last administration. A

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minor increase in group mean neutrophils was measured on day 1 after the last GLASSIA administration. Recovery was observed after 14 days.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Inactive ingredients*

- Monobasic sodium phosphate dihydrate
- Sodium chloride
- Water for injection

GLASSIA contains no preservatives and no latex.

### 6.2 Incompatibilities

Administer GLASSIA alone; do not mix with other agents or diluting solutions.

### 6.3 Shelf life

30 months from date of manufacture stored at 2° to 8°C (Refrigerate, do not freeze).

1 month from date of manufacture stored at or below 25°C, with no return to refrigeration permitted.

### 6.4 Special precautions for storage

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

Product may be stored at temperatures not exceeding 25 °C (77 °F) for up to one month.

Product removed from refrigeration must be used within one month.

Keep vial in carton until required for use. Do not use beyond the expiration date printed on the label or carton.

### 6.5 Nature and contents of container

Each carton of GLASSIA contains a single use vial containing approximately 1 gram of functional Alpha1-PI in 50mL (20mg/mL) of solution and a sterile filter needle.

Each vial of GLASSIA has the functional activity stated on the label.

### 6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MEDICINE SCHEDULE

Prescription Only Medicine.

## 8 SPONSOR

GLASSIA is distributed in New Zealand by:

Shire New Zealand Ltd  
C/o Crowe Horwath  
PO Box 158  
Shortland Street  
Auckland 1010

Shire New Zealand Ltd  
C/o Crowe Horwath  
Level 29, 188 Quay Street  
Auckland Central  
Auckland 1010

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Telephone: 0508 169 077.

GLASSIA is manufactured by:  
Kamada Ltd  
Beit Kama  
MP Negev 85325  
ISRAEL.

## 9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:  
DD MONTH YYYY

## 10 DATE OF REVISION OF THE TEXT

(DRAFT) 27 November 2017

## SUMMARY TABLE OF CHANGES

<i>Section changed</i>	<i>Summary of new information</i>
All	Entire document reformatted to new standard format based on the European Summary of Product Characteristics (SPC).
8	Sponsor name and address changed to Shire.
10	Date of <i>Revision of Text</i> updated.

*Based on US PI June 2012 (US Licence no. 1826).*

*Please refer to the Medsafe website ([www.medsafe.govt.nz](http://www.medsafe.govt.nz)) for most recent data sheet.*

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