ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 1,000 mg powder and solvent for solution for infusion.
Respreeza 4,000 mg powder and solvent for solution for infusion.
Respreeza 5,000 mg powder and solvent for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Respreeza 1,000 mg powder and solvent for solution for infusion
One vial contains approximately 1,000 mg of human alpha$_1$-proteinase inhibitor*, as determined by its capacity to neutralize human neutrophil elastase.
After reconstitution with 20 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.
The total protein content is approximately 1,100 mg per vial.

Respreeza 4,000 mg powder and solvent for solution for infusion
One vial contains approximately 4,000 mg of human alpha$_1$-proteinase inhibitor*, as determined by its capacity to neutralize human neutrophil elastase.
After reconstitution with 76 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.
The total protein content is approximately 4,400 mg per vial.

Respreeza 5,000 mg powder and solvent for solution for infusion
One vial contains approximately 5,000 mg of human alpha$_1$-proteinase inhibitor*, as determined by its capacity to neutralize human neutrophil elastase.
After reconstitution with 95 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.
The total protein content is approximately 5,500 mg per vial.

*Produced from the plasma of human donors.

Excipients with known effect
Respreeza contains approximately 1.9 mg sodium per ml of reconstituted solution (81 mmol/l).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

The powder is white to off-white. The solvent is a clear and colourless solution.
The reconstituted solution has an approximate osmolality of 279 mOsmol / kg and a pH of 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha$_1$-proteinase inhibitor deficiency (*e.g.* genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (*e.g.* lower forced expiratory volume per second

(FEV_1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of $alpha_1$-proteinase inhibitor deficiency.

4.2 Posology and method of administration

First infusions should be administered under the supervision of a healthcare professional experienced in the treatment of $alpha_1$-proteinase inhibitor deficiency. Subsequent infusions can be administered by a caregiver or by the patient (see section 4.4).

Posology
The recommended dose of Respreeza is 60 mg / kg body weight (bw) administered once weekly.

Elderly population
The safety and efficacy of Respreeza in elderly patients (65 years of age or older) have not been established in specific clinical trials.

Patients with renal or hepatic impairment
No special investigations have been performed. No alternative dose regimen can be recommended in those patients.

Paediatric population
The safety and efficacy of Respreeza in the paediatric population (below 18 years) have not been established. No data are available.

Method of administration
Respreeza should only be administered intravenously by infusion after reconstitution.
The powder must be reconstituted with water for injections (see instructions on reconstitution in section 6.6) and administered using an intravenous administration set (supplied with the 4,000 and 5,000 package).

The reconstituted solution should be infused intravenously at an infusion rate of about 0.08 ml / kg bw / min. This infusion rate may be adjusted, based upon patient tolerability. The recommended dose of 60 mg / kg bw will take approximately 15 minutes to infuse.
One vial of Respreeza is for single use only.

For detailed information regarding the administration of the reconstituted solution, see the instructions at the end of section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.4).
- IgA deficient patients with known antibodies against IgA, due to the risk of severe hypersensitivity and anaphylactic reactions.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

The recommended infusion rate given under section 4.2 should be adhered to. During the first infusions, patient's clinical state, including vital signs, should be closely monitored throughout the infusion period. If any reaction takes place that might be related to the administration of Respreeza, the rate of infusion should be decreased or the administration should be stopped, as required by the clinical condition of the patient. If symptoms subside promptly after stopping, the infusion may be resumed at a lower rate that is comfortable for the patient.

Hypersensitivity
Hypersensitivity reactions may occur, including in patients who have tolerated previous treatment with human alpha$_1$-proteinase inhibitor.

Respreeza may contain trace amounts of IgA. Patients with selective or severe IgA deficiency can develop antibodies to IgA and, therefore, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

Suspected allergic or anaphylactic type reactions may require immediate discontinuation of the infusion, depending on the nature and severity of the reaction. In case of shock, emergency medical treatment should be administered.

Home-treatment / self-administration
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 handling and administration of the medicinal product as well as to the handling of adverse reactions, particularly hypersensitivity. Patients should be informed of signs of hypersensitivity reactions.

The decision of whether a patient is suitable for home-treatment / self-administration is made by the treating doctor, who should ensure appropriate training is provided (e.g. regarding reconstitution, use of Mix2Vial® set, assembly of intravenous tubing, infusion techniques, maintenance of a treatment diary, identification of adverse reactions and measures to be taken in case such reactions occur) and the use is reviewed at regular intervals.

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation / removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A (HAV) and parvovirus B19 virus.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived proteinase inhibitors.

Smoking
Tobacco smoke is an important risk factor for the development and progression of emphysema. Therefore, cessation of smoking and the avoidance of environmental tobacco smoke are strongly recommended.

Sodium content
Respreeza 1,000 mg powder and solvent for solution for infusion
This medicine contains approximately 37 mg (1.6 mmol) sodium per 1,000 mg Respreeza vial. This is equivalent to 1.9% of the recommended maximum daily dietary intake of sodium for an adult.

Respreeza 4,000 mg powder and solvent for solution for infusion
This medicine contains approximately 149 mg (6.5 mmol) sodium per 4,000 mg Respreeza vial. This is equivalent to 7.4% of the recommended maximum daily dietary intake of sodium for an adult.

Respreeza 5,000 mg powder and solvent for solution for infusion

This medicine contains approximately 186 mg (8.1 mmol) sodium per 5,000 mg Respreeza vial. This is equivalent to 9.3% of the recommended maximum daily dietary intake of sodium for an adult.

That should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
No animal reproduction studies have been conducted with Respreeza and its safety for use in human pregnancy has not been established in controlled clinical trials. Since alpha$_1$-proteinase inhibitor is an endogenous human protein, it is considered unlikely that Respreeza will cause harm to the foetus when given at recommended doses. However, Respreeza should be given with caution to pregnant women.

Breast-feeding
It is unknown whether Respreeza / metabolites are excreted in human milk. The excretion of human alpha$_1$-proteinase inhibitor in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Respreeza should be made, taking into account the benefit of breast-feeding to the child and the benefit of human alpha$_1$-proteinase inhibitor therapy to the woman.

Fertility
No animal fertility studies have been conducted with Respreeza and its effect on human fertility has not been established in controlled clinical trials. Since human alpha$_1$-proteinase inhibitor is an endogenous human protein, no adverse effects on fertility are expected when given at recommended doses.

4.7 Effects on ability to drive and use machines

Dizziness may occur following the administration of Respreeza (see section 4.8). Therefore, Respreeza may have a minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions have been observed during the treatment. In the most serious cases, allergic reactions may progress to severe anaphylactic reactions even when the patient has shown no hypersensitivity to previous administrations (see section 4.4).

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions
The adverse reactions (ARs) collected from six clinical studies in 221 patients and post-marketing experience are presented in the table below according to the MedDRA system organ classification (SOC and Preferred Term (PT) Level). Frequency per patient (based on six months of exposure during clinical trials) has been evaluated according to the following convention: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). The frequency of ARs during post marketing only is considered as “not known (cannot be estimated from the available data)”.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency of adverse reactions (ARs) in clinical studies and post-marketing experience with Respreeza

System organ class (SOC)	Frequency of ARs			
	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Very rare (<1/10,000)	Not known
Blood and lymphatic system disorders				Lymph node pain
Immune system disorders		Hypersensitivity reactions (including tachycardia, hypotension, confusion, syncope, oxygen consumption decreased and pharyngeal oedema)	Anaphylactic reactions	
Nervous system disorders	Dizziness, headache	Paraesthesia	Hypoaesthesia	
Eye disorders				Eye swelling
Vascular disorders		Flushing		
Respiratory, thoracic and mediastinal disorders	Dyspnoea			
Gastrointestinal disorders	Nausea			Lip swelling
Skin and subcutaneous tissue disorders		Urticaria, rash (including exfoliative and generalized)	Hyperhidrosis, pruritus	Face swelling
General disorders and administration site conditions		Asthenia, infusion-site reactions (including infusion site hematoma)	Chest pain, chills, pyrexia	

Paediatric Population
Safety and effectiveness in the paediatric population have not been established. No data are available.

Geriatric population
The safety and efficacy of Respreeza in elderly patients (65 years of age or older) have not been established in clinical trials.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Consequences of overdose are unknown.

In the event of overdose, the patient should be observed closely for the occurrence of adverse reactions and supportive measures should be available as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, proteinase inhibitor, ATC code: B02AB02

Human alpha$_1$-proteinase inhibitor is a normal constituent of human blood. Human alpha$_1$-proteinase inhibitor has a molecular weight of 51 kDa and belongs to the family of serine protease inhibitors.

Mechanism of action
Human alpha$_1$-proteinase inhibitor is understood to be the primary anti-protease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient alpha$_1$-proteinase inhibitor to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of lung tissue by NE. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of NE. However, individuals deficient in endogenous alpha$_1$-proteinase inhibitor are unable to maintain appropriate antiprotease defence and experience more rapid proteolysis of the alveolar walls starting prior to the development of clinically evident chronic obstructive lung disease in the third or fourth decade.

Pharmacodynamic effects
The administration of Respreeza increases and maintains serum levels and lung epithelial lining fluid (ELF) levels of alpha$_1$-proteinase inhibitor leading to a slowdown of the progression of emphysema.

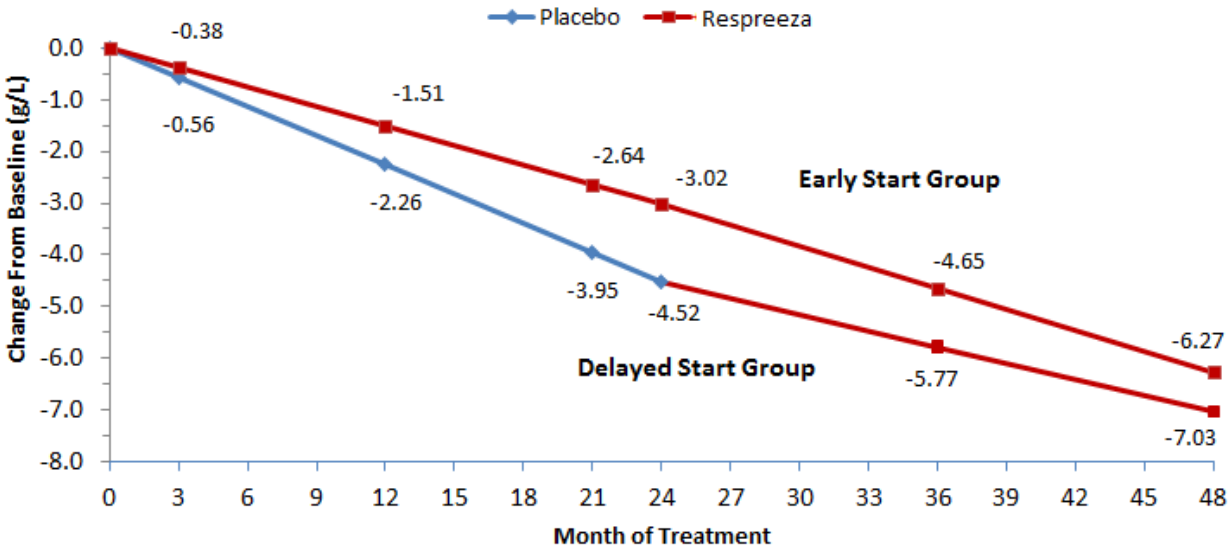
Clinical efficacy and safety

RAPID studies
The safety and efficacy of Respreeza was evaluated in a randomized, double-blind, placebo-controlled, multi-center study (RAPID) followed by a 2-year open-label extension study (RAPID extension study). A total of 180 subjects with alpha$_1$-proteinase inhibitor deficiency characterized by a serum alpha$_1$-proteinase inhibitor level < 11 µM (*i.e.* < 50 mg/dL as determined by nephelometry) and clinical evidence of emphysema, were randomized to receive a weekly 60 mg / kg bw intravenous dose of either Respreeza (93 subjects) or placebo (87 subjects) for up to 24 months. The subjects ranged in age from 31 to 67 years (median age 54 years) with average baseline alpha$_1$-proteinase inhibitor levels of approximately 6.15 µM, and average volume-adjusted CT lung density of 47 g/L /50 g/L for Respreeza and placebo subjects, respectively.
One-hundred forty subjects (76 Respreeza-treated subjects and 64 subjects treated with placebo in the RAPID Study) continued into the RAPID extension study and were treated with a weekly 60 mg / kg bw intravenous dose of Respreeza for up to 24 months.

The studies investigated the effect of Respreeza on the progression of emphysema, assessed by the decline of lung density, measured by computer tomography (CT).
Respreeza-treated subjects demonstrated a consistent pattern of slower lung density decline than those receiving placebo (see Figure 1). The annual rate of lung density decline, as measured by CT scan at total lung capacity (TLC) over 2 years was lower with Respreeza (-1.45 g/L) as compared with placebo (-2.19 g/L), reflecting a 34% reduction ($p = 0.017$, 1-sided).

The RAPID extension study demonstrated that the reduced rate in lung density decline was maintained for subjects continuously treated with Respreeza for 4 years (see Figure 1).

Figure 1: Changes in Lung Density (TLC) from baseline in the RAPID and RAPID Extension studies



Single doses of 120 mg / kg bw have been administered to 137 subjects treated with Respreeza.

Pediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Respreeza in all subsets of the pediatric population in chronic obstructive pulmonary disease (COPD) due to alpha$_1$-proteinase inhibitor deficiency (see section 4.2 for information on pediatric use).

5.2 Pharmacokinetic properties

Four clinical studies were conducted with Respreeza in 89 subjects (59 males and 30 females) to evaluate the effect of Respreeza on serum levels of alpha$_1$-proteinase inhibitor. The subjects ranged in age from 29 to 68 years (median age 49 years). At screening, serum alpha$_1$-proteinase inhibitor levels were between 3.2 and 10.1 µM (mean of 5.6 µM).

A double-blind, randomized, active-controlled, crossover pharmacokinetic study was conducted in 13 males and 5 females with alpha$_1$-proteinase inhibitor deficiency, ranging in age from 36 to 66 years. Nine subjects received a single 60 mg / kg bw dose of Respreeza followed by a comparator product, and 9 subjects received comparator product followed by a single 60 mg / kg bw dose of Respreeza, with a wash-out period of 35 days between doses. A total of 13 post-infusion serum samples were taken at various time points up to Day 21. Table 1 shows the mean results for the Respreeza pharmacokinetic parameters.

Table 1: Pharmacokinetic parameters for alpha$_1$-proteinase inhibitor following a single 60 mg / kg bw dose of Respreeza

Pharmacokinetic Parameter	Mean (standard deviation)*
Area under the curve ($AUC_{0-\infty}$)	144 (±27) µM x day
Maximum concentration (C_{max})	44.1 (±10.8) µM
Terminal half-life ($t_{1/2ß}$)	5.1 (±2.4) days
Total clearance	603 (±129) mL/day
Volume of distribution at steady state	3.8 (±1.3) L

* n=18 subjects.

A population pharmacokinetic analysis was conducted using data from 90 Respreeza-treated subjects from the RAPID trial. The population estimate of mean half-life was 6.8 days. The model predicted mean steady-state concentration was 21.8 µM after a 60 mg /kg bw / week dose. The population

pharmacokinetic analysis did not indicate that there were any significant effects of age, gender, weight, or baseline serum antigenic alpha$_1$-proteinase inhibitor concentrations on the clearance of Respreeza.

Pharmacokinetic/pharmacodynamic relationship
In a double-blind, controlled clinical study to evaluate the safety and biochemical efficacy of Respreeza 44 subjects were randomized to receive 60 mg / kg bw intravenous dose of Respreeza once weekly for 24 weeks. The mean trough serum alpha$_1$-proteinase inhibitor levels at steady state (weeks 7-11) were maintained above 11 μM. The mean (standard deviation) of the steady state trough serum alpha$_1$-proteinase inhibitor level for Respreeza-treated subjects was 17.7 μM (2.5).
In a subgroup of subjects enrolled in this study (10 Respreeza-treated subjects) broncho-alveolar lavage was performed. Epithelial lining fluid measurements (ELF) of alpha$_1$-proteinase inhibitor levels showed a consistent increase following treatment. ELF levels of antigenic alpha$_1$-proteinase inhibitor and alpha$_1$-proteinase inhibitor: NE complexes increased from baseline. Free elastase was immeasurably low in all samples.
Following the completion of the RAPID study, an analysis of achieved median alpha$_1$-proteinase inhibitor levels and lung density decline was conducted. This analysis revealed an inverse linear relationship between trough serum alpha$_1$-proteinase inhibitor levels and the annual decline in lung density as measured by volume adjusted CT scans for subjects receiving 60 mg / kg bw intravenous dose of Respreeza.

5.3 Preclinical safety data

The safety of Respreeza has been assessed in several preclinical studies. Non-clinical data reveal no special risk for humans based on safety pharmacology and short-term toxicity studies. Repeat dose toxicity studies longer than 5 days, reproductive toxicity studies and carcinogenicity studies, have not been performed. Such studies are not considered meaningful due to the production of antibodies against the heterologous human protein in animals. Since human alpha$_1$-proteinase inhibitor is a protein and a physiological constituent of human blood, it is not expected to present carcinogenic, genotoxic, or teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sodium chloride
Sodium dihydrogen phosphate monohydrate
Mannitol

Solvent:
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

Respreeza 1,000 mg powder and solvent for solution for infusion
3 years

Respreeza 4,000 mg powder and solvent for solution for infusion
30 months

Respreeza 5,000 mg powder and solvent for solution for infusion
30 months

From a microbiological point of view, the product should be used immediately after reconstitution. However chemical and physical in-use stability has been demonstrated for 3 h at room temperature (up to 25 °C). Do not freeze the reconstituted solution.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for administration

Respreeza 1,000 mg powder and solvent for solution for infusion
Respreeza 1,000 mg of powder in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.
20 ml of water for injections in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.

Respreeza 4,000 mg powder and solvent for solution for infusion
Respreeza 4,000 mg of powder in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.
76 ml of water for injections in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.

Respreeza 5,000 mg powder and solvent for solution for infusion
Respreeza 5,000 mg of powder in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.
95 ml of water for injections in a glass vial (type I), closed with a rubber (butyl) stopper and an aluminium seal with a plastic flip-off cap.

Presentations
Each pack contains:

Respreeza 1,000 mg powder and solvent for solution for infusion:
One single-use powder vial
One solvent vial of 20 ml water for injections
One transfer set 20/20 (Mix2Vial set) for reconstitution

Respreeza 4,000 mg powder and solvent for solution for infusion:
One single-use powder vial
One solvent vial of 76 ml water for injections
One transfer set 20/20 (Mix2Vial set) for reconstitution
Administration set (inner box):
One IV infusion set
One butterfly set
Three alcohol swabs

Respreeza 5,000 mg powder and solvent for solution for infusion:
One single-use powder vial
One solvent vial of 95 ml water for injections
One transfer set 20/20 (Mix2Vial set) for reconstitution
Administration set (inner box):
One IV infusion set
One butterfly set

Three alcohol swabs

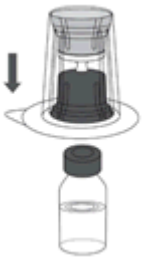
Not all pack sizes may be marketed.

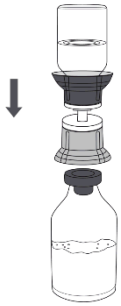
6.6 Special precautions for disposal and other handling

General instructions

- The reconstitution should be performed according to the instructions provided below.
- The product must be reconstituted, administered and handled with caution using aseptic technique to maintain product sterility.
- Do not use provided sterile ancillaries for reconstitution and administration if their package is opened or if they are damaged.
- The powder must be reconstituted with solvent (water for injections).
- Total reconstitution of the powder should be obtained within 5 minutes (1,000 mg presentation) or 10 minutes (4,000 mg and 5,000 mg presentation).
- Inspect the reconstituted solution for particulate matter and discoloration prior to administration.
- The reconstituted solution should be clear, colorless to slightly yellow, and free from visible particles.

Follow the steps provided below for the preparation and reconstitution of Respreeza:

1. Ensure that the Respreeza vial and water for injections vial are at room temperature (up to 25°C).	
2. Remove the plastic flip-off cap from the water for injections vial.	
3. Wipe the rubber stopper of the **water for injections** vial with an antiseptic like an alcohol swab and allow it to dry.	
4. Open the Mix2Vial set by peeling off the lid (Figure 1). Do not remove the Mix2Vial set from the blister package.	 Figure 1
5. Place the **water for injections** vial on an even, clean surface and hold the vial tight. Take the Mix2Vial set together with the blister package and vertically pierce the **water for injections** vial with the **blue** tip of the Mix2Vial set (Figure 2).	 Figure 2
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim and pulling vertically upwards. Make sure that you only pull away the blister package and not the Mix2Vial set (Figure 3).	 Figure 3
7. Remove the plastic flip-off cap from the **Respreeza** vial.	
8. Wipe the rubber stopper of the **Respreeza** vial with an antiseptic like an alcohol swab and allow it to dry.	

9. Place the **Respreeza** vial on an even and firm surface. Invert the water for injections vial with the Mix2Vial set attached and vertically pierce the **Respreeza** vial with the **clear** tip of the Mix2Vial set (Figure 4). The water for injections will automatically flow into the Respreeza vial. NOTE: Ensure all water has transferred into the Respreeza vial.	 Figure 4
10. Follow steps below to remove entire Mix2Vial set from Respreeza vial: • With one hand tightly grasp the Respreeza vial as shown in Figure 5. • With the other hand tightly grasp the water for injections vial and the blue part of the Mix2Vial set. • Bend **the entire Mix2Vial set** to the side until it disconnects from the Respreeza vial (Figure 5). Discard the water for injections vial with the entire Mix2Vial set.	 Figure 5
11. Gently swirl the Respreeza vial until the powder is completely dissolved (Figure 6). DO NOT SHAKE. Take care not to touch the rubber vial stopper.	 Figure 6
12. Inspect visually the reconstituted solution. The solution should be clear, colourless to slightly yellow, and free from visible particles. Do not use solutions that are discoloured, cloudy or have particles.	
13. If more than 1 vial of Respreeza is needed to achieve the required dose, repeat instructions 1 to 12 above using an additional package containing an unused Mix2Vial set. **Use a separate, unused Mix2Vial set, and a water for injections vial for each Respreeza vial.**	
14. The reconstituted solutions can be sequentially administered directly from the vial, or the reconstituted solutions can alternatively be transferred into an infusion container (e.g., empty intravenous bag or glass bottle; (not supplied) via a commercially available intravenous fluid tubing transfer set (not supplied)) prior to administration. Use aseptic technique to transfer the reconstituted solution into an infusion container.	

Administration

The reconstituted solution must be administered using an IV infusion set.

1. Make sure that the air vent cap and the roller clamp of the IV infusion set are closed. VERTICALLY pierce the Respreeza vial with the IV infusion set spike while twisting the IV infusion set spike gently or connect it to an infusion container.
2. Elevate the Respreeza vial/infusion container or hang on an infusion stand.
3. Prime the drip chamber by squeezing it until the Respreeza solution has filled the chamber roughly half-way.

4. Open the air vent cap of the IV infusion set.
5. Slowly open the roller clamp of the IV infusion set and let the Respreeza solution flow until it reaches the end of the tubing with no air bubbles.
6. Close the roller clamp.
7. Disinfect the injection site with an antiseptic like an alcohol swab before carefully inserting the needle into the vein. Make sure that there is no more air in the butterfly tube left.
8. Connect the end of the IV infusion set to the butterfly set and open the roller clamp again.
9. Infuse the reconstituted solution into the vein. The solution should be infused at an infusion rate of about 0.08 ml per kg body weight each min, as determined by your response and your comfort. The recommended dose of 60 mg per kg of body weight will take approximately 15 minutes to infuse.

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

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/001
EU/1/15/1006/002
EU/1/15/1006/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 August 2015
Date of latest renewal: 23 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CSL Behring LLC
Route 50 North 1201 N. Kinzie
Bradley, IL 60915
United States

Name and address of the manufacturer responsible for batch release

CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): A randomized, long-term PAES has been agreed to study the dose-relationship if the higher API levels achieved in the blood might influence the rate of lung density decline and whether that would support an increased dose of 120mg/kg the MAH should conduct and submit the results of a randomized, long term, efficacy study conducted according to an agreed protocol.	Submission of final clinical study report by 31 March 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 1,000 mg powder and solvent for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 1,000 mg
After reconstitution with 20 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

1 single-use powder vial
1 solvent vial of 20 ml water for injections
1 transfer set 20/20 (Mix2Vial set) for reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Respreeza 1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 1,000 mg powder for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 1,000 mg

3. LIST OF EXCIPIENTS

Excipients : Sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1,000 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SOLVENT VIAL

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Respreeza

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Water for injections

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 4,000 mg powder and solvent for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 4,000 mg
After reconstitution with 76 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

1 single-use powder vial
1 solvent vial of 76 ml water for injections
1 transfer set 20/20 (Mix2Vial set) for reconstitution
Administration set (inner box):
1 IV infusion set
1 butterfly set
3 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Respreeza 4,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 4,000 mg powder for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 4,000 mg

3. LIST OF EXCIPIENTS

Excipients : Sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

4,000 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SOLVENT VIAL

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Respreeza

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Water for injections

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

76 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 5,000 mg powder and solvent for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 5,000 mg
After reconstitution with 95 ml solvent, the solution contains approximately 50 mg/ml of human alpha$_1$-proteinase inhibitor.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion

1 single-use powder vial
1 solvent vial of 95 ml water for injections
1 transfer set 20/20 (Mix2Vial set) for reconstitution
Administration set (inner box):
1 IV infusion set
1 butterfly set
3 alcohol swabs

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, 35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Respreeza 5,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT

Respreeza 5,000 mg powder for solution for infusion
Human alpha$_1$-proteinase inhibitor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human alpha$_1$-proteinase inhibitor 5,000 mg

3. LIST OF EXCIPIENTS

Excipients : Sodium chloride, sodium dihydrogen phosphate monohydrate, mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

5,000 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

SOLVENT VIAL

1. NAME OF THE MEDICINAL PRODUCT

Solvent for Respreeza

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Water for injections

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

95 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1006/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton administration set (inner box)

1. NAME OF THE MEDICINAL PRODUCT

Administration set

2. STATEMENT OF ACTIVE SUBSTANCE(S)

-not applicable-

3. LIST OF EXCIPIENTS

-not applicable-

4. PHARMACEUTICAL FORM AND CONTENTS

-not applicable-

5. METHOD AND ROUTE(S) OF ADMINISTRATION

-not applicable-

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

-not applicable-

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-not applicable-

8. EXPIRY DATE

Exp. date

9. SPECIAL STORAGE CONDITIONS

-not applicable-

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-not applicable-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring

12. MARKETING AUTHORISATION NUMBER(S)

-not applicable-

13. BATCH NUMBER

Lot No.

14. GENERAL CLASSIFICATION FOR SUPPLY

-not applicable-

15. INSTRUCTIONS ON USE

-not applicable-

16. INFORMATION IN BRAILLE

-not applicable-

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Respreeza 1,000 mg powder and solvent for solution for infusion
Respreeza 4,000 mg powder and solvent for solution for infusion
Respreeza 5,000 mg powder and solvent for solution for infusion

Human alpha$_1$-proteinase inhibitor

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Respreeza is and what it is used for

What Respreeza is

This medicine contains the active substance human alpha$_1$-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 alpha$_1$-proteinase inhibitor deficiency).

What Respreeza is used for

This medicine is used in adults with known severe alpha$_1$-proteinase inhibitor deficiency (an inherited condition also called alpha$_1$ antitrypsin deficiency) who have developed a lung condition called emphysema.

Emphysema develops when the lack of alpha$_1$-proteinase inhibitor results in a condition in which neutrophil elastase is not being properly controlled, damaging the tiny air sacs in the lungs through which oxygen passes into the body. Because of this damage, the lungs do not work properly.

Using this medicine regularly increases the blood and lung levels of alpha$_1$-proteinase inhibitor, thus slowing the progression of emphysema.

2. What you need to know before you use Respreeza

Do NOT take Respreeza
- if you are allergic to human alpha$_1$-proteinase inhibitor or any of the other ingredients of this medicine (listed in section 6).

- if you have been found to have a deficiency of certain blood proteins called immunoglobulin type A (IgA) and have developed antibodies against them.

Warnings and precautions

➔ Talk to your doctor or healthcare professional before using Respreeza.

Information on allergic reactions: when slowing or stopping the infusion may be required?
You may be allergic to human alpha$_1$-proteinase inhibitor even if you have previously received human alpha$_1$-proteinase inhibitors and had tolerated them well. In some cases, severe allergic reactions may occur. 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) (see also section 4).

➔ Tell your doctor or healthcare professional **immediately** if you notice such reactions during the infusion of this medicine. Depending on the nature and severity of the reaction, your doctor may decide whether to slow or stop the infusion completely and start the appropriate treatment.

➔ In case of self-administration / home-treatment, stop the infusion **immediately** and contact your doctor or healthcare professional.

Information on safety with respect to infections
Respreeza is made from human blood plasma (this is the liquid part of the blood with the blood cells removed).
Because blood can carry infections, when medicines are made from human blood or plasma certain measures are put in place to prevent these from being present in the medicine and passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of samples of donated blood and plasma to try to avoid use of material with signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

The measures taken are considered effective for viruses such as human immunodeficiency virus (HIV), hepatitis A virus, hepatitis B virus, hepatitis C virus, and parvovirus B19 virus.

However, despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived proteinase inhibitors.

➔ It is strongly recommended that every time you receive a dose of Respreeza the name and batch number of the product are recorded in order to maintain a record of the batches used.

Smoking
Since tobacco smoke is an important risk factor for the development and progression of emphysema, you are strongly advised to stop smoking and avoid passive smoking.

Children and adolescents

This medicine is not for use in children or adolescents below 18 years of age.

Other medicines and Respreeza

➔ Tell your doctor or healthcare professional if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility

➔ 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.

Since alpha$_1$-proteinase inhibitor is a normal component of human blood, recommended dose of this medicine is not expected to cause harm to the developing foetus. However, as there is no information available regarding the safety of Respreeza use during pregnancy, if you are pregnant, this medicine should only be given to you with caution.
It is unknown whether Respreeza 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 but as alpha$_1$-proteinase inhibitor is a normal component of human blood, no adverse effects on fertility are expected if you use Respreeza at the recommended dose.

Driving and using machines

Dizziness may occur after the administration of this medicine. If you experience dizziness, you should not drive or use machines until the dizziness has passed (see section 4).

Respreeza contains sodium

This medicinal product contains approximately 37 mg sodium per 1,000 mg Respreeza vial, 149 mg sodium per 4,000 mg Respreeza vial and 186 mg sodium per 5,000 mg Respreeza vial, equivalent to 1.9%, 7.4% and 9.3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult. Your doctor or healthcare professional will take that into consideration if you are on a controlled sodium diet.

3. How to use Respreeza

After reconstitution, Respreeza is given by infusion into a vein. A healthcare professional experienced in the treatment of alpha$_1$-proteinase inhibitor deficiency will supervise the first infusions.

Home treatment / Self-administration
After the first infusions, you or your caregiver might also administer Respreeza, but only after receiving adequate training. If your doctor decides that you are suitable for such home-treatment / self-administration, he or she will instruct you in:

- how to prepare and give this medicine (see the illustrated instructions at the end of this leaflet in "Information for health-care professionals and for patients suitable for home-treatment / self-administration"),
- how to keep the product sterile (aseptic infusion techniques),
- how to keep a treatment diary,
- how to identify side effects, including signs of allergic reactions, and measures to be taken in case such effects occur (see also section 2 and section 4).

Your doctor or your healthcare professional will regularly review your / your caregiver's infusion technique to ensure continued appropriate handling.

Dose
The amount of Respreeza you are given is based on your body weight. The recommended dose is 60 mg per kg of body weight and should be administered once per week. The infusion solution is normally given over about 15 minutes (about 0.08 ml of solution per kg body weight each min). Your doctor will determine the appropriate infusion rate for you by taking into account your weight and your tolerability to infusion.

If you use more Respreeza than you should
Consequences of an overdose are unknown.
➔ Tell your doctor or healthcare professional if you think you have used more Respreeza as you should. He or she will take the appropriate measures.

If you forget to use Respreeza
➔ 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.

If you stop using Respreeza
➔ Do no stop using this medicine without consulting your doctor or healthcare professional. If treatment with Respreeza is stopped, your condition may worsen.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Such side effects may occur even if you previously received human alpha$_1$-proteinase inhibitors and had tolerated them well.

Some side effects may be serious:
Uncommonly (may affect up to 1 in 100 people), allergic reactions have been observed. They may progress in some very rare cases (may affect up to 1 in 10,000 people) to severe allergic reactions even when you have shown no signs of allergy on previous infusions.
➔ Tell your doctor or healthcare professional **immediately** if you notice any sign 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) during the administration of Respreeza. Depending on the nature and severity of the reaction, your doctor or healthcare professional may decide whether to slow or stop the administration completely and give appropriate treatment for the reaction.
In case of self-administration / home-treatment, stop the infusion **immediately** and contact your doctor or healthcare professional.

The other side effects may include:

Commonly (may affect up to 1 in 10 people)
Dizziness, headache, shortness of breath (dyspnoea), nausea.

Uncommonly (may affect up to 1 in 100 people)
Altered sense of touch like burning, tingling or feeling of numbness in your hands, arms, legs, or feet (paraesthesia), flushing, hives (urticaria), scaly rash and rash all over the body, physical weakness (asthenia), infusion-site reactions (such as burning, stinging, pain, swelling or redness at the infusion site (haematoma)).

Very rarely (may affect up to 1 in 10,000 people)
Decreased sense of touch like burning, tingling or feeling of numbness in your hands, arms, legs, or feet (hypoaesthesia), excessive sweating (hyperhidrosis), itching, chest pain, chills, fever (pyrexia).

Frequency not known (frequency cannot be estimated from the available data)
Pain to the lymph glands (oval-shaped masses of tissue that are distributed throughout the body and which may be palpable for example in the armpit, groin or neck), swollen face, swollen eyes and lips.

Reporting of side effects
➔ If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the

national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Respreeza

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the outer carton and the vial labels after EXP. The expiry date refers to the last day of that month.
Do not store above 25 °C. Do not freeze.
After reconstitution, the solution should be used immediately. If this is not possible, solutions can be stored up to 3 hours at room temperature (up to 25 °C). Do not freeze the reconstituted solution.

6. Contents of the pack and other information

What Respreeza contains

The **active substance** is human alpha$_1$-proteinase inhibitor. One vial contains approximately 1,000 mg, 4,000 mg or 5,000 mg of human alpha$_1$-proteinase inhibitor.
The **other ingredients** are sodium chloride, sodium dihydrogen phosphate monohydrate and mannitol (see section 2).
Solvent: Water for injections.

What Respreeza looks like and contents of the pack

This medicine is a white to off-white powder.
After it has been reconstituted with water for injections, the solution should be clear, colourless to slightly yellow and free from visible particles.

Presentations

One pack contains:

Respreeza 1,000 mg powder and solvent for solution for infusion:
- 1 single-use powder vial
- 1 solvent vial of 20 ml water for injections
- 1 transfer set 20/20 (Mix2Vial set) for reconstitution

Respreeza 4,000 mg powder and solvent for solution for infusion:
- 1 single-use powder vial
- 1 solvent vial of 76 ml water for injections
- 1 transfer set 20/20 (Mix2Vial set) for reconstitution
  Administration set (inner box):
- 1 IV infusion set
- 1 butterfly set
- 3 alcohol swabs

Respreeza 5,000 mg powder and solvent for solution for infusion:
- 1 single-use powder vial
- 1 solvent vial of 95 ml water for injections
- 1 transfer set 20/20 (Mix2Vial set) for reconstitution
  Administration set (inner box):
- 1 IV infusion set
- 1 butterfly set
- 3 alcohol swabs

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

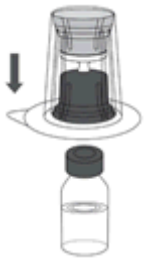
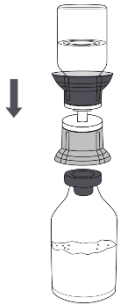
The following information is intended for health-care professionals and for patients suitable for home-treatment / self-administration

General instructions

- The reconstitution should be performed according to the instructions provided below.
- The product must be reconstituted, administered and handled with caution using aseptic technique to maintain product sterility.
- Do not use provided sterile ancillaries for reconstitution and administration if their package is opened or if they are damaged.
- The powder must be reconstituted with solvent (water for injections).
- Total reconstitution of the powder should be obtained within 5 minutes (1,000 mg presentation) or 10 minutes (4,000 mg and 5,000 mg presentation).
- Inspect the reconstituted solution for particulate matter and discoloration prior to administration.
- The reconstituted solution should be clear, colorless to slightly yellow, and free from visible particles.

Follow the steps provided below for the preparation and reconstitution of Respreeza:

1. Ensure that the Respreeza vial and water for injections vial are at room temperature (up to 25°C).	
2. Remove the plastic flip-off cap from the water for injections vial.	
3. Wipe the rubber stopper of the **water for injections** vial with an antiseptic like an alcohol swab and allow it to dry.	
4. Open the Mix2Vial® set by peeling off the lid (Figure 1). Do not remove the Mix2Vial set from the blister package.	 Figure 1
5. Place the **water for injections** vial on an even, clean surface and hold the vial tight. Take the Mix2Vial set together with the blister package and	

vertically pierce the **water for injections** vial with the **blue** tip of the Mix2Vial set (Figure 2).	 Figure 2
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim and pulling vertically upwards. Make sure that you only pull away the blister package and not the Mix2Vial set (Figure 3).	 Figure 3
7. Remove the plastic flip-off cap from the **Respreeza** vial.	
8. Wipe the rubber stopper of the **Respreeza** vial with an antiseptic like an alcohol swab and allow it to dry.	
9. Place the **Respreeza** vial on an even and firm surface. Invert the water for injections vial with the Mix2Vial set attached and vertically pierce the **Respreeza** vial with the **clear** tip of the Mix2Vial set (Figure 4). The water for injections will automatically flow into the Respreeza vial. NOTE: Ensure all water has transferred into the Respreeza vial.	 Figure 4
10. Follow steps below to remove entire Mix2Vial set from Respreeza vial: • With one hand tightly grasp the Respreeza vial as shown in Figure 5. • With the other hand tightly grasp the water for injections vial and the blue part of the Mix2Vial set. • Bend **the entire Mix2Vial set** to the side until it disconnects from the Respreeza vial (Figure 5). Discard the water for injections vial with the entire Mix2Vial set.	 Figure 5
11. Gently swirl the Respreeza vial until the powder is completely dissolved (Figure 6). DO NOT SHAKE. Take care not to touch the rubber vial stopper.	 Figure 6

12. Inspect visually the reconstituted solution. The solution should be clear, colourless to slightly yellow, and free from visible particles. Do not use solutions that are discoloured, cloudy or have particles.
13. If more than 1 vial of Respreeza is needed to achieve the required dose, repeat instructions 1 to 12 above using an additional package containing an unused Mix2Vial set. **Use a separate, unused Mix2Vial set, and a water for injections vial for each Respreeza vial.**
14. The reconstituted solutions can be sequentially administered directly from the vial, or the reconstituted solutions can alternatively be transferred into an infusion container (e.g., empty intravenous bag or glass bottle; (not supplied) via a commercially available intravenous fluid tubing transfer set (not supplied)) prior to administration. Use aseptic technique to transfer the reconstituted solution into an infusion container.

Administration

The reconstituted solution must be administered using an IV infusion set (supplied with the 4,000 and 5,000 package).

1. Make sure that the air vent cap and the roller clamp of the IV infusion set are closed. VERTICALLY pierce the Respreeza vial with the IV infusion set spike while twisting the IV infusion set spike gently or connect it to an infusion container.
2. Elevate the Respreeza vial/infusion container or hang on an infusion stand.
3. Prime the drip chamber by squeezing it until the Respreeza solution has filled the chamber roughly half-way.
4. Open the air vent cap of the IV infusion set.
5. Slowly open the roller clamp of the IV infusion set and let the Respreeza solution flow until it reaches the end of the tubing with no air bubbles.
6. Close the roller clamp.
7. Disinfect the injection site with an antiseptic like an alcohol swab before carefully inserting the needle into the vein. Make sure that there is no air in the butterfly tube left.
8. Connect the end of the IV infusion set to the butterfly set and open the roller clamp again.
9. Infuse the reconstituted solution into the vein. The solution should be infused at an infusion rate of about 0.08 ml per kg body weight each min, as determined by your response and your comfort. The recommended dose of 60 mg per kg of body weight will take approximately 15 minutes to infuse.

One vial of Respreeza is for single use only.

Any unused medicinal product or waste material should be disposed as instructed by your doctor or healthcare professional.