**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains approximately 1,000 mg of human alpha$_1$-proteinase inhibitor*, as determined by its capacity to neutralize human neutrophil elastase (NE).

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 1100 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.

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

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.

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 filtered during administration using an intravenous administration set with a suitable infusion filter (recommended pore size 5 micrometers (µm); not supplied).
The reconstituted solution should be infused intravenously using a separate dedicated infusion line 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 the package leaflet.

## 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

The recommended infusion rate given under section 4.2 should be adhered. 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.

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 transfer device or filter, 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.

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

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 contains approximately 1.9 mg (<1 mmol) sodium per ml of reconstituted solution. 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).

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) 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 |

| 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 |
| General disorders and administration site conditions | | Asthenia, infusion-site reactions (including infusion site hematoma) | Chest pain, chills, pyrexia | |

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.

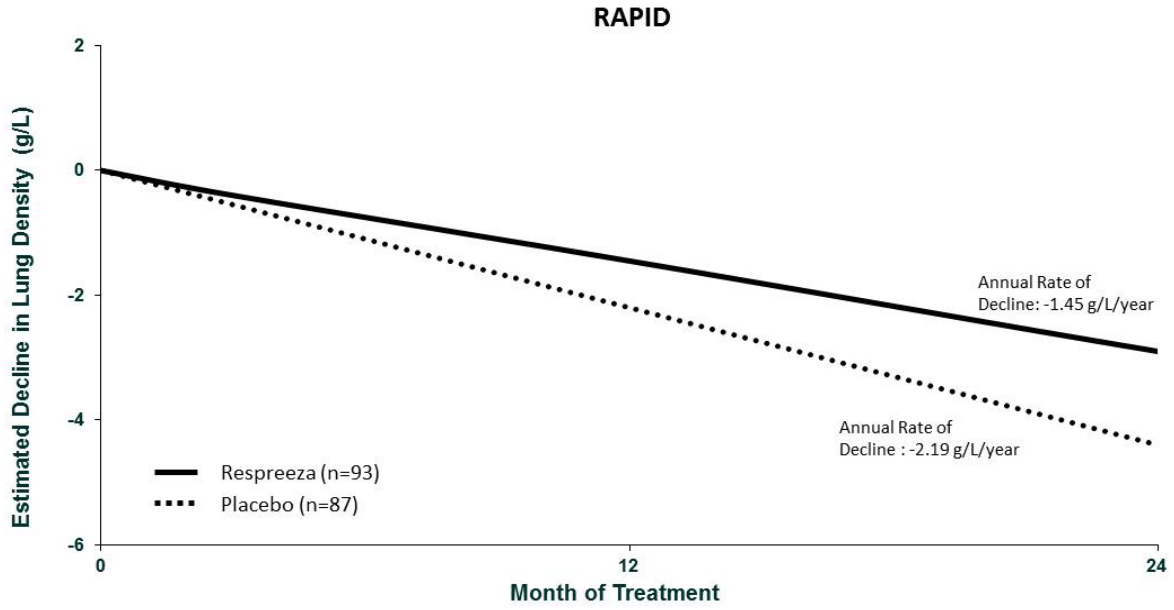
Pharmacodynamic effects
The administration of Respreeza increases and maintains serum levels and lung epithelial lining fluid (ELF) levels of alpha$_1$-proteinase inhibitor leading to a slowdown of the progression of emphysema.

Clinical efficacy and safety

*RAPID study*
The safety and efficacy of Respreeza was evaluated in a randomized, double-blind, placebo-controlled, multi-center study (RAPID). 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 study investigated the effect of Respreeza on the progression of emphysema, assessed by the decline of lung density, measured by computer tomography (CT). 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.
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).

**Figure 1: Changes in Lung Density (TLC) from baseline in the RAPID study**




Single doses of 120 mg / kg bw have been administered to 75 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) bronco-alveolar lavage have been 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 unmeasurably 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

3 years.
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

1,000 mg of powder in a glass vial (type I), closed with a rubber (bromobutyl) 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 (chlorobutyl) stopper and an aluminium seal with a plastic flip off cap.

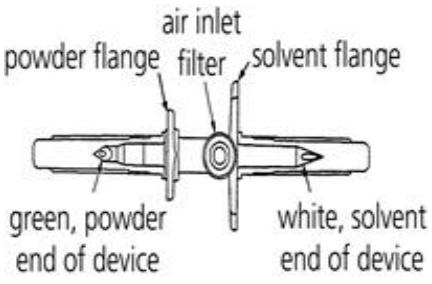
Each pack contains:
One powder vial
One solvent vial
One vented transfer device.

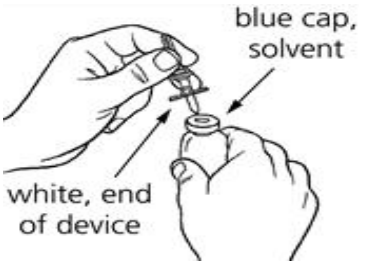
## 6.6 Special precautions for disposal and other handling

The product must be reconstituted, administered and handled with caution using aseptic technique to maintain product sterility.

Reconstitution using the transfer device and solvent vial:
The powder must be reconstituted with 20 ml of solvent (water for injections). Total reconstitution should be obtained within 5 minutes.

➔ Please follow the instructions given below:

<table>
<tr><td>Notes on using the transfer device:<br>• The transfer device provided in the Respreeza carton has a white end (for the solvent) with a double orifice and a green end (for the powder) with a single orifice.<br>• Incorrect use of the transfer device will result in loss of vacuum and prevent transfer of the solvent, thereby prolonging or preventing reconstitution of Respreeza.<br>• The transfer device is sterile. Once the protective covers have been removed (Steps 3 and 4), do not touch the exposed ends of the spikes.</td><td> 
</td></tr>
<tr><td colspan="2">1. Ensure that the powder vial (green cap) and solvent vial (blue cap) are at room temperature (up to 25°C).<br>This can be done either by leaving the vials at room temperature for about an hour or by holding them in your hands for a few minutes.</td></tr>
<tr><td colspan="2">2. Remove the plastic flip-top caps from each of the vials being used. Clean each of the rubber stoppers with antiseptic solution and allow them to dry.</td></tr>
</table>

| | |
|---|---|
| 3. Remove the protective cover from the white end of the transfer device. Place the solvent vial on a flat surface and insert the white end of the transfer device into the center of the stopper of the upright solvent vial (blue cap). |  |
| 4. Place the powder vial (green cap) on a flat surface. Remove the protective cover from the green end of the transfer device. Invert the solvent vial with the attached transfer device and, gently, insert the green end of the transfer device into the center of the rubber stopper of the upright powder vial (green top). The flange of the transfer device should rest on the surface of the stopper so that the solvent flows into the powder vial. |  |
| 5. Allow the solvent to flow into the powder vial. This happens automatically because of a vacuum in the powder vial. If there is no vacuum in the vial, the solvent will not flow into the powder vial. In this case, do not use the product. | |
| 6. During solvent transfer, wet the powder completely by gently tilting the powder vial. | |
| 7. When solvent transfer is complete, withdraw the transfer device from the powder vial and discard the solvent vial and transfer device. | |
| 8. Gently swirl the powder vial until the powder is completely dissolved. **Do not shake to avoid foaming.** |  |
| 9. Inspect visually the reconstituted solution. The solution should be clear, colorless to slightly yellow, and free from visible particles. Do not use solutions that are discoloured, cloudy or have particles. | |
| 10. As more than 1 vial of powder will be needed to achieve the required dose, repeat instructions 1 to 9 above using an additional package containing a transfer device. **Do not reuse the transfer device**. | |
| 11. Use aseptic technique to transfer the reconstituted solutions from the vials into the administration container (e.g. empty intravenous bag or glass bottle; not supplied) via a commercially available intravenous tubing transfer set (not supplied). | |

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

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 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**

The requirements for submission of periodic safety update reports 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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 powder vial
1 solvent vial
1 vented transfer device 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

**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

1000 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

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**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.

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 medicine contains 1.9 mg sodium per ml of reconstituted solution. 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.

**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, shortness of breath (dyspnea), nausea, 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 (hematoma)).

**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 (see details

below). By reporting side effects you can help provide more information on the safety of this medicine.

**UK:**
Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

**Ireland:**
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
Email: medsafety@hpra.ie

**Malta**
ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

## 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 alpha$_1$-proteinase inhibitor. One vial contains approximately 1,000 mg of alpha$_1$-proteinase inhibitor.
The **other ingredients** are sodium chloride, sodium dihydrogen phosphate monohydrate and mannitol (see last paragraph of 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.

One pack contains:
- 1 vial with powder
- 1 vial with 20 ml water for injections
- 1 transfer device for reconstitution

**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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Tél/Tel: +32 15 28 89 20

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

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

Reconstitution and administration of Respreeza

The product must be reconstituted, administered and handled with caution **using aseptic technique to maintain product sterility.**

➔ Please follow the instructions given below:

Reconstitution
The powder must be reconstituted with 20 ml of solvent (water for injections). Total reconstitution should be obtained within 5 minutes.

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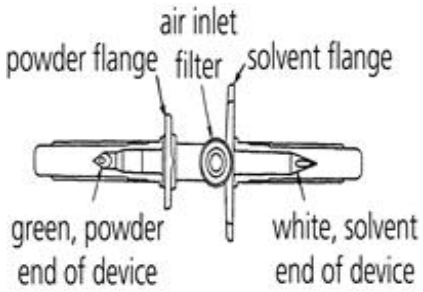
| Notes on using the transfer device:<br>• The transfer device provided in the Respreeza carton has a white end (for the solvent) with a double orifice and a green end (for the powder) with a single orifice.<br>• Incorrect use of the transfer device will result in loss of vacuum and prevent transfer of the solvent, thereby prolonging or preventing reconstitution of Respreeza.<br>• The transfer device is sterile. **Once the protective covers have been removed** (Steps 3 and 4), **do not touch the exposed ends of the spikes.** |  |
| 1. Ensure that the powder vial (green cap) and solvent vial (blue cap) are at room temperature (up to 25°C).<br>This can be done either by leaving the vials at room temperature for about an hour or by holding them in your hands for a few minutes. | |
| 2. Remove the plastic flip-top caps from each of the vials being used. Clean each of the rubber stoppers with antiseptic solution and allow them to dry. | |

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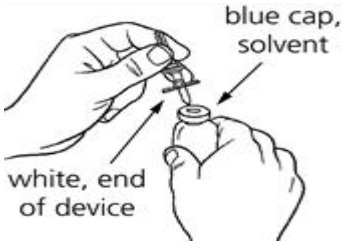
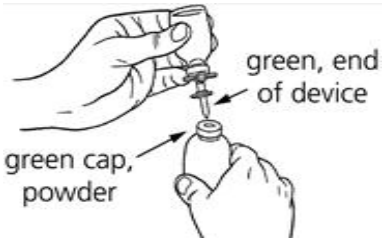
| 3. Remove the protective cover from the white end of the transfer device. Place the solvent vial on a flat surface and insert the white end of the transfer device into the center of the stopper of the upright solvent vial (blue cap). |  |
| 4. Place the powder vial (green cap) on a flat surface. Remove the protective cover from the green end of the transfer device. Invert the solvent vial with the attached transfer device and, gently, insert the green end of the transfer device into the center of the rubber stopper of the upright powder vial (green top). The flange of the transfer device should rest on the surface of the stopper so that the solvent flows into the powder vial. |  |
| 5. Allow the solvent to flow into the powder vial. This happens automatically because of a vacuum in the powder vial. If there is no vacuum in the vial, the solvent will not flow into the powder vial. In this case, do not use the product. | |
| 6. During solvent transfer, wet the powder completely by gently tilting the powder vial. | |
| 7. When solvent transfer is complete, withdraw the transfer device from the powder vial and discard the solvent vial and transfer device. | |
| 8. Gently swirl the powder vial until the powder is completely dissolved. **Do not shake to avoid foaming.** |  |
| 9. Inspect visually the reconstituted solution. The solution should be clear, colorless to slightly yellow, and free from visible particles. Do not use solutions that are discoloured, cloudy or have particles. | |
| 10. As more than 1 vial of powder will be needed to achieve the required dose, repeat instructions 1 to 9 above using an additional package containing a transfer device. **Do not reuse the transfer device**. | |
| 11. Use aseptic technique to transfer the reconstituted solutions from the vials into the administration container (e.g. empty intravenous bag or glass bottle; not supplied) via a commercially available intravenous tubing transfer set (not supplied). | |

Administration

The reconstituted solution must be filtered during administration using a suitable infusion filter (recommended pore size 5 micrometers; not supplied) and an intravenous administration set (not supplied).

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| 1. Attach the administration set to the administration container.<br>Make sure that the roller clamp on the administration set is closed.<br>Elevate the administration container (if intravenous bag, hang on an intravenous. pole).<br>Prime the chamber by squeezing the drip chamber until Respreeza has filled the chamber half-way.<br>Slowly open the roller clamp on the administration set and let Respreeza flow until it reaches the end of the tubing with no air bubbles.<br>Close the roller clamp. |
| 2. Attach the 5 micrometers filter onto the end of the administration set.<br>Again open the roller clamp and let Respreeza flow until the filter is saturated. |
| 3. Connect the other end of the filter to the injection set (e.g. butterfly / winged infusion needle or infusion catheter). |

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| 4. Inject/infuse the reconstituted solution into the vein following the instructions given to you by your doctor. 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. |
| 5. If you notice that the infusion stops or slows, you may need to change the filter as it can be clogged. Repeat then the steps 2-4. |

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.