ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 400 Units* of velaglucerase alfa**.
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

*An enzyme unit is defined as the amount of enzyme that is required to convert one micromole of p-nitrophenyl β-D-glucopyranoside to p-nitrophenol per minute at 37 ºC.
**produced in an HT-1080 human fibroblast cell line by recombinant DNA technology.

Excipient with known effect

Each vial contains 12.15 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VPRIV is indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.

4.2 Posology and method of administration

VPRIV treatment should be supervised by a physician experienced in the management of patients with Gaucher disease.

Posology

The recommended dose is 60 Units/kg administered every other week.

Dose adjustments can be made on an individual basis based on achievement and maintenance of therapeutic goals. Clinical studies have evaluated doses ranging from 15 to 60 Units/kg every other week. Doses higher than 60 Units/kg have not been studied.

Patients currently treated with imiglucerase enzyme replacement therapy for type 1 Gaucher disease may be switched to VPRIV, using the same dose and frequency.

Special populations

Elderly (≥65 years old)
Elderly patients may be treated within the same dose range (15 to 60 units/kg) as other adult patients (see section 5.1).

Renal impairment
No dosing adjustment is recommended in patients with renal impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of velaglucerase alfa (see section 5.2).

Hepatic impairment
No dosing adjustment is recommended in patients with hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of velaglucerase alfa (see section 5.2).

Paediatric population
Twenty of the 94 patients (21%) who received velaglucerase alfa during clinical studies were in the paediatric and adolescent age range (4 to 17 years). The safety and efficacy profiles were similar between paediatric and adult patients (see section 5.1 for further information).

The safety and efficacy of velaglucerase alfa in children below the age of 4 years have not yet been established. No data are available.

Method of administration

For intravenous infusion use only.
To be administered as a 60-minute intravenous infusion.
Must be administered through a 0.2 or 0.22 µm filter.

Home administration under the supervision of a healthcare professional may be considered only for those patients who have received at least three infusions and were tolerating their infusions well. Appropriate medical support, including adequately trained personnel in emergency measures, should be readily available when velaglucerase alfa is administered. If anaphylactic or other acute reactions occur, immediately discontinue the infusion and initiate appropriate medical treatment (see section 4.4).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Severe allergic reaction to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

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

Hypersensitivity

Hypersensitivity reactions, including symptoms consistent with anaphylaxis, have been reported in patients in clinical studies and in post-marketing experience. The majority of hypersensitivity reactions usually occur up to 12 hours post infusion. The most frequently reported symptoms of hypersensitivity include nausea, rash dyspnoea, back pain, chest discomfort (including chest tightness), urticaria, arthralgia, and headache.

Infusion-related reactions

An infusion-related reaction is defined as any adverse drug reaction occurring within 24 hours after the initiation of velaglucerase alfa infusion. Infusion-related reactions (IRR) were the most commonly observed adverse reactions in patients treated in clinical studies. An IRR often appears as a

hypersensitivity reaction. The most frequently reported symptoms of hypersensitivity include nausea, rash, dyspnoea, back pain, chest discomfort (including chest tightness), urticaria, arthralgia, and headache. Symptoms consistent with anaphylaxis have been reported in patients in clinical studies and in post-marketing experience. Apart from symptoms associated with hypersensitivity reactions IRRs might show as fatigue, dizziness, pyrexia, blood pressure increase, pruritus, vision blurred, or vomiting. In treatment-naïve patients, the majority of infusion-related reactions occurred during the first 6 months of treatment.

Prevention and management of infusion related reactions including hypersensitivity reactions

The management of infusion-related reactions should be based on the severity of the reaction, and include slowing the infusion rate, treatment with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time.

Due to the risk for hypersensitivity reactions including anaphylaxis, appropriate medical support, including adequately trained personnel in emergency measures, should be readily available when velaglucerase alfa is administered. If anaphylactic or other acute reactions occur, in the clinic or home setting, immediately discontinue the infusion and initiate appropriate medical treatment. For patients developing anaphylaxis in a home setting it should be considered to continue treatment in a clinical setting.

Treatment should be approached with caution in patients who have exhibited symptoms of hypersensitivity to velaglucerase alfa or other enzyme replacement therapy.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required.

Immunogenicity

Antibodies may play a role in treatment-related reactions found with the use of velaglucerase alfa. To further evaluate the relationship, in cases of severe infusion-related reactions and in cases of lack or loss of effect, patients should be tested for the presence of antibodies and the results reported to the company.

In the clinical studies for Marketing Authorisation one of 94 (1%) patients developed IgG-class antibodies to velaglucerase alfa. In this one event, the antibodies were determined to be neutralising in an *in vitro* assay.

No patients developed IgE antibodies to velaglucerase alfa.

No infusion related reactions were reported.

Post-marketing phase
During a post marketing extension study, one patient developed IgG antibodies to VPRIV. In addition, a few events of positive neutralising antibodies and lack of effect were reported post marketing.

Sodium

This medicinal product contains 12.15 mg sodium per vial. This is equivalent to 0.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Patients who have Gaucher disease and become pregnant may experience a period of increased disease activity during pregnancy and the puerperium. A risk-benefit assessment is required for women with Gaucher disease who are considering pregnancy.

Pregnancy

There are no or limited amount of data from the use of velaglucerase alfa in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualisation of therapy. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

There is insufficient information on the excretion of velaglucerase alfa or its metabolites in human milk. Velaglucerase is a synthetic form of beta-glucocerebrosidase, which is a normal component of human milk. Studies with other forms of the enzyme have found very low levels of the enzyme in breastmilk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VPRIV taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies show no evidence of impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

VPRIV has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions in patients in clinical studies were hypersensitivity reactions (2.1%).

The most common adverse reactions were infusion-related reactions (39.4%). The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased (see section 4.4 for further information). The only adverse reaction leading to discontinuation of treatment was an infusion-related reaction.

Tabulated list of adverse reactions

Adverse reactions reported in patients with type 1 Gaucher disease are listed in Table 1. Information is presented by system organ class and frequency according to MedDRA convention. Frequency is defined as very common (≥1/10), common (≥1/100 to <1/10), and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with VPRIV in patients with type 1 Gaucher disease

System organ class	Adverse reaction		
	Very common	**Common**	**Uncommon**
Immune system disorders		hypersensitivity reactions (includes dermatitis allergic and anaphylactic*/anaphylactoid reactions)	
Nervous system disorders	headache, dizziness		
Eye disorders			vision blurred*
Cardiac disorders		tachycardia	
Respiratory, thoracic and mediastinal disorders		dyspnoea*	
Vascular disorders		hypertension, hypotension, flushing	
Gastrointestinal disorders	abdominal pain/abdominal pain upper,	nausea	vomiting*
Skin and subcutaneous tissue disorders		rash, urticaria, pruritus*	
Musculoskeletal and connective tissue disorders	bone pain, arthralgia, back pain		
General disorders and administration site conditions	infusion-related reaction, asthenia/fatigue, pyrexia/body temperature increased	chest discomfort*	
Investigations		activated partial thromboplastin time prolonged, neutralizing antibody positive	

*Adverse reactions derived from post-marketing reports

Description of selected adverse reactions

Vomiting

In some cases vomiting can be serious and severe. Vomiting most often occurs during the infusion and up to 24 hours after the infusion.

Other special populations

Elderly population (≥65 years)

The safety profile of VPRIV in clinical studies involving patients aged 65 years and above was similar to that observed in other adult patients.

Paediatric population

The safety profile of VPRIV in clinical studies involving children and adolescents aged 4 to 17 years was similar to that observed in adult patients.

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

There is limited information available regarding overdose with velaglucerase alfa. In the majority of the cases reporting overdose, no additional adverse events were observed. However, in the event of accidental or intentional overdose, patients should be carefully observed and treatment should be symptomatic and supportive. There is no antidote available. The maximum dose of velaglucerase alfa in clinical studies was 60 Units/kg (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB10.

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene which results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. This enzymatic deficiency causes an accumulation of glucocerebroside primarily in macrophages, giving rise to foam cells or "Gaucher cells". In this lysosomal storage disorder (LSD), clinical features are reflective of the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebroside in the liver and spleen leads to organomegaly. Bone involvement results in skeletal abnormalities and deformities as well as bone pain crises. Deposits in the bone marrow and splenic sequestration lead to clinically significant anaemia and thrombocytopenia.

The active substance of VPRIV is velaglucerase alfa, which is produced by gene activation technology in a human cell line. Velaglucerase alfa is a glycoprotein. The monomer is approximately 63 kDa, has 497 amino acids, and the same amino acid sequence as the naturally occurring human enzyme, glucocerebrosidase. There are 5 potential N-linked glycosylation sites, four of which are occupied. Velaglucerase alfa is manufactured to contain predominantly high-mannose-type glycans to facilitate internalisation of the enzyme by the phagocytic target cells via the mannose receptor.

Velaglucerase alfa supplements or replaces beta-glucocerebrosidase, the enzyme that catalyses the hydrolysis of glucocerebroside to glucose and ceramide in the lysosome, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of Gaucher disease. Velaglucerase alfa increases haemoglobin concentration and platelet counts and reduces liver and spleen volumes in patients with type 1 Gaucher disease.

In studies 025EXT and 034, patients were offered home therapy. In study 025EXT, 7 of 10 patients received home therapy at least once during 60 months of treatment. In study 034, 25 of 40 patients received home therapy at least once during the 12-month study.

Clinical efficacy and safety

Studies in treatment naïve patients

Study 025 was a 9 month, open-label study in 12 adult (≥18 years) patients who were naïve to ERT (defined as having not been treated with ERT for at least 12 months prior to study entry). Velaglucerase alfa was initially administered in a dose-escalating fashion in the first 3 patients (15, 30, 60 Units/kg) and the 9 remaining patients began treatment with 60 Units/kg.

Clinically meaningful improvements from baseline were observed in haemoglobin concentration and platelet counts as early as 3 months and in liver and spleen volumes at both 6 months and 9 months following the initiation of treatment with velaglucerase alfa.

Ten patients who completed Study 025 enrolled in an open-label extension study (025EXT), 8 of whom completed the study. After a minimum of 12 months of continuous treatment with velaglucerase alfa, all patients qualified to have the dose of velaglucerase alfa reduced in a step-wise fashion from 60 to 30 Units/kg after achieving at least 2 of the 4 "Year 1" therapeutic goals of ERT for type 1 Gaucher disease. Patients received doses ranging from 30 to 60 Units/kg (median dose 35 Units/kg) every other week for up to 84 months (7 years). Sustained clinical activity continued to be demonstrated during treatment as observed by improvements in haemoglobin concentrations and platelet counts and reduced liver and spleen volumes.

By month 57, 8 out of the 8 patients had achieved a reduction of at least 2 points in the lumbar spine Bone Marrow Burden (BMB) score as assessed by MRI scan. Improvement from baseline in mean lumbar spine and femoral neck bone mineral density (BMD) Z-scores were observed at month 24 (0.4; 95% CI 0.1, 0.7) and month 33 (0.4; 95% CI 0.2, 0.6), respectively. After seven years of treatment, the mean increase from baseline in Z-scores were 0.7 (95% CI 0.4, 1.0) for the lumbar spine and 0.5 (95% CI 0.2, 0.7) for the femoral neck. No patients were classified at a more severe WHO classification of bone density compared to baseline.

Study 032 was a 12-month, randomised, double-blind, parallel-group efficacy study that enrolled 25 patients aged 4 years and older who were naïve to ERT (defined as having not been treated with ERT for at least 30 months prior to study entry). Patients were required to have Gaucher disease-related anaemia and either thrombocytopenia or organomegaly. Patients were randomised to receive velaglucerase alfa at a dose of either 45 Units/kg (N=13) or 60 Units/kg (N=12) every other week.

Velaglucerase alfa 60 Units/kg given intravenously every other week demonstrated clinically meaningful increases from baseline in mean haemoglobin concentration (+2.4 g/dl) and platelet count (+50.9 x 10^9/l), liver volume was reduced from 1.46 to 1.22 times normal (mean reduction of 17%) and spleen volume was reduced from 14.0 to 5.75 times normal (mean reduction of 50%). Meaningful increases from baseline were observed in the 45 Units/kg dose group in haemoglobin concentration (+2.4 g/dl) and platelet count (+40.9 x 10^9/l), liver volume was reduced from 1.40 to 1.24 times normal (mean reduction of 6%) and spleen volume was reduced from 14.5 to 9.50 times normal (mean reduction of 40%).

Study 039 was a 9-month, randomised, double-blind, non-inferiority, active-comparator (imiglucerase) controlled, parallel-group efficacy study that enrolled 34 patients aged 4 years and older who were naïve to ERT (defined as having not been treated with ERT for at least 12 months prior to study entry). Patients were required to have Gaucher disease-related anaemia and either thrombocytopenia or organomegaly. Patients received either 60 Units/kg of velaglucerase alfa (N=17) or 60 Units/kg of imiglucerase (N=17) every other week.

The mean absolute increase from baseline in haemoglobin concentrations was 1.624 g/dl (±0.223 SE) following 9 months of treatment with velaglucerase alfa. This increase in haemoglobin concentration was demonstrated to be clinically and statistically non-inferior to imiglucerase (mean treatment difference of change from baseline to 9 months [velaglucerase alfa – imiglucerase]: 0.135 g/dl). There were no statistically significant differences between velaglucerase alfa and imiglucerase in changes in platelet counts and liver and spleen volumes after 9 months of velaglucerase alfa treatment, and in the time to first haemoglobin response (defined as 1 g/dl increase from baseline).

Study in patients switching from imiglucerase treatment to VPRIV

Study 034 was a 12-month, open-label safety study that enrolled 40 patients aged 4 years and older who had been receiving treatment with imiglucerase at doses ranging from 15 to 60 Units/kg for a minimum of 30 consecutive months. Patients were required to have a stable dose of imiglucerase for at least 6 months prior to study enrolment. Treatment with velaglucerase alfa was administered as the same number of units and regimen as their imiglucerase dose. Haemoglobin concentration and platelet counts were evaluated as changes from baseline, which was defined as the end of the patient's treatment with imiglucerase.

In patients who switched from imiglucerase to velaglucerase alfa, haemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment.
Study 058 was an open-label clinical safety study in 211 patients including 205 patients previously treated with imiglucerase 6 treatment-naïve patients and 57 patients aged 65 years or older (56/57 had switched from imiglucerase to velaglucerase alfa). Patients transferring from imiglucerase were administered velaglucerase alfa infusions every other week at the same number of units as imiglucerase within the range of 15 to 60 Units/kg. Patients transferring from a dose of <15 Units/kg imiglucerase were administered 15 Units/kg of velaglucerase alfa.

Patients previously treated with imiglucerase received a median of 8 velaglucerase alfa infusions with median duration of treatment of 15.1 weeks. The safety profile in these patients was similar to that observed in other clinical studies. Only 1 out of 163 patients assessed developed anti-velaglucerase alfa antibodies during the study.

The mean haemoglobin concentration and platelet count of patients previously treated with imiglucerase were maintained throughout the study and remained within the reference intervals.

Extension study 044

A total of 95 patients (73 adult and 22 paediatric) who participated in studies 032, 034, and 039 enrolled in the open label extension study and were treated with velaglucerase alfa. 57 patients were treatment naïve. All patients received at least 2 years of ERT and were followed for a mean of 4.5 years (min. 2.3 years, max 5.8 years).

In this study, haemoglobin concentration, platelet count, liver volume and spleen volume were assessed in treatment-naïve patients after 24 months of treatment. The results are presented in Table 2.

Table 2: Results at 24 months - change from baseline – study 044 ITT population

Clinical parameters	**Overall** velaglucerase alfa **group (N=39)** - **Mean change from baseline (95% CI)**	**Patients treated with imiglucerase for 9 months and then** velaglucerase alfa **for 15 months (N=16)** - **Mean change from baseline (95% CI)**	**Patients who switched from long-term imiglucerase treatment to** velaglucerase alfa **(N=38)** - **Mean change from baseline (95% CI)**
Haemoglobin concentration (g/dL)	2.75 (2.28, 3.22)	2.00 (1.25, 2.75)	-0.05 (-0.34, 0.25)
Platelet count ($x10^9$/L)	87.85 (72.69, 103.00)	160.94 (117.22, 204.66)	9.03 (-2.60, 20.66)
Normalised liver volume* (%BW)	-1.21 (-1.50, -0.91)	-1.69 (-2.16, -1.21)	-0.03 (-0.10, 0.05)
Normalised spleen volume* (%BW)§	-2.66 (-3.50, -1.82)	-3.63 (-7.25, - 0.02)	-0.11 (-0.19, -0.03)
§ Excludes patients with splenectomy. N=30, 6 and 34 for the 3 above groups. *Liver and spleen volume are normalised as a percentage of body weight. Normal spleen is defined as 0.2% of body weight; normal liver as 2.5% of body weight Note: Imputation was applied to intermittent missing data.			

In this study, BMD was assessed using dual x-ray absorptiometry of the lumbar spine and femoral neck. Among 31 treatment-naïve adult patients treated with velaglucerase alfa, the mean lumbar spine BMD Z-score at baseline was -1.820 (95% CI: -2.21, -1.43) and increased by 0.62 (95% CI: 0.39, 0.84) from baseline following 24 months of treatment with velaglucerase alfa. Similar results were seen in treatment-naïve patients who received 9 months of imiglucerase followed by velaglucerase alfa for 15 months. In patients who switched from long-term imiglucerase to velaglucerase alfa, lumbar spine BMD was maintained at 24 months. In contrast, no significant change in femoral neck BMD was observed.

In the paediatric population (ages 4 to 17 years studied), increases in the mean height Z-score were seen through 60 months of treatment in the overall treatment-naïve population, suggesting a beneficial treatment effect with velaglucerase alfa on linear growth. Similar treatment effects were seen through 48 months in the paediatric population who received 9 months of imiglucerase followed by velaglucerase alfa. Paediatric subjects who switched from long-term imiglucerase to velaglucerase alfa in study 034 had greater mean height Z-scores at baseline and their mean height Z-scores remained stable over time.

These treatment effects on haemoglobin, platelet count, organ volumes, bone mineral density and height were maintained through the end of the study.

Paediatric population

Use in the age group 4 to 17 is supported by evidence from controlled studies in adults and paediatric [20 of 94 (21%)] patients. The safety and efficacy profiles were similar between paediatric and adult patients. The studies allowed the inclusion of patients 2 years and older and the safety and efficacy profiles are expected to be similar down to the age of 2 years. However, no data are available for children under the age of 4 years. The effect on height was assessed in the study 044 (see section 5.1, extension study 044).

Phase I/II study HGT-GCB-068 was conducted to explore the efficacy and safety of velaglucerase alfa ERT in treatment naïve children and adolescents with type 3 Gaucher disease. This was a multicentre, open-label study in which 60 U/kg of velaglucerase alfa was administered by intravenous infusion every other week (EOW) over 12 months in 6 patients (2 to 17 years of age at enrolment) with a confirmed diagnosis of type 3 Gaucher disease.

In this small, exploratory study, the non-neurological efficacy findings and the safety profile of intravenous velaglucerase alfa in type 3 Gaucher patients were consistent with those observed in patients with type 1 Gaucher disease. There was no indication of significant improvements of the neurological manifestations of type 3 Gaucher disease except for one patient in this study.

The European Medicines Agency has waived the obligation to submit the results of studies with VPRIV in all subsets of the paediatric population in type 2 Gaucher disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

There were no apparent pharmacokinetic differences between male and female patients with type 1 Gaucher disease. None of the subjects in the pharmacokinetic studies were positive for anti-velaglucerase alfa antibodies on the days of pharmacokinetic evaluation. Therefore, it was not possible to evaluate the effect of antibody response on the pharmacokinetic profile of velaglucerase alfa.

Absorption

Velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes of the 60-minute infusion before levelling off, and C_{max} was typically attained between 40 and 60 minutes after the start of the infusion. After the end of the infusion, velaglucerase alfa serum concentrations fell rapidly in a monophasic or biphasic fashion with a mean $t_{1/2}$ ranging from 5 to 12 minutes at doses of 15, 30, 45, and 60 Units/kg.

Distribution

Velaglucerase alfa exhibited an approximately linear (i.e. first-order) pharmacokinetic profile, and C_{max} and AUC increased approximately proportional to the dose over the dose range 15 to 60 Units/kg. The steady state volume of distribution was approximately 10% of the body weight. The high clearance of velaglucerase alfa from serum (mean 6.7 to 7.6 ml/min/kg) is consistent with the rapid uptake of velaglucerase alfa into macrophages via mannose receptors.

Elimination

The range of velaglucerase alfa clearance in paediatric patients (N=7, age range 4 to 17 years) was contained within the range of clearance values in adult patients (N=15, age range 19 to 62 years).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and toxicity to reproduction and development (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate dihydrate (E331)
Citric acid monohydrate (E330)
Polysorbate 20

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Reconstituted and diluted solution for infusion:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C under protection from light.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not exceed 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml vial (type I glass) with a stopper (fluoro-resin coated butyl rubber), one-piece seal, and flip-off cap.

Pack sizes of 1, 5 and 25 vials. Each vial contains 400 Units powder for solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

VPRIV requires reconstitution and dilution, and is intended for intravenous infusion only. It is for single use only and is administered through a 0.2 or 0.22 µm filter.

Aseptic technique must be used.

VPRIV has to be prepared as follows:
1. The number of vials to be reconstituted is determined based on the individual patient's weight and the prescribed dose.
2. The required vials are removed from the refrigerator. Each 400 Units vial is reconstituted with 4.3 ml of sterile water for injections.

3. Upon reconstitution, vials should be mixed gently. Vials should not be shaken. Each vial will contain an extractable volume of 4.0 ml (100 Units/ml).
4. Prior to further dilution, the solution in the vials should be visually inspected; the solution should be clear to slightly opalescent and colourless; the solution should not be used if it is discoloured or if foreign particulate matter is present.
5. The calculated volume of medicinal product is withdrawn from the appropriate number of vials and the total volume required is diluted in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion. The diluted solution should be mixed gently. It should not be shaken. The infusion should be initiated within 24 hours from the time of reconstitution.

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

7. MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/646/002
EU/1/10/646/005
EU/1/10/646/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2010
Date of latest renewal: 23 July 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Cell Bank storage and Drug Substance Manufacture
Shire Human Genetic Therapies, Inc
205 Alewife Brook Parkway, Cambridge, Massachusetts 02138
USA

Drug Substance Manufacture
Shire Human Genetic Therapies, Inc
400 Shire Way, Lexington, Massachusetts 02421
USA

Name and address of the manufacturers responsible for batch release

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

Shire Pharmaceuticals Ireland Limited
Block 2 & 3 Miesian Plaza
50 – 58 Baggot Street Lower
Dublin 2
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 authorization 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.

If the dates of submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH must agree on the content and format of the educational materials for use of VPRIV in home infusion, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use of VPRIV in home infusion are aimed at providing guidance on how to manage risk of infusion-related reactions including allergic-type hypersensitivity reactions in a home setting.

The MAH shall ensure that in each Member State where VPRIV is marketed, all healthcare professionals, nurses and patients/carers who are expected to prescribe, dispense or use VPRIV have access to/are provided with the following educational package:

- Educational materials for nurses and for patients with Gaucher Disease who receive home infusion;
- Guide for Healthcare Professionals Treating Patients with Gaucher Disease;

The educational materials for nurses and for patients with Gaucher Disease who receive home infusion should contain the following key elements:

- A description of the correct preparation and administration technique
- Information about risks of the product, particularly hypersensitivity reactions
- Infusion diary should be used as the communication tool between all involved in the infusion. It includes:
    - Infusion plan with dose, infusion rate etc. determined and filled in by the physician
    - Information about antibody testing
    - Documentation of the individual infusions, adverse events and measures by the person infusing
- In the emergency plan, the physician determines for the individual patient how to act in an emergency.

The Guide for Healthcare Professionals Treating Patients with Gaucher Disease should contain the following key elements:

- Checklist to determine patient eligibility prior to initiation of home infusion:
    - Patient had at least 3 consecutive well-tolerated VPRIV infusions (no infusion related reactions) in the clinic.
    - Patient assessed to be medically stable.
    - History of adherence to infusion schedule.
    - The homecare nurse, patient and/or caregiver have been trained about home infusion, the associated risks, how to act in an emergency.
    - The homecare nurse, patient and/or caregiver has received the educational material for nurses/patients
- Detailed description of the administration procedures of VPRIV

- Instructions indicating when to notify healthcare nurse or prescriber for adverse event reporting and antibody testing.
- Information on antibodies testing even in a home infusion setting in case of a hypersensitivity reaction or decreasing efficacy. Information on when to take samples, where they can be analysed and how to communicate test results.
- Infusion diary is the communication tool for all involved in the infusion. It should be provided to patient/caregiver. It should include:
    - The infusion plan determined by the treating physician including dose, infusion rate etc. and any changes
    - A record of the actual infusions administered by the infusing person including health status of the patient before, during and after infusion and measures taken in response to an adverse event
- In the emergency plan, the treating physician should provide details on how to recognize and manage hypersensitivity reactions. The emergency plan should be suitable for the specific patient.
- The physician is responsible that the homecare nurse, patient and/or caregiver is adequately trained in preparing, administering and documenting the infusions; they are aware of risks and trained to act in emergencies adequately including communication of adverse events to the treating physician.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 400 UNITS (1 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units powder for solution for infusion
velaglucerase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 Units of velaglucerase alfa.
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

3. LIST OF EXCIPIENTS

Also contains:
Sucrose
Sodium citrate dihydrate
Citric acid monohydrate
Polysorbate 20
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
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

After reconstitution and dilution

Use immediately. Do not exceed 24 hours at 2 °C to 8 °C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Do not use, if it is discoloured or if foreign particulate matter is present.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharmaceuticals International AG Ireland Branch
Block 2 Miesian Plaza
50-58 Baggot Street Lower
Dublin 2
D02 HW68
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/646/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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 OUTER PACKAGING

OUTER CARTON – 400 UNITS (5 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units powder for solution for infusion
velaglucerase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 Units of velaglucerase alfa.
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

3. LIST OF EXCIPIENTS

Also contains:
Sucrose
Sodium citrate dihydrate
Citric acid monohydrate
Polysorbate 20
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
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

After reconstitution and dilution

Use immediately. Do not exceed 24 hours at 2 °C to 8 °C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Do not use, if it is discoloured or if foreign particulate matter is present.

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/646/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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 OUTER PACKAGING

OUTER CARTON – 400 UNITS (25 vial pack)

1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units powder for solution for infusion
velaglucerase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 Units of velaglucerase alfa.
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

3. LIST OF EXCIPIENTS

Also contains:
Sucrose
Sodium citrate dihydrate
Citric acid monohydrate
Polysorbate 20
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
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

After reconstitution and dilution

Use immediately. Do not exceed 24 hours at 2 °C to 8 °C.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Do not use, if it is discoloured or if foreign particulate matter is present.

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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/646/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL – 400 UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VPRIV 400 Units powder for solution for infusion
velaglucerase alfa
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

VPRIV 400 Units powder for solution for infusion
velaglucerase alfa

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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet

1. What VPRIV is and what it is used for

VPRIV is a long-term enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease.

Gaucher disease is a genetic disorder caused by a missing or defective enzyme named glucocerebrosidase. When this enzyme is missing or does not work properly, a substance called glucocerebroside builds up inside cells in the body. The build-up of this material causes the signs and symptoms found in Gaucher disease.

VPRIV contains a substance called velaglucerase alfa which is designed to replace the missing or defective enzyme, glucocerebrosidase, in patients with Gaucher disease.

2. What you need to know before VPRIV is used

Do not use VPRIV
- if you are severely allergic to velaglucerase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before VPRIV is used
- If you are treated with VPRIV, you may experience side effects during or following the infusion (see section 4, possible side effects). These are called infusion related reactions and might appear as a hypersensitivity reaction with symptoms like nausea, rash, difficulty in breathing, back pain, chest discomfort (chest tightness), hives, joint pain or headache.
- Apart from symptoms of hypersensitivity reactions infusion-related reactions might show as dizziness, high blood pressure, tiredness, fever, itching, blurry vision, or vomiting.
  If you experience any of the symptoms, **you must tell your doctor immediately**.
- You may be given additional medicines to treat or help prevent future reactions. These medicines may include antihistamines, antipyretics, and corticosteroids.
- If the reaction is severe, your doctor will stop the intravenous infusion immediately and start giving you appropriate medical treatment.
- If the reactions are severe and/or there is a loss of effect from this medicine, your doctor will perform a blood test to check for antibodies which may affect the outcome of your treatment

- Your doctor or nurse may decide to continue to administer VPRIV even if you experience any infusion related-reaction. Your condition will be closely monitored.

Tell your doctor if you have previously experienced an infusion-related reaction with other ERT for Gaucher disease.

Children
Do not use in children under the age of 4 years because there is no experience of using the medicine in this age group.

Other medicines and VPRIV
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy
Gaucher disease may become more active in a woman during pregnancy and for a few weeks after birth. Women with Gaucher disease who are pregnant or considering pregnancy should talk with their doctor before this medicine is used.

Breast-feeding
It is not known whether VPRIV can pass into breast milk. If you are breast-feeding or considering breast-feeding, you should talk to your doctor before this medicine is used. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop using VPRIV, considering the benefit of breast-feeding to the baby and the benefit of VPRIV to the mother.

Driving and using machines
VPRIV has no or negligible influence on your ability to drive or use machines.

VPRIV contains sodium
This medicine contains 12.15 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 0.6% of the recommended maximum daily dietary intake of sodium for an adult.

3. How VPRIV is used

This medicine is only to be used under appropriate medical supervision of a doctor who is knowledgeable in the treatment of Gaucher disease. It is given by a doctor or nurse by intravenous infusion.

Dose
The recommended dose is 60 Units/kg given every other week.

If you are currently being treated for Gaucher disease with another ERT and your doctor wants to change you to VPRIV, you can initially receive VPRIV at the same dose and frequency you had been receiving the other ERT.

Use in children and adolescents
VPRIV may be given to children and adolescents (4 to 17 years of age) at the same dose and frequency as in adults.

Use in elderly
VPRIV may be given to the elderly (aged over 65 years) at the same dose and frequency as in adults.

Response to treatment
Your doctor will monitor your response to treatment and may change your dose (up or down) over time.

If you are tolerating your infusions well in the clinic, your doctor or nurse may administer your infusions at home.

Administration
VPRIV is supplied in a vial as a packed powder which is mixed with sterile water and further diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion prior to intravenous infusion.

After preparation, your doctor or nurse will give the medicine to you through a drip into a vein (by intravenous infusion) over a period of 60 minutes.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Commonly (may affect up to 1 in 10 people), patients experienced a severe allergic reaction, with difficulty breathing, chest discomfort (chest tightness), feeling sick (nausea), swelling of the face, lips, tongue or throat (anaphylactic/anaphylactoid reactions), common is also an allergic skin reaction such as hives, severe rash or itching. If any of these happen tell your doctor immediately.

Most side effects, including the allergic reactions, occurred during the infusion or shortly after. These are called infusion related reactions. Other infusion related reactions that occurred very commonly (may affect more than 1 in 10 people) include headache, dizziness, fever/body temperature increased, back pain, joint pain and tiredness, as well as high blood pressure (commonly reported), blurry vision, and vomiting (uncommonly reported). If any of these happen tell your doctor immediately.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people) are:
- bone pain
- weakness/loss of strength
- stomach ache

Common side effects (may affect up to 1 in 10 people) are:
- lengthening of the time it takes for a cut to stop bleeding may lead to easy/spontaneous bleeding/easy bruising
- skin flushing
- rapid heart beat
- developing antibodies to VPRIV (see section 2)
- decreased blood pressure

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 VPRIV

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 carton and label after ‘EXP’. The expiry date refers to the last day of that month.

Store in the refrigerator (2 ºC – 8 ºC).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Reconstituted and diluted solution for infusion:
Use immediately. Do not exceed 24 hours at 2 °C to 8 °C.

Do not use if the solution is discoloured or if foreign particles are present.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throwaway medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What VPRIV contains
- The active substance is velaglucerase alfa.
  Each vial contains 400 Units of velaglucerase alfa.
  After reconstitution, one ml of solution contains 100 Units of velaglucerase alfa

- The other ingredients are sucrose, sodium citrate dihydrate, citric acid monohydrate and polysorbate 20 (see section 2 “VPRIV contains sodium”).

What VPRIV looks like and contents of the pack
20 ml glass vial containing a white to off-white powder for solution for infusion.

Packs of 1, 5 or 25 vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only.

VPRIV is a powder for solution for infusion. It requires reconstitution and dilution and is intended for intravenous infusion only. VPRIV is for single–use only and is administered through a 0.2 or 0.22 µm filter. Discard any unused solution. VPRIV should not be infused with other medicines in the same infusion as the compatibility in solution with other medicines has not been evaluated. The total volume of infusion should be delivered over a period of 60 minutes.

Use aseptic technique.
Prepare VPRIV as follows:

1. Determine the number of vials to be reconstituted based on the individual patient's weight and the prescribed dose.
2. Remove the required vials from the refrigerator. Reconstitute each vial using sterile water for injections:

Vial size	Water for injections
400 Units	4.3 ml

3. Upon reconstitution, mix vials gently. Do not shake.
4. Prior to dilution, visually inspect the solution in the vials; the solution should be clear to slightly opalescent and colourless; do not use if the solution is discoloured, or if foreign particulate matter is present.
5. Withdraw the calculated volume of medicine from the appropriate number of vials. Some solution will remain in the vial:

Vial size	Extractable volume
400 Units	4.0 ml

6. Dilute the total volume required in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion. Mix gently. Do not shake. Initiate the infusion within 24 hours from the time of reconstitution.

From a microbiological point of view, use the medicine immediately. If you do not immediately, in-use storage times and conditions prior to use are the responsibility of the user. Do not exceed 24 hours at 2 °C to 8 °C.

Do not dispose of the medicine via waste water or household waste. Dispose of any unused medicine or waste material in accordance with local requirements.

Keeping a record
In order to improve the traceability of biological medicine, record the name and batch number of the administered medicine clearly.