# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units
Lyophilized 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

Lyophilized powder for solution for infusion.
White to off-white powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VPRIV is a hydrolytic glucocerebroside – specific enzyme indicated for the long term replacement therapy (ERT) for pediatric and adult 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 0.22 µm filter.

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 Authorization 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

### 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)**<br>-<br>**Mean change from baseline (95% CI)** | **Patients treated with imiglucerase for 9 months and then** velaglucerase alfa **for 15 months (N=16)**<br>-<br>**Mean change from baseline (95% CI)** | **Patients who switched from long-term imiglucerase treatment to** velaglucerase alfa **(N=38)**<br>-<br>**Mean change from baseline (95% CI)** |
|---|---|---|---|
| Haemoglobin concentration (g/dL) | 2.75<br>(2.28, 3.22) | 2.00<br>(1.25, 2.75) | -0.05<br>(-0.34, 0.25) |
| Platelet count (x$10^9$/L) | 87.85<br>(72.69, 103.00) | 160.94<br>(117.22, 204.66) | 9.03<br>(-2.60, 20.66) |
| Normalised liver volume*<br>(%BW) | -1.21<br>(-1.50, -0.91 ) | -1.69<br>(-2.16, -1.21) | -0.03<br>(-0.10, 0.05) |
| Normalised spleen volume* | -2.66 | -3.63 | -0.11 |

| | | | |
|---|---|---|---|
| (%BW)[§] | (-3.50, -1.82) | (-7.25, - 0.02) | (-0.19, -0.03) |
| [§] Excludes patients with splenectomy. N=30, 6 and 34 for the 3 above groups.<br>*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.<br>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).

## 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
Citric acid monohydrate
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

The expiry date of the product is indicated on the packaging materials.

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 lyophilized 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 0.22 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. MANUFACTURER

Shire Human Genetic Therapies, Inc
300 Shire Way
Lexington, MA 02421, USA

## 8. LICENSE HOLDER

Takeda Israel Ltd., Efal 25 st., Petach Tikva 4951125.

## 9. REGISTRATION NUMBER(S)

Vpriv 400 : 146-02-33234

- This leaflet was revised in April 2021 according to MoHs guidelines