

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

VPRIV 200 Units powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 200 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  $\beta$ -D-glucopyranoside to p-nitrophenol per minute at 37°C.

Velaglucerase alfa is produced in an HT-1080 human fibroblast cell line by recombinant DNA technology.

### Excipients:

One vial contains 6.07 mg sodium.

For a 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. Home administration under the supervision of a healthcare professional may be considered only for patients who have received at least three infusions and were tolerating their infusions well.

### 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.

### Special populations

#### *Current enzyme replacement therapy*

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

#### *Renal or hepatic impairment*

No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of velaglucerase alfa. See section 5.2.

#### *Elderly (≥65 years old)*

Four of the 94 patients (5%) who received velaglucerase alfa during clinical studies were age 65 years or older. The limited data do not indicate a need for a dose adjustment in this age group.

#### 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.

#### 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 VPRIV, see section 6.6 and the end of the leaflet.

### **4.3 Contraindications**

Severe allergic reaction to the active substance or to any of the excipients.

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

#### Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies. As with any intravenous protein medicinal product, hypersensitivity reactions are possible. Therefore, appropriate medical support should be readily available when velaglucerase alfa is administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed.

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

#### Infusion related-reactions

Infusion-related reactions were the most commonly observed adverse reactions in patients treated in clinical studies. Most of the infusion-related reactions were mild. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased. In treatment-naïve patients, the majority of infusion-related reactions occurred during the first 6 months of treatment.

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.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of velaglucerase alfa during clinical studies.

#### 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 trials, 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 infusion-related reactions were reported for this patient. No patients developed IgE antibodies to velaglucerase alfa.

### Sodium

This medicinal product contains 6.07 mg sodium per vial. To be taken into consideration by 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**

### Women of child bearing 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 each pregnancy. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualisation of therapy.

### Pregnancy

There are no 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. Caution should be exercised when prescribing to pregnant women.

### Breast-feeding

There are no data from studies in breast-feeding women. It is not known whether velaglucerase alfa is excreted in human milk. Because many active substances are excreted in human milk, caution should be exercised when prescribing to a breast-feeding woman.

### Fertility

Animal studies show no evidence of impaired fertility.

## **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**

The data described below reflect exposure of 94 patients with type 1 Gaucher disease who received velaglucerase alfa at doses ranging from 15 to 60 Units/kg every other week in 5 clinical studies. Fifty-four patients were naïve to ERT and 40 patients switched from imiglucerase to VPRIV. Patients were between 4 and 71 years old at the time of first treatment with VPRIV, and included 46 male and 48 female patients.

The most serious adverse reactions in patients in clinical trials were hypersensitivity reactions.

The most common adverse reactions were infusion-related reactions. 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.

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 ( $\geq 1/10$ ) and common ( $\geq 1/100$  to  $< 1/10$ ). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

System organ class	Adverse reaction	
	Very common	Common
Immune system disorders		hypersensitivity reactions
Nervous system disorders	headache, dizziness	
Cardiac disorders		tachycardia
Vascular disorders		hypertension, hypotension, flushing
Gastrointestinal disorders		abdominal pain/abdominal pain upper, nausea
Skin and subcutaneous tissue disorders		rash, urticaria
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	
Investigations		activated partial thromboplastin time prolonged, neutralizing antibody positive

#### Paediatric population

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

#### **4.9 Overdose**

There is no experience with overdose of velaglucerase alfa. 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 catalyzes 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 ( $\geq 18$  years) patients who were naïve to ERT (defined as having not been treated with ERT for at least 12 months prior to study entry). VPRIV 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 VPRIV.

Ten patients who completed Study 025 enrolled in an open-label extension study (025EXT). After a minimum of 12 months of continuous treatment with VPRIV, all patients qualified to have the dose of VPRIV 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 60 months (5 years). Sustained clinical activity continued to be demonstrated during 5 years of treatment as observed by improvements in haemoglobin concentrations and platelet counts and reduced liver and spleen volumes.

Study 032 was a 12-month, randomized, double-blind, parallel-group efficacy study in 25 patients aged 2 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 randomized to receive VPRIV 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 IV every other week demonstrated clinically meaningful increases from baseline in mean haemoglobin concentration (+2.4 g/dl) and platelet count ( $+50.9 \times 10^9/l$ ), 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 ( $+40.9 \times 10^9/l$ ), 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, randomized, double-blind, non-inferiority, active-comparator (imiglucerase) controlled, parallel-group efficacy study in 34 patients aged 2 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 VPRIV (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 ( $\pm 0.223$  SE) following 9 months of treatment with VPRIV. 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 [VPRIV – imiglucerase]: 0.135 g/dl). There were no statistically significant differences between VPRIV and imiglucerase in changes in platelet counts and liver and spleen volumes after 9 months of VPRIV 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 in 40 patients aged 2 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 VPRIV 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 VPRIV, haemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment.

#### 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 European Medicines Agency has waived the obligation to submit the results of studies with VPRIV in all subsets of the paediatric population with type 2 Gaucher disease and has deferred the obligation to submit the results of studies with VPRIV in one or more subsets of the paediatric population in Gaucher disease type 1 and 3, as per the PIP decision.

## **5.2 Pharmacokinetic properties**

Velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes of the 60-minute infusion before leveling 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.

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.

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). Additionally, 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.

### **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.

## **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**

18 months

#### 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 of the reconstituted and/or diluted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

200 Units of velaglucerase alfa in a 5 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.

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. VPRIV is for single-use only and is administered through a 0.22 µm filter.

Use aseptic technique.



Prepare VPRIV 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 200 Units vial is reconstituted with 2.2 ml of sterile water for injections.
3. Upon reconstitution, mix vials gently. Do not shake. Each vial will contain an extractable volume of 2.0 ml (100 Units/ml).
4. Prior to further 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. 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. Mix gently. Do not shake. 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**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/001  
EU/1/10/646/003  
EU/1/10/646/004

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

Date of first authorisation: 26/08/2010

## **10. DATE OF REVISION OF THE TEXT**

03/11/10

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

## 1. NAME OF THE MEDICINAL PRODUCT

VPRIV 400 Units powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 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  $\beta$ -D-glucopyranoside to p-nitrophenol per minute at 37°C.

Velaglucerase alfa is produced in an HT-1080 human fibroblast cell line by recombinant DNA technology.

### Excipients:

One vial contains 12.15 mg sodium.

For a 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. Home administration under the supervision of a healthcare professional may be considered only for patients who have received at least three infusions and were tolerating their infusions well.

### 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.

### Special populations

#### *Current enzyme replacement therapy*

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

#### *Renal or hepatic impairment*

No dosing adjustment is recommended in patients with renal or hepatic impairment based on current knowledge of the pharmacokinetics and pharmacodynamics of velaglucerase alfa. See section 5.2.

#### *Elderly (≥65 years old)*

Four of the 94 patients (5%) who received velaglucerase alfa during clinical studies were age 65 years or older. The limited data do not indicate a need for a dose adjustment in this age group.

#### 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.

#### 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 VPRIV, see section 6.6 and the end of the leaflet.

### **4.3 Contraindications**

Severe allergic reaction to the active substance or to any of the excipients.

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

#### Hypersensitivity

Hypersensitivity reactions have been reported in patients in clinical studies. As with any intravenous protein medicinal product, hypersensitivity reactions are possible. Therefore, appropriate medical support should be readily available when velaglucerase alfa is administered. If a severe reaction occurs, current medical standards for emergency treatment are to be followed.

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

#### Infusion related-reactions

Infusion-related reactions were the most commonly observed adverse reactions in patients treated in clinical studies. Most of the infusion-related reactions were mild. The most commonly observed symptoms of infusion-related reactions were: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia, and pyrexia/body temperature increased. In treatment-naïve patients, the majority of infusion-related reactions occurred during the first 6 months of treatment.

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.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of velaglucerase alfa during clinical studies.

#### 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 trials, 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 infusion-related reactions were reported for this patient. No patients developed IgE antibodies to velaglucerase alfa.

### Sodium

This medicinal product contains 12.15 mg sodium per vial. To be taken into consideration by 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**

#### Women of child bearing 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 each pregnancy. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualisation of therapy.

#### Pregnancy

There are no 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. Caution should be exercised when prescribing to pregnant women.

#### Breast-feeding

There are no data from studies in breast-feeding women. It is not known whether velaglucerase alfa is excreted in human milk. Because many active substances are excreted in human milk, caution should be exercised when prescribing to a breast-feeding woman.

#### Fertility

Animal studies show no evidence of impaired fertility.

### **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**

The data described below reflect exposure of 94 patients with type 1 Gaucher disease who received velaglucerase alfa at doses ranging from 15 to 60 Units/kg every other week in 5 clinical studies. Fifty-four patients were naïve to ERT and 40 patients switched from imiglucerase to VPRIV. Patients were between 4 and 71 years old at the time of first treatment with VPRIV, and included 46 male and 48 female patients.

The most serious adverse reactions in patients in clinical trials were hypersensitivity reactions.

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Cardiac disorders		tachycardia
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Skin and subcutaneous tissue disorders		rash, urticaria
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General disorders and administration site conditions	infusion-related reaction, asthenia/fatigue, pyrexia/body temperature increased	
Investigations		activated partial thromboplastin time prolonged, neutralizing antibody positive

#### 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.

#### **4.9 Overdose**

There is no experience with overdose of velaglucerase alfa. 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.

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Velaglucerase alfa supplements or replaces beta-glucocerebrosidase, the enzyme that catalyzes 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 ( $\geq 18$  years) patients who were naïve to ERT (defined as having not been treated with ERT for at least 12 months prior to study entry). VPRIV 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 VPRIV.

Ten patients who completed Study 025 enrolled in an open-label extension study (025EXT). After a minimum of 12 months of continuous treatment with VPRIV, all patients qualified to have the dose of VPRIV 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 60 months (5 years). Sustained clinical activity continued to be demonstrated during 5 years of treatment as observed by improvements in haemoglobin concentrations and platelet counts and reduced liver and spleen volumes.

Study 032 was a 12-month, randomized, double-blind, parallel-group efficacy study in 25 patients aged 2 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 randomized to receive VPRIV 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 IV every other week demonstrated clinically meaningful increases from baseline in mean haemoglobin concentration (+2.4 g/dl) and platelet count ( $+50.9 \times 10^9/l$ ), 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 ( $+40.9 \times 10^9/l$ ), 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, randomized, double-blind, non-inferiority, active-comparator (imiglucerase) controlled, parallel-group efficacy study in 34 patients aged 2 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 VPRIV (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 ( $\pm 0.223$  SE) following 9 months of treatment with VPRIV. 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 [VPRIV – imiglucerase]: 0.135 g/dl). There were no statistically significant differences between VPRIV and imiglucerase in changes in platelet counts and liver and spleen volumes after 9 months of VPRIV 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 in 40 patients aged 2 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 VPRIV 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 VPRIV, haemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment.

#### 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 European Medicines Agency has waived the obligation to submit the results of studies with VPRIV in all subsets of the paediatric population with type 2 Gaucher disease and has deferred the obligation to submit the results of studies with VPRIV in one or more subsets of the paediatric population in Gaucher disease type 1 and 3, as per the PIP decision.

## **5.2 Pharmacokinetic properties**

Velaglucerase alfa serum concentrations rose rapidly for the first 20 minutes of the 60-minute infusion before leveling 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.

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.

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). Additionally, 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.

## **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.

## **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 of the reconstituted and/or diluted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

400 Units of velaglucerase alfa in a 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.

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. VPRIV is for single-use only and is administered through a 0.22 µm filter.

Use aseptic technique.

Prepare VPRIV 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, mix vials gently. Do not shake. Each vial will contain an extractable volume of 4.0 ml (100 Units/ml).
4. Prior to further 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. 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. Mix gently. Do not shake. 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**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
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: 26/08/2010

## **10. DATE OF REVISION OF THE TEXT**

03/11/10

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND  
MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH  
RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer 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 manufacturer responsible for batch release

Shire Human Genetic Therapies AB  
Åldermansgatan 13  
227 64 Lund  
Sweden

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 OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING**

**OUTER CARTON – 200 UNITS (single vial pack)**

**1. NAME OF THE MEDICINAL PRODUCT**

VPRIV 200 Units powder for solution for infusion  
velaglucerase alfa

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 200 Units of velaglucerase alfa.  
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**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**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING**

**OUTER CARTON – 200 UNITS (5 vial pack)**

**1. NAME OF THE MEDICINAL PRODUCT**

VPRIV 200 Units powder for solution for infusion  
velaglucerase alfa

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 200 Units of velaglucerase alfa.  
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
5 vials  
Not for individual sale

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**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**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING**

**OUTER CARTON – 200 UNITS (25 vial pack)**

**1. NAME OF THE MEDICINAL PRODUCT**

VPRIV 200 Units powder for solution for infusion  
velaglucerase alfa

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One vial contains 200 Units of velaglucerase alfa.  
After reconstitution, one ml of the solution contains 100 Units of velaglucerase alfa.

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
25 vials  
Not for individual sale

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**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**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/004

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL – 200 UNITS**

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

VPRIV 200 U powder for solution for infusion  
velaglycerase alfa  
Intravenous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

200 Units

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON – 400 UNITS (single vial pack)**

**1. NAME OF THE MEDICINAL PRODUCT**

VPRIV 400 Units powder for solution for infusion  
velaglucerase alfa

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

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

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**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****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE 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)**

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

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
5 vials  
Not for individual sale

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP



**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**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/005

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE 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)**

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

**3. LIST OF EXCIPIENTS**

Sucrose  
Sodium citrate dihydrate  
Citric acid monohydrate  
Polysorbate 20  
Contains sodium, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder for solution for infusion  
25 vials  
Not for individual sale

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Intravenous use.

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

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**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**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/646/006

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

**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 U powder for solution for infusion  
velaglucerase alfa  
Intravenous use

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

400 Units

**6. OTHER**

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET: INFORMATION FOR THE USER

### VPRIV 200 Units powder for solution for infusion VPRIV 400 Units powder for solution for infusion velaglucerase alfa

**Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**In this leaflet:**

1. What VPRIV is and what it is used for
2. Before you use VPRIV
3. How to use VPRIV
4. Possible side effects
5. How to store VPRIV
6. Further information

#### **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 is designed to replace the missing or defective enzyme, glucocerebrosidase, in patients with Gaucher disease.

#### **2. BEFORE YOU USE VPRIV**

**Do not use VPRIV**

- If you are allergic (hypersensitive) to velaglucerase alfa or any of the other ingredients of VPRIV.

**Take special care with VPRIV**

- If you are treated with VPRIV, you may experience a side effect during or following the infusion (see section 4, possible side effects). This is known as an infusion-related reaction and can sometimes be severe.
- Infusion-related reactions include dizziness, headache, nausea, low or high blood pressure, tiredness, and fever. If you experience an infusion-related reaction, **you must tell your doctor immediately.**
- If you have an infusion-related reaction you may be given additional medicines to treat or help prevent future reactions. These medicines may include antihistamines, antipyretics, and corticosteroids.
- If the infusion-related reaction is severe, your doctor will stop the intravenous infusion immediately and start giving you appropriate medical treatment.
- Most of the time you can still be given VPRIV even if you experience an infusion-related reaction.

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

### **Children**

VPRIV should not be used in children under the age of 2 years.

### **Using other medicines**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

### **Pregnancy and breast-feeding**

Gaucher disease may become more active in a woman during pregnancy and for a few weeks after birth. Women with Gaucher disease who are considering pregnancy should talk with their doctor.

VPRIV has not been studied in pregnant women. Studies in animals do not show harmful effects from VPRIV. Caution should be exercised when using VPRIV in pregnancy.

VPRIV has not been studied in women who are breast-feeding and it is not known whether VPRIV appears in breast milk. However, VPRIV contains a protein that may be digested by the child. Cautious use of VPRIV during breast feeding is recommended.

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

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

### **Important information about one of the ingredients of VPRIV**

Each 200 Units vial of this medicine contains 6.07 mg sodium. Each 400 Units vial of this medicine contains 12.15 mg sodium. This should be taken into consideration by patients on a controlled sodium diet.

## **3. HOW TO USE VPRIV**

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

### **Dose**

The usual 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. In clinical studies, doses ranging from 15 Units/kg to 60 Units/kg have been used.

### **Use in children and adolescents**

VPRIV may be given to children and adolescents (2 to  $\leq 17$  years of age) 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 prior to intravenous infusion.

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

### **If you use more VPRIV than you should**

If you feel ill whilst receiving the infusion, tell your doctor or nurse immediately.

### **If you forget to have VPRIV**

If you have missed an infusion, please contact your doctor.

### **If you stop using VPRIV**

Discuss changes in treatment with your doctor.

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

## **4. POSSIBLE SIDE EFFECTS**

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

In studies with VPRIV, side effects were mainly seen while patients were being infused with the medicine or shortly after (infusion-related reactions). These side effects have included headache, dizziness, decreased blood pressure, increased blood pressure, nausea, tiredness, and fever/body temperature increased. If you experience any side effect like these, please tell your doctor immediately. The majority of these side effects were mild in intensity.

However a few patients experienced an allergic skin reaction such as severe rash or itching. A severe allergic reaction, with difficulty breathing, swelling of the face, lips, tongue or throat occurred. If any of these happen tell your doctor immediately.

The frequency of possible side effects listed below is defined using the following convention:

Very common	affects more than 1 user in 10
Common	affects 1 to 10 users in 100
Uncommon	affects 1 to 10 users in 1,000
Rare	affects 1 to 10 users in 10,000
Very rare	affects less than 1 user in 10,000
Not known	frequency cannot be estimated from the available data.

In studies with VPRIV the following side effects were reported:

The very common side effects are:

- headache
- dizziness
- bone pain
- joint pain
- back pain
- infusion-related reaction
- weakness/loss of strength/fatigue
- fever/body temperature increased

The common side effects are:

- abdominal pain/nausea
- abnormal blood clotting
- decreased blood pressure



- increased blood pressure
- flushing
- rapid heart beat
- rash/hives
- serious allergic reactions
- developing antibodies to VPRIV

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

## **5. HOW TO STORE VPRIV**

Keep out of the reach and sight of children.

Do not use VPRIV after the expiry date which is stated on the outer carton and vial after 'EXP'. The expiry date refers to the last day of that month.

Store in the refrigerator (2°C - 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER INFORMATION**

### **What VPRIV contains**

- The active substance is velaglucerase alfa.  
One vial of VPRIV 200 Units powder contains 200 Units of velaglucerase alfa.  
One vial of VPRIV 400 Units powder contains 400 Units of velaglucerase alfa.  
After reconstitution the solution contains 100 Units of velaglucerase alfa per ml.
- The other ingredients are sucrose, sodium citrate dihydrate, citric acid monohydrate, and polysorbate 20.

### **What VPRIV looks like and contents of the pack**

VPRIV is a powder for solution for infusion which comes as a white to off-white powder.

VPRIV 200 Units powder is packaged in a 5 ml glass vial, with 1, 5 or 25 vials per carton.

VPRIV 400 Units powder is packaged in a 20 ml glass vial, with 1, 5 or 25 vials per carton.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

#### Marketing Authorization Holder

Shire Pharmaceuticals Ireland Limited  
5 Riverwalk  
Citywest Business Campus  
Dublin 24  
Ireland

Manufacturer  
Shire Human Genetic Therapies AB  
Åldermansgatan 13  
227 64 Lund  
Sweden

**This leaflet was last approved in**

03/11/10

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.

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The following information is intended for medical or healthcare professionals only.

VPRIV is a powder for solution for infusion. VPRIV requires reconstitution and dilution and is intended for intravenous infusion only. VPRIV is for single-use only and is administered through a 0.22 µm filter. Vials are single-use only. 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. 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 vial is reconstituted using sterile water for injections:

Vial size	Water for Injections
200 Units	2.2 ml
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. The calculated volume of medicinal product is withdrawn from the appropriate number of vials. Some solution will remain in the vial:

Vial size	Extractable volume
200 Units	2.0 ml
400 Units	4.0 ml

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

From a microbiological point of view, the medicine 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.

Medicines should not be disposed of via waste water or household waste. Any unused medicine or waste material should be disposed of in accordance with local requirements