VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Gaucher disease is a rare genetic illness due to the absence of a specific enzyme in the body. About 30,000 persons worldwide have type 1 Gaucher disease. People from both sexes and all races may develop this disease but some like the Ashkenazi Jewish are more affected.

If untreated, Gaucher disease can cause anemia, fatigue, easier bruising, bleeding, bone breaking; bone loss, bone pain and swollen abdomen due to enlarged liver and/or spleen. At birth, infants with type 1 Gaucher disease appear normal. In severe cases, an enlarged liver/spleen appears after the first years of life and may progress for some years thereafter. Patients with untreated type 1 Gaucher disease may have a life expectancy up to 60 year and their life-span is generally shortened due to affected bone and blood. Presently, in many parts of the world symptomatic patients with Gaucher disease are generally receiving enzyme replacement therapy.

VI.2.2 Summary of Treatment Benefits

Velaglucerase alfa has been evaluated using consistent measures for treatment effect and safety 334 patients from 10 completed clinical studies (TKT025, TKT025EXT, TKT032, TKT033 NPU, TKT034, HGT-GCB-039, HGT-GCB-044, HGT-GCB-058, HGT-GCB-087 and HGT-GCB-091) and 1 ongoing clinical study (HGT-GCB-068). Treatment with velaglucerase alfa has been shown to be effective in key therapeutic goals for Gaucher disease: increase in hemoglobin concentration, increase in platelet count, reduction of liver volume and reduction of spleen volume. Effect on these 4 parameters was maintained after 24 months with continued velaglucerase alfa treatment.

Clinical stability in these 4 parameters is maintained when patients are switched from long-term treatment with imiglucerase to treatment with velaglucerase alfa. No safety issues were observed after switching patients who were clinically stable on imiglucerase to treatment with velaglucerase alfa at the same dose.

Velaglucerase alfa is generally well-tolerated.

VI.2.3 Unknowns Relating to Treatment Benefits

The velaglucerase alfa clinical development program was carefully planned to look at the safety and efficacy of velaglucerase alfa as long-term enzyme replacement therapy for patients with a confirmed diagnosis of type 1 Gaucher disease. Because this illness is rare and thus few patients were available for study, there needed to be a development program that used broad eligibility criteria and that was also international in scope. The program did not include children less than 2 years of age because few patients are diagnosed below this age and telling apart the different types of Gaucher disease is often not possible in children younger than 2 years. A study, currently ongoing and assessing the efficacy and safety of velaglucerase alfa ERT in children and adolescents with Type 3 Gaucher disease will help gather more information in the paediatric population. In addition, the ongoing extension study in Japanese patients will enable to assess long-term safety and efficacy in this specific population.

VI.2.4 Summary of Safety Concerns

Table 1: Important Identified Risks

Risk	What is Known	Preventability
Allergic reaction (Infusion-related reactions and hypersensitivity)	Up to 50% of patients in clinical studies had an allergic reaction to velaglucerase alfa. Most of the reactions were mild to moderate and were improved by slowing or stopping the medication or by taking certain medications.	Allergic reactions treatment should be based on the severity of the reaction, and include slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with increased infusion time. In patients who have had symptoms of allergy during velaglucerase alfa administration, pre-treatment with drugs such as antihistamines and/or corticosteroids may prevent future reactions.

Table 2: Important Potential Risks

Risk	What is Known
Velaglucerase alfa does not work because the body produces antibodies that reduce the effect of velaglucerase alfa	In clinical studies 1 of 94 patients treated with velaglucerase alfa tested positive for anti-velaglucerase alfa antibodies. The development of antibodies was not linked with any evident loss of effect, and no adverse events were reported for this patient.
Increased activated partial thromboplastin time (aPTT) (blood test that measures risk of bleeding)	Six of 94 patients (6.4%) treated with velaglucerase alfa developed a prolonged aPTT. Five of the 6 patients had high aPTT values before taking velaglucerase. The prolonged aPTT in all 6 patients were not associated with any bleeding complications.

Table 3: Important Missing Information

Risk	What is Known
Lack of information on non approved indication	Velaglucerase alfa does not reach the brain, and thus is unlikely to have any effect on the symptoms of the central nervous system usually found Gaucher disease type 2 and 3. Given the very small size of populations affected with type 2 and 3 disease, and taking the safety profile of velaglucerase alfa into account, it is unlikely that sporadic treatment attempts will give rise to any new safety findings of concern.
Lack of information in patients with a history of significant adverse reactions to other enzyme replacement therapy	Patients who have previously been treated with and have experienced anaphylactic reactions to other enzyme replacement therapy were excluded from clinical studies with velaglucerase alfa. Therefore, there are no data on the tolerability of velaglucerase alfa in those patients. Because such prior experiences do not constitute a contraindication for treatment, these patients may potentially be treated with velaglucerase alfa.

VI.2.5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for velaglucerase alfa can be found in the velaglucerase alfa's EPAR page.

Additionally Shire (the company that makes velaglucerase alfa) has developed educational materials for healthcare professionals and patients or caregivers to address the risks of serious allergic reactions (infusion related reactions and hypersensitivity) in patients receiving velaglucerase alfa at home. The educational materials were developed to remind healthcare professionals about the screening to be performed before deciding if the patient is a candidate to receive velaglucerase alfa at home and provide information to both healthcare professionals and patients/caregivers on dosing, administration and safety as well as emergency measures for patients/caregivers if such events occur at home.

VI.2.6 Planned post Authorisation Development Plan

Table 4: Summary of Ongoing and Planned Post-authorisation Studies

Study (Type and Study Number)	Objectives	Efficacy Uncertainties Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Study Report
Paediatric Investigational Plan	Assess the efficacy and safety of velaglucerase alfa ERT in children and adolescents withType 1 and Type 3 Gaucher disease.	Efficacy in Type I and Type 3 Gaucher disease as part of the PIP	Ongoing	June-July 2015
HGT-GCB-068/A Multicenter, Open-label, Efficacy and Safety Study of Velaglucerase Alfa Enzyme Replacement Therapy in Children and Adolescents with Type 3 Gaucher Disease	Explore the efficacy and safety of velaglucerase alfa enzyme replacement therapy (ERT) in children and adolescents	Efficacy in Type 3 Gaucher disease	Ongoing	Final study report Dec 2015 (estimated)

	with Type 3 Gaucher disease.			
GOS: An Observational, International, Multi-Center, Long-Term, Registry of Patients	To monitor the safety and effectiveness of velaglucerase alfa	Effectiveness in all patients	Ongoing	Interim findings reported in PSURs
A survey among healthcare professionals, patients and caregivers to assess knowledge and attitudes on prescribing and home administration conditions of VPRIV in the EU (3)	To measure the effectiveness of the educational material	Effectiveness of the Education material	Planned	Final report Q4 2017 (estimated)

VI.6.2.1 Studies which are a Condition of the Marketing Authorisation.

None of the above studies are conditions of the marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 5: Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
9.2 9.1 9.0	April 2016 March 2016 November 2015	Hypersensitivity and IRR	Addition of risk minimization measures for home administration Annexes 6, 7, 10 and 11 updated accordingly
8.2	April 2015	Not Applicable	Updated to address the comments from the Rapporteur assessment report on the renewal of the marketing authorisation of VPRIV (Procedure no. EMEA/H/C/001249/R/0021)
8.1	April 2014	Not applicable	Updated to address the comments from the PRAC assessment report (dated 10 October 2013) for RMP v8.0 Updated MedDra preferred terms for identified and potential risks Updated information from completed study HGT-GCB-044
8.0	June 2013	Not applicable	The RMP v.7.1 was reformatted to the new EU template and updated to address comments in the assessment report for version 7.1 of the RMP (dated 28 January 2013) Reinstated short summary of HGT-GCB-058
7.1	07 December 2012	Increased aPTT reinstated as an important potential risk	Updated to address the comments in the assessment report for version 7.0 of RMP (dated 03 October 2012). Deleted short summary of HGT-GCB-058
7.0	16 April 2012	Increased aPTT removed as Important identified risk Off-label use removed as an “Important Potential	Included short summary of HGT-GCB-058A Multicenter Open-Label Treatment Protocol to Observe the Safety of Gene-Activated®

		Risk" and added to "Important missing information" Important missing information "Lack of safety data for patients who transition to velaglucerase alfa and have a prior history of significant adverse drug reactions to other ERT, and insufficient safety data for patients who transition to velaglucerase alfa and who developed antibodies to previous ERT" was modified to the following: "Lack of safety data for patients who transition to velaglucerase alfa and have a prior history of significant adverse drug reactions to other ERT"	Human Glucocerebrosidase (GA-GCB, Enzyme Replacement Therapy in Newly Diagnosed or Previously Treated (with Imiglucerase) Patients with type 1 Gaucher Disease
6.0	23 June 2010	Identified risk:Infusion-related reactions Potential risks:1) Potential for reduced efficacy due to development of neutralizing antibodies to velaglucerase alfa, 2) Increased activated partial thromboplastin time (aPTT) and 3) off-label use Missing information: "Lack of safety data for patients who transition to velaglucerase alfa and have a prior history of significant adverse drug reactions to other ERT, and insufficient safety data for patients who transition to velaglucerase alfa and who developed antibodies to previous ERT	