Summary Report of Benefit-Risk Assessment

VPRIV POWDER FOR SOLUTION FOR INFUSION 400 UNITS/VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Velaglucerase alfa
Product Registrant	Takeda Pharmaceuticals (Asia Pacific) Pte Ltd
Product Registration Number	SIN16107P
Application Route	Abridged evaluation
Date of Approval	24 February 2021

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A INTRODUCTION

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

The active substance, velaglucerase alfa, is a human β-glucocerebrosidase that is produced by gene activation in a human cell line using proprietary gene activation technology. In Gaucher disease, the naturally occurring lysosomal enzyme β-glucocerebrosidase that catalyses the breakdown of glucosylcerebroside (GlcCer) is deficient. The therapeutic goal is to reduce storage and accumulation of GlcCer in affected tissues of patients.

Vpriv is available as vials containing 400 units of velaglucerase alfa as lyophilised powder. Other ingredients in the vial are sucrose, sodium citrate dihydrate, citric acid monohydrate and polysorbate 20.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, velaglucerase alfa, is manufactured at Shire Human Genetic Therapies, Inc, Cambridge, USA, and Shire Human Genetic Therapies, Inc., Lexington, USA. The drug product, Vpriv Powder for Solution for Infusion 400 units/vial, is manufactured at Vetter Pharma-Fertigung GmbH & Co., Ravensburg, Germany and Emergent Biosolutions, Baltimore, USA (previously known as Cangene bioPharma LLC).

Drug substance:
Adequate controls have been presented for the cell substrate, cell banks, unpurified bulk intermediate and raw materials used. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance were considered appropriate. The drug substance manufacturers are compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches from each of the manufacturing sites.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for both manufacturers were adequate to support the approved storage condition and shelf life. The drug substance is stored in 2 L polycarbonate vial with polypropylene closures. The drug substance is approved for storage at -65 to -85^{o}C with a shelf life of 36 months.

Drug product:
The manufacturing of the drug product comprises of formulation, sterile filtration, aseptic filling, lyophilisation, followed by packing and labelling.

All manufacturing sites involved are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored between 2-8 ºC. The in-use period following reconstitution and dilution with sterile water for injection is approved for up to 24 hours when stored between 2-8 ºC under protection from light. The container closure system is a 20 ml Type I glass vial fitted with a butyl rubber stopper.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Vpriv in the treatment of type 1 Gaucher's disease (GD) was mainly based on one pivotal Phase III study, HGT-GCB-039, and three supportive studies, TKT032, TKT034 and HGT-GCB-044.

Study HCT-GCB-039 was a multicentre, Phase III, randomised, double-blind, parallel-group study which compared the efficacy and safety of velaglucerase alfa with imiglucerase in treatment-naïve adult and paediatric patients with type 1 GD. Patients were randomised in 1:1 ratio to receive continuous intravenous (IV) infusions of either velaglucerase alfa 60 U/kg or imiglucerase 60U/kg every other week for 39 weeks (20 infusions). Imiglucerase is a currently approved therapy for type 1 GD, in this regard the choice of active comparator was considered acceptable.

The primary efficacy analysis was conducted in the intent-to-treat (ITT) population. The primary efficacy endpoint was the difference in the mean change in haemoglobin (Hgb) from baseline to week 41 between groups. Non-inferiority of velaglucerase alfa to imiglucerase was tested using a one-sided 97.5% confidence interval of the treatment difference (velaglucerase alfa minus imiglucerase) at a non-inferiority margin of -1 g/dL. Secondary endpoints included differences in the mean and the percentage changes from baseline in platelet count, liver and spleen volumes measured by magnetic resonance imaging.

A total of 35 patients were randomised in the study, of which 34 who received at least one dose of study treatment (velaglucerase alfa: 17; imiglucerase: 18) were included into the ITT and safety populations. Demographics and baseline disease characteristics were similar between the treatment arms. The median age of the total population was 30.5 years (range: 3-73 years), the majority were White (64.7%) with a smaller proportion of Asians (23.5%). Paediatric patients (2-17 years) made up 26.5% of the study population (n=9). Of the 9 patients, 4 were 2-4 years old and all were randomised to imiglucerase treatment. Approximately 58.8% of patients were splenectomised.

In the ITT population, the mean increase from baseline in Hgb concentration was 1.624 g/dL for patient treated with velaglucerase alfa and 1.488 g/dL with imiglucerase. The estimated mean treatment difference was 0.135 g/dL with the lower bound of the one-sided 97.5% CI of

-0.596 g/dL, which was above the non-inferiority margin of -1 g/dL and demonstrated non-inferiority of velaglucerase alfa to imiglucerase. The key secondary endpoints such as mean platelet counts, liver volume and spleen volume demonstrated comparable responses for both treatments.

Summary of Key Efficacy Results (Study HGT-GCB-039) (ITT Population)

	Velaglucerase alfa 60 U/kg	Imiglucerase 60 U/kg
Primary endpoint – Change from baseline in mean Hgb (g/dL)		
n	17	17
Baseline: mean (SE)	11.512 (0.299)	10.459 (0.329)
Change from baseline at Week 41: mean (SE)	1.624 (0.223)	1.488 (0.281)
Mean treatment difference (97.5%CI)	0.135 (-0.596, inf)	
Secondary endpoint – Change from baseline in mean platelet count (10^9 cells/L)		
n	17	17
Baseline mean (SE)	161.12 (22.068)	181.21 (24.580)
Change from baseline at Week 41: mean (SE)	110.41 (17.159)	144.38 (22.760)
Mean treatment difference[a] (97.5%CI)	-38.71 (-88.42, 10.99)	
Secondary endpoint – Change from baseline in mean normalised liver volume (% body weight)		
n	17	17
Baseline mean (SE)	4.44 (0.555)	4.16 (0.335)
Change from baseline at Week 41: mean (SE)	-1.31 (0.347)	-1.10 (0.182)
Mean treatment difference[a] (95% CI)	-0.07 (-0.43, 0.29)	
Secondary endpoint – Change from baseline in mean normalised spleen volume (% body weight)		
n	7	7
Baseline mean (SE)	2.53 (0.641)	4.24 (1.475)
Change from baseline at Week 41: mean (SE)	-1.34 (0.424)	-2.46 (0.966)
Mean treatment difference[b] (95% CI)	0.08 (-0.52, 0.68)	

inf: infinity; Hgb: haemoglobin; SE: standard error; CI: confidence interval
[a] Based on a mixed model adjusting for age at informed consent, splenectomy status and baseline values
[b] Based on a mixed model adjusting for age at informed consent and baseline values

The subgroup analyses of the primary efficacy endpoint in terms of age (2 to 17 years old; ≥18 years old), gender and splenectomy status consistently demonstrated comparable treatment responses from both study treatments.

Subgroup Analyses of the Primary Endpoint (ITT Population; Study HGT-GCB-039)

	Change from baseline[a] in mean Hgb (g/dL) at Week 41		
Subgroup	**n**	**Mean Treatment Difference[b]**	**95% 2-sided CI**
Age			
2 to 17 years old	9	-0.355	(-1.909, 1.199)
≥18 years old	25	0.378	(-0.444, 1.200)
Gender			
Male	16	-0.031	(-1.310, 1.248)
Female	18	0.283	(-0.424, 0.991)
Splenectomy status			
Yes	20	0.525	(-0.385, 1.435)
No	14	-0.421	(-1.593, 0.750)

[a] Baseline is the modified baseline haemoglobin concentration
[b] treatment difference reflects velaglucerase alfa compared to imiglucerase

Study TKT032 was a supportive multi-centre, Phase III, randomised, double-blinded, parallel group, 2-dose study conducted in adult and paediatric patients with type 1 GD. Patients were either treatment naïve or have not been treated for Gaucher disease within 30 months prior to study entry. Splenectomised patients were excluded from this study. A total of 25 patients were randomised 1:1 to receive either fixed dose velaglucerase alfa 45 U/kg or 60 U/kg EOW over 12 months (45 U/kg: 13 patients; 60 U/kg: 12 patients). The primary efficacy endpoint was the mean change in Hgb concentration from baseline to 12 months in the 60 U/kg treatment group. Secondary efficacy endpoints were the change from baseline to 12 months in mean platelet counts, normalised liver and spleen volumes for both treatment groups.

The demographics and baseline characteristics between the 2 dose groups were generally similar. The median age was 25.0 years (range: 4 to 62 years) with 7 patients aged <18 years (28.0%, range: 2-17 years). Baseline Hgb concentrations and platelet counts were similar between both groups (overall mean: 10.65 g/dL and 97.0 x 10^9 cells/L respectively).

After 12 months of treatment, velaglucerase alfa at 60 U/kg EOW demonstrated statistically significant increases from baseline in the mean Hgb concentration, platelet counts, normalised spleen and liver volumes. Also, the 60 U/kg dose was observed to elicit a numerically larger platelet response than the 45 U/kg dose (60 U/kg: 50.88 x 10^9 cells/L; 45 U/kg: 40.92 x 10^9 cells/L) and a numerically larger reduction in mean normalised liver volume by Month 12 (60 U/kg: -0.84%; 45 U/kg: -0.30%).

Summary of Key Efficacy Results at Week 53 (Study TKT032) (ITT Population)

	Velaglucerase alfa	
	60 U/kg	**45 U/kg**
Primary endpoint – Change from baseline in mean Hgb (g/dL)		
n	12	13
Baseline: mean (SE)	10.688 (0.367)	10.723 (0.354)
Change from baseline: mean (SE)	2.429 (0.324)	2.438 (0.436)
%change from baseline: mean (SE)	23.25 (3.371)	23.81 (4.641)
Secondary endpoint – Change from baseline in mean platelet count (10^9 cells/L)		

n	12	13
Baseline: mean (SE)	107.96 (31.026)	84.38 (19.036)
Change from baseline: mean (SE)	50.88 (12.223)	40.92 (13.640)
%change from baseline: mean (SE)	65.93 (16.932)	66.38 (23.815)
Secondary endpoint – Change from baseline in mean normalised liver volume (% body weight)[a]		
n	12	13
Baseline: mean (SE)	3.89 (0.444)	3.95 (0.375)
Change from baseline: mean (SE)	-0.84 (0.333)	-0.30 (0.286)
%change from baseline: mean (SE)	-17.02 (4.538)	-6.22 (5.429)
Secondary endpoint – Change from baseline in mean normalised spleen volume (% body weight)[a]		
n	12	13
Baseline: mean (SE)	3.40 (0.692)	4.05 (0.979)
Change from baseline: mean (SE)	-1.92 (0.511)	-1.87 (0.595)
%change from baseline: mean (SE)	-50.35 (5.339)	-39.88 (5.513)

[a] Results at Week 51

Study TKT034 was a multi-centre, Phase II/III, open-label, 12-month, uncontrolled study designed to evaluate the safety of velaglucerase alfa in adult and paediatric patients previously treated with imiglucerase therapy for at least 30 consecutive months and on stable doses for at least 6 months prior to study entry. Patients received the same dose of velaglucerase alfa as their prior imiglucerase dose (range: 15-60 U/kg). Clinical efficacy was a secondary objective in this study and the efficacy endpoints included the mean change from baseline in Hgb concentration, platelet counts, and normalised liver and spleen volumes after transitioning to velaglucerase alfa treatment.

A total of 41 subjects were enrolled and 40 patients received at least 1 full or partial dose. Most of the patients were White (92.5%) and there was one Asian patient (2.5%). The median age was 36.5 years (range: 9-71 years) and there were 9 paediatric patients (<18 years; 22.5%). All patients were treated with imiglucerase for a median of 67 months (range: 22.0-191.5 months) before beginning the study and 3 patients (7.5%) tested positive for anti-imiglucerase antibodies prior to receiving study treatment. Overall, patients were treated for a median of 50.1 weeks (range: 0.1-51.6 weeks).

For the efficacy endpoints, the mean change in Hgb from baseline was -0.101 g/dL (90% CI -0.272, 0.070), which was within the predefined efficacy criterion of ±1 g/dL. The mean change in platelet count from baseline was 5.956×10^9 cells/L and the percentage change from baseline after 1 year was 7.04% (90% CI 0.54, 13.53), which was within the predefined efficacy criterion of ±20%. The mean percentage decrease from baseline in normalised liver volume was -0.03% (90% CI -2.62, 2.56), and that in normalised spleen volume was -5.56% (90% CI

-10.77, -0.35). Both were within the predefined efficacy criterion of ±15%. The switch study showed that the baseline Hgb, platelets, normalised liver and spleen volume were maintained over the long term (51 weeks) within predefined efficacy criterions, suggesting that the efficacy was comparable.

Summary of Key Efficacy Results at Week 53 (Study TKT034) (ITT Population)

	Velaglucerase alfa 15 to 60 U/kg
Change from baseline in mean Hgb (g/dL)	
n	40
Baseline: mean (SE)	13.578 (0.193)
Change from baseline: mean (SE)	-0.101 (0.101)
%change from baseline: mean (SE)	-0.57 (0.752)
Change from baseline in mean platelet count (10^9 cells/L)	
n	40
Baseline: mean (SE)	174.713 (13.354)
Change from baseline: mean (SE)	5.956 (8.141)
%change from baseline: mean (SE)	7.04 (3.853)
Change from baseline in mean normalised liver volume (% body weight) [a]	
n	40
Baseline: mean (SE)	2.09 (0.092)
Change from baseline: mean (SE)	0.00 (0.034)
%change from baseline: mean (SE)	-0.03 (1.536)
Change from baseline in mean normalised spleen volume (% body weight) [a]	
n	36
Baseline: mean (SE)	0.75 (0.110)
Change from baseline: mean (SE)	-0.09 (0.032)
%change from baseline: mean (SE)	-5.56 (3.086)

[a] Results at Week 51

All patients who completed studies TKT032, TKT034 and HGT-GCB-039 were recruited into the Phase III open-label extension study HGT-GCB-044, which comprised a total of 95 patients made up of 25 patients from study TKT032, 38 patients from TKT034 and 32 patients from HGT-GCB-039 study (velaglucerase alfa: 16; imiglucerase: 16). All patients received IV velaglucerase alfa EOW at doses ranging between 15 U/kg and 60 U/kg. Those who had transitioned from studies TKT032 (dose finding) and HGT-GCB-039 received the 60 U/kg dose, while those from TKT034 received the same dose as in TKT034. Patients from HCT-GCB-039 previously on imiglucerase 60U/kg were switched to velaglucerase alfa at the same dose (60 U/kg). Patients were eligible to remain in the study until velaglucerase alfa became

commercially available, the study was discontinued, or until early discontinuation from the study.

The endpoints for HGT-GCB-044 were similar to HGT-GCB-039 and assessed after 24 months of treatment, and also included an assessment of GD disease-related bone disease. For the 2-year analyses, baseline was defined as data captured before the first dose in the earlier pivotal studies. Subjects were analysed in 3 treatment groups – the overall velaglucerase alfa treatment naïve population (n=39), those who were randomised to receive imiglucerase in HGT-GCB-039 (n=16) and those from TKT034 who transitioned from imiglucerase to velaglucerase alfa (n=38). The median duration in these 3 populations was 4.60 years (range: 2.3-5.8 years), 4.35 years (range: 1.9-4.8 years) and 2.80 years (range: 2.0-5.3 years), respectively.

For the overall velaglucerase alfa treatment naïve population, there was an increase in mean Hgb concentration and mean platelet count and a decrease in mean normalised liver and spleen volumes by Month 24. Similarly, increases in mean Hgb concentration and mean platelet count and decreases in mean normalised liver and spleen volumes were seen in patients who switched from imiglucerase in HGT-GCB-039 to velaglucerase alfa. The change in the clinical parameters for both populations are maintained up to Month 24. For patients who switched from imiglucerase to velaglucerase alfa in TKT034, mean Hgb concentrations, platelet count, normalised liver volume and spleen volume were generally maintained.

Summary of Key Efficacy Results (Study HGT-GCB-044) (ITT Population)

	Overall velaglucerase alfa naïve group	HCT-GCB-039 IMI -> velaglucerase alfa	TKT034 switch population
n	39	16	38
Change from baseline at Month 24 in Hgb (g/dL): mean (SE)	2.75 (0.232)	2.00 (0.352)	-0.05 (0.146)
Change from baseline at Month 24 in platelet count ($x10^9$/L): mean (SE)	87.85 (7.488)	160.94 (20.512)	9.03 (5.740)
Change from baseline at Month 24 in normalised liver volume (% body weight): mean (SE)	-1.206 (0.1454)	-1.688 (0.2237)	-0.026 (0.0363)[a]
Change from baseline at Month 24 in normalised spleen volume (% body weight): mean (SE)	-2.662 (0.4108)[b]	-3.633 (1.4057)[c]	-0.110 (0.0399)[d]

[a] based on n=37
[b] based on n=30
[c] based on n=6
[d] based on n=34

These results suggest that velaglucerase alfa had a beneficial effect on the 4 key clinical parameters of GD: anaemia, thrombocytopenia, hepatomegaly and splenomegaly, which were

defined as the primary efficacy variables of the study by Month 24, and the effect was maintained until study completion.

For the overall velaglucerase alfa treatment naïve population, there was an overall improvement in bone mineral density (BMD) Z-scores for the lumbar spine. This improvement was less significant for subjects who switched from imiglucerase to velaglucerase alfa, although there was no worsening of scores up to Month 24. A similar trend was observed for the 8 children included in the study population. For the patients who switched from imiglucerase in HGT-GCB-039, there was numerical improvement in the mean change in lumbar spine BMD Z-score at Month 24 . For the patients who switched from imiglucerase to velaglucerase alfa in TKT034, the Z-score was maintained up to Month 24. No notable change to femoral neck bone mineral density was observed for all three populations.

Summary of Key Skeletal Endpoints (Lumbar Spine BMD) for HGT-GCB-044

	Overall velaglucerase alfa naïve group	**HCT-GCB-039 IMI -> velaglucerase alfa**	**TKT034 switch population**
Z-score – Month 24			
n	31	11	29
Change from baseline: Mean (95% CI)	0.62 (0.39, 0.84)	0.47 (0.19, 0.75)	0.08 (-0.08, 0.24)
g/cm^2 – Month 24			
n	31	11	29
Change from baseline: Mean (95% CI)	0.067 (0.042, 0.092)	0.05 (0.021, 0.079)	0.003 (-0.015, 0.022)
g/cm^2 – Month 24			
n	28	7	11
Change from baseline: Mean (95% CI)	0.952 (0.898, 1.007)	1.110 (0.931, 1.289)	1.023 (0.970, 1.075)
g/cm^2 – Month 63			
n	6	0	4
Change from baseline: Mean (95% CI)	0.965 (0.902, 1.028)	-	0.977 (0.916, 1.039)

Overall, the results of the four studies were consistent in meeting the primary and secondary efficacy endpoints, and adequately supported the efficacy of velaglucerase alfa for the enzyme replacement therapy for Gaucher disease.

D ASSESSMENT OF CLINICAL SAFETY

The overall safety population comprised 321 patients including 33 patients from study HCT-GCB-039, 25 patients from TKT032, 40 patients from TKT 034, 211 patients from an open-label clinical safety study HGT-GCB-058 as well as 12 patients from TKT025. A total of 60 patients were treatment naïve and 261 patients switched from imiglucerase to velaglucerase alfa. Patients were between 4 and 71 years old at the time of first treatment with velaglucerase

alfa. There were 47 paediatric patients and 27 were treatment naïve, while 20 were switched from imiglucerase.

Overview of safety profile (Treatment-Naïve Population) – 0-9 months exposure

	Velaglucerase Alfa			Imiglucerase
AE n (%)	**Overall N=54**	**45 U/kg N=13**	**60 U/kg N=41**	**60 U/kg N=17**
Any TEAE	51 (94.4)	11 (84.6)	40 (97.6)	16 (94.1)
Treatment-related TEAE	33 (61.1)	9 (69.2)	24 (58.5)	6 (35.3)
SAE	4 (7.4)	0	4 (9.8)	0
Treatment-related SAE	1 (1.9)	0	1 (2.4)	0
Discontinuations due to AE	0	0	0	0
Deaths due to AE	0	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
Source: studies TKT025, TKT032, HGT-GCB-039

Overview of velaglucerase alfa safety profile (Treatment-Naïve Population) – 0-12 months exposure

AE n (%)	**Overall N=51**	**45 U/kg N=13**	**60 U/kg N=38**
Any TEAE	48 (94.1)	11 (84.6)	37 (97.4)
Treatment-related TEAE	31 (60.8)	9 (69.2)	22 (57.9)
SAE	6 (11.8)	0	6 (15.8)
Treatment-related SAE	1 (2.0)		1 (2.6)
Discontinuations due to AE	0	0	0
Deaths due to AE	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
Source: studies TKT025, TKT025EXT, TKT032, HGT-GCB-039, HGT-GCB-044

Overview of velaglucerase alfa safety profile (Switched from Imiglucerase; Studies TKT034 and HGT-GCB-044)

	Study TKT034					Study HGT-GCB-044
AE n (%)	**Overall N=40**	**15 U/kg N=15**	**30 U/kg N=12**	**45 U/kg N=6**	**60 U/kg N=7**	**60 U/kg N=16**
Any TEAE	34 (85.0)	12 (80.0)	11 (91.7)	5 (83.3)	6 (85.7)	15 (93.8)
Treatment-related TEAE	11 (27.5)	6 (40.0)	3 (25.0)	1 (16.7)	1 (14.3)	7 (43.8)
SAE	4 (10.0)	1 (6.7)	1 (8.3)	2 (33.3)	0	4 (25.0)
Treatment-related SAE	0	0	0	0	0	0
Discontinuations due to AE	1 (2.5)	1 (6.7)	0	0	0	0
Deaths due to AE	0	0	0	0	0	1 (6.3)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Overview of velaglucerase alfa safety profile (Switched from Imiglucerase; Study HGT-GCB-058)

	Previously treated					Treatment naïve
AE n (%)	**Overall N=205**	**15 U/kg N=5**	**30 U/kg N=93**	**45 U/kg N=32**	**60 U/kg N=75**	**60 U/kg N=6**
Any TEAE	89 (34.4)	4 (80.0)	36 (38.7)	12 (37.5)	37 (49.3)	3 (50.0)

Treatment-related TEAE	35 (17.1)	2 (40.0)	7 (7.5)	6 (18.8)	20 (26.7)	1 (16.7)
SAE	11 (5.4)	0	2 (2.2)	0	9 (12.0)	0
Treatment-related SAE	7 (3.4)	0	2 (2.2)	0	5 (6.7)	0
Discontinuations due to AE	3 (1.5)	0	0	1 (3.1)	2 (2.7)	0
Deaths due to AE	0	0	0	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

Adverse events (AEs) considered related to the use of velaglucerase alfa included headache, dizziness, abdominal pain/upper abdominal pain, bone pain, arthralgia, pyrexia and infusion related reactions. Most of the treatment-emergent adverse events which occurred with velaglucerase alfa were of mild or moderate in intensity.

There were no discontinuations due to adverse events in the treatment-naïve population. For patients who were switched from imiglucerase to velaglucerase alfa, one discontinuation was due to an anaphylactoid reaction, one was due to nausea and two were due to increased blood pressure. There were no deaths attributed to velaglucerase alfa. There was one treatment-related serious adverse event (SAE) in a treatment-naïve patient, consisting of a mild allergic skin reaction which did not recur with treatment rechallenge. One treatment related SAE of mild migraine was also reported in previously treated patient. All other SAEs were considered to be unrelated to velaglucerase alfa.

The AEs of special interest were infusion-related reactions and immunogenicity. Most infusion-related AEs were mild or moderate in intensity and did not result in study discontinuation. Among treatment-naïve patients with up to 12 months exposure to velaglucerase alfa, 27 of 51 (52.9%) patients reported infusion-related AEs and all were of mild severity. Among patients who switched from imiglucerase to velaglucerase alfa in study TKT034, 9 of 40 (22.5%) patients reported infusion-related AEs; of these 9 patients, 6 were mild and the remaining 3 were moderate in severity. In study HGT-GCB-058, 27 patients (13.2%) who were previously treated and 1 treatment naïve patient (16.7%) reported infusion-related adverse events.

The incidence rates of immunogenicity reactions were low. Of the 321 patients (treatment-naïve and switched) treated with velaglucerase alfa in Phase I/II/III studies, 2 treatment-naive patients developed anti-velaglucerase alfa antibodies. Among patients who switched from imiglucerase to velaglucerase alfa, 11 patients who developed anti-velaglucerase alfa antibodies were positive for anti-imiglucerase antibodies at baseline, while 9 previously treated patients reported anti-velaglucerase antibodies at baseline and this could be attributed to cross-reactivity.

Overall, velaglucerase alfa presented an acceptable safety profile for the target patient population which appeared similar to that of imiglucerase. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Gaucher disease is a rare, pan-ethnic disease, which occurs when an inherited deficiency of the lysosomal enzyme, glucocerebrosidase, leading to progressive accumulation of glucocerebroside within macrophages and subsequent tissue and organ damage, typically of the liver, spleen, bone marrow, and brain. The clinical features reflective of type 1 Gaucher disease include anaemia, thrombocytopenia, hepatomegaly, splenomegaly, skeletal pathology, growth retardation, and decreased quality of life. Enzyme replacement therapy has been the mainstay of treatment that aims to reduce organomegaly, improve haematological parameters and prevent skeletal complications.

The efficacy of velaglucerase alfa in treatment-naïve type 1 Gaucher disease patients was demonstrated to be non-inferior to imiglucerase in terms of mean increase in Hgb, and supported by improvements in other clinical parameters including platelets count, liver volume and spleen volume. The extension study HGT-GCB-044 also provided efficacy data up to 2 years, including long term efficacy on skeletal complications which are associated with Gaucher disease.

The safety profile of velaglucerase alfa was considered acceptable and similar to alternative enzyme replacement therapies. Adverse events generally occurred at a similar incidence in the velaglucerase alfa subjects compared to those who received imiglucerase. The most notable safety concerns were infusion-related reactions and immunogenicity, which have been adequately addressed in the package insert.

Overall, the benefit-risk profile of velaglucerase alfa for the long-term enzyme replacement therapy in patients with type 1 Gaucher disease was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of velaglucerase alfa for the long-term enzyme replacement therapy in patients with type 1 Gaucher disease was deemed favourable and approval of the product registration was granted on 24 February 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

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 β-D-glucopyranoside to p-nitrophenol per minute at 37ºC.
** produced in an HT-1080 human fibroblast cell line by recombinant DNA technology.

Excipient with known effect:
One vial contains 12.15 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

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

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

Special populations
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)
Elderly patients may be treated within the same dose range (15 to 60 units/kg) as other adult patients. See section 5.1.

Paediatric population
Twenty of the 94 patients (21%) who received velaglucerase alfa during clinical studies were in the paediatric and adolescent age range. The studies allowed inclusion of patients 2 years and older; however, no data are available for children under the age of 4 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 0.2 µm or 0.22 µm filter.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 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.

One additional patient developed IgG antibodies to velaglucerase alfa that were reported as having neutralizing activity during an extension study. No adverse events considered related to velaglucerase alfa 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 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. Caution should be exercised when administering 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

Summary of the safety profile
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.

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. Adverse drug reactions derived from post-marketing reports other than interventional clinical trials are printed in italics.

Table 1: Adverse reactions reported with VPRIV observed in patients with type 1 Gaucher disease Italic text denotes post-marketing event.

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		*Dyspnea*	
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	

Description of selected adverse reactions
Vomiting
In some cases vomiting can be serious (reported from post-marketing experience).

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.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

There is limited information available regarding overdose with velaglucerase alfa. 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..

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 (≥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, randomized, 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 randomized 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, randomized, 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 trials. Only 1 out of 163 patients assessed developed anti-velaglucerase alfa antibodies during the study.

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

Extension Study 044
A total of 95 patients (73 adult and 22 paediatric) who participated in studies 032, 034, and 039 enrolled in the open label extension study and were treated with velaglucerase alfa. 57 patients were treatment-naïve. All patients received at least 2 years of ERT and were followed for a mean of 4.5 years (min. 2.3 years, max 5.8 years).

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

Table 2: Results at 24 months - Change from Baseline – Study 044 ITT Population

Clinical Parameters	**Overall** velaglucerase alfa **group (N=39)** - **Mean change from baseline (95% CI)**	**Patients treated with imiglucerase for 9 months and then** velaglucerase alfa **for 15 months (N=16)** - **Mean change from baseline (95% CI)**	**Patients who switched from long-term imiglucerase treatment to** velaglucerase alfa **(N=38)** - **Mean change from baseline (95% CI)**
Haemoglobin concentration (g/dL)	2.75 (2.28, 3.22)	2.00 (1.25, 2.75)	-0.05 (-0.34, 0.25)
Platelet count (x 10^9/L)	87.85 (72.69, 103.00)	160.94 (117.22, 204.66)	9.03 (-2.60, 20.66)
Normalized Liver Volume* (%BW)	-1.21 (-1.50, -0.91)	-1.69 (-2.16, -1.21)	-0.03 (-0.10, 0.05)
Normalized Spleen Volume* (%BW)[§]	-2.66 (-3.50, -1.82)	-3.63 (-7.25, - 0.02)	-0.11 (-0.19, -0.03)

[§] Excludes patients with splenectomy. N=30, 6 and 34 for the 3 above groups.
*Liver and spleen volume is normalized as a percentage of body weight. Normal spleen is defined as 0.2% of body weight; normal liver as 2.5% of body weight
Note: Imputation was applied to intermittent missing data.

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

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

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

Paediatric population

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

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

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

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 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.

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.

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.

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6.3 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.

6.4 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 and 5 vials. Not all pack sizes may be marketed.

6.5 Special precautions for disposal and other handling

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

Aseptic technique must be used.

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, 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 product should be mixed gently. It should not be shaken. The infusion should be initiated within 24 hours from the time of reconstitution.

Chemical and physical in-use stability of the reconstituted and diluted solution 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.

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

7. Local Product Registrant

Takeda Pharmaceuticals (Asia Pacific) Pte Ltd
21 Biopolis Road
Nucleos North Tower, Level 4
Singapore 138567

8. DATE OF REVISION

Dec 2020