

New Drug

Velaglucerase Alfa for the Management of Type 1 Gaucher Disease

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ABSTRACT

Background: Gaucher disease (GD) is the most common lysosomal storage disease, (frequency of 1:40,000 to 1:60,000). Ninety-Five percent of patients have type 1 (nonneuropathic type). Symptomatic patients with type 1 GD are treated with enzyme replacement therapy (ERT) to improve disease-induced effects on hemoglobin, platelets, and liver and spleen volume. Currently, several ERTs are available.

Objective: The goal of this article was to review the pharmacology, efficacy, and safety data available for the use of a recently approved ERT, velaglucerase alfa, for the treatment of type 1 GD in symptomatic pediatric and adult patients.

Methods: Serial searches of MEDLINE, EMBASE, and Cochrane databases for English-language, peer-reviewed, clinical data (using the search term *velaglucerase alfa*) were completed, with the final search in November 2011. All identified, peer-reviewed published human data were used for this review. Due to minimal peer-reviewed published data, those data reported via clinical trial registries or in the form of published abstracts were included. The manufacturer was contacted and given the opportunity to submit supplemental data for consideration of inclusion by the author.

Results: Velaglucerase alfa is produced through gene activation technology and is identical to wild-type enzyme. As with other ERTs for type 1 GD, velaglucerase alfa targets accumulated glucocerebroside primarily within the lysosome of the macrophages in the affected organs and systems. When administered at doses of 60 U/kg intravenously, velaglucerase alfa follows linear pharmacokinetics and is rapidly eliminated, with a mean (SD) residence time or time for 63% of the dose to be cleared from systemic circulation of 14 (4) minutes. Four trials and early access program data reporting efficacy were identified for this review: 5

peer-reviewed publications, 3 clinical trial registry reports, and 1 abstract-only publication. Phase I/II data with an extension phase ($n = 12$) showed significant improvements (all, $P < 0.004$) in hemoglobin concentrations (21.7%), platelet counts (157.8%), and hepatic (−42.8%) and spleen (−79.3%) volumes at 48 months. Bone mineral density data reported out to 69 months for this extension population noted significant improvements in z score slope for both lumbar spine (0.14 z score unit per year; $P < 0.01$) and femoral head (0.08 z score unit per year; $P < 0.01$). Benchmarking of 7 patients with complete clinical datasets at 57 months identified achievement and maintenance of therapeutic goals set by the International Collaborative Gaucher Group for anemia, platelet counts, hepatosplenomegaly, and bone mineral density. Thirty-eight patients enrolled in an open-label, therapy-switch trial who received velaglucerase alfa at doses consistent with current doses of imiglucerase maintained hemoglobin (−0.101 g/dL [95% CI, −0.272 to 0.07]) and platelet counts (7.04% [95% CI, 0.54% to 13.53%]) at 53 weeks after therapy change. Phase III data evaluating 2 dosing regimens of velaglucerase alfa 60 and 45 U/kg intravenously every other week reported significant improvements in most measured clinical parameters at 12 months: hemoglobin concentrations (60 U/kg, 2.429 [0.324] g/dL [$P < 0.0001$]; 45 U/kg, 2.438 g/dL [95% CI, 1.488 to 3.389]), platelet counts (60 U/kg, $50.88 \times 10^9/L$ [95% CI, 23.97 to 77.78]; 45 U/kg, $40.92 \times 10^9/L$ [95% CI, 11.2 to 70.64]), spleen volumes (60 U/kg, −1.92% of body weight [95% CI, −3.04 to −0.79]; 45 U/kg, −1.87% of body weight [95% CI, −3.17 to −0.57]), and hepatic volumes (60 U/kg, −0.84% of body weight [95% CI, −1.58 to

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–0.11]). A subanalysis of the pediatric population showed clinical improvements at 12 months in both dosing groups: hemoglobin concentrations (60 U/kg, 1.74 g/dL [95% CI, 0.72 to 2.78]; 45 U/kg, 2.77 g/dL [95% CI, –0.99 to 6.53]), platelet counts (60 U/kg, $49.9 \times 10^9/L$ [95% CI, –32.1 to 131.9]; 45 U/kg, $60.3 \times 10^9/L$ [95% CI, –103.1 to 223.7]), spleen volumes (60 U/kg, -2.1 cm^3 [95% CI, –5.3 to 1.1]; 45 U/kg, -0.7 cm^3 [95% CI, –2.6 to 1.2]), and hepatic volumes (60 U/kg, -0.7 cm^3 [95% CI, –1.4 to 0.0]; 45 U/kg, -0.3 cm^3 [95% CI, –1.7 to 1.1]). Data comparing velaglucerase alfa with imiglucerase identified similar changes in hemoglobin concentrations at 1.624 g/dL and 1.488 g/dL, respectively, after 9 months of therapy. Safety was reported in 3 identified studies and in data reported from the early access program: 3 peer-reviewed publications, 3 studies reported in clinical trial registries, and 1 abstract publication. Patients experienced a minimal number of adverse effects, and most reactions were mild to moderate in severity; 1 patient developed an anaphylactoid reaction and was discontinued from the trial. Antibody formation has been described with velaglucerase alfa but when compared with that of imiglucerase, seroconversion is less frequent (1% and 23%, respectively). Dosing regimens, from 30 to 60 U/kg intravenously every other week, have been assessed. Currently, the manufacturer recommends 60 U/kg intravenously every other week; however, further studies and evaluation of current study dosing regimens are needed to determine if there is a lower effective dose.

Conclusions: Although a minimal amount of data are available for this relatively new biological agent, velaglucerase alfa reportedly is effective in the achievement and maintenance of therapeutic goals in type 1 GD in both treatment-naïve and patients previously treated with imiglucerase. This agent has been reasonably well tolerated in clinical trials and may be considered for use in symptomatic patients with type 1 GD. (*Clin Ther.* 2012;xx:xxx) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: enzyme replacement therapy, Gaucher disease, type 1 Gaucher disease velaglucerase alfa.

INTRODUCTION

Gaucher disease (GD) is the most prevalent lysosomal storage disease. This autosomal recessive inherited condition, occurring at a frequency of 1:40,000 to

1:60:000 within the general population, results in multisystem accumulation for glucocerebrosidase due to deficiency of the enzyme β -glucocerebrosidase.^{1–3} Accumulation of glucocerebrosidase in macrophages (Gaucher cells) results in organomegaly of the liver and spleen as well as dysfunction within the bone marrow, skeleton, lungs, and, with certain types, within the central nervous system.⁴ Three types of GD have been described. Type 1 GD, also referred to as nonneuropathic GD, is the most common; it occurs in 95% of patients, is the least severe type, and has no effects on the central nervous system.³ Type 2 GD, otherwise termed infantile GD, has a more acute onset, affects both the visceral and the central nervous systems, and generally results in death by 2 years of age. Type 3 GD generally presents later in childhood but, as with infantile disease, it affects both the visceral and central nervous systems.¹ Enzyme replacement therapy (ERT) is the mainstay of therapy for type 1 GD. Due to the inability of ERT compounds to cross into the central nervous system, ERT is only used in type 1 GD because it is unlikely to alter the disease progression of type 2 or 3 GD.¹ Alglucerase (placental-derived glucocerebrosidase), which received orphan drug status in 1991, was the first ERT available for the treatment of type 1 GD. Shortly after the introduction of alglucerase, imiglucerase, a recombinant product from Chinese hamster ovary cells, was approved by the US Food and Drug Administration (FDA) in 1994. Imiglucerase, which differs from wild-type glucocerebrosidase amino acid sequence by a single amino acid substitution, has been the primary treatment agent for patients with type 1 GD since its approval.⁴ In February 2010, the FDA approved velaglucerase alfa, a new ERT agent, for the treatment of type 1 GD in both pediatric and adult patients.⁵ This approval was timely and important as ERT has become the standard of therapy for patients with symptomatic type 1 GD, and velaglucerase alfa provides an alternative to imiglucerase, which has recently been in short supply.⁶ This review focuses on the pharmacology, safety, and efficacy data available for the use of velaglucerase alfa in the treatment of type 1 GD in symptomatic pediatric and adult patients.*

*Trademark: VPRIV™ (Shire Human Genetic Therapies, Inc., Cambridge, Massachusetts).

METHODS

Serial searches of MEDLINE, Cochrane databases, and EMBASE (all dates posted through November 2011), using the search term *velaglycerase alfa*, were limited to clinical trials in the English language, with the final search occurring on November 21, 2011, to ensure inclusion of all indentified, published, peer-reviewed data for this new ERT. All identified prospective human trials, including those reported in clinical trial registries with results and abstract-only publications, were included in the review. Due to the limited amount of published prospective data, the manufacturer of velaglycerase alfa (Shire Human Genetic Therapies, Inc) was contacted and provided the opportunity to submit unpublished data for review by the author for potential inclusion in the review. Personal contact with the manufacturer did not result in any additional data not previously published in at least abstract form. One pharmacokinetic analysis, 1 report from early access program data, and 4 Phase I through III investigations were identified that correlate with 5 peer-reviewed publications, 3 investigations with completed results reported in clinical trial registries, and 2 abstract-only publications. Secondary to the minimal peer-reviewed published data for this ERT, the product labeling was used to supplement published data in this review.

PHARMACOLOGY

Velaglycerase alfa for injection, a hydrolytic lysosomal glucocerebrosidase, is indicated for long-term ERT in pediatric and adult patients with type 1 GD. It is a glycoprotein comprising 497 amino acids with a molecular weight of ~63 kDa.⁵ Velaglycerase alfa is produced via gene activation technology in a human fibroblast cell line. Unlike imiglucerase, the amino acid sequence of velaglycerase alfa is identical to the wild-type enzyme.^{4,5}

Velaglycerase alfa degrades accumulated glucocerebroside to glucose and ceramide within the lysosomes

of macrophages in the affected organs and systems. Velaglycerase alfa contains predominantly high mannose-type N-linked glycan chains. Macrophages are targeted, and velaglycerase alfa is internalized into the macrophages via the mannose receptors, providing access to accumulated glucocerebrosides.^{4,5}

PHARMACOKINETICS

Patients enrolled in a safety and efficacy analysis of velaglycerase alfa were assessed using pharmacokinetic modeling with initial doses of this human β -glucocerebrosidase.⁷ The initial 3 patients underwent dose escalation every other week; with each subsequent dose of velaglycerase alfa, patients received 15 U/kg intravenously followed by 30 U/kg intravenously and 60 U/kg intravenously. After the tolerated administration of maximally escalated doses in these 3 patients, 9 additional patients were enrolled and received velaglycerase alfa at a dose of 60 U/kg intravenously every other week. The first 3 patients were sampled at weeks 1, 3, and 5 of therapy (with each dose escalation); 1 of these patients was excluded from the pharmacokinetic analysis secondary to inconsistent patterns of enzyme activity after administration of 30 and 60 U/kg intravenously. The remaining 9 patients were sampled at week 1 with the initial dose of 60 U/kg. WinNonlin (Professional Version 4.1 or 5.0 Pharsight Corporation, Mountain View, California) was used for modeling 1-compartment model serum concentration curves. Individual patient samples were evaluated for the following pharmacokinetic parameters: AUC, C_{max} , T_{max} , mean residence time or time required for clearance of at least 63% of the dose, serum clearance, and apparent volume at steady state. Both serum clearance and apparent volume at steady state were also reportedly normalized for body weight. Mean values of pharmacokinetic parameters for a dose of 60 U/kg intravenously for each of the 11 evaluated patients are

Table I. Mean (SD) pharmacokinetic parameters after administration of 60 U/kg intravenous infusion.⁷

C_{max} (mU/mL)	AUC (min*mU/mL)	CL (mL/min)	CL per BW (mL/min/kg)	MRT (min)	$t_{1/2}$ (min)	V_{ss} (% BW)
80.6 (20.3)	5116 (1322)	717 (161)	12.6 (3.7)	14 (4)	9.8 (2.8)	17.5% (5.1%)

CL = serum clearance; CL per BW = serum clearance normalized to body weight; MRT = mean residence time; V_{ss} (% BW) = apparent volume normalized to BW.

reported in Table I.⁷ At the clinically relevant dose administered in the pharmacokinetic analysis, velaglucerase alfa followed first-order, linear pharmacokinetics. As with other ERTs for type 1 GD, velaglucerase alfa was rapidly cleared from systemic circulation, with a mean (SD) residence time of 14 (4) minutes.

No notable gender differences were identified in the pharmacokinetics of males versus females. Description of the pharmacokinetics of this agent in populations with end-organ impairment (eg, renal or hepatic) is not available either within the literature or the product labeling.⁵ Evaluation of pharmacodynamic properties of the enzyme at the level of the affected tissue is likely to correlate most closely with the drug effect; however, the invasive nature of such analysis, which would likely require tissue sampling, would be difficult in human subjects.

EFFICACY

Four peer-reviewed publications, results from 3 investigations reported in clinical trial registries, and 1 abstract-only publication of Phase I–III trials of velaglucerase alfa were identified for this review (Table II^{2,4,8–12}). Four of these reports include the same patient sets, and they report a subset of the original population (eg, extension phase, pediatric patients). Much of the currently available data for this biological agent are only available in abstract form or from results reported within clinical trial registries. Only 4 peer-reviewed publications concerning the efficacy of this agent in humans were identified in the literature search.

A defined set of therapeutic goals for evaluation of treatment effectiveness were identified in 2004 by the International Collaborative Gaucher Group. These goals, derived from the extensive treatment experience with imiglucerase, are used to assess improvement in the organs and systems effected by type 1 GD.^{4,13} Using these goals, clinical response is assessed during the first 12 months, 12 to 24 months, and >24 months of treatment. Therapeutic goals include improvement in and resolution of anemia and thrombocytopenia, decreases in hepatomegaly and splenomegaly, and improvement in skeletal pathology (Table III).^{3,13} Not all prospective efficacy studies used these specific criteria for assessment; each study assessed a compilation of these outcomes. These criteria are helpful, however, in understanding the overall goal of ERT treatment in type 1 GD.

Zimran et al² reported Phase I/II and extension data for ERT with velaglucerase alfa in 12 adult patients with type 1 GD (same patient population assessed in pharmacokinetic analysis). Symptomatic adult patients with enzymatically confirmed type 1 GD >17 years old were included and received 60 U/kg intravenously every other week if they had an intact spleen, anemia, thrombocytopenia, and negative screen for hepatitis B and C and HIV. Patients had to be ERT naive or had not received imiglucerase or miglustat in the previous 12 months. Patients receiving other investigational agents or who were unable to comply with the study protocol were excluded. Patients were initially enrolled in a 9-month Phase I/II trial and then given the option to continue into a 39-month extension trial. Eleven of the 12 patients completed the Phase I/II trial, and 10 patients consented to continue into the extension phase; 9 of 10 completed the extension phase. The primary objective of this study was to assess the safety of velaglucerase alfa; that data are reported in the Safety section of this review. Effect of velaglucerase alfa on key disease features was assessed as a secondary objective of the investigation. Hemoglobin concentration and platelet counts were evaluated at tri-monthly intervals. Statistically significant improvements in hemoglobin concentrations (19.2%; $P < 0.003$) and platelet counts (67.6%; $P < 0.003$) at 9 months and hemoglobin normalization were seen in all patients at 24 months. Normalization of liver (−18.2%; $P < 0.003$) and spleen (−49.5%; $P < 0.003$) volumes were also identified after 9 months of therapy, with continued improvement throughout the extension phase. Although 5 of the 13 patients in this trial had received previous therapies for GD, conclusions from their separate data were not addressed in the study.

Elstein et al^{4,8} further analyzed the data from the previous study reported by Zimran et al² to identify early achievement and maintenance of therapeutic goals with the previously determined treatment goals from the International Collaborative Gaucher Group. Patients from the earlier study were included in the extension phase if they had complete clinical dataset to 57 months after initial enrollment and received treatment with 60 U/kg intravenously every other week, with a dose reduction to 30 U/kg between 15 and 18 months of therapy. Assessments from baseline, 9 months, and yearly thereafter were included in the analysis. Clinical dataset needed for inclusion was as follows: hemoglobin concentration; platelet count;

Table II. Efficacy data from prospective human clinical data.

Reference No.	Design	No. of Patients	Patient Population	Dosing Regimen (Intravenous for all)	Results
2,4,8	Phase I/II and extension study Single group Not blinded	12	Symptomatic, enzymatically confirmed adult patients with intact spleen, disease-related anemia, and thrombocytopenia Negative for hepatitis B and C and HIV	Patients naive to ERT or imiglucerase-free for >12 months 60 U/kg every other week for first 12 months Extension phase de-escalation dosing: 6-9 months into extension: 45 U/kg every other week $\times$ 3 months; then 30 U/kg As above	Statistically significant (all, $P < 0.003$) mean percentage change at 9 months in hemoglobin (19.2%), platelet counts (67.6%), hepatic volume normalization (-18.2%), and spleen volume normalization (-49.5%) Continuous/maintenance of improvement of clinical outcomes throughout the extension phase Statistically significant (all, $P < 0.004$) improvements at 48 months in hemoglobin (21.7%), platelet counts (157.8%), hepatic volume normalization (-42.8%), and spleen volume normalization (-79.3%)
	Analysis of early and maintenance treatment goals from above patients	7 (complete clinical data at 57 months for analysis)	As above		Goals as previously defined by the ICGG ⁷ All patients achieved goal improvement in all clinical outcomes at 48 months of therapy All patients either maintained or achieved goal hemoglobin by 9 months of therapy (goal, ≥ 11.0 g/dL for females; ≥ 12.0 g/dL for males) All patients achieve platelet count goals by 36 months of therapy (goal, for mild to moderate thrombocytopenia—approach low normal values; for severe thrombocytopenia—2-fold increase from baseline) Hepatosplenomegaly improved at 24 months in all patients and was maintained throughout 57 months (goal: liver volumes— $\leq 1.5 \times$ normal or reduction by 30%–40% from baseline; spleen volumes— $\leq 8 \times$ normal or reduction by 50%–60% from baseline) Increased BMD (goal) seen in all patients by 48 months Of note, 3 patients received bisphosphonates during the study period Maintenance of BMD improvements at 69 months Significant improvement in z scores Lumbar spine slope, 0.14 z score unit per year ($P < 0.01$) Femoral head slope, 0.08 z score unit per year ($P < 0.01$) Subgroup of patients not receiving bisphosphonates Lumbar spine slope, 0.16 z score unit per year ($P < 0.01$) Femoral head slope, 0.1 z score unit per year ($P < 0.01$)
	BMD extension data	10 (7 with complete data)	As above (4 receiving concurrent bisphosphonate therapy)	As above	
9	Open-label Multicenter Therapy switch Extension phase	38	Imiglucerase- treated patients with stable hemoglobin concentrations >2 years	Dose equivalent to imiglucerase dose Range: 15–60 U/kg every other week	53 weeks Stable clinical parameters as demonstrated by negligible mean change in hemoglobin concentrations (-0.101 g/dL [95% CI, -0.272 to 0.07]) and platelet counts (7.04% [95% CI, 0.54% to 13.53%]) 51 weeks Stable hepatic mass (-0.03% [95% CI, -2.62% to 2.56%]) Significant decrease in splenic mass (-5.05% [95% CI, -10.77% to -0.35%])

(continued)

Table II (continued).

Reference No.	Design	No. of Patients	Patient Population	Dosing Regimen (intravenous for all)	Results
10,11	12 month Phase III Double blind Randomized Global	25	Symptomatic, enzymatically confirmed ≥2 years Treatment naive	Randomized 1:1 60 U/ kg every other week 45 U/kg every other week	12-month results Statistically significant improvements in the 60-U/kg group for hemoglobin concentrations (2.429 [0.324] g/dL); platelet count ($50.88 \times 10^9/L$ [95% CI, 23.97 to 77.78]); spleen volume (−1.92% of body weight [95% CI, −3.04 to −0.79]); and liver volume (−0.84% of body weight [95% CI, −1.58 to −0.11]) Statistically significant improvements in the 45-U/kg group for hemoglobin concentrations (2.438 g/dL [95% CI, 1.488 to 3.389]); platelet count ($40.92 \times 10^9/L$ [95% CI, 11.2 to 70.64]); and spleen volume (−1.87% of body weight [95% CI, −3.17 to −0.57])
	Pediatric subset of 12-month Phase III trial Double-blind Randomized Global	7	As above	As above	12-month results Clinically relevant improvements in the 60-U/kg group for hemoglobin concentrations (1.74 g/dL [95% CI, 0.72 to 2.78]); platelet count ($49.9 \times 10^9/L$; [95% CI, −32.1 to 131.9]); spleen volume (−2.1 cm ³ [95% CI, −5.3 to 1.1]); and liver volume (−0.7 cm ³ [95% CI, −1.4 to 0]) Clinically relevant improvements in the 45-U/kg group for hemoglobin concentrations (2.77 g/dL [95% CI, −0.99 to 6.53]); platelet count ($60.3 \times 10^9/L$ [95% CI, −103.1 to 223.7]); spleen volume (−0.7 cm ³ [95% CI, −2.6 to 1.2]); and liver volume (−0.3 cm ³ [95% CI, −1.7 to 1.1])
12	Phase III Multicenter Randomized Double-blind Parallel	34	Adult and pediatric patients with type 1 GD (previous treatment not denoted)	Randomized 1:1 Velaglucerase alfa 60 U/kg every other week Imiglucerase 60 U/kg every other week	9-month endpoints (mean [SEM]) Change in hemoglobin Velaglucerase alfa, 1.624 (0.223) g/dL Imiglucerase, 1.624 (0.223) g/dL Change in platelets Velaglucerase alfa, $110.41 (17.159) \times 10^9/L$ Imiglucerase, $144.38 (22.76) \times 10^9/L$ Change in liver mass Velaglucerase alfa, −1.31 (0.347) cm ³ Imiglucerase, −1.10 (0.182) cm ³ Change in splenic mass Velaglucerase alfa, −1.34 (0.424) cm ³ Imiglucerase, −2.46 (0.966) cm ³

ERT = enzyme replacement therapy; ICGG = International Collaborative Gaucher Group; BMD = bone mineral density; GD = Gaucher disease.

Table III. Therapeutic goals for treatment of type 1 Gaucher disease.^{3,13}

Disease Effect	Short-Term Goals		Long-Term Goals
	Within 12 Months	12–24 Months	24–60 Months (Ongoing)
Anemia	NA	Women and children: ≥ 11 mg/dL Men: ≥ 12 mg/dL	Maintain hemoglobin values achieved in first 12–24 months
Thrombocytopenia	All patients: increase platelet count Splenectomy: normalization of platelet count Intact spleen and moderate baseline thrombocytopenia: 1.5- to 2-fold increase Intact spleen and severe baseline thrombocytopenia [†] : 1.5-fold increase	Intact spleen and moderate baseline thrombocytopenia*: approaching low normal by year 2 Intact spleen and severe baseline thrombocytopenia [†] : double from baseline	All patients: maintenance of stable platelet counts Intact spleen and severe baseline thrombocytopenia [†] : continued slight increase; not anticipated to normalize
Splenomegaly	Reduce spleen volume by 30%–50% from baseline	NA	Reduce spleen volume by 50%–60% from baseline Maintain spleen volume at ≤ 2 to $8 \times$ normal
Hepatomegaly	NA	Reduce liver volume by 20%–30% from baseline	Reduce liver volume by 30%–50% from baseline Maintain liver volume at 1 – $1.5 \times$ normal
Skeletal [‡]	NA	Lessen or eliminate bone pain BMD Pediatric patients: Increase cortical and trabecular BMD	BMD Adult patients: increase trabecular BMD

BMD = bone mineral density; NA = not applicable.

*Baseline platelet count: $< 120,000/\mu\text{L}$ and $> 60,000/\mu\text{L}$.

[†]Baseline platelet count: $< 60,000/\mu\text{L}$.

[‡]Additional skeletal goals (not time dependent): prevent bone crises, prevent osteonecrosis, prevent subchondral joint collapse, and attain normal or ideal peak skeletal mass in pediatric patients.

spleen and liver volumes, assessed by using magnetic resonance imaging); and skeletal pathology, assessed by using bone mineral density (BMD; dual-energy X-

ray absorption). In addition, BMD data were reported out to 69 months.⁸ Seven of the 10 patients who entered the extension study had a complete clinical data-

set for analysis. All 7 patients achieved all 5 therapeutic goals: resolution of anemia (goal, ≥ 11.0 g/dL for females, ≥ 12.0 g/dL for males), thrombocytopenia (goal, for mild to moderate thrombocytopenia—approach low normal values; for severe thrombocytopenia—2-fold increase from baseline), hepatomegaly (goal, liver volumes $\leq 1.5 \times$ normal or reduction by 30%–40% from baseline), splenomegaly (goal, spleen volumes $\leq 8 \times$ normal or reduction by 50%–60% from baseline), and improvement in skeletal pathology (goal, increase in BMD) by 48 months and maintained outcomes at 57 months.⁴ BMD extension data were reported in 10 intention-to-treat subjects; 7 with complete data at 69 months showed maintenance of improvements. Four patients were concurrently receiving bisphosphonates at initiation of the study. Of the 6 not receiving bisphosphonate therapy at initiation of the study, 3 showed improvement in BMD status (2 lumbar spine and 1 femoral head improved from osteopenic to normal, and 1 femoral head improved from osteoporotic to osteopenic); clinical status changes were not recognized in those subjects receiving bisphosphonate therapy. The 3 patients without clinical improvement data have no information reported beyond 9 months of therapy.⁸ Benchmarking of patient outcomes, compared with previously determined therapeutic goals, showed that velaglucerase alfa was an effective treatment for establishing early achievement at 9 months and maintenance at 57 months of clinical outcomes.⁴

In a manufacturer study, the efficacy of velaglucerase alfa was reported in patients 35.6 (18.37) years of age with stable hemoglobin while receiving treatment with imiglucerase.⁹ These data, only available via clinical trial registry (ClinicalTrials.gov), describe the results at 51 to 53 weeks for 38 patients (18 males) enrolled in the open-label, multicenter, therapy-switch trial for patients who received doses of velaglucerase alfa equal to the dose of imiglucerase the patient had been receiving; doses ranged from 15 to 60 U/kg intravenously every other week. Hemoglobin concentrations remained stable in mean change from baseline, before velaglucerase alfa initiation, to 53 weeks (-0.101 g/dL [95% CI, -0.272 to 0.07]), as did platelet counts (7.04% [95% CI, 0.54% to 13.53%]). Liver and spleen volume changes from baseline were reported at 51 weeks. Liver volumes remained stable (-0.03% [95% CI, -2.62% to 2.56%]), whereas splenic volume decreased significantly (-5.05% [95% CI, -10.77% to -0.35%]).

At this time, Phase III data are reported via clinical trial registry, abstract publication, and personal communication from the manufacturer only. Data provided by the manufacturer provided no information not already available on the clinical trial registry; therefore, those communications are not cited in this review. A randomized, double-blind, global study evaluated the efficacy of 2 dosing regimens of velaglucerase alfa in 25 anemic, treatment-naïve type 1 GD patients aged ≥ 2 years.¹⁰ Patients were randomized to either 60 U/kg ($n = 12$; mean age, 23.5 years [age range, 4–42 years]) or 45 U/kg ($n = 13$; mean age, 30.0 years [age range, 6–62 years]) intravenously every other week for 12 months. Treatment groups did not differ in baseline characteristics. All efficacy parameters showed a statistically significant improvement at 12 months in both dosing groups, with the exception of reduction of liver mass in the 45-U/kg group. Hemoglobin increased 2.429 (0.324) g/dL ($P < 0.0001$) and 2.438 g/dL (95% CI, 1.488 to 3.389) in the 60- and 45-U/kg groups, respectively. Improvements in platelet count at 12 months were increased by $50.88 \times 10^9/L$ (95% CI, 23.97 to 77.78) in the 60-U/kg group and $40.92 \times 10^9/L$ (95% CI, 11.2 to 70.64) in the 45-U/kg group. Hepatic and splenic masses decreased in both groups; the 60-U/kg dose realized a hepatic mass reduction of -0.84% of body weight (95% CI, -1.58 to -0.11) and a splenic mass reduction of -1.92% of body weight (95% CI, -3.04 to -0.79); the 45-U/kg group reported a hepatic mass reduction of -0.3% of body weight (95% CI, -0.92 to 0.32) and a splenic mass reduction of -1.87% of body weight (95% CI, -3.17 to -0.57). Skeletal goals were not reported.

The group completing the aforementioned Phase III study¹⁰ also reported separately a subanalysis of pediatric patients within the trial.¹¹ Seven of the 25 patients were classified as pediatric (patient ages not noted in abstract); as described earlier, patients were randomized to receive either 60 U/kg or 45 U/kg intravenously every other week for 12 months. Improvements were seen in all clinical parameters assessed; P values were not reported for any outcomes. However, data were reported with 95% CIs, which are used to assess statistical significance for the purpose of this review. Although not statistically significant, hemoglobin and platelet counts increased in both groups: the 60-U/kg group showed a 1.74-g/dL (95% CI, 0.72 to 2.78) increase in hemoglobin and an increase of $49.9 \times 10^9/L$ (95% CI, -32.1 to 131.9) in platelet count. The

45-U/kg group hemoglobin and platelet count increases were 2.77 g/dL (95% CI, -0.99 to 6.53) and $60.3 \times 10^9/L$ (95% CI, -103.1 to 223.7), respectively. Splenic mass, normalized to body weight, showed a nonsignificant decrease in both groups by 2.1 cm^3 (95% CI, -5.3 to 1.1) in the 60-U/kg group and 0.7 cm^3 (95% CI, -2.6 to 1.2) in the 45-U/kg group. Hepatic mass reduction of 0.7 cm^3 (95% CI, -1.4 to 0) in the 60 U/kg group was the only statistically significant clinical outcome change identified in this subanalysis, with the 45-U/kg group experiencing a 0.3 cm^3 (95% CI, -1.7 to 1.1) decrease in hepatic mass. Again, skeletal assessment was not reported. Due to the small number of patients in this subanalysis, it is not surprising that statistical significance was not realized for most clinical outcomes despite clinically relevant improvement in all areas, as it is unlikely that 7 patients is a large enough sample size to overcome the risk of a type II error.

One active comparator trial of velaglucerase alfa and imiglucerase was completed, with results available in a clinical trial registry.¹² This clinical trial is a non-inferiority, multicenter, randomized, double-blind study including 34 patients with type 1 GD randomized 1:1 to receive either 60 U/kg intravenously every other week of velaglucerase alfa ($n = 17$) or imiglucerase ($n = 17$) for 9 months. The primary endpoint was comparison of increases in hemoglobin at 41 weeks; secondary endpoints were effects on platelet counts as well as liver and spleen volumes. Each group contained 8 males (47.1%). The majority of the patients were white (70.6% velaglucerase alfa; 58.8% imiglucerase) and >18 years of age (mean age, 36 years [age range, 7–60 years] for velaglucerase alfa; mean age, 27 years [age range, 3–73 years] for imiglucerase). Nine pediatric patients ages 2 to 7 years were included (4, velaglucerase alfa; 5, imiglucerase alfa). Results at 9 months of therapy are available, but no statistical analysis was reported. The majority of patients treated responded with a 1-g/dL increase in hemoglobin from baseline at 9 months, with 92% in the velaglucerase alfa group (mean change, $1.624 [0.223] \text{ g/dL}$) and 100% in the imiglucerase group (mean change, $1.624 [0.223] \text{ g/dL}$). Change in platelet count was $110.41 (17.159) \times 10^9/L$ and $144.38 (22.76) \times 10^9/L$ for the velaglucerase alfa and imiglucerase groups, respectively. Liver and splenic mass changes were similar at 9 months, with liver mass decreasing by $-1.31 (0.347) \text{ cm}^3$ in the velaglucerase alfa group and by

$-1.10 (0.182) \text{ cm}^3$ in the imiglucerase group; splenic mass decreased $-1.34 (0.424) \text{ cm}^3$ in the velaglucerase alfa arm and $-2.46 (0.966) \text{ cm}^3$ in the imiglucerase arm.

Elstein et al¹⁴ reported the use of velaglucerase alfa as part of the early access program launched secondary to shortages of imiglucerase alfa late in the last decade. Seventy-one patients, either ERT naive or previously treated with imiglucerase, were enrolled in this program and treated. No specific clinical monitoring protocol was in place because this program was not initiated as a study; therefore, only the 44 patients with clinical assessment of hemoglobin, platelets, and organ volume within 6 months of velaglucerase alfa initiation are included in the report of efficacy. Eight of these patients were considered treatment naive and received 15 U/kg intravenously every other week. The remaining 36 were therapy-switch patients who initiated treatment with 15 to 30 U/kg intravenously every other week. After 12 months of follow-up, improvements in hemoglobin (percentage with increase of $>1 \text{ g/dL}$) were similar between the therapy-switch patients [9 of 36 (25%)] and the treatment-naive patients [2 of 6 (33.3%)], as were the decreases in hepatic mass, with a decrease $>15\%$ from baseline in 12 of 33 (36.4%) therapy-switch patients and 3 of 6 (50%) treatment-naive patients. Greater improvement was seen in the treatment-naive patients for platelet count, with increases of 20% from baseline (6 of 7 [85.7%]), than in the therapy-switch patients (15 of 36 [41.7%]). In addition, spleen volume $>15\%$ from baseline was more apparent in the treatment-naive group (6 of 6 [100%]) than in the therapy-switch group.

On the basis of currently available data, velaglucerase alfa seems to be effective in achieving reasonable, previously defined clinical goals for type 1 GD. This efficacy translates across an array of patient populations, including pediatrics, treatment-naive, and previously treated individuals. Additional Phase III data will be helpful in identifying velaglucerase alfa's place in therapy, especially once supply limitations of imiglucerase are resolved. Although Phase III data comparing velaglucerase alfa with the current standard of therapy, imiglucerase, are complete, evaluation of these data before full-peer review should be done with caution.

Table IV. Common adverse reactions reported in $\geq 10\%$ * of patients.^{2,5,10,12}

Central nervous system
Dizziness
Headache
Tremor
Gastrointestinal
Nausea
Epistaxis
Abdominal pain
Vomiting
Musculoskeletal
Back pain
Bone pain
Extremity pain
Arthralgia
Infections
Upper respiratory tract
General/administration reaction
Infusion reaction
Pyrexia
Asthenia/fatigue
Cough
Miscellaneous
Prolonged activated partial thromboplastin time

*As categorized by any available reference.

SAFETY AND TOLERABILITY

Velaglucerase alfa, as with previous ERTs, has been generally well tolerated with mild to moderate adverse effects reported (Table IV^{2,5,10,12}). The primary objective of the Phase I/II and extension study reported by Zimran et al² was the safety of velaglucerase alfa 60 U/kg every other week for 9 months; the study included 12 patients with type 1 GD. Safety assessment for adverse and infusion-related reactions was performed every other week during and after infusions. Additional safety assessments were completed every 12 weeks, including physical examination, laboratory testing, ECGs, and echocardiograms. No serious adverse events related to the study drug were reported in either the Phase I/II or extension study. No premedication was administered before the infusion. All patients experienced at least 1 re-

ported adverse event. Events occurring in $\geq 10\%$ of the patients in the initial Phase I/II trial included dizziness (n = 3 [25%]), headache (n = 2 [16.7%]), nausea (n = 2 [16.7%]), back pain (n = 2 [16.7%]), bone pain (n = 2 [16.7%]), and pyrexia (n = 2 [16.7%]). Those events occurring in $\geq 10\%$ of the extension phase population of 10 patients included tremor (n = 1 [10%]), epistaxis (n = 2 [20%]), abdominal pain (n = 2 [20%]), pain in extremity (n = 1 [10%]), and fatigue (n = 1 [10%]).

Safety data reported in the clinical trials registry from noncomparator studies report a total of 5 serious adverse effects in 65 exposed patients. Serious adverse effects reported include anaphylactoid-infusion reaction (n = 1), allergic reaction to alteplase (n = 1), ankle pain (n = 1), facial swelling (n = 1), hives (n = 1), and seizure (n = 1).^{9,10} A total of 26 adverse events were reported in the combined 65 exposed participants of these 2 noncomparator trials. No adverse effects occurred in $>10\%$ of all exposed patients when reported adverse events for both of these completed noncomparator trials were combined. Several adverse events were reported in $>10\%$ of exposed patients in one of the trials (n = 25): headache (n = 4 [16%]), petechiae (n = 3 [12%]), and hypotension (n = 3 [12%]).¹⁰ A few notable adverse effects were reported at a greater frequency in the 45-U/kg group (n = 13) in this study than in the higher dose group; those adverse events included arthralgia (2 [15.4%] vs 0%) and back pain (2 [15.4%] vs 0%).

Safety data from the 71 early access program patients reported no serious adverse events or withdrawal symptoms (for therapy-switch patients).¹⁴ One patient was reported to have an allergic reaction; this patient had previously reported an allergic reaction to taliglucerase alfa, another ERT for type 1 GD. The patient was able to continue to receive velaglucerase alfa with premedication before infusion. One other patient developed a fixed drug eruption after the first infusion, which resolved without treatment and has never reappeared despite continued treatment with velaglucerase alfa. No other adverse events were reported from these data.

A total of 5 serious adverse events were reported in the 1 available comparator trial, with 3 events occurring in the velaglucerase alfa group (thrombocytopenia, convulsions, and allergic dermatitis) and 2 in the imiglucerase group (thrombocytopenia and sepsis).¹² Headache was the only adverse effect reported in $>10\%$ of patients in both groups. Two patients

(11.8%) in both the velaglucerase alfa and imiglucerase groups reported headache, making it the most commonly reported adverse event in this comparator trial. Other adverse reactions were reported at similar frequencies.

A report of the pediatric subset of this study resulted in no severe or serious treatment-emergent adverse events, and no patients discontinued therapy due to adverse events.¹¹

There have been reports of a clinically relevant number of infusion-related adverse reactions, generally mild in severity, in the prescribing information for this treatment.⁵ No peer-reviewed, published data are available to analyze type or severity of these reactions, however. The trial registry provides no likelihood of association data for these adverse reactions, although based on an understanding of biological medications and the mechanism of velaglucerase alfa on the pathophysiology of GD, it is likely that several of these reactions, including some classified as serious, were associated with the medication or its administration. Depending on the severity of these reactions, management of infusion-related adverse effects is consistent with standard practice, including slowing the rate of infusion or pretreatment with medications such as antipyretics, corticosteroids, and/or antihistamines.

Antibody Development

Antibody development and risk of anaphylaxis or anaphylactic-like reactions have been reported with previous ERTs for type 1 GD. Antibody concentration assessment occurred every 3 months during the published Phase I/II and extension study.² None of the 12 study patients developed antibodies to velaglucerase alfa. Data available from a published abstract, which reported development of antidrug antibodies in patients receiving imiglucerase ($n = 17$) versus velaglucerase alfa ($n = 82$), showed a 23% (4 of 17) and 1% (1 of 82) seroconversion rate, respectively.¹⁵ Although only minimal data exist and risk for antibody development should be considered, it seems that velaglucerase alfa is less likely to induce antibody development, thus decreasing concern for serious administration-related reactions after antibody development.

Pregnancy and Lactation

Animal studies in both rats and rabbits, at doses exceeding those recommended for treatment in hu-

mans (1.8 and $4.3 \times$ the recommended human doses, respectively), have failed to show prenatal or postnatal development adverse events in animal models.⁵ No studies on the effects on the human fetus have been conducted. Velaglucerase alfa should only be used during pregnancy when the benefits to the mother's health clearly outweigh the potential, unknown risk to the fetus. In addition, it is not known whether velaglucerase alfa is transmitted via breast milk.

DOSAGE AND ADMINISTRATION

Velaglucerase alfa is administered via intermittent intravenous infusion, which should optimally occur within an infusion center or, if in the patient's home, with a health care professional present. Although infusion reactions, with or without antibody development, are rare, these precautions for administration should be done as a safety measure.

After reconstitution of the 400-U vial of lyophilized powder, the manufacturer recommends further dilution of velaglucerase alfa in 100 mL of 0.9% sodium chloride, which may be infused over 1 hour.⁵ Additional assessment of maximum stable concentrations would be useful for pediatric administration. Pediatric patients as young as 3 years old have received this agent; however, to administer such a volume to pediatric patients may result in fluid balance issues, especially in patients who may be fluid restricted or receiving numerous other intravenous intermittent or continuous medications. No data concerning further concentration of this medication could be identified for review.

Although studies have shown long-term efficacy and suggest reasonable tolerability for both initial and de-escalated dosing regimens (using doses lowered every other week), the current FDA-approved and manufacturer-recommended dosing regimen is 60 U/kg intravenously every other week.⁵ Zimran et al used a dose de-escalation strategy for treatment of 12 patients treated in a Phase I/II and extension study as described earlier.^{2,4} Following up the initial 3 study patients, all patients received an initial dose of 60 U/kg every other week, for a total of 20 doses. Patients entering the extension study underwent dose de-escalation to 45 U/kg intravenously every other week after 6 to 9 months in the extension study if they had met 2 of the 4 predetermined therapeutic goals and to 30 U/kg every other week 3 months later. Only one patient required dose escalation to 60 U/kg after de-escalation;

this was the result of increased bone pain, which the primary investigator believed to be potentially secondary to skeletal pathology of the patient's disease. All other patients maintained therapeutic goals with dose de-escalation.

Phase III studies have assessed the efficacy of an initial dosing strategy of 45 U/kg intravenously every other week as described earlier.¹⁰ In both adults and pediatric patients, this dosing regimen resulted in statistically significant and clinically relevant improvements of clinical outcomes (see Efficacy section) with this lower dose. Secondary to both cost and risk of shortages with such specialty therapies, these dose de-escalation strategies or lower initial dosing regimens warrant further investigation.

DISCUSSION

Currently, only a minimal amount of peer-reviewed published data is available regarding the use of velaglucerase alfa for the treatment of type 1 GD. The majority of the published data are available only as abstract publications, yet to have been subject to full peer-review. These factors result in both limitations of the data and the current review. Given the nature of much of these data, readers should use caution and appropriate clinical reasoning when drawing conclusions from such data. However, secondary to the low occurrence rate of GD, the unique nature of its treatment options, and the recent shortage of imiglucerase, with appropriate clinical knowledge in the treatment of type 1 GD, velaglucerase alfa should be considered for treatment of symptomatic patients.

On the basis of currently available published data, velaglucerase alfa is likely to have a reasonable safety profile and to be effective in the treatment of type 1 GD. Data for both treatment-naïve and previously treated patients are positive for achieving and maintaining clinical outcomes. However, to this point, only a small number of patients have been treated with this agent. Phase III studies available in published abstracts and made available from the manufacturer show promising data; however, these data await further peer review, and conclusions based on these data, for clinical practice, should be made with caution. Animal studies comparing the pharmacokinetics, efficacy within the affected organ systems, and safety—especially in terms of antibody development—are also promising.¹⁶

Velaglucerase alfa was generally well tolerated in published studies. Common adverse reactions (occurring in

>10% of patients) were generally mild to moderate in severity, and no studies reported life-threatening adverse reactions. Infusion-associated reactions do seem to be somewhat common, but no peer-reviewed data discussing mitigation strategies for such reactions are available. Thus, caution should be undertaken, and this agent should be administered within a health care setting or, if in the home, with a health care provider present. Patient who experience non-life-threatening infusion-related adverse reactions may be premedicated or have infusions rates slowed to attempt to prevent such reactions. Antibody development and risk of subsequent anaphylaxis or anaphylactic-like reactions seem to be less likely with velaglucerase alfa than with imiglucerase. Reported anaphylactic-like reactions were rare.

Although cost should not drive the final decision for treatment, it must be considered. Average wholesale price for a velaglucerase alfa 400-unit vial and an imiglucerase 400-unit vial are \$1620.00 and \$1903.20, respectively. Because the dosing strategies for velaglucerase alfa and imiglucerase are similar, drug costs may be comparable when initiating therapy in a treatment-naïve patient or when switching from one agent to the other. Thus, at a dose of 60 U/kg intravenously every other week, for either agent, drug costs would be similar for a patient of equal weight. Identification of the lowest effective dose or optimal dose titration strategies (including dose reductions in patients with clinically stable disease) for velaglucerase alfa may help to mitigate some drug costs associated with this treatment. Optimally, pharmacoeconomic analysis of velaglucerase alfa would be used to identify whether cost differences exist compared with imiglucerase. Unfortunately, to date, no pharmacoeconomic analyses comparing velaglucerase alfa with imiglucerase have been published.

CONCLUSIONS

Currently, there are no treatment guidelines for GD; therefore, the place in therapy of velaglucerase alfa would be determined by the currently available data and experience of those clinicians versed in the treatment of this disease. Velaglucerase alfa has been shown to be effective in the achievement and maintenance of therapeutic goals in type 1 GD and has been generally well tolerated in clinical trials. On the basis of the available published data, including those available in abstract form, and considering the potential availability issues with ERT treatment options, velaglucerase alfa should be considered for use in symptomatic type

1 GD patients, including both treatment-naïve patients and those previously treated with imiglucerase.

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CONFLICT OF INTEREST

The author has indicated that she has no conflicts of interest regarding the content of this article.

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