HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 December 2010

VPRIV 400 Units, powder for solution for infusion
B/1 (CIP code: 578 188-7)

Applicant: SHIRE FRANCE, HGT division

Velaglucerase alfa
ATC code: A16AB10

List I

Orphan drug (designation granted on 9 June 2010)

Date of Marketing Authorisation (centralised procedure): 26 August 2010
This proprietary drug is being monitored as part of a risk management plan.

Reason for request: Inclusion on the list of medicines approved for hospital use.

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Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Velaglucerase alfa

1.2. Background
Velaglucerase alfa is the first human recombinant enzyme replacement (of glucocerebrosidase) manufactured by genetic activation of fibroblasts of human origin in culture.
The technique used to produce VPRIV could help overcome the risks of interruptions in the production of imiglucerase (a recombinant enzyme replacement obtained from hamster ovary cells).

1.3. Indications
“VPRIV is indicated for long-term enzyme replacement therapy in patients with type 1 Gaucher disease".

1.4. Dosage
“VPRIV treatment should be supervised by a physician experienced in the management of Gaucher disease. Home administration under the supervision of a healthcare professional may be considered only for patients who have received at least three infusions and were tolerating their infusions well.

Dosage: the recommended dosage is 60 units/kg administered every other week.
Dosage 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.

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

Renal or hepatic impairment: No dosage 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. of the SPC

Elderly (≥ 65 years old): Four of the 94 patients (5%) who received velaglucerase alfa during clinical studies were aged 65 or older. The limited data does not indicate a need for a dosage adjustment in this specific age group.

Paediatric population: Twenty of the 94 patients (21%) who received velaglucerase alfa during clinical studies were in the paediatric and adolescent age range (4 to ≤ 17 years). The safety and efficacy profiles were similar between paediatric/adolescent and adult patients. See section 5.1 of the SPC for further information.

Method of administration: For intravenous infusion use only. To be administered as a 60-minute intravenous infusion, using a 0.22 µm filter. For instructions on reconstitution and dilution, see section 6.6 of the SPC”.

1.5. Special precautions for storage
“Store in a refrigerator (2℃ - 8℃). Do not freeze . Keep the vial in the outer carton in order to protect from light”.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

A: Alimentary tract and metabolism
A16: Other medicinal products for the alimentary tract and metabolism
A16A: Other medicinal products for the alimentary tract and metabolism
A16AB: Enzymes
A16AB10: Velaglucerase alfa

2.2. Medicines in the same pharmacotherapeutic category

A different enzyme indicated for the treatment of Gaucher disease: CEREZYME (imiglucerase), indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease and who have clinically significant non-neurological manifestations of the disease. This is the standard treatment.

2.3. Medicines with a similar therapeutic aim

The other drugs indicated in the treatment of Gaucher disease: ZAVESCA (miglustat): indicated in “the treatment of mild to moderate type 1 Gaucher disease. ZAVESCA must only be used to treat patients for whom enzyme replacement therapy is not suitable".

3. ANALYSIS OF AVAILABLE DATA

The efficacy and tolerance of VPRIV have been analysed in four studies on patients suffering from type 1 Gaucher disease:

- two phase III studies: one comparing VPRIV 60 U/kg* with imiglucerase 60 U/kg*, and the other comparing two doses (45 U/kg and 60 U/kg) of VPRIV.
- two studies with the principal aim of assessing the tolerance of VPRIV at doses of 15 to 60 U/kg*; these studies will be discussed in the “adverse effects” section.

Studies referred to in the dossier submitted by the pharmaceutical company that have not yet been concluded will not be discussed in this opinion.

3.1. Efficacy

3.1.1. Study HGT-GCB-039: pivotal study

Method: Randomised, double-blind, parallel-group non-inferiority phase III study comparing VPRIV 60 U/kg every other week with imiglucerase (CEREZYME) 60 U/kg every other week conducted on 34 patients with type 1 Gaucher disease who were monitored for 41 weeks.
Non-inferiority was demonstrated if the lower margin of the confidence interval of the difference exceeded a limit set at -1 g/dl.

Inclusion criteria: patients who have had type 1 Gaucher disease, determined by the following aspects, for over two years:
- Glucocerebrosidase (GCB) enzyme activity deficiency measured by leucocyte or genotype testing,
- disease-related anaemia, defined as a haemoglobin level below the lower limit of the interval defined according to the patient's age and sex,
- at least one of the following criteria:
  - moderate splenomegaly on palpation (2 to 3 cm below the left edge of the ribs),
  - disease-related thrombocytopenia, defined as a platelet count of ≤ 120 x 10^3/ mm^3
  - disease-related hepatomegaly.

who have not had enzyme replacement therapy for Gaucher disease within the past 12 months.

Treatments:
- VPRIV 60U/kg, continuous infusion for one hour every other week, n=17,
- CEREZYME (imiglucerase) 60U/kg, continuous infusion for one hour every other week, n=17.

The patients received 20 infusions during the study.

Primary endpoint: average variation in the haemoglobin (Hb) level after 41 weeks of treatment.

RESULTS: ITT and PP analysis (see table 1).
The patient characteristics on inclusion were similar, apart from the following aspects:
The breakdown of the paediatric population included (< 17 years), which was:
- VPRIV group: four patients over 5 years and no patients aged from 2 to 4 years,
- CEREZYME group: one patient over 5 years and four patients aged from 2 to 4 years.

The haemoglobin levels on inclusion, which were 11.34 g/dl in the VPRIV group versus 10.39 g/dl in the CEREZYME group.

Table 1: average variation in the Hb level (g/dl) after 41 weeks.

	VPRIV (velaglucerase) 60 U/kg	CEREZYME (imiglucerase) 60 U/kg
ITT analysis	N=17	N=17
Hb level on inclusion Variation of Hb levels at W41 Difference versus CEREZYME [lower level of 95% CI]	11.51 [9.65; 14.35] 1.62 [-0.15; 3.6] 0.135 [-0.596]	10.46 [8.10; 13.05] 1.49 [-0.55; 3.5]
PP analysis	N=15	N=15
Hb level on inclusion Variation of Hb levels at W41 Difference versus CEREZYME [lower level of 95% CI]	11.34 [9.65; 13.20] 1.68 [-0.15; 3.6] **0.157 [-0.599]**	10.39 [9.10; 11.95] 1.52 [-0.55; 3.5]

After 41 weeks of treatment, the haemoglobin levels had increased by 1.68 g/dl [-0.15; 3.6] in the VPRIV group and 1.52 g/dl [-0.55; 3.5] in the CEREZYME group (per-protocol analysis) in relation to the initial values: average difference of 0.157 g/dl, lower limit of the 95% CI -0.599. The lower limit of the confidence interval of the difference was above the limit which had been set (-1 g/dl), and consequently the non-inferiority of VPRIV was established.
These results were confirmed by the ITT analysis.
No data is available for children under 4 years of age.

3.1.2. Study TKT032

Method: Randomised, double-blind, parallel-group phase III study comparing VPRIV 60 U/kg every other week with VPRIV 45 U/kg every other week conducted on 25 patients with type 1 Gaucher disease who were monitored for 12 months.

Inclusion criteria: patients who have had type 1 Gaucher disease, determined by the following aspects, for over two years:
- Glucocerebrosidase (GCB) enzyme activity deficiency measured by leucocyte or genotype testing,
- disease-related anaemia, defined as a haemoglobin level below the lower limit of the interval defined according to the patient's age and sex,
- at least one of the following criteria:
  - moderate splenomegaly on palpation (2 to 3 cm below the left edge of the ribs),
  - disease-related thrombocytopenia, defined as a platelet count of $< 90 \times 10^3 / mm^3$
  - disease-related hepatomegaly.

who have not had enzyme replacement therapy for Gaucher disease within the 30 months prior to inclusion.

Treatments:
- VPRIV 60 U/kg, continuous infusion for one hour every other week, n=12
- VPRIV 45 U/kg, continuous infusion for one hour every other week, n=13

The patients received 26 infusions during the study.

Primary endpoint: average variation in the Hb level after 12 months of treatment with VPRIV 60 U/kg. An increase of > 1 g/dl in the Hb level was defined as clinically significant.
The variation in Hb levels in patients receiving VPRIV 45 U/kg was assessed as a secondary criterion.

RESULTS: ITT analysis
Patients in the VPRIV 60 U/kg group had an average Hb level on inclusion of 10.69 g/dl [7.05; 12.25]. The haemoglobin levels of patients treated with VPRIV 60 U/kg rose by 2.43 g/dl compared with the baseline figure after 12 months of treatment (95% CI [1.72; 3.14], p<0.0001 (primary endpoint)).

Patients in the VPRIV 45 U/kg group had an average Hb level on inclusion of 10.72 g/dl [8.45; 12.85]. The haemoglobin levels of patients treated with VPRIV 45 U/kg rose by 2.44 g/dl compared with the baseline figure after 12 months of treatment (95% CI [1.49; 3.39], p<0.0001 (secondary endpoint)).

The findings need to be interpreted with caution given the methodology of the study (before-and-after study with no inter-group comparison, small cohort).

3.2. Adverse effects

3.2.1. HGT-GCB-039

32 of the 34 patients taking part in this study experienced adverse events: 16/17 (94.1%) in the VPRIV group and 16/17 (94.1%) in the CEREZYME group. The most frequently observed events (> 15%) were:

- infections (flu, nasopharyngitis, rhinitis): 9 versus 8 patients,
- headache: 3 versus 3 patients,
- diarrhoea: 3 patients versus 1 patient,
- arthralgia: 4 versus 3 patients,
- fever: 4 versus 2 patients.

Four serious events (three grade 3 and one grade 4) were observed in patients treated with VPRIV: one case of dorsalgia, one allergic dermatosis, one TPA extension and one convulsion.

3.2.2. Study TKT 025

This phase I/II open-label study assessed the tolerance of VPRIV at doses of 15 to 60 U/kg in 12 patients with type 1 Gaucher disease who were monitored for 40 weeks (20 infusions) and had never had enzyme replacement treatment before.

The patients (aged over 18) who were included had type 1 Gaucher disease diagnosed on the basis of clinical features (anaemia and thrombopenia) and biochemical tests (GCB enzyme activity deficiency), a platelet count lower than normal, with no hepatitis B or C antigen.

A total of 22 adverse events were observed in 10 of the 12 patients taking part. The most common (> 15%, n=2) were: vertigo, headache, nausea, arthralgia, dorsalgia and fever.

3.2.3. Study TKT 034

This phase II/III open-label study assessed the tolerance of VPRIV at doses of 15 to 60 U/kg in 40 patients with type 1 Gaucher disease who were monitored for 12 months (26 infusions) and had previously been treated with CEREZYME for 30 months.

The patients taking part (aged over two) had type 1 Gaucher disease, determined by GCB enzyme activity deficiency measured by leucocyte or genotype tests.

Eleven of the 40 patients taking part (27.5%) experienced adverse events. The most common adverse events (> 5%, n=2) were: vertigo, headache, hypertension, nausea, arthralgia and fatigue.

3.2.4. SPC

According to the SPC, the tolerance data is based on the exposure of 94 patients suffering from type 1 Gaucher disease. The most common adverse events (> 10%) are: headache, vertigo, arthralgia, dorsalgia, reaction to the infusion (asthenia, fever, hypotension, hypertension, nausea).

3.3. Immunogenicity

During clinical studies, one patient being treated with VPRIV (1.1%) versus four patients being treated with CEREZYME (23.5%) developed anti-velaglucerase and anti-imiglucerase antibodies. Only the patient being treated with VPRIV presented a neutralising antibody.

The immunogenicity differences that have been observed need to be investigated in more depth and monitored, particularly as neutralising antibodies can have consequences for product efficacy. Furthermore, the potential for cross-reactions between these two products is not yet known.

3.4. Conclusion

The efficacy (increase in haemoglobin levels) and tolerance of VPRIV have been assessed on the basis of four studies conducted on patients with type 1 Gaucher disease. One of these studies was a randomised double-blind clinical study versus CEREZYME (HGT-GCB-039) and three of them were dose-finding studies (TKT032, TKT025 and TKT034).

In one randomised double-blind study comparing VPRIV to imiglucerase at the same dose (60 U/kg every other week) in 34 patients with type 1 Gaucher disease, VPRIV was found to be not inferior to imiglucerase after 41 weeks of treatment in terms of changes to haemoglobin levels. In fact, haemoglobin levels increased compared to baseline values by 1.68 g/dl [-0.15; 3.6] in the VPRIV group and by 1.52 g/dl [-0.55; 3.5] in the imiglucerase group, or an average difference of 0.157 g/dl, with a lower limit of the 95% CI of -0.599 and an upper limit set at -1 g/dl; VPRIV was consequently shown to be not inferior to CEREZYME. These results were confirmed by the ITT analysis.
No data is available for children under 4 years of age.

In a study carried out on 25 patients with type 1 Gaucher disease, haemoglobin levels rose after 12 months of treatment by 2.43 g/dl, 95% CI [1.72; 3.14], $p<0.0001$ in the VPRIV 60 U/kg group (primary endpoint) and by 2.44 g/dl, 95% CI [1.49; 3.39], $p<0.0001$ in the VPRIV 45 U/kg group (secondary endpoint). The findings need to be interpreted with caution given the methodology of the study (before-and-after study, small cohort).

In the study versus imiglucerase, 94.1% of patients in the VPRIV group and 94.1% of patients in the imiglucerase group experience adverse events. Four serious adverse events were observed with VPRIV: dorsalgia, allergic dermatosis, TPA extension and convulsion.
In the two studies carried out primarily to assess the tolerance of VPRIV at doses ranging from 15 U/kg to 60 U/kg (60 patients), the most common events (> 5%, n=2) were: vertigo, headache, hypertension, nausea, arthralgia, fatigue.

According to the SPC, the tolerance data is based on the exposure of 94 patients suffering from type 1 Gaucher disease. The most common adverse events (> 10%) are: headache, vertigo, arthralgia, dorsalgia, reaction to the infusion (asthenia, fever, hypotension, hypertension, nausea).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Gaucher disease is a rare and serious condition which involves deterioration in the quality of life and is life-threatening.

This drug comes within the area of replacement therapy.

The efficacy/adverse effects ratio for this drug is high.

It is a first-line drug.

Alternative medicinal products exist: CEREZYME (first-line) and ZAVESCA (second-line).

Public health benefit:
The public health burden of type 1 (non-neurological) Gaucher disease is low, particularly because it varies in severity and the number of patients with the condition is small (approximately 500).
Management of rare diseases is a public health need which forms part of the 2010-2014 National Rare Diseases Plan.
Alternative treatments are available: imiglucerase (the standard enzyme replacement treatment) and miglustat (second-line treatment which acts by reducing the substrate). In addition, the need is already partly met.
The efficacy of VPRIV was shown in a non-inferiority study versus imiglucerase on intermediate criteria (increase in haemoglobin level). Also, it is impossible to quantify the impact of VPRIV in terms of morbidity and mortality and quality of life. The applicability of the results of the studies into clinical practice is acceptable.
Consequently, VPRIV is not expected to have any public health benefit in the long-term enzyme replacement treatment indicated for patients suffering from type 1 Gaucher disease.

The actual benefit of VPRIV in type 1 Gaucher disease is **substantial**.

4.2. Improvement in actual benefit (IAB)

In patients with type 1 Gaucher disease, VPRIV is an alternative that provides no improvement in actual benefit (IAB V) compared to CEREZYME.

4.3. Therapeutic use[1][2]

Gaucher disease is an autosomal recessive transmission hereditary disease of glycosphingolipid metabolism. It is caused by a deficit in the enzyme glucocerebrosidase, which leads to the multivisceral accumulation of glucocerebrosides, affecting the spleen (causing anaemia and thrombopenia), liver and bones (destroying the architecture of the bones and causing pain, sometimes leading to infarction and demineralisation). This non-neurological deterioration is observed in the chronic form of the disease (type 1) which is often diagnosed in

1 Drs T. Billette, J. Stirnemann and N. Belmatoug, ORPHANET - October 2006
2 Vellodi et al. Guidelines of the European working group on Gaucher disease - consensus-building conference - 2001

adulthood. The forms which feature acute (type 2) or subacute (type 3) neurological progression are seen in children.

Drug treatment is indicated only for patients with type 1 or type 3 Gaucher disease who have clinically significant non-neurological manifestations of the disease. Patients with type 2 are not treated, as treatment has no effect on the rapid and severe neurological course of the disease.
Gaucher disease must be treated as soon as possible once the diagnosis has been made and before consequences which cannot be resolved by these treatments have occurred.

Two drugs specifically designed for Gaucher disease are on the market:
- a replacement drug, which is the standard treatment (imiglucerase for infusion: CEREZYME) in type 1 and type 3,
- a drug which reduces the substrate (oral miglustat: ZAVESCA), which is a second-line alternative indicated for mild to moderate type 1 Gaucher disease.

A bone marrow transplant could be effective for some patients.

Palliative measures can be offered in conjunction with CEREZYME: analgesics, bisphosphonates, orthopaedic surgery.

VPRIV is an alternative to CEREZYME for patients with type 1 Gaucher disease.

4.4. Target population

The target population for VPRIV is made up of patients with type 1 Gaucher disease. It can be estimated on the basis of the following data:
- The prevalence of Gaucher disease is around 1 in 100,000. 95% of cases are type 1 (chronic, non-neurological). The condition is normally classified into three main phenotypes.
- The French National Institute for Statistics and Economic Studies INSEE puts the French population at around 66 million.
- 456 patients have been registered on the national French Gaucher Disease Treatment Assessment Committee register.

This means that the target population for VPRIV is between 450 and 630 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at dosages in the Marketing Authorisation.

The Transparency Committee would like the pharmaceutical company to supply data on VPRIV. This data should allow the following factors to be described:
- the reasons for initiating treatment
- the characteristics of patients being treated
- their progress in terms of their clinical condition (hepato-splenomegaly, events affecting the bones), biological status (haemoglobin level, platelets) and quality of life
- tolerance of treatment and data relating to the development of neutralising antibodies, with cross-comparison between various forms of enzyme therapy where necessary

This data could be taken from the National Gaucher Disease Register. The first data to become available must be submitted to the Committee within two years.