Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

velaglucerase alfa 400 units powder for solution for infusion (VPRIV®). SMC No. (681/11)

Shire Pharmaceuticals Limited

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

velaglucerase alfa (VPRIV®) is accepted for use within NHS Scotland.

Indication under review: Long-term enzyme replacement therapy in patients with type 1 Gaucher disease.

Velaglucerase alfa has been shown to be non-inferior to another enzyme replacement treatment in patients with type 1 Gaucher disease.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of velaglucerase. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Long-term enzyme replacement therapy in patients with type 1 Gaucher disease.

Dosing Information

The recommended dose is 60 units/kg administered every other week as a 60-minute intravenous (IV) infusion. 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.

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

Product availability date

01 September 2010. Designated orphan medicine for use in the European Union for the treatment of Gaucher's disease in 2010.

Summary of evidence on comparative efficacy

Gaucher disease is a rare, inherited, lysosomal glycosphingolipid storage disorder which develops due to a deficiency in the enzyme beta-glucocerebrosidase that catalyses the breakdown of glucocerebroside. This results in intracellular accumulation of glucocerebroside, mainly in macrophages. Gaucher disease is categorised into types 1 to 3, with type 1 (non-neuropathic) being the most common. The pathological consequences of type I Gaucher disease include hepatomegaly, splenomegaly, skeletal abnormalities including deformities and bone pain crises, anaemia and thrombocytopenia.

Velaglucerase alfa is a recombinant glucocerebrosidase enzyme developed to replace the physiological enzyme. It is produced by gene activation technology in a human cell line and has an amino acid sequence identical to the naturally occurring enzyme. Velaglucerase alfa was designated an orphan medicinal product by the European Medicines Agency (EMA) in June 2010.

The main evidence supporting the marketing authorisation is from a phase III, randomised, double-blind, non-inferiority study comparing velaglucerase alfa with the current standard treatment, imiglucerase.[1,2] Patients were included if they had a documented diagnosis and clinical manifestation of type 1 Gaucher disease, were at least two years old, had not received treatment for Gaucher disease within the preceding 12 months, had anaemia related to Gaucher disease and either thrombocytopenia or organomegaly.

A total of 34 patients were randomised equally to intravenous (IV) infusion every other week for 39 weeks of velaglucerase alfa 60 units/kg or imiglucerase 60 units/kg. The median age was 36 years (7 to 60) in the velaglucerase alfa group and 27 years (3 to 73) in the imiglucerase group.

Mean baseline haemoglobin was 11.5g/dL in the velaglucerase alfa and 10.5g/dL in the imiglucerase group and this difference between groups was maintained throughout the study.

The primary endpoint was mean change in haemoglobin concentration from baseline to week 41. The study was designed to demonstrate that velaglucerase alfa was non-inferior to imiglucerase if the lower limit of the one-sided 97.5% confidence interval (CI) of the treatment difference (velaglucerase alfa minus imiglucerase) was greater than -1 g/dL. Analyses were in both the intention to treat (ITT) population, defined as randomised patients who received at least one partial or full study drug infusion, and in the per protocol (PP) population, defined as patients who completed the study, had both baseline and week 41 measurements of haemoglobin concentration collected, had no protocol violations, and had received at least 80% of their scheduled dose of infusion.

The mean change (standard error) in haemoglobin concentration from baseline to end of study was 1.624g/dL (0.223) for velaglucerase alfa and 1.488g/dL (0.281) for imiglucerase with an estimated mean treatment difference of 0.135g/dL (lower limit of one-sided 97.5% CI: -0.596g/dL) in the ITT population. Similar results were reported for the PP population: 1.677g/dL (0.249) for velaglucerase alfa and 1.520g/dL (0.273) for imiglucerase with an estimated mean treatment difference of 0.157g/dL (lower limit of one-sided 97.5% CI: -0.599). Non-inferiority was demonstrated in both analysis populations.

Secondary outcomes included changes from baseline in platelet count, liver and spleen volumes measured by magnetic resonance imaging (MRI), plasma chitotriosidase activity, plasma chemokine (C-C motif) ligand 18 (CCL18) levels, and time to response for haemoglobin ≥1g/dL from baseline. The treatment effect with velaglucerase alfa was comparable to imiglucerase for all of these outcomes.

Quality of life was measured in 19 adult patients using the Short Form-36 (SF-36) and treatment groups showed comparable improvement although the low patient numbers make interpretation difficult.

A 12-month, open-label safety study indicated preservation of treatment effect after switching from imiglucerase to velaglucerase alfa. A total of 40 patients with type 1 Gaucher disease aged at least 2 years who had previously received treatment with imiglucerase (dose range 15 to 60 units/kg) were switched to velaglucerase alfa at the same dose regimen. After switching, haemoglobin concentrations and platelet counts were sustained at therapeutic levels through 12 months of treatment.[1,3]

Summary of evidence on comparative safety

In the pivotal study,[2] 16 of the 17 patients in each treatment group experienced at least one adverse event (AE). In the velaglucerase alfa and imiglucerase groups, AE considered to be drug-related occurred in eight and six patients, respectively, and AE considered to be infusion-related occurred in five and four patients, respectively. There was one treatment-related serious AE: allergic dermatitis in a patient receiving velaglucerase alfa.

Three patients receiving velaglucerase alfa had a severe or life-threatening AE: severe back pain plus severe allergic dermatitis, severe prolonged activated partial thromboplastin time

(aPTT) and life-threatening convulsion. Two patients on imiglucerase experienced severe AE: severe arthralgia and severe chills.

No unexpected safety issues were reported from the open-label safety study in patients switched from imiglucerase to velaglucerase alfa.[1,3]

The EMA noted that velaglucerase alfa, like imiglucerase, appears to induce antibodies including neutralising antibodies. Antibody formation appears to be numerically higher in patients on imiglucerase than on velaglucerase alfa. However absolute numbers are low and thus no firm conclusion is possible.[1]

The EMA concluded that the overall AE profile appeared to be comparable between treatment groups. It noted that prolongation of aPTT is a potential risk and it is included in the Risk Management Plan.[1]

Summary of clinical effectiveness issues

Gaucher disease is a rare condition that affects an estimated 30,000 people worldwide. It can present at any age, however, approximately half of Gaucher disease patients are diagnosed in childhood or adolescence. It is estimated that there are five to ten patients in Scotland.

Enzyme replacement therapy is the current first line treatment for type 1 Gaucher disease. Imiglucerase is the only other licensed enzyme replacement therapy; it is also a recombinant glucocerebrosidase that is administered every two weeks by intravenous infusion. Velaglucerase alfa is structurally similar to imiglucerase.

Velaglucerase alfa is an orphan medicinal product and consequently in this rare indication the evidence base is limited. The pivotal, phase lll, 9-month, active comparator study demonstrated that treatment with velaglucerase alfa was non-inferior to imiglucerase in treatment-naïve patients for the primary endpoint of improvement in haemoglobin concentration, and it is comparable to imiglucerase for several secondary endpoints. However the study included only 17 patients per treatment group. In addition, a 12-month open label study investigating the safety and efficacy of switching from imiglucerase to velaglucerase alfa provided evidence of maintenance of treatment effect and safety.

Initial treatment with both velaglucerase alfa and imiglucerase is required to be undertaken in hospital. The supervision, training and administration requirements for home administration differ between the products and may meet differing patient circumstances.

The submitting company has advised that although two vial strengths (200 and 400 units) are licensed, only the higher strength will be available in the UK. Imiglucerase is available in both 200 and 400 unit strengths providing more flexibility and potentially less wastage which may impact on cost.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing velaglucerase alfa versus imiglucerase as long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease. A lifetime time horizon was used.

The clinical evidence to underpin the assumption of comparable efficacy, as necessary for a cost-minimisation analysis, came from the randomised, study comparing the efficacy and safety of velaglucerase alfa to imiglucerase (Cerezyme®) previously described.

The analysis compared the total cost per patient for velaglucerase alfa versus the total cost per patient for imiglucerase. Costs included both medicine and administration costs. Imiglucerase was costed using its list price.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. Under the PAS a discount was offered on the list price of the medicine.

The results showed that without the PAS the total estimated lifetime cost per patient for velaglucerase alfa was £5,206,513 compared to imiglucerase at £3,973,868 indicating velaglucerase would be associated with an incremental cost of £1,232,645 and therefore would not be the preferred treatment on cost minimisation grounds. Without the PAS, the results showed that the total cost per patient per year for velaglucerase alfa was £226,067 compared to imiglucerase at £173,198 indicating velaglucerase alfa would be associated with an incremental cost of £52,869 and therefore would not be the preferred treatment on cost minimisation grounds. However, when the PAS was taken into account, velaglucerase became a cost-effective treatment option.

The sensitivity analysis showed that velaglucerase alfa remained cost saving in all scenarios, under the conditions of the PAS.

There were no major weaknesses in the analysis. As such, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group submission was received from The Gaucher Association.

Additional information: guidelines and protocols

Paediatric Gaucher disease in England: Guidelines for assessment, monitoring and enzyme replacement therapy, compiled by a multidisciplinary group including paediatricians and the Gaucher Association, were published in March 2012. These guidelines state that all children with types I Gaucher disease should commence treatment with enzyme replacement therapy; imiglucerase (Cerezyme®) or velaglucerase (VPRIV®) which appear to be equally effective.

The recommended starting dose in children is 60 units/kg every two weeks by intravenous infusion. Once the therapeutic goals have been achieved, the dose can be reduced to a minimum maintenance dose of 30 units/kg every two weeks and should be reviewed every six months. Reduction should not take place more frequently than this.

A UK National Guideline for Adult Gaucher Disease was written by clinicians of Addenbrooke's Hospital, Cambridge and The Royal Free Hospital, Hampstead at the invitation of the National Specialist Commissioning Advisory Group of the UK and published in April 2005. It recommends the use of imiglucerase as enzyme replacement therapy. The guideline predates the licensing of velaglucerase alfa.

Additional information: comparators

Imiglucerase is licensed for use as long-term enzyme replacement therapy in patients with non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease.

Miglustat is licensed for the treatment of mild to moderate type 1 Gaucher disease in patients for whom enzyme replacement therapy is unsuitable.

Cost of relevant comparators

Drug	Dose Regimen (for adults and children)	Cost per year (£)**
Velaglucerase alfa	**15 to 60 units/kg by intravenous infusion every two weeks***	**36,665 to 439,982**
Imiglucerase alfa	15 to 60 units/kg by intravenous infusion every two weeks*	13,927 to 334,242

Doses are for general comparison and do not imply therapeutic equivalence. Costs from British National Formulary March 2012. *Dose range cited in summary of product characteristics **Costs based on body weight range 12 to 80kg (lower limit is average weight of a 2 year old child as this was the minimum age in pivotal study; upper limit extends beyond the 75kg body weight used in the economic model).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 8 in year 1 rising to 14 in year 5, with an estimated uptake rate of 50% in year 1 and 75% in year 5. Without PAS the gross impact on the medicines budget was estimated to be £925k in year 1 and £2.337m in year 5. As other drugs were assumed to be displaced the net medicines budget impact is estimated to be £222k in year 1 and £562k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

1) The European Medicines Agency (EMEA) European Public Assessment Report. Velaglucerase alfa (VPRIV®) 2010, EMEA/H/C/001249

2) Shire HGT, I. Study of gene-activated human glucocerebrosidase (GA-GCB) ERT compared with imiglucerase in Type 1 Gaucher disease (HGT-GCB-039). 2012 Feb 07; Clinical Trials.Gov.

3) Shire HGT, I. Study of GA-GCB enzyme replacement therapy in Type 1 Gaucher disease patients previously treated with imiglucerase (TKT034). 2012 Feb 07]; Clinical Trials.Gov.

This assessment is based on data submitted by the applicant company up to and including **16 August 2012.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the

considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.