

# velmanase alfa 10mg powder for solution for infusion (Lamzede®)

Chiesi Limited

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The Scottish Medicines Consortium (SMC) has completed its initial assessment of the evidence for the above product using the ultra-orphan framework:

**Indication under review:** enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

## Key points:

- Alpha-mannosidosis is a very rare progressive lysosomal storage disorder which results in the accumulation of mannose-rich oligosaccharides in all tissues leading to cell and tissue dysfunction affecting multiple systems. This causes a broad range of cognitive and physical symptoms which vary widely in range, severity and rate of progression between patients.
- Evidence from a double-blind, randomised, phase III study demonstrated significant reductions in serum oligosaccharide levels after 52 weeks of treatment with velmanase alfa compared with placebo.
- The placebo-controlled study was limited by a lack of power calculation and small patient numbers leading to uncertainty in the magnitude of treatment effect. There was no significant improvement in the clinical outcome of 3-minute stair climb test. The 52-week duration was considered too short to adequately assess the longer term benefits of velmanase alfa on clinically relevant outcomes including disease progression and complications as well as long term safety.
- There were no significant differences between velmanase alfa and placebo for quality of life measurements assessed after 52 weeks.
- The submitting company has positioned the use of velmanase alfa for patients aged 6 years and over, for whom treatment with allogeneic haematopoietic stem cell transplant (HSCT) is unsuitable/not possible. Although the use of velmanase alfa is not restricted by age, there is agreement generally that HSCT is likely to be targeted towards younger children less than aged 6 years, based on clinical judgement, so HSCT has been excluded as a comparator in this submission.

- There were a number of uncertainties in the economic analysis, and while this is to be expected to some extent given the sample sizes available from the clinical data, several key assumptions about the utility benefit conferred by treatment with velmanase alfa, the longer-term effect of treatment on quality of life and delays to deterioration in functional status (as determined by walking ability) among responders remain difficult to validate beyond expert opinion.
- Despite a PAS that improves the cost-effectiveness of velmanase alfa, the treatment's cost in relation to its health benefits remains high.

**Chairman**  
**Scottish Medicines Consortium**

## Indication

Enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.<sup>1</sup>

## Dosing Information

The recommended dose of velmanase alfa is 1mg/kg of bodyweight administered once every week by intravenous infusion at a controlled speed. Refer to the summary of product characteristics (SPC) for details.

The treatment should be supervised by a physician experienced in the management of patients with alpha-mannosidosis or in the administration of other enzyme replacement therapies (ERT) for lysosomal storage disorders. Administration of velmanase alfa should be carried out by a healthcare professional with the ability to manage ERT and medical emergencies.<sup>1</sup>

## Product availability date

Launched: 23 March 2018

## SMC ultra-orphan designation

Velmanase alfa has been validated as meeting SMC ultra-orphan criteria:

- The prevalence of alpha-mannosidosis is estimated to be  $\leq 1$  in 50,000 (or around 100 people in Scotland).
- Velmanase alfa was granted GB orphan designation for enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis at the time of marketing authorisation (PLGB 08829/0188/OD1).
- Alpha-mannosidosis is chronic and severely disabling due to the severe clinical features which include intellectual disability, immune deficiency, myopathy, skeletal abnormalities and hearing impairment.
- Alpha-mannosidosis requires highly specialised management which will be delivered by the nationally designated service for people of all ages with inherited metabolic disorders.

## Background

Velmanase alfa is a recombinant form of human alpha-mannosidase which is intended to support or replace natural alpha-mannosidase. In patients with alpha-mannosidosis, velmanase alfa will act as an endogenous enzyme, catalysing the sequential degradation of hybrid and complex high-mannose oligosaccharides in the lysosomes and reducing the amount of accumulated mannose-rich oligosaccharides.<sup>1,2</sup>

Velmanase alfa is the first enzyme replacement therapy available for the treatment of alpha-mannosidosis.

## Nature of condition

Alpha-mannosidosis is a progressive lysosomal storage disorder caused by mutations in the MAN2B1 gene which codes for the lysosomal enzyme, alpha-mannosidase. A deficiency in this enzyme results in accumulation of mannose-rich oligosaccharides in all tissues leading to cell and tissue dysfunction affecting multiple systems. It is a very rare condition with a reported prevalence ranging from 1 in 500,000 to 1 in 1,000,000.<sup>2,3,4</sup>

Alpha-mannosidosis causes a broad range of cognitive and physical symptoms including coarse facial features, skeletal abnormalities, ataxia, muscle pain and weakness, hearing impairment and impaired speech. Intellectual disabilities can range from mild cognitive impairment to profound mental deficiency. The immune system may be affected making patients more susceptible to bacterial infections. The range, severity and rate of progression of symptoms varies widely between patients. Alpha-mannosidosis is generally classified into three subtypes: mild which is often diagnosed in patients  $\geq 10$  years old and progresses slowly with symptoms generally including muscle weakness; moderate, which is the most common subtype, may be diagnosed in patients  $< 10$  years old with signs of progressive skeletal abnormalities and muscle weakness; and severe which presents prenatally or in infancy and is characterised by rapid progression of intellectual disability, hydrocephalus, progressive ataxia and hepatosplenomegaly. In severe cases, alpha-mannosidosis is life-threatening.<sup>2,3,4</sup>

Patients may have reduced functional capacity and impaired motor function with some patients eventually becoming wheelchair-bound. Impairment of cognitive function, hearing and sight can have a profound effect on the patient's ability to perform daily activities and self-care. Patients with alpha-mannosidosis are expected to experience a substantial quality of life burden due to their progressive symptoms. This subsequently has a considerable impact on carers to support patients with daily living.

Patients with alpha-mannosidosis are managed with symptomatic and supportive treatments which may include antibiotics to suppress bacterial infections, hearing aids, physiotherapy for muscle weakness, devices or surgery to treat skeletal abnormalities. The most severely affected patients may be considered for haematopoietic stem cell transplantation (HSCT) or bone marrow transplantation.<sup>2,4</sup>

## Impact of new technology

### Comparative efficacy

Evidence for velmanase alfa comes from one randomised, double-blind, phase III study (rhLAMAN-05). This enrolled 25 patients, aged 5 to 35 years, with a confirmed diagnosis of alpha-mannosidosis with alpha-mannosidase activity  $< 10\%$  of normal on blood leucocytes. They were able to co-operate with tests physically and mentally and to walk without support.

Eligible patients were randomised 3:2 to receive velmanase alfa (1mg/kg by intravenous infusion, n=15) or placebo (n=10) once weekly for 52 weeks. Randomisation was stratified according to age.<sup>2,5</sup>

The study had two co-primary outcomes which assessed the change from baseline to week 52 in serum oligosaccharides and in the 3-minute stair climb test (3MSCT). Efficacy analyses were performed in the full analysis population, which included all randomised patients who received at least one dose of study medicine and had at least one post-baseline efficacy measurement. After 52 weeks of treatment, there was a significant improvement in serum oligosaccharide levels in patients treated with velmanase alfa compared with placebo. However, there was no significant difference between velmanase alfa and placebo in change in 3MSCT. The study included two prioritised, secondary outcomes which assessed change from baseline to week 52 in 6-minute walk test (6MWT) and in forced vital capacity (FVC) percentage predicted; results numerically favoured velmanase alfa. Details are presented in table 1.

**Table 1. Results for the co-primary and prioritised secondary outcomes in the full analysis population of the rhLAMAN-05 study<sup>1,2,5</sup>**

	Velmanase alfa (n=15)	Placebo (n=10)	Adjusted mean difference versus placebo (95% CI)
<b>Change from baseline to week 52 in serum oligosaccharide (micromol/L)</b>			
Baseline	6.8	6.6	
Absolute mean change	-5.11	-1.61	-3.50 (-4.37 to -2.62) p<0.001
Adjusted mean relative change	-78%	-24%	-70% (-78% to -60%) p<0.001
<b>Change from baseline to week 52 in 3MSCT (steps/minute)</b>			
Baseline	52.9	55.5	
Absolute mean change	0.46	-2.16	2.62 (-3.81 to 9.05)
Adjusted mean relative change	-1.1%	-4.0%	-3.0% (-9.9% to 18%)
<b>Change from baseline to week 52 in 6MWT (metres)</b>			
Baseline	459.6	465.7	
Absolute mean change	3.74	-3.61	7.35 (-30.8 to 45.5)

Adjusted mean relative change	0.64%	-1.20%	1.9% (-6.6% to 11%)
<b>Change from baseline to week 52 in FVC % predicted</b>			
Baseline	82	90	
Absolute mean change	8.2	2.3	5.9 (-4.8 to 16.6)
Adjusted mean relative change	10%	1.6%	8.4% (-6.1% to 25%)

CI=confidence interval; 3MSCT=3-minute stair climb test; 6MWT=6-minute walk test; FVC=forced vital capacity

Additional secondary outcomes assessed respiratory, motor and cognitive function, hearing and cerebrospinal (CSF) levels of oligosaccharide and other biomarkers. The changes from baseline to week 52 were small with slight numerical improvements in the velmanase alfa group compared with placebo, except for CSF levels and cognitive function. Quality of life was assessed using Childhood Health Assessment Questionnaire disability index (CHAQ-DI) and pain visual analogue scale (VAS) scores and the Euroqol 5-dimensions 5-levels (EQ-5D-5L). There were minimal changes in these measures during the study period and between the treatment groups.<sup>2</sup>

Post hoc responder analyses, using responder criteria defined in terms of minimal clinically important differences for individual outcomes, were performed to consider the clinical relevance of the study results. Results were reported by outcome and were also arranged by domains. The pharmacodynamics domain (serum oligosaccharide) response was achieved by 100% of velmanase alfa patients and 20% of placebo patients; combined functional domain (3MSCT, 6MWT and FVC%) response by 60% and 30% of patients respectively and combined quality of life domain (CHAQ-DI and CHAQ-VAS) response by 40% of patients in each group.<sup>1,2</sup>

The rhLAMMAN-10 study was an open label, phase III study to assess the long-term efficacy of velmanase alfa as an integrated analysis of patients with alpha-mannosidosis who had enrolled in previous velmanase alfa studies (phase I and II and rhLAMMAN-05) and continued to receive velmanase alfa 1 mg/kg once weekly (n=33, 14 adults and 19 paediatric). The primary outcomes were the change from baseline in serum oligosaccharides and in the 3MSCT. Data were analysed as change from baseline to last observation and the time-point of this analysis varied with duration of follow-up to a maximum of 48 months in nine patients. At the last observation, there were improvements in the percentage change from baseline in serum oligosaccharides (-63% [95% CI: -75% to -51%]) and the 3MSCT (14% [95% CI: 4.6% to 23%]). There were also improvements from baseline to last observation in the secondary outcomes of 6MWT and FVC percentage predicted. There was no or minimal change in the CHAQ disability index and general VAS from baseline and a small improvement in the CHAQ pain VAS and EQ-5D-5L scores. Of note, there were ten patients who required walking assistance at baseline and

seven (4/5 paediatric and 3/5 adult patients) became assistance independent at last observation. Post hoc responder analyses of rhLAMAN-10, using the criteria as in rhLAMAN-05, found that a pharmacodynamics domain response was achieved by 91% of patients, combined functional domain response by 73% of patients and combined quality of life domain response by 67% of patients.<sup>1,2,6</sup>

## Comparative safety

In rhLAMAN-05, any treatment-emergent adverse event (AE) was reported by 100% (15/15) of patients in the velmanase alfa group and 90% (9/10) in the placebo group and these were considered treatment-related in 47% and 50% respectively. In the velmanase alfa and placebo groups respectively, patients reporting a serious AE were 33% versus 0%. No patients discontinued study treatment due to treatment emergent AEs.<sup>5</sup>

The most frequently reported treatment-emergent AEs of any grade occurring in more than one patient in the velmanase alfa group versus the placebo group were: nasopharyngitis (67% versus 70%), pyrexia (40% versus 50%), vomiting (20% versus 40%), diarrhoea (13% versus 30%), headache (33% versus 30%), syncope (13% versus 0%), dizziness (6.7% versus 20%), ear discomfort (0% versus 20%), arthralgia (20% versus 10%), back pain (13% versus 10%), ear infection (13% versus 10%), acute tonsillitis (13% versus 0%), influenza (13% versus 10%) and gastroenteritis (13% versus 10%).<sup>2,7</sup>

In the velmanase alfa group, there was one serious treatment-emergent AEs of moderate acute renal failure was considered possibly related to velmanase alfa; the patient had also received long-term ibuprofen.<sup>2,5</sup>

Overall, most AEs in patients treated with velmanase alfa were mild and transient. However, further data is required to evaluate long-term safety, particularly infusion related reactions, immunogenicity and hypersensitivity and this will be collected in an alpha-mannosidosis disease registry.<sup>2</sup>

## Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below:

### *Key strengths:*

- There is evidence from rhLAMAN-05 that velmanase alfa significantly reduced serum oligosaccharide levels compared with placebo demonstrating the pharmacodynamic efficacy of velmanase alfa. This was supported by uncontrolled, longer term data from rhLAMAN-10.<sup>2,5,6</sup>
- Velmanase alfa is the first medicine to receive a marketing authorisation for alpha-mannosidosis and offers a disease modifying treatment for patients who would otherwise receive supportive treatments to manage symptoms and complications of progression.

*Key uncertainties:*

- The only controlled evidence comes from the rhLAMAN-05 study which had no power calculation, hypothesis for testing and hierarchy to control for testing of co-primary and prioritised secondary outcomes. Although there was a significant improvement in serum oligosaccharides in patients treated with velmanase alfa compared with placebo, the statistical robustness of the treatment effect is limited by the weak statistical methods used. The duration of 52 weeks was considered too short to adequately assess the longer term benefits of velmanase alfa on clinical relevant outcomes including disease progression and complications as well as its long-term safety. A disease registry of alpha-mannosidosis has been established to evaluate the long term treatment effect of velmanase alfa.<sup>2,5</sup>
- The responder analysis, which was conducted at the request of the regulator, suggested benefit in terms of minimal clinically important differences but these results should be treated with caution as they were performed post hoc and given that this is such a rare disease, there was limited evidence to support the criteria used to define a response to each outcome.<sup>2</sup>
- In rhLAMAN-05, there was little or no treatment effect with velmanase alfa on the levels of oligosaccharides or proteins in the cerebrospinal fluid or on cognitive function. Since velmanase alfa does not cross the blood brain barrier, this lack of treatment effect was not unexpected. However, this is of clinical relevance to patients (85% of patients in the rhLAMAN-05 study had intellectual disability at baseline). The marketing authorisation restricts the use of velmanase alfa to the treatment of non-neurological manifestations of alpha-mannosidosis.<sup>1,2</sup>
- Study patients in rhLAMAN-05 and -10 were aged  $\geq 6$  years but the marketing authorisation does not restrict the use of velmanase alfa by age. Post hoc subgroup analysis (according to  $< 18$  years or  $\geq 18$  years) suggested that the treatment effect of velmanase alfa was greatest in younger patients and an ad hoc expert advisory group suggested that it would be reasonable to expect clinical benefits in patients aged  $< 6$  years. Therefore, the regulatory authorities considered that it was important for treatment to be started as early as possible and instead of an age restriction, the marketing authorisation was limited to patients with mild to moderate disease to prevent damage from prolonged accumulation of oligosaccharides in various tissues. It was considered that patients with the most severe type of alfa-mannosidosis, which progresses rapidly and with likely neurological deterioration, would be unlikely to be treatable with velmanase alfa. A small, single-arm, open-label study (rhLAMAN-08) has supported the efficacy and safety of velmanase alfa in patients aged  $< 6$  years ( $n=5$ ).<sup>1,2,8, 10</sup>
- Patients with more advanced disease and those who were wheelchair bound were excluded from the rhLAMAN-05 and -10 studies. Therefore, the efficacy of velmanase alfa in these patients in practice is unknown.<sup>2,5,6</sup>
- The study population in rhLAMAN-05 was heterogeneous and there were some differences between treatment groups particularly in baseline 3MSCT and 6MWT values. This suggests

that patients in the velmanase alfa group had lower endurance and were possibly more compromised than patients in the placebo group. This imbalance may affect study results.<sup>2,5</sup>

- Recurrent infections due to immune deficiency are a common complication of alpha-mannosidosis. The rhLAMAN-05 and -10 studies did not assess the rates of infection as a clinical outcome but post hoc analysis found increased immunoglobulin G level in patients treated with velmanase alfa, suggesting improved immune response. However, there is currently limited clinical evidence published to support reduced infection rates with velmanase alfa.<sup>2,5,6</sup>
- Within the clinical case, the company considered the use of velmanase alfa plus best supportive care (BSC) versus BSC alone as the most relevant comparator. Stem cell transplantation may also be used in a small number of suitable patients but was considered more likely to be used in younger patients with severe disease. The company positioned velmanase alfa for use with BSC in patients with alpha-mannosidosis for the treatment of non-neurological manifestations, in those for whom allogeneic HSCT is unsuitable and / or not possible. The clinical evidence from rhLAMAN-05 and rhLAMAN-10 excluded patients with a history of stem cell transplantation.

The efficacy of velmanase alfa looks promising and is associated with significant reductions in serum oligosaccharide levels compared with placebo. However, the longer term effect on clinically relevant outcomes assessing disease progression and complications and the long-term safety of velmanase alfa remain uncertain.

### Impact beyond direct health benefits and on specialist services

The availability of velmanase alfa may stabilise progression of alpha-mannosidosis and may allow patients to participate in activities of daily living, self-care, education and employment for longer. Family and carers may experience a reduced burden of disease if patients maintain mobility and functioning for longer.

The availability of velmanase alfa results in benefits in direct and indirect costs to patients, caregivers and wider social services. Treatment with velmanase alfa may allow patients and caregivers an increased ability and opportunity to work, work for longer hours and maintain employment for longer periods, with fewer absences due to illness and medical appointments. Younger patients may require reduced educational support to access school or college. Treatment may reduce the need for out-of-pocket expenses on patients and carers including mobility aids, electric wheelchairs, vehicles with disabled access, home alterations and private carers or respite providers and to local or central government for home adaptations and welfare benefits.

It is expected that treatment with velmanase alfa would be managed by the national inherited metabolic disease service.

## Patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The MPS Society, which is a registered charity.
- The MPS Society has received 16% pharmaceutical company funding in the past two years, including from the submitting company.
- Alpha mannosidosis is a very rare and highly heterogeneous progressive, debilitating disease. Symptoms include: progressive issues with motor function, problems with bone growth and formation often resulting in osteoarthritis, severe joint stiffness and swelling that restricts movement and causes acute pain, spinal difficulties such as scoliosis and kyphosis, impaired pulmonary and respiratory function with patients suffering from frequent infections and some patients needing ventilation. Hearing loss is also common, with many patients requiring hearing aids. Many carers have to give up work to undertake their caring roles, either to accommodate frequent hospital trips or to become the patient's full-time carer.
- Best supportive care such as management of pain, orthopaedic/ skeletal problems, infections, hearing and therapeutic care such as physiotherapy, speech and language therapy is the only current option for most patients. These do not address the underlying disease pathology.
- Presentation of symptoms at diagnosis could have an impact on treatment outcomes and patients will respond in different ways. They added that whilst treating early will give the best outcomes, it is important to consider that stabilisation is as good a response rate, as improvements. Treated teenagers and adults have shown positive improvements. Age and timely treatment is critical whether it is treating a child or an adult.
- Treatment with velmanase alfa had a positive impact on the quality of life of patients and carers. A patient reported a range of benefits including: improvements in respiratory function, reduced need for mobility aids, reduced ear infections leading to improvements in communication, overall improvements in self-esteem and greater independence. Parents reported improvements in their mental health, relationships and their social and working lives. A treating clinician consulted by the patient group reported that the outcomes seen in their patient were better than the clinical trial data would suggest as the trial does not reflect the positive impact on cognitive function, daily living and carers.
- Regarding disadvantages the patient group noted that patients may need a portacath to avoid weekly cannulation for difficult veins or needle phobia. There is also a small possibility of an allergic reaction and serious AEs. They added that most patients treated with enzyme replacement therapy have indicated that benefits of treatment far outweigh the potential risk of a severe adverse event.

## Value for money

The submitting company provided a cost-utility analysis assessing the cost effectiveness of velmanase alfa in the treatment of non-neurological manifestations in patients, aged 6 years and over, with mild-to-moderate alpha-mannosidosis for whom allogeneic haematopoietic stem cell transplant (HSCT) is unsuitable and/or not possible.

The primary comparison was between velmanase alfa plus BSC and BSC alone. An alternative comparator of HSCT was not included as the submitting company argued this would be a more relevant treatment for those aged under 6 years old (the model starting age). Experts consulted by SMC agreed that younger children are more likely to receive HSCT owing to the risks and benefits of HSCT, and the clinical manifestations of alpha-mannosidosis being more severe in those diagnosed at younger ages. The submitting company confirmed that extension of the license of velmanase alfa to children of all ages was approved in November 2021 but was too late to include in this submission to SMC in December 2021.

A state transition Markov structure was used whereby patients are followed up over a lifetime time horizon (cycle length 12 months) with health states depending on their functional walking ability (walking unaided, walking with assistance, wheelchair dependent and severely immobile). Patients progress towards the states with poorer mobility over time, in addition they can experience surgical events or severe infections. Patients can die from all-cause mortality directly from any state in the model or from a severe infection. Severe infections were modeled as tunnel states, as opposed to side effects within the main health states, as was done for surgical events. This allowed for the infection-specific short end-stage state to apply the costs and disutilities associated with intensive, end of life care (average duration of 4 weeks).

Improvement in functional response was taken from rhLAMAN-10 data. Data used from rhLAMAN-10 included backwards transitions through the model (i.e. defying progression) from wheelchair dependence to walking with assistance (for velmanase alfa patients only), as well as transition probabilities for adults, the model starting state (baseline data from rhLAMAN-10), and the probability of non-response to velmanase alfa at follow up (year 1 or at the end of the first model cycle). Otherwise, most parameters in the model were sourced from expert opinion. Notably, an assumption was made that deterioration in responders is delayed for the first five years (this was tested in scenario analysis). This was based on available data from the Etoile Alpha retrospective registry<sup>9</sup> and validated by a Scottish clinician consulted by the submitting company.

Utility data for the model came from the clinical data collected in rhLAMAN-10 (walking unassisted and walking with assistance only as patients who could not walk did not meet the inclusion criteria for rhLAMAN-05) and an external study by Adam et al 2019<sup>11</sup>. Within the base case modelling, the utility values were 0.652 for walking unassisted, 0.577 for walking with assistance, 0.100 for wheelchair dependent state and -0.011 for severe immobility.

An assumption was also made that patients gain a specific “on-treatment” utility benefit from receiving velmanase alfa of 0.1. This was done to account for the benefit of treatment on minor infections, minor surgeries, psychiatric complications, ventilator dependency and intra-ambulatory health state improvements (e.g. a reduction in ambulatory aids required for walking even though assistance is still needed). This was tested in scenario analysis (where it was removed or reduced to 0.05).

The EQ-5D data from the rhLAMAN-10 study also showed improvements in mean EQ-5D index and VAS scores over time, but 95% confidence intervals included negative values in most cases, except relative percent change over time in EQ-5D index score. Subgroup data for these EQ-5D index score gains indicate improvements over time were larger for paediatric patients.

Costs included medicines, administration costs of infusion (of which it was assumed 98% of infusions would take place at home although this was tested in scenario analysis to assume all infusions were hospital-based), surgical treatment, infection treatment and ventilation, as well as Personal Social Services (PSS) caregiver costs and BSC costs. Adult healthcare costs were assumed to apply to adult patient at age 16 years and over.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

The main economic results, shown in the tables below, are inclusive of the PAS discount and are broken down according to patient age ranges. Both costs and QALYs are predominantly gained in the “walking unaided” state and so it is expected that assumptions about transitions to and from this state could have a large impact (see scenario analyses below). In univariate sensitivity analyses the main parameters influencing the size of the incremental cost-effectiveness ratio (ICER) were the costs of velmanase alfa, although other parameters including the annual probability of withdrawal, progression from the walking with assistance to the wheelchair state, backwards progression from the walking with assistance to the walking unaided state and the utility value for the walking unaided state, also had an influence.

**Table 2: With PAS Base case results (excluding carer disutility) at each age group of patients**

Paediatrics	ICER vs. BSC Paediatrics	ICER vs. BSC Adolescents	ICER vs. BSC Adults
<b>BSC</b>			
<b>Velmanase Alfa</b>	£181,224	£250,245	£269,767

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio;

The submitting company also provided some additional results on request, using an overall age-weighted ICER and according to assuming an under or over age 18 population split, as shown in table 3.

Table 3: With PAS ICER values (excluding carer utilities) for a single overall cohort and separate ICERs for paediatric (<18 years old) and adult (18 years old and over) groups

Age group	% weighting	Overall ICER	Paediatric (<18 years)/Adult (18 years +) ICERs
<b>Paediatric (6-11 years old)</b>	40%	£231,426	£204,608
<b>Adolescent (12-17 years old)</b>	20%		
<b>Adult (18 years and over)</b>	40%		£269,767

Abbreviations: ICER = incremental cost-effectiveness ratio.

Table 4: Scenario analyses (inclusive of the PAS discount on velmanase alfa)

Scenario Number	Scenario	Scenario detail	Paediatric ICER	Adolescent ICER	Adult ICER
1	Include personal and caregiver expenditure		£183,678	£252,644	£272,108
2	Include caregiver productivity loss	Include caregiver productivity losses due to reduced earnings	£236,968	£307,024	£329,073
3	Time horizon 20 years		£428,950	£692,871	£980,722
4	No annual withdrawal	No treatment discontinuation for responders until they enter the 'wheelchair dependent' health state	£363,988	£410,757	£423,694
5	No delay in progression in VA responders		£252,577	£336,383	£364,933
6	Permanent delay in progression in VA responders	A permanent delay in disease progression in VA responders until treatment discontinuation	£127,664	£184,665	£199,196
7	Discontinue if wheelchair dependent	Treatment is discontinued upon entering the 'wheelchair dependent' health state	£173,177	£243,144	£262,235

<b>8</b>	No reduction in severe infection probability	No treatment effect for VA in terms of reducing the probability of a severe infection occurring, and in reducing the mortality risk of a severe infection	£174,225	£248,306	£268,440
<b>9</b>	No reduction in surgery benefit	No treatment effect for VA in terms of reducing the probability of mortality or serious complications arising from a surgical procedure	£191,952	£268,256	£288,288
<b>10</b>	No homecare administration	No homecare administration, all VA infusions provided in hospital	£213,974	£282,120	£300,423
<b>11</b>	MPS Health State Utilities	MPS Society Survey utility values are used for the health state utility values	£156,458	£215,458	£231,021
<b>12</b>	Include carer disutility	Include carer disutility (NB: company submitted base case)	£179,671	£247,939	£267,146
<b>13</b>	On-treatment utility = 0.00	On-treatment utility benefit for VA = 0	£241,007	£329,893	£351,359
<b>14</b>	On-treatment utility = 0.05	On-treatment utility benefit for VA = 0.05	£206,883	£284,602	£305,204

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; VA = velmanase alfa; MPS = mucopolysaccharidosis

The key strengths and uncertainties of the economic case are summarised below:

*Key strengths:*

- The economic analysis drew on comparative data from the clinical study rhLAMAN-05 and additional data on change over time from the rhLAMAN-10 study and Etoile Alpha registry to support the analysis.
- The company had made significant efforts to co-design the model structure with experts and ensure inputs that reflect clinical practice for this population.
- Extensive scenario analyses was undertaken to explore areas of uncertainty.
- The primary comparator appeared to be appropriate and the justification for excluding HSCT as a comparator was judged as sound.

*Key weaknesses:*

- Although data from rhLAMAN-10 (inclusive of rhLAMAN-05) were used to inform the model, most parameters have been informed by expert opinion. The efforts made to elicit

expert opinions have been extensive but while the methods used have been summarised, results were not well reported and so there remained uncertainty regarding the extent of agreement across the experts consulted. This, coupled with the lack of long-term data being inputted into the model with a lifetime time horizon, made it difficult to know how well the model reflected what is likely to happen to patients in practice. As shown in table 3, the cost-effectiveness estimate was upwardly sensitive to a range of aspects where the data are uncertain, such as the effect of treatment on infections, the need for surgery, the extent of delay in disease progression and treatment discontinuation.

- The model split data from the rhLAMAN-05 and rhLAMAN-10 studies (already with small sample sizes) into three separate subgroups to provide separate ICERs for a paediatric, adolescent and adult cohort. Within the clinical effectiveness results, some subgroup data were available for paediatric (<18 years old) patients and adult (aged 18 years old and over) but the additional use of an adolescent cohort for the economic evaluation may have only exacerbated existing uncertainties.
- As noted, the model assumed an additional on-treatment utility of 0.1 for velmanase alfa in an attempt to incorporate other quality of life impacts that are not captured due to the model being structured around ambulatory status. While potentially a plausible approach, there is uncertainty associated with the true quality of life impact of the treatment in practice, and this has a key impact on the cost-effectiveness results (see table 3, scenarios 13 and 14).
- Structurally the model cycle length was long, although it had been validated by experts. There were insufficient data to confirm the validity of the assumed reduction in the duration of disutility by 50% for patients receiving velmanase alfa (based on expert opinion), particularly for infection events, where clinical data on these outcomes was not captured in the rhLAMAN studies.

The cost of velmanase alfa in relation to its health benefits remains high and there are outstanding uncertainties relating to the clinical data and utility values used in the model.

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

## Costs to NHS and Personal Social Services

The submitting company estimated there would be three patients eligible for treatment with velmanase alfa each year. The estimated uptake rate was 50% annually to year 5. This resulted in one patient estimated to receive treatment annually to year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

Other data were also assessed but remain confidential.\*

## Additional information: guidelines and protocols

No treatment guidelines have been published for the treatment of alpha-mannosidosis. In 2019, a consensus document was published “Recognition of alpha-mannosidosis in paediatric and adult patients: presentation of a diagnostic algorithm from an international working group”. The aim of this document is to aid early diagnosis and no recommendations were made for the treatment of patients. The clinical management of alpha-mannosidosis is discussed, noting that it is based on treating disease manifestations and preventing complications, while optimising the patient’s quality of life as much as possible. This may include the early use of antibiotics for bacterial infections, hearing aids, glasses, physiotherapy, use of a wheelchair, orthopaedic interventions and shunting for hydrocephalus. HSCT may be a targeted option but procedure-related mortality and rate of complications must be considered. Long term enzyme replacement therapy with velmanase alfa is associated with clinically meaningful and continued benefit for many patients with alpha-mannosidosis.<sup>4</sup>

## Additional information: comparators

Best supportive care.

## Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
<b>Velmanase alfa</b>	<b>1mg/kg by intravenous infusion once weekly</b>	<b>92,207 to 322,726</b>

*Costs from MIMS online on 9 June 2022. Costs calculated based body weight ranging from 20kg to 70kg and on a using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.*

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10. Guffon NK, V; Hennermann, J; Muschol, N.; Bruno, I.; Tummolo, A.; Ceravolo, F.; Zardi, G; and Lund, A., editor Long-term safety and efficacy of velmanase alfa (VA) treatment in children under 6 years of age with alpha-mannosidosis (AM)2021 21-24 November; Abstract presented at ICIEM (International Congress of Inborn Errors of Metabolism).
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This assessment is based on data submitted by the applicant company up to and including 15 July 2022.

*\*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:<https://www.scottishmedicines.org.uk/about-us/policies-publications/>*

Medicine prices are those available at the time the papers were issued to SMC for consideration. 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 assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine 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 NHSScotland 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 a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

### **Assessment report context:**

*No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.*

*This assessment 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. 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.*