Enclosure No:	**4**/AWMSG/0524
Agenda Item No:	8 – Alglucosidase alfa for long term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency)
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Alglucosidase alfa for long term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency)

Action:

AWMSG members are requested to review and endorse an update to existing AWMSG advice for alglucosidase alfa for Pompe disease.

Situation:

The All Wales Medicines Strategy Group (AWMSG) appraised alglucosidase alfa (Myozyme®) for the above indication in 2006 and recommended it for restricted use in NHS Wales for infantile and juvenile onset Pompe disease (see Appendix 1). At the time AWMSG concluded there was insufficient evidence of clinical effectiveness for late onset Pompe disease (LOPD) in adults. Clinical experts in Wales and the Welsh Health Specialised Services Committee (WHSSC) contacted AWTTC to highlight the unmet need which exists for adult patients with LOPD and request AWMSG advice is reviewed. They highlight that since the original appraisal a number of studies conclude that alglucosidase alfa has a beneficial effect in LOPD in adults as demonstrated by improvements in survival and ambulation maintained over time, as well as prevention of deterioration in respiratory function. Alglucosidase alfa for the treatment of LOPD is available in NHS Scotland and NHS England. National Services Scotland funds alglucosidase alfa for the treatment of Pompe disease if prescribed by the Scottish inherited metabolic services. NHS England commissions services for adults and children with Pompe disease from Highly Specialised Lysosomal Storage Disorder Centres. In NHS Wales WHSSC commissions alglucosidase alfa within its marketing authorisation, for the treatment of Pompe disease in line with AWMSG restricted advice (see Specialised Services Commissioning Policy CP55 Drug treatment for lysosomal storage disorder (All ages)).

Background:

Pompe disease (acid alpha-glucosidase deficiency) is a rare, genetic, chronic and progressive metabolic disease resulting in severe disability and a reduced life expectancy. Pompe disease is estimated to affect approximately 0.3 in 10,000 people with a reported birth prevalence of 0.8 per 100,000 people for the infantile onset form and 1.75 per 100,000 for the late-onset form according to European Orphanet data. There is a range of phenotypes of Pompe disease which can be broadly classed as infantile-onset (IOPD) i.e. patients ≤ 12 months of age, and LOPD i.e. childhood, juveniles and adults. Earlier onset compared to later onset is associated with more rapid progression and greater disease severity. The most severely affected infants usually present within the first three months of life and have characteristic cardiac problems. Less severe forms with onset during childhood, adolescence or adulthood, rarely manifest cardiac problems, but lead to walking disability and reduced respiratory function. The monitoring of patients with Pompe disease requires a coordinated approach by a specialist and individuals who have expertise in the care of these patients. Management of care is often coordinated by a neuromuscular physician, neurologist or metabolic disease specialist. The only treatment for Pompe disease is enzyme replacement therapy (ERT) that targets enzyme deficiency. Although ERT is not curative, it is the only treatment that has been shown to modify the disease course in patients with Pompe disease. Currently there are two National Institute for Health and Care Excellence (NICE) approved alternatives to alglucosidase alfa for LOPD; avalglucoside alfa (TA821) and cipaglucosidase alfa with miglustat for treating LOPD (TA912). NICE confirms that the standard treatment for LOPD is with alglucosidase alfa or avalglucosidase alfa. In line with the current AWMSG advice, adult patients in Wales with LOPD do not have routine access to alglucosidase alfa, unlike patients in England and Scotland.

Assessment:

In 2016 the market authorisation holder, Sanofi Genzyme, approached AWTTC with new evidence in the LOPD group. The company were asked to prepare a full submission but decided not to submit due to the lack of available studies available for the LOPD population due to the rare nature of the disease. AWTTC conducted a routine review of the AWMSG recommendation in 2019. WHSSC has since approached AWTTC to review the advice again, in line with a recent review of their commissioning policy for lysosomal storage disorders.

The treatment of lysosomal storage disorders, such as Pompe disease falls under the remit of National Specialist Commissioning Groups. National guidelines exist for the treatment and monitoring of these patients, including the use of enzyme replacement therapies. These guidelines are written by the physicians working within the Highly Specialised Lysosomal Storage Disorder Centres and are reviewed on a regular basis.

Clinical experts have highlighted that alglucosidase alfa is considered established practice for the treatment of Pompe disease across the rest of the UK. Patient organisations such as Association for Glycogen Storage Disease UK (AGSD-UK), patients and clinical experts in Wales have continued to highlight the high unmet need for the treatment of LOPD. The AGSD-UK highlights the significant impact of Pompe disease as a serious, debilitating, degenerative condition that can affect every aspect of daily life. Given the heterogeneity of response to ERTs, full access to all effective treatment options should be considered to enable the clinician, in partnership with the individual, to select the most appropriate therapy at every stage, following close monitoring and review. Experts have stated not all patients respond equally to the different ERTs, thus clinicians wish to have alglucosidase as an available option for patients. It’s place in therapy, if approved, is likely to be as a second line treatment option. Alglucosidase alfa for LOPD is currently accessed by clinicians applying for IPFR funding, which requires additional NHS Wales resource to submit and process, and patients have to wait for a decision before they can commence treatment. WHSCC confirm that in the year 2021-2022 there were 10 patients on alglucosidase alfa treatment for LOPD in Wales.

The clinical efficacy and safety for the use of alglucosidase alfa for LOPD is based on a number of clinical studies. In 2006, the applicant company highlighted study

AGLU02704 was ongoing, and interim results were not available at that time. The results for this and the extension study have since been published (van der Ploeg et al., 2010, 2012, and 2017). Other studies identified were observational, longitudinal cohort surveys (follow up to five years). Most were prospective, investigating clinical outcomes such as mortality, motor (six-minute walk test) and respiratory function (% predicted Forced Vital Capacity). There was one systematic review and meta-analysis (Schoser et al.2017) which showed a nearly five-fold lower mortality rate in alglucosidase alfa-treated patients than in untreated patients. All studies concluded that alglucosidase alfa had a beneficial effect in LOPD in adults. An updated literature search since 2019 includes a systematic review and meta-analysis (Bereli S et al. 2022). The available data showed that ERT has a significant beneficial effect in the improvement of walking distance in LOPD patients and a non-significant improvement of muscle strength and respiratory function stabilised.

No post marketing pharmacovigilance concerns of note have been identified (other than infusion-associated reactions). Such reactions are well tolerated, and managed by interrupting or reducing the infusion rate, as well as treatment with antihistamines and antipyretics.

Prescribing data for the years January to December 2022 and January to December 2023 showed costs of £1,640,409 and [Confidential text removed]. Dosing of alglucosidase alfa is individualised and weight-based. The average cost per patient per year, based on the list price and assuming an average weight of 60 kg and the recommended dose of 20mg/kg is £222,181. WHSSC records have confirmed that in 2021-2022 ten patients were being treated with alglucosidase alfa and over the period 2022-2023 [Confidential text removed]. Given the low number of patients already being treated, the low incidence of the condition and the proposed usage as a second line treatment there is unlikely to be any additional patients receiving the medicine as a result of the proposed change in the recommendation over the next 5 years. As an alternative scenario the net yearly impact of a single 60kg patient moving from cipaglucosidase alfa plus miglustat (taking account of the patient access scheme for cipaglucosidase alfa) to alglucosidase alfa is [Commercial in confidence text removed]. The budget impact for a patient switching from avalglucosidase alfa to alglucosidase alfa is [Commercial in confidence text removed] per year (taking account of the patient access scheme for avalglucosidase).

Recommendation:

AWMSG members are asked to endorse an update to the existing recommendation for alglucosidase alfa to include LOPD in adult patients, in accordance with the licensed indication (see Appendix 2). The recommendation will then be forwarded to Welsh Government for ratification.

References:

A full reference list is available on request.

Appendix 1

Current AWMSG advice (date of issue 30/12/2006).

> ***Status:*** *Recommended with restrictions*
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> Alglucosidase alfa (Myozyme™) should be endorsed within NHS Wales for the treatment of Pompe disease in accordance with the licensed indication but with the specific restriction. That there is presently insufficient evidence of clinical effectiveness in late-onset disease and AWMSG does not endorse its use in this group of patients at this stage. AWMSG endorsed the use of alglucosidase alfa (Myozyme™), but with the specific exclusion of alglucosidase alfa (Myozyme™) in Late-onset Pompe disease of the Adult Onset form (Adult Onset disease) because of insufficient evidence of clinical effectiveness. The Committee was however persuaded that alglucosidase alfa (Myozyme™) should be available for the treatment of Late Onset Pompe disease of the Juvenile Onset form (Juvenile Onset Disease).
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> AWMSG recommends that:
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> 1. Patients receiving alglucosidase alfa (Myozyme™) will be entered into the Pompe registry.
> 2. Treatment will be administered under the supervision of a physician experienced in the management of Pompe disease or other neuromuscular disorders.
> 3. Treatment will be administered according to agreed guidelines at appropriate centres.
> 4. The AWMSG recommendation will be reviewed in light of further evidence becoming available.

Appendix 2

Final Appraisal Recommendation
Advice number: 0224 – May 2024

Alglucosidase alfa (Myozyme®)

50 mg powder for concentrate for solution for infusion

Submission by Sanofi Genzyme

Recommendation of the All Wales Medicines Strategy Group

Alglucosidase alfa (Myozyme®) is recommended as an option for use within NHS Wales for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).

(Myozyme®) is indicated in adults and paediatric patients of all ages.

Additional note(s):

- This advice incorporates and replaces the AWMSG recommendation for algluosidase alfa (Myozyme®) for the treatment of infantile on-set and juvenile onset Pompe disease (originally published October 2006).

In reaching the above recommendation AWMSG has taken account of the appraisal documentation prepared by the AWMSG Secretariat (reference number 17). The original decision was made in 2006 then updated in 2024 to align with current evidence and clinical practice.

This recommendation has been ratified by Welsh Government. The All Wales Therapeutics and Toxicology Centre (AWTTC) reviewed this appraisal recommendation in February 2024. Following this update this recommendation has been transferred to AWMSG's static list of medicine recommendations.

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All Wales Medicines Strategy Group Final Appraisal Recommendation – 0224: Alglucosidase alfa (Myozyme®) 50 mg powder for concentrate for solution for infusion May 2024