Technology Guidance

Enzyme replacement therapies

for Fabry disease

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Agalsidase alfa 3.5 mg/3.5 mL concentrate for solution for infusion as an enzyme replacement therapy in patients with Fabry disease. The treatment may be initiated only in:
  a) Male patients with classical Fabry disease; or
  b) Male patients with non-classical Fabry disease, or female patients with classical or non-classical Fabry disease, who have signs/symptoms of organ involvement (e.g. kidney, heart or nervous system) consistent with Fabry disease and which are not fully explained by other pathology.

Funding status

Agalsidase alfa 3.5 mg/3.5 mL concentrate for solution for infusion is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 August 2024.

Agalsidase alfa should be used in line with the additional clinical criteria listed in the Annex.

MAF assistance **does not** apply to agalsidase beta for treating Fabry disease.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the March 2024 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of two enzyme replacement therapies (ERTs), agalsidase alfa and agalsidase beta, for Fabry disease. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for the ERTs was considered in line with their registered indications.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. Fabry disease (FD) is a genetic disorder where a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A) leads to progressive accumulation of glycolipids, primarily globotriaosylceramide (Gb3), in the blood vessels and a wide range of cells throughout the body. This accumulation causes cell abnormalities, organ dysfunction, and serious complications such as kidney failure, heart failure and stroke.

2.2. There are two main phenotypes of FD. The more severe, classical phenotype is most often seen in males with no alpha-Gal A enzyme activity, and who usually experience symptoms before they are 18 years old. The less severe, non-classical phenotype occurs in patients with limited alpha-Gal A enzyme activity and has a later onset.

2.3. In line with international guidelines, local clinicians recommend timely treatment of FD to prevent progression to irreversible tissue damage and organ failure. Hence, treatment should be considered in males with classical FD even if asymptomatic. For males with non-classical FD, and all females with FD, treatment should be considered when there are signs or symptoms of organ involvement.

2.4. The Committee noted that two ERTs, agalsidase alfa and agalsidase beta, are approved by the Health Sciences Authority (HSA) to provide an exogenous source of the deficient alpha-Gal A enzyme for patients with FD.

2.5. The Committee heard there are at least 15 current cases of diagnosed FD in Singapore. They acknowledged the high clinical need for a subsidised treatment option for FD to ensure appropriate patient care and improve treatment affordability.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence for agalsidase alfa and agalsidase beta in adults and children with FD. The evidence came from single-arm and randomised controlled trials, open-label extension studies, observational studies, and meta-analyses of randomised trials and cohort studies.

3.2. The Committee noted several limitations with the evidence base. For example, most trials had small sample sizes, and the observational studies lacked a control arm which limited the interpretation of their results. Additionally, many studies reported outcomes following late initiation of ERT, when substantial organ damage had already occurred.

3.3. Based on the totality of evidence, the Committee acknowledged that ERTs may halt or attenuate disease progression in patients with FD. The studies showed that ERT reduced Gb3 levels in various body tissues, and stabilised renal function and left ventricular hypertrophy. ERT-treated patients also appeared to have a lower incidence of severe clinical events (stroke, renal or cardiac events) and to live longer than untreated patients.

3.4. In terms of safety, both ERTs were generally well-tolerated. The most common adverse reactions reported were infusion-related reactions, thus pre-treatment with antipyretics, antihistamines or corticosteroids may be necessary.

3.5. The Committee noted that two head-to-head trials between agalsidase alfa and agalsidase beta reported no significant differences in efficacy or safety outcomes. Hence, the two ERTs are considered clinically comparable, in line with local clinical expert opinion.

Cost effectiveness

4.1. The Committee heard there was limited information on economic evaluations by overseas HTA agencies for the two ERTs, and that available evaluations were conducted many years ago. The Committee also noted that ERTs are funded in reference jurisdictions to enable patient access to treatment.

4.2. Given agalsidase alfa and agalsidase beta have comparable clinical effectiveness and safety, the Committee agreed that a cost-minimisation approach was appropriate to identify the ERT with lower treatment cost for funding consideration. Based on the companies' proposed prices and the HSA-approved doses, the cost-minimisation analysis showed that agalsidase alfa had a lower treatment cost than agalsidase beta.

4.3. When compared with prices in overseas reference jurisdictions, the Committee considered agalsidase alfa likely to represent an acceptable use of healthcare resources for treating FD.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system was estimated to be less than SG$1 million in the first year, and between SG$1 million and SG$3 million in the fifth year of listing agalsidase alfa on the MOH List of Subsidised Drugs for treating FD.

Recommendations

6.1. Given the high clinical need, the totality of clinical evidence, and that agalsidase alfa is considered an acceptable use of healthcare resources, the Committee recommended agalsidase alfa 3.5 mg/3.5 mL concentrate for solution for infusion be listed on the Medication Assistance Fund (MAF) for treating FD. They also recommended that agalsidase alfa be used in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice.

6.2. The Committee recommended not listing agalsidase beta on the MOH List of Subsidised Drugs due to unfavourable cost-effectiveness compared with agalsidase alfa at the proposed prices.

ANNEX

MAF clinical criteria for agalsidase alfa

For enzyme replacement therapy in patients with Fabry disease. Diagnosis of Fabry disease must be confirmed by the demonstration of specific deficiency of alpha-galactosidase enzyme activity in the blood or white cells, or the presence of genetic mutations known to result in deficiency of alpha-galactosidase enzyme activity.

The treatment may be initiated only in:

a) Male patients with classical Fabry disease; or

b) Male patients with non-classical Fabry disease, or female patients with classical or non-classical Fabry disease, who have signs/symptoms of organ involvement (e.g. kidney, heart or nervous system) consistent with Fabry disease and which are not fully explained by other pathology.

Patient must be treated by, or in consultation with, a specialist physician experienced in the diagnosis and management of Fabry disease. The treatment must be ceased when there is evidence of disease progression as shown by any of the following:

- End-stage renal disease, without an option for renal transplantation, in combination with advanced heart failure (NYHA class IV); or
- End-stage Fabry disease or other comorbidities, with a life expectancy of less than 1 year; or
- Severe cognitive decline of any cause.