

Guidelines for Eligibility to Receive Treatment with Agalsidase through the Lifesaving Drugs Program

Introduction

Fabry disease is an X-linked disorder caused by the deficiency of the lysosomal enzyme α -Galactosidase A (α -Gal). Patients with this disorder suffer in childhood from severe pains in hands and feet and develop progressive multi-system complications later in life (usually in early adulthood), such as renal failure, cerebrovascular accidents (CVAs) and cardiovascular complications. Patients with Fabry disease have a reduced life expectancy. Age of onset of Fabry-related symptoms, and rate of disease progression and severity, is variable and cannot be definitively predicted for each individual.

Prior to the introduction of enzyme replacement therapy, treatment of Fabry disease was symptomatic and included dialysis, renal transplantation, and neurotropic analgesics. Recent surveys have highlighted complications in female Fabry carriers, occurring on average 10 to 20 years later than their male counterparts.

Two α -Galactosidase enzyme preparations have received marketing authorisation in Australia and both have orphan drug status: ReplagalTM and FabrazymeTM. The nature of the pivotal trials did not facilitate comparisons between these products, with regard to safety and clinical efficacy, because of their different dosage and evaluation methods. Therefore, treatment should ideally be performed according to a standardised approach, with centralised data collection, to allow ongoing comparison of both drugs. There have been a number of Fabry treatment centres established in Australia (see Attachment 1). Patients wishing to receive treatment with agalsidase through the Lifesaving Drugs Program must be under the care of one of these centres.

Patient Definition

All patients (of all ages and either sex) with biochemical (α -Galactosidase enzyme activity) or mutation-proven Fabry disease who meet the criteria listed below should be considered for therapy. Testing should be performed by a NATA accredited laboratory. The patient must be a permanent Australian resident and be eligible for Medicare benefits.

In women, particularly those from Fabry families, even if enzyme studies are normal, mutation analysis should be performed if clinical suspicion is high. Review of data in symptomatic women from WCH Adelaide¹ and other centres around the world² has revealed that α -Galactosidase enzyme activity is often normal in Fabry heterozygotes.

¹ Fletcher JM Nelson PV Muller V Clements P. Harrison JR Hopwood JJ. Fietz M. α -Galactosidase enzymology does not predict symptomatic Fabry heterozygotes. *J. inherit. Metab. Dis.* 25 (2002) Suppl 1; 114

² Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. *J Inherit Metab Dis.* 2003;26(7):617-27.

Clinical criteria for funded enzyme replacement therapy

Male Fabry patients must have evidence of 1 major criterion, or 2 or more minor criteria

Major criteria (males)

- Severe Fabry-related renal disease as evidenced by:
 - proteinuria >300 mg/24 hours. Renal biopsy is recommended to exclude other causes of nephropathy, *or*
 - albumin excretion rate > 20 µg/min or albumin: creatinine ratio greater than upper limit of normal, in 2 separate samples, at least 24 hours apart, in presence of renal biopsy showing Fabry glomerulopathy on electron microscopy; *or*
 - history of renal transplant, with prior biopsy evidence excluding other causes of nephropathy.
- Left ventricular hypertrophy, (wall thickness greater than 12 millimetres on echocardiogram) in the absence of hypertension. If hypertension is present, it should be treated for at least 6 months and myocardial biopsy is recommended to differentiate the cause of the hypertrophy.
- Cerebral ischaemic vascular damage at age less than 50 with no other cause identified
- Documented CVA with no other cause identified and correlated with MRI findings
- Uncontrolled chronic pain despite the use of maximum doses of appropriate neurotropic analgesics.

Female Fabry patients must have evidence of 1 major criterion, or 2 or more minor criteria

Major criteria (females)

- GFR < 70 ml/min/1.73m² on 2 successive readings *OR* fall of more than 20% in 2 successive readings at least 6 months apart, with second reading below 80 ml/min/1.73m², with renal biopsy to exclude other causes of nephropathy and with proteinuria >300 mg/24 hours.
- Left ventricular hypertrophy, (wall thickness greater than 13 millimetres on echocardiogram) in the absence of hypertension. If hypertension is present, it should be treated for at least 6 months and myocardial biopsy is recommended to differentiate the cause of the hypertrophy.
- Cerebral ischaemic vascular damage at age less than 50 with no other cause identified.
- Documented CVA with no other cause identified and correlated with MRI findings.
- Uncontrolled chronic pain despite the use of maximum doses of appropriate neurotropic analgesics.

Minor criteria (Males and Females)

- 3 documented transient ischaemic attacks with no other cause identified.
- Abnormal cerebral MRI scans with no clinical symptoms of CNS disease and no other cause identified.
- Episodic severe disabling vertigo.

Patients receiving enzyme replacement therapy as at 11 May 2004 will be continued on therapy even though their disease severity at time of assessment may not meet the above criteria due to the protective/reversal effect of the therapy they have already received. It should be noted that these patients met entry criteria for clinical trials or were judged to have severe enough disease to warrant compassionate use therapy.

Dosage

There is as yet no unequivocal data on the optimum dose or preparation of α -Galactosidase A. In the first instance, dosage will depend on the preparation used. As more data on the outcomes of treatment with different regimens become available, dosage schedules may be altered, in line with this information. Dosage of agalsidase beta will not exceed 1.0 mg/kg per fortnight (FabrazymeTM) or agalsidase alfa 0.2 mg/kg per fortnight (ReplagalTM) in adults with Fabry disease. Fortnightly dose is calculated on BMI of 27 or actual body weight, whichever is lower.

Monitoring of therapy

- Patients must agree to conditions of monitoring, review and data collection as specified in this document
- The first 12 infusions should be undertaken at a designated treatment centre.
- The results of treatment will be re-evaluated every six months at a designated treatment centre, according to the schedule below and provided to the central committee.
- In the event of severe drug reaction, treatment may be discontinued.

Adjunctive therapy

Enzyme replacement therapy may be supplemented by optimal treatment with analgesics, reno-protective, cardio-protective and vasculo-protective medications as indicated. A complete record of such therapy must be kept.

Withdrawal of therapy

The recommendation to provide financial support for Fabry enzyme replacement therapy may be withdrawn:

- In the event that the patient fails to comply adequately with treatment or measures taken to evaluate the effectiveness of therapy;
- If therapy fails to relieve symptoms of disease or fails to arrest progression of those signs that originally resulted in the patient being classified as severely affected.

Treating physicians should note that failure to comply with the protocol for data collection may jeopardise their patient remaining on the program.

Dose may be adjusted by the committee who oversees treatment of Fabry disease, based on response to therapy and evolution of evidence.

After 2 years of therapy, the following may be considered on the basis of the patient's response to treatment:

- Increase in dosage up to the approved maximum dose for the given therapy.
- Reduce dosage.
- Change product.
- Stop treatment.

Safety end-points

Monitored by:

- Clinical examination
- Vital signs.
- Routine bloods.

Adverse events should be reported to ADRAC and the drug's sponsor.

Audit

There is a requirement for centralised data management through the Fabry committee. Referring physicians should be encouraged, with consent, to enrol their patients in the appropriate Fabry registry.

These guidelines may be revised by the Fabry Committee from time to time.

Protocol for Investigations of patients receiving Fabry enzyme replacement therapy

Baseline

- Medical history and family pedigree.
- Vital signs including weight and height and blood pressure.
- Pain score – Brief Pain Inventory (short form)
- ECG, echocardiogram. Patients with short PR interval should have baseline electrophysiological study to determine the maximum AV conduction during atrial pacing and in AF.
- Cardiac MRI is desirable
- MRI brain scan
- Quality of life score (SF-36).
- Standardised neurological examination including temperature and vibration sensation.
- Hearing test.
- Exercise capacity
- Respiratory function tests

Laboratory Tests

- Full blood count.
- Urea and electrolytes.
- Liver function tests.
- Fasting lipid profile.
- Timed urine collection for creatine clearance, proteinuria, albumin excretion rate
- Urine and plasma GL₃ (optional)
- Blood group

Additional Baseline investigations in selected patients, depending on indications for ERT

- Renal biopsy in patients with nephropathy
- Myocardial biopsy in patients with left ventricular hypertrophy, particularly those with associated hypertension
- Electrophysiological study in patients with short PR interval to determine the maximum AV conduction during atrial pacing and in AF.

At each infusion

- Vital signs
- Adverse events
- Concomitant medications
- patient diary of pain and relevant symptoms
- Routine baseline bloods and urine with exception of GFR
- Pain score (if abnormal)

At 6 months

- ECG and echocardiograph
- Full blood count.
- Urea and electrolytes.
- Liver function tests.
- Fasting lipid profile.
- timed urine collection for creatine clearance, proteinuria, albumin excretion rate
- Urine and plasma GL₃ (optional)

At 12 months, then annually

- vital signs
- routine baseline bloods and urine
- pain scores
- GFR
- ECG and Echocardiogram
- cardiac MRI if available
- MRI brain scan if abnormal at baseline (2 years if normal at baseline)
- quality of life score (SF-36)

ATTACHMENT 1

ROYAL ADELAIDE HOSPITAL –

Contact: Dr Ian Chapman, Department of Medicine

ROYAL BRISBANE AND WOMEN'S HOSPITAL –

Contact: Dr Charles Denaro, Department of Internal Medicine

ROYAL MELBOURNE HOSPITAL –

Contact: Dr Kathy Nicholls, Department of Nephrology

ROYAL PERTH HOSPITAL –

Contact: Professor John Jack Goldblatt, Genetics Services of WA

WESTMEAD HOSPITAL –

Contact: Professor David Sillence, Department of Medical Genetics