GUIDELINES FOR ELIGIBILITY TO RECEIVE TREATMENT OF MUCOPOLYSACCHARIDOSIS Type 1 (MPS1) WITH LARONIDASE THROUGH THE LIFE SAVING DRUGS PROGRAM

Effective date: August 2007

Also available at:
**Aim**
The main aim of therapy is to improve the quality of life and survival in MPS1 patients who do not have neurological involvement.

These guidelines were prepared for the Department of Health by Dr Jim McGill (chair) Metabolic Physician (Qld), Prof David Sillence, Clinical Geneticist (NSW) and Dr Janice Fletcher, Metabolic Physician and Biochemical Geneticist (SA).

**MPS Advisory Committee**
The MPS Advisory Committee will include one physician from each state in which there is a patient under treatment. The Committee will include the following:
Dr Jim McGill
Prof David Sillence
Dr David Ketteridge
Dr Heidi Peters

**Centres of Excellence**
Each patient will be seen in a Centre of Excellence to collect data for monitoring the progress of therapy. These visits will be at baseline and 6 monthly thereafter. It is the responsibility of the Committee member at the Centre of Excellence to submit the required documentation to the Life Savings Drug Program and to liaise with the local paediatrician/adult physician and general practitioner who are responsible for administering the enzyme and the general care of the patient.

**Centres of Excellence will be:**
Children’s Hospital, Westmead/ Genetic Medicine Westmead Hospital, Westmead, NSW – Prof David Sillence (adolescents and adults)/ Prof John Christodoulou (children)
Royal Children’s Hospital, Parkville, Vic – Dr Heidi Peters / Dr Joy Lee
Royal Children’s Hospital, Herston, Qld – Dr Jim McGill
Women’s and Children’s Hospital, North Adelaide, SA – Dr Janice Fletcher / Dr David Ketteridge
Princess Margaret Hospital for Children, Subiaco, WA – Dr Geoff Knight
BACKGROUND

Mucopolysaccharidosis Type 1 (MPS1) is an inherited disorder due to deficiency of the lysosomal enzyme, alpha-iduronidase (1). There is a spectrum of disease which historically has been divided into:

**Hurler Syndrome (MPS1H)** which is the most severe form and which has onset in the first year of life. Involvement of the central nervous system always occurs, resulting in intellectual impairment. Lifespan is shortened, and children with Hurler syndrome rarely survive the first decade.

**Hurler-Scheie (MPS 1HS)** is the intermediate form with onset in the first few years of life. Intellect is usually preserved in this form. Lifespan is shortened but people with Hurler Schie syndrome usually survive to the second or third decade until cardiorespiratory problems intervene.

**Scheie Syndrome (MPS 1S)** is the mildest form and may not be detected until adulthood. The major problem in Schie syndrome is joint disease.

Modern nomenclature refers to severe (MPS 1H) and attenuated (MPS 1HS and MPS 1S) forms of MPS 1.

The diagnosis of MPS 1 must be confirmed by the demonstration of a deficiency of alpha-iduronidase in white blood cells with the assay performed in a NATA-accredited laboratory. Confirmation of the diagnosis should be made by repeat enzyme assay in cultured skin fibroblasts or by detection of 2 disease-causing mutations in the alpha-iduronidase gene.

It is sometimes difficult to distinguish between Hurler and Hurler-Scheie early in life. This distinction is critical as the treatment of Hurler Syndrome is stem cell transplantation (cord blood or bone marrow) with the best outcomes occurring with early transplantation. Hurler disease must be excluded by mutation analysis (2,3) or specialised protein studies (4).

INDICATIONS

Commonwealth government-funded Laronidase therapy will be available to **MPS 1 patients without neurological disease (Hurler-Scheie (MPS 1HS)).** Treatment in this group is supported by published studies (5-7). Planning for therapy should start at the time of diagnosis and should be part of a holistic management program.

Commonwealth government-funded therapy will be available to patients likely to benefit from the therapy. Generally these patients will be early in their disease trajectory as experience with other ERT programs has shown that end-stage disease rarely responds to treatment. Patients with other medical or surgical conditions which would significantly impair response to or benefit from ERT will not qualify for therapy.
CRITERIA for funded ERT in patients with non-neurological MPS1:
any of the following complications of MPS 1:

Sleep Disordered Breathing
Patients with an Apnoea/Hypopnoea Incidence of > 5 events/hour of total sleep time or more than 2 severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study (8)

Respiratory Function Tests
Patients with FVC less than 80% of predicted value for height. (Hibbert et al (9); Zapletal et al (10) and Eigen et al (11)).

Cardiac

Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 56% (Normal Range 56-78%) OR a reduction in fraction shortening to <25% (normal range 25-46%) (7,8,12).

Joint Contractures:
Patients developing restricted range of movement of joints of greater than 10 degrees from normal in shoulders, neck, hips, knees, elbows or hands.

These guidelines will be reviewed on a biennial basis or if new information becomes available.
CURRENT RESEARCH

The following uses of laronidase (*Aldurazyme*) are outside current TGA approved indications for laronidase, and will need to be funded by Genzyme Australasia. The Committee believe that they should act in an advisory capacity for such uses of the product.

**MPS 1H (Hurler syndrome) (severe end of spectrum)**

As laronidase has only been shown to treat the non-neurological features of MPS 1, there is no indication for long term treatment in MPS 1H patients who have not had or are not planning to have a bone marrow transplant. Bone marrow transplant remains the treatment of choice for the severe form of Hurler syndrome (13).

There is world wide support for the use of enzyme replacement therapy for short periods in two clinical settings in patients with MPS 1H. Although there are few published studies to date, the Committee strongly supports both (i) and (ii) and believe they are cost-effective short term uses of enzyme replacement therapy. Potential savings include improved survival and outcome for patients receiving bone marrow transplantation and shorter ICU stays and faster recovery for older patients receiving surgery.

i) Treatment for children who are being scheduled for bone marrow transplantation. Pre-transplant therapy for a maximum of 12 weeks and post-transplant therapy usually for 15-17 weeks.

- The duration of the pre-transplant therapy may be shorter than 12 weeks and this will depend on the health of the affected child, the rate of response and the availability of a suitable donor.
- The duration of the post-transplant therapy will depend upon the respiratory status of the patient and the recovery of haematological parameters. The Committee realises the importance of some flexibility in the duration of post-transplantation ERT based on the status of the patient.

Studies are underway to assess the benefits of this adjunctive therapy (11). Comparisons will be made with historical controls, the data for which has been prospectively collected and is published.

At this stage there is no data, published or otherwise, to support long term enzyme replacement therapy (ERT) in patients who have had a bone marrow transplant. Studies to determine whether or not such patients would benefit from ERT are underway at present and others are planned. The Committee awaits the outcome of these studies.

ii) Adjunctive supportive therapy for patients with MPS 1H to condition their airway and improve post-operative recovery for major neurosurgical, orthopaedic and cardiac therapy. Usual period of therapy is 8 weeks (divided 4 weeks pre and post surgery) for each procedure. With anterior and posterior spinal fusion the patient may require two periods of support.
At this stage there is only strong anecdotal evidence to support this application of enzyme replacement therapy (Prof David Sillence, personal communication).
REFERENCES

1. OMIM – Online Mendelian Inheritance in Man.


5. Wraith, JE; Clarke, LA; Beck, M; Kolodny, EH; Pastores, GM; Muenzer, J; Rapoport, DM; Berger, KI; Swiedler, SJ; Kakkis, ED; Braakman, T; Chadbourne, -E; Walton-Bowen, K; Cox, GF Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J-Pediatr. 2004 May; 144(5):581-8.


