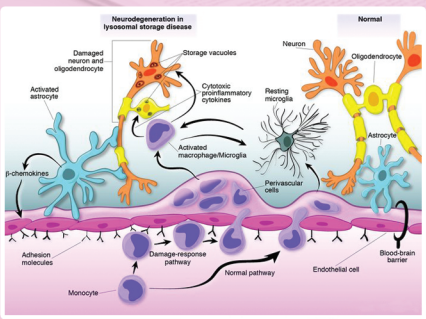
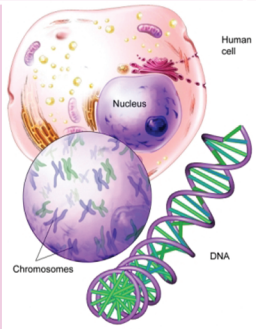
MOH / P / PAK / 216.11 (GU)

MINISTRY OF HEALTH MALAYSIA

Guidelines for Treatment of Lysosomal Storage Diseases by Enzyme Replacement Therapy in Malaysia





Medical Development Division
Ministry of Health Malaysia

MOH/P/PAK/216.11(GU)

Guidelines for Treatment of Lysosomal Storage Diseases by Enzyme Replacement Therapy in Malaysia

MEDICAL DEVELOPMENT DIVISION
MINISTRY of HEALTH MALAYSIA

Guidelines for Treatment of Lysosomal Storage Diseases by Enzyme Replacement Therapy In Malaysia

First published in Malaysia in January 2012 by

The Technical Committee on Enzyme Replacement Therapy
in collaboration with
Obstetric & Gynaecological and Paediatric Services Unit,
Medical Services Department Section,
Medical Development Division, Ministry of Health Malaysia.
www.moh.gov.my

A catalogue record of this document is available from the Library and Resource Unit of the Institute of Medical Research, Ministry of Health;
MOH/P/PAK/216.11(GU)

And also available from the National Library of Malaysia;
ISBN 978-983-44999-9-0

ISBN 978-983-44999-9-0
9 789834 499990

CONTENTS

1	Foreword	4
2	Introduction	5
3	Guideline on Gaucher disease	9
4	Guideline on Pompe disease	17
5	Guideline on Mucopolysaccharidosis Type I	25
6	Guideline on Mucopolysaccharidosis Type II	33
7	Guideline on Mucopolysaccharidosis Type VI	41
8	Guideline on Fabry disease	47
9	Appendix	55
	A: General conditions for eligibility	56
	B: Patient's consent form (Borang Persetujuan Pesakit)	58
	C: Monitoring requirements and data submission form for Gaucher disease	63
	D: Monitoring requirements and data submission form for Pompe disease	69
	E: Monitoring requirements and data submission form for MPS diseases	80
	F: Monitoring requirements and data submission form for Fabry disease	88
	G: SF-36 health survey score sheet	96
	H: Gross motor function measure score sheet	103
	I : Brief pain inventory (short form)	110
	J : MRC scale for assessment of muscle power	114
10	Drafting Committee	117
11	Acknowledgement	118

FOREWORD

Rare inherited Lysosomal Storage Diseases (LSD) pose diagnostic and therapeutic challenge. They are also increasingly becoming a health care and economic challenge, mainly due to the development and availability of enzyme replacement therapy (ERT) for some LSDs. Currently ERT are available for six LSDs: Mucopolysaccharidosis Type 1(MPS I), MPS II, MPS VI, Fabry disease, Pompe disease and Gaucher disease.

The Malaysian Government, through the Ministry of Health, has approved the funding for Enzyme Replacement Therapy Program for LSDs, and provides subsidized access to expensive and potentially lifesaving drugs for these life-threatening diseases. It would appear rational to have a national guideline to ensure consistency and a sustainable program. This is also to ensure careful spending of public funding.

A candidate must fully satisfy the eligibility criteria of the relevant disease as stated in this guideline before a consideration for the subsidized drugs is to be made. Patient eligibility will be reviewed in accordance with the frequency stated in this guideline, generally 12 months after commencing therapy and every 12 months thereafter. Continued eligibility will be subjected to the evaluation of evidence for

1. clinical improvement in the patient, or

2. stabilisation of the patient's condition.

We hope this guideline will be a valuable reference document to clinicians, pharmacists, patients, families as well as the general public.

Y.Bhg. Datuk Dr. Noor Hisham bin Abdullah
Deputy Director General of Health (Medical)
November 2011

INTRODUCTION

Lysosomal Storage Diseases (LSD) are a heterogenous group of more than 40 inborn errors of metabolism that are due to specific defects of lysosomal enzymes, lysosomal membrane proteins or transporters. All LSDs are inherited autosomal recessively with the exception of MPS II (Hunter disease) and Fabry Disease that are inherited as X-linked traits. As a group, LSDs occur in approximately 1 in 5000 to 8000 births.[1,2]

LSDs in general are progressive multi organ disorder with about 50% having significant central nervous system involvement. Each LSD comprises a more or less unique clinical spectrum with patients at the more severe end showing increased morbidity and mortality whereas patients at the milder end of the spectrum having only subtle clinical signs. Patients with mild disease may often go unrecognized for many years.

In the past, no specific treatment was available for the affected patients; management mainly consisted of supportive care and treatment of complications. Allogeneic bone marrow transplantation (BMT) was the first specific therapeutic approach to be used in LSDs. The vast majority of clinical experience is in treating patients with mucopolysaccharidoses, particularly MPS I. Because of the risks associated with the procedure, allogeneic BMT has generally been used in the more severe, Hurler form of MPS I and the vast majority of children have been transplanted before the age of three. In the last 2 decades, remarkable progress has been achieved in the field of LSD with the development of innovative therapies including enzyme replacement therapies (ERT) and substrate reduction therapy(SRT). Additional therapies such as chaperone therapy and gene therapy are currently under preclinical investigations. Currently ERT are available for MPS I, II, VI, Fabry, Pompe and Gaucher diseases. In addition SRT has been licensed for Gaucher disease.[3,4,5]

Enzyme replacement therapy for LSD is expensive compared to treatment modalities for other rare inborn errors of metabolism (dietary therapy, co-factor substitution). The development of these effective but very expensive therapies presents special problems for health care policy-makers, who are committed to ensuring access to new therapies which are life saving for affected patients; but who at the same time are also under pressure to control overall health care spending. Therefore, a national policy and guideline is deemed necessary to determine which patients should be treated with this very costly treatment.

The aim of this guideline is to provide guidance judged to be necessary for the selection of patients for ERT. The candidate must meet all the eligibility criteria and none of the exclusion criteria in order to be considered for government funded ERT. Government funded ERT will only be provided where the patient agrees to participate in the evaluation of the efficacy of the treatment by periodic medical assessment. Continued eligibility will be subjected to clinical improvement in the patient, and/or stabilisation of the patient's condition. Separate guidelines are written for each of the following LSDs:

- Gaucher disease
- Pompe disease
- Mucopolysaccharidosis type I
- Mucopolysaccharidosis type II
- Mucopolysaccharidosis type VI
- Fabry disease

The committee will review and revise these guidelines periodically in line with any new medical development and evidence in the field of LSD.

References :-

1. Poorthuis BJ, Wevers RA, Kleijer WJ, Groener JE, de Jong JG, van Weely S,Niezen-Koning KE, van Diggelen OP. 1999. The frequency of lysosomal storage diseases in The Netherlands. Hum Genet 105:151–156.

2. Lin HY, Lin SP, Chuang CK, Niu DM, ChenMR, Tsai FJ, Chao MC, Chiu PC, Lin SJ, Tsai LP, Hwu WL, Lin JL. 2009. Incidence of the mucopolysaccharidoses in Taiwan,1984–2004 Am J Med Genet Part A 149A:960–964.

3. Beck M. 2007. New therapeutic options for lysosomal storage disorders: Enzyme replacement, small molecules and gene therapy. Hum Genet 121:1–22.

4. P.M. Hoogerbrugge, O.F. Brouwer, P. Bordigoni, O. Ringden, P. Kapaun, J.J. Ortega, A.O'Meara, G. Cornu, G. Souillet, D. Frappaz, et al., Allogeneic bone marrow transplantation for lysosomal storage diseases. The European Group for Bone Marrow Transplantation, Lancet 345 (1995) 1398–1402 issn: 0140–6736.

5. R.O Brady, Enzyme replacement for lysosomal diseases, Annu. Rev. Med. 57 (2006) 283–296

GAUCHER DISEASE

INTRODUCTION

Gaucher Disease (GD) is an autosomal recessive disorder, caused by deficiency of the lysosomal enzyme β-glucosylceramidase. This deficiency results in a decreased breakdown of the glycosphingolipid and glucocerebroside, which accumulate in the lysosomes of the monocyte-macrophage system.[1,2] The prevalence of type 1 GD is 1:40 000 to 60 000 in the general population.[3]

Gaucher Disease encompasses a continuum of clinical findings from a perinatal lethal disorder to an asymptomatic type. The identification of three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular) is useful in determining prognosis and management. Type 1 Gaucher Disease is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. Types 2 and 3 Gaucher Disease is characterized by the presence of primary neurologic disease. In the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute. Disease with onset before two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years is classified as type 2 Gaucher Disease. Individuals with type 3 Gaucher Disease may have onset before age two years, but often have a more slowly progressive course and may live into the third or fourth decade. The perinatal-lethal form is associated with ichthyosiform or collodion skin abnormalities or with nonimmune hydrops fetalis. The cardiovascular form is characterized by calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia. Cardiopulmonary complications have been described in all the clinical subtypes, although varying in frequency and severity.[1,4]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY

In the past, treatment of Gaucher Disease has focused on symptomatic treatment of pain, surgical treatment of fractures, infections and avascular necrosis of the bone; surgical removal of the spleen to relieve thrombocytopenia caused by hypersplenism; and blood transfusions to correct anaemia. Patients with very severe disease have also been treated by bone marrow transplantation (BMT). However, this requires the availability of a suitable bone marrow donor, and the procedure is associated with prolonged hospitalisation and significant morbidity and mortality.[1]

An effective treatment of Gaucher Disease has now been available since 1991 in the form of enzyme replacement therapy (ERT). The two recombinant β-glucosylceramidase enzyme preparations are currently available commercially and are distinguished according to the cell

type involved in their production: imiglucerase (Cerezyme®, Genzyme) generated in Chinese hamster ovary cells; velalglucerase alfa (VPRIV®, Shire) from human cell line. Each formulation is modified to expose the alpha-mannosyl (carbohydrate) residues for enhanced uptake by the macrophage.[5-6] Currently, imiglucerase has been approved by National Pharmaceutical Control Bureau for treatment of Gaucher Disease in Malaysia.

In clinical studies, ERT is effective for treatment of the haematologic, visceral and bone complications of the Gaucher Disease. The efficacy of ERT for neurologic complications is not proven conclusively and still under investigation.[7-11] Individuals with chronic neurologic GD and progressive disease despite ERT may be candidates for BMT or a multi-modal approach (i.e., combined ERT and BMT). Miglustat, an inhibitor of glucosylceramide synthetase, which is administered orally, may be an alternative for the treatment of individuals with mild to moderate Gaucher Disease for whom ERT is not a therapeutic option because of constraints such as allergy, hypersensitivity, or poor venous access.[12]

While ERT is effective, such chronic treatment places a burden on the individual patient, and is costly for society. Therefore, some guidance was judged to be necessary for the selection of patients for treatment.

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of Gaucher Disease

The diagnosis of Gaucher Disease must have been established by the demonstration of specific deficiency of β-glucosylceramidase in leukocytes or cultured skin fibroblasts. The diagnosis can also be confirmed by the presence of glucocerebrosidase gene mutations known to result in severe deficiency of enzyme activity.

3. Severity of Gaucher Disease

a. ERT is only for Type I Gaucher Disease with clinically significant symptoms.

Children (under 18 years of age)	Adults (18 Years of Age or Over)
i. Any of the following symptoms :- - Bone pain - Abdominal pain - Fatigue - Exertion limitations - Weakness - Cachexia - Hepatosplenomegaly - Growth failure **And** ii. Presents with one or more of the following :- - Thrombocytopenia, defined as platelet count≤ 60 x10^9/l; - Anemia, defined as Hemoglobin < 2g/dl below the lower limit of normal for age and sex; **OR** iii. Evidence of skeletal involvement as confirmed by radiographic examination, including :- - EFD (Erlenmeyer Flask Deformity) - Avascular Necrosis of Bone - Destructive lesions of bone	i. One of the following :- Symptomatic manifestations of skeletal disease as confirmed by radiological examination, including :- - Joint deterioration - Pathological fracture - Avascular necrosis - Definite Osteopenia - Marrow infiltration **OR** ii. Presents with two or more of the following :- - Anemia ≤12.5g/dl for males and ≤11.5g/dl for females - Platelet count ≤ 120 x10^9/l - Hepatomegaly, defined as liver volume 25% greater than normal - Splenomegaly, defined as spleen volume 5 times normal or greater

b. Type II and III patients exhibiting primary neurological disease due to Gaucher disease would not be considered eligible for treatment with ERT. Exception to this is children with oculomotor apraxia as their only neurological finding.

4. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. The treatment of asymptomatic patients is not generally granted unless the disease is of sufficient severity to suggest a severe course or impending complications (this could be determined through mutation analysis in the asymptomatic patient), or the presence of a family history of severe, accelerated course of the disease during childhood.

2. Potentially confounding serious disorders such as Hodgkin's Disease.

3. The patient should not have any Gaucher Disease related or any other medical condition that might reasonably be expected to compromise their response to ERT.

4. In some patients with Gaucher disease, secondary pathologic changes, such as avascular necrosis of bone, may already have occurred that would not be expected to respond to ERT. In such patients, reversal of the pathology is unlikely. Treatment of patients with significant secondary pathology would be directed at preventing further progression of the disease. In these cases, the extent to which symptoms, such as bone pain, are due to active progression of the disease, rather than the secondary pathology, can only be established by a trial of therapy.

5. ERT should not be given to a pregnant woman unless it is clearly needed.

DOSING RECOMMENDATIONS

The dose of imiglucerase generally ranges between 15 and 60 units of enzyme per kilogram body weight by intravenous infusion every 2 weeks. The enzyme dose may be increased or decreased after initiation of treatment and during the maintenance phase, based on clinical response – i.e., hematopoietic reconstitution, reduction of liver and spleen volumes, and stabilization or improvement in skeletal findings.

CONSENT FORMS

Patients or their parents/guardians (if patient is younger than 18 years old) are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

REVIEW OF THERAPY

Patient who is on subsidized ERT should be reviewed at regular intervals by the ERT Technical Committee, based on the haematological, biochemical and radiological data that are to be collected by the treating doctor **(see Appendix C)**.

WITHDRAWAL OF THERAPY

Subsidized imiglucerase treatment could be withdrawn in any of the following situations:

a. the patient fails to comply adequately with treatment (defaults 2 or more infusions over 6 months period without acceptable reason) or monitoring requirements, taken to evaluate the effectiveness of the therapy

b. if therapy fails to relieve the symptoms that originally resulted in the patient being approved for subsidized treatment

c. young children with severe visceral manifestations of Gaucher disease may be considered for therapy prior to the possible development of primary neurological complications, with the understanding of the treating doctor and parents/guardians that there should be close neurodevelopmental follow-up. Development of the following features consistent with a neuronopathic form of Gaucher Disease would result in therapy being withdrawn :-

   - Opisthotonus
   - Seizures
   - Bulbar dysfunction (manifested by swallowing difficulties)
   - Deteriorating intellectual function (determined by age-appropriate psychometric testing)
   - Deterioration in motor skills

d. development of a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

REFERENCES

1. Grabowski GA, Kolodny EH, Weinreb NJ, Rosenbloom BE, Prakash-Cheng A, Kaplan P, Charrow J, Rastores GM, Mistry PK. Gaucher disease: phenotypic and genetic variation. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, eds.*The Metabolic and Molecular Bases of Inherited Disease (OMMBID).* New York: McGraw-Hill; Chap 146.1. Available at www.ommbid.com.

2. Grabowski GA, Horowitz M. Gaucher's disease: molecular, genetic and enzymological aspects. Baillieres Clin Haematol.1997;10:635–56.

3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281:249–54.

4. Grabowski GA, Andria G, Baldellou A, Campbell PE, Charrow J, Cohen IJ, Harris CM, Kaplan P, Mengel E, Pocovi M, Vellodi A. Pediatric non-neuronopathic Gaucher disease: presentation, diagnosis and assessment. Consensus statements.Eur J Pediatr. 2004;163:58–66.

5. Pastores GM (2003) Enzyme therapy for the lysosomal storage disorders: principles, patents, practice and prospects. Expert Opin Ther Patents 13:1157-72.

6. Zimran A, Altarescu G, Philips M, Attias D, Jmoudiak M, Deeb M, Wang N, Bhirangi K, Cohn GM, Elstein D. Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience.Blood. 2010;115:4651–6.

7. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, Rosenbloom BE, Scott CR, Wappner RS, Zimran A. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med. 2002;113:112–9.

8. Mistry PK, Cappellini MD, Lukina E, Ozsan H, Mach Pascual S, Rosenbaum H, Helena Solano M, Spigelman Z, Villarrubia J, Watman NP, Massenkeil G. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. Am J Hematol. 2011;86:110–5.

9. Baldellou A, Andria G, Campbell PE, Charrow J, Cohen IJ, Grabowski GA, Harris CM, Kaplan P, McHugh K, Mengel E, Vellodi A. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr.2004;163:67–75.

10. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, Prakash-Cheng A, Rosenbloom BE, Scott CR, Wappner RS, Weinreb NJ. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr. 2004;144:112–20.

11. Hughes D, Cappellini MD, Berger M, Van Droogenbroeck J, de Fost M, Janic D, Marinakis T, Rosenbaum H, Villarubia J, Zhukovskaya E, Hollak C. Recommendations for the management of the haematological and onco-haematological aspects of Gaucher disease. Br J Haematol. 2007;138:676–86.

12. Pastores GM, Elstein D, Hrebicek M, Zimran A. Effect of miglustat on bone disease in adults with type 1 Gaucher disease: a pooled analysis of three multinational, open-label studies. Clin Ther. 2007;29:1645–54.

Website resources

1. Dr A Vellodi, Dr JE Wraith, Dr K McHugh and Mr A Cooper for the National Specialist Commissioning Advisory Group (NSCAG).guidelines for the management of Paediatric Gaucher disease in the united kingdom (August 2005). www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4118411.pdf

2. P Deegan, D Hughes, A Mehta, TM Cox. UK National Guideline for Adult Gaucher Disease (April 2005). www.specialisedservices.nhs.uk/.../Guidelines_for_Adult_Gauchers_Disease.pdf

3. *Department of Health and Ageing, Australia* Guidelines for the treatment of Gaucher Disease through the Life Saving Drugs Program (September 2009). www.commcarelink.health.gov.au/.../Guidelines%20Gaucher%20Disease.pdf

4. Canadian guidelines for treatment of Gaucher Disease by enzyme replacement with imiglucerase or substrate reduction therapy with miglustat (Version 8; March 26, 2007) www.garrod.ca/data/.../RevisedGaucherGuidelinesV8Mar26-07.pdf

POMPE DISEASE

INTRODUCTION

Pompe Disease is a rare autosomal recessive disease caused by the deficiency of acid α-glucosidase (GAA), which is needed for the degradation of lysosomal glycogen. The disease causes lysosomal glycogen to accumulate in various tissues, particularly muscle, resulting in progressive muscle dysfunction.[1] Incidence data for Pompe Disease is limited with reports ranging from 1 in 14,000 to 1 in 300,000 depending upon ethnicity or the geographic area studied.[2]

Clinically, Pompe Disease encompasses a range of phenotypes. The infantile form presents with a generalized muscle weakness, hypotonia and a severe hypertrophic cardiomyopathy followed by death from cardio-respiratory failure or respiratory infection usually by age 1 year. Late onset Pompe Disease (juvenile and adult-onset) primarily presents with skeletal and respiratory muscle weakness with minimal to no cardiac involvement and longer survival.

Symptoms with late onset Pompe Disease may start at any age and rate of disease progression is variable. It is associated with significant morbidity, and as the disease advances patients often become wheelchair bound and require artificial ventilation due to respiratory insufficiency. Most patients with infantile-onset disease have undetectable to minimal GAA activity, whereas those with the late-onset phenotype tend to have a limited amount of residual GAA activity.[1,3,4]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY (ERT)

Until 2006, there has been no specific treatment for Pompe Disease, other than supportive care such as symptomatic treatment of cardiomyopathy and respiratory support. A high-protein, low-carbohydrate diet or, alternatively, a diet rich in L-alanine has shown benefit in some but not all patients with late-onset Pompe Disease.

Since 1999 enzyme therapy with recombinant human alpha-glucosidase was investigated as treatment for the disease. In 2006, enzyme replacement therapy with Chinese hamster ovary cell derived recombinant human acid alpha glucosidase (alglucosidase alfa, Genzyme) was approved by both the European Union and the US Food and Drug Administration for treatment of patients with this otherwise devastating and lethal disease. It degrades glycogen by catalyzing the hydrolysis of alpha 1, 4 and alpha 1, 6 glycosidic linkages of lysosomal glycogen. Till now, ERT using alglucosidase alfa is the only approved specific treatment available for Pompe Disease. Alglucosidase alfa has been approved by National Pharmaceutical Control Bureau for treatment of Pompe Disease in Malaysia.

A majority of infants in whom ERT was initiated before the age of six months and before the need for ventilatory assistance demonstrated improved survival, ventilator-independent survival, and acquisition of motor skills, and reduced cardiac mass compared to untreated controls.[5,6,7] The individual response to enzyme replacement therapy may vary due to development of rhGAA specific antibodies, age of presentation and progression of disease. The development of rhGAA antibodies may be more frequent in patients with absent GAA protein or cross-reacting immunological material (CRIM). The absence of CRIM (CRIM negative) may have an impact on the prognosis of patients with infantile disease. In patients with late-onset disease, ERT may stabilize ventilatory function and motor ability, measured by six-minute walk and upright pulmonary function testing.[8,9]

While ERT is effective, such chronic treatment places a burden on the individual patient, and is costly for society. Therefore, some guidance was judged to be necessary for the selection of patients for treatment.

DEFINITION OF INFANTILE AND LATE-ONSET DISEASE

Infantile disease:

All patients become symptomatic and diagnosed in the first two years of life with a documented deficiency of acid alpha-glucosidase measured in lymphocytes, muscle, skin fibroblasts. This will include “classic” infantile patients presenting with severe cardiomyopathy in the first few months of life and also variant patients who present outside the first year of life but suffering from early onset cardiomyopathy.

Late-onset disease:

All patients become symptomatic and diagnosed over the age of 2 years with a documented deficiency of acid alpha-glucosidase measured in lymphocytes, muscle or skin fibroblasts.

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY (ERT)

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of Pompe Disease

The diagnosis of Pompe disease must have been established by one of the following methods:

a. demonstration of specific deficiency of acid alpha-glucosidase measured in dry blood spots, lymphocytes, skin fibroblasts or muscle;

b. the presence of acid alpha-glucosidase gene mutations known to result in severe deficiency of enzyme activity.

3. Severity of Pompe disease

Infantile disease

a. All patients with infantile disease with cardiomyopathy, muscle weakness and/or respiratory compromise are eligible for ERT except for patients who are already on long term invasive ventilation for respiratory failure or in such an advance stage of disease that will not benefit from treatment.

b. CRIM status: patients who are CRIM negative are not excluded from ERT but may need a modified plan for enzyme therapy.

Late-onset disease

Late-onset patient with muscle weakness and/or respiratory compromise, leading to an impaired quality of life are eligible for ERT except for patients who are already on long term invasive ventilation for respiratory failure or in a too advance stage of the disease prior to starting ERT.

4. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. Patients with another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy would not be considered eligible for treatment with ERT.

2. The presence of severe or irreversible muscle/cardiac end organ damage that is not likely to improve with ERT.

3. Refusal of the patients or caretakers to comply with the following:-

    a. To be compliant with the lifelong therapy, as recommended by the ERT committee, currently in the form of two weekly intravenous infusion.

    b. To comply with the requirement to undergo regular follow up, evaluation and, monitoring procedures as stated in the ERT guidelines.

DRUG DOSAGE

Recommended dose regimen for alglucosidase alfa is 20 mg/kg/every other week via intravenous infusion.

CONSENT FORMS

Patients or their parents/ guardians are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

MONITORING OF THERAPY

Patient who is on subsidized ERT are monitored at regular intervals by the Technical Committee on ERT, basing on the data that are to be collected by the treating doctor **(see Appendix D)**.

WITHDRAWAL OF THERAPY

Subsidized ERT treatment could be withdrawn in any of the following situations: -

a. patient fails to comply adequately with treatment (defaults 2 or more infusions over 6 months period without acceptable reason) or monitoring taken to evaluate the effectiveness of the therapy

b. if therapy fails to relieve the symptoms of the disease that originally resulted in the patient being approved for subsidized treatment

c. evidence of disease progression despite regular therapy including the development of the need for 24 hour invasive ventilation indicating that the cardiorespiratory failure is progressive

d. the muscle tone is so poor that there is no useful movement or motor development

e. development of a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

REFERENCES

1. Hirschhorn R, Reuser AJJ. Glycogen storage disease type II: (acid maltase) deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, eds. *The Metabolic and Molecular Bases of Inherited Disease (OMMBID)*. New York: McGraw-Hill. Chap 135. Available at www.ommbid.com.

2. Lin CY, Hwang B, Hsiao KJ, Jin YR. Pompe's disease in Chinese and prenatal diagnosis by determination of alpha-glucosidase activity. J Inherit Metab Dis. 1987;10:11–7

3. van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, Bakker HD, Loonen MC, de Klerk JB, Reuser AJ, van der Ploeg AT. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics. 2003;112:332–40.

4. Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain 2005;128(Pt 3):671–7.

5. Kishnani PS, Corzo D, Nicolino M, et al. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology 2007;68(2):99–109.

6. Kishnani PS, Corzo D, Leslie ND, Gruskin D, Van der Ploeg A, Clancy JP, Parini R, Morin G, Beck M, Bauer MS, Jokic M, Tsai CE, Tsai BW, Morgan C, O'Meara T, Richards S, Tsao EC, Mandel H. Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res. 2009;66:329–35.

7. Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR, Arnold GL, Pivnick EK, Ottinger CJ, Robinson PH, Loo JC, Smitka M, Jardine P, Tatò L, Chabrol B, McCandless S, Kimura S, Mehta L, Bali D, Skrinar A, Morgan C, Rangachari L, Corzo D, Kishnani PS. Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. Genet Med. 2009;11:210–9.

8. Strothotte S, Strigl-Pill N, Grunert B, Kornblum C, Eger K, Wessig C, Deschauer M, Breunig F, Glocker FX, Vielhaber S, Brejova A, Hilz M, Reiners K, Müller-Felber W, Mengel E, Spranger M, Schoser B. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol. 2010;257:91–7.

9. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, Herson S, Kishnani PS, Laforet P, Lake SL, Lange DJ, Leshner RT, Mayhew JE, Morgan C, Nozaki K, Park DJ, Pestronk A, Rosenbloom B, Skrinar A, van Capelle CI, van der Beek NA, Wasserstein M, Zivkovic SA. A randomized study of alglucosidase alfa in late-onset Pompe's disease.N Engl J Med. 2010;362:1396–406.

10. American College of Medical Genetics. Pompe disease diagnosis and management guideline. Available at www.acmg.net(pdf). 2006

11. Pompe Disease Diagnostic Working Group; Methods for a prompt and reliable laboratory diagnosis of Pompe disease: report from an international consensus meeting. Mol Genet Metab. 2008;93:275–81.

12. Kishnani PS, Goldenberg PC, DeArmey SL, Heller J, Benjamin D, Young S, Bali D, Smith SA, Li JS, Mandel H, Koeberl D, Rosenberg A, Chen YT. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants.Mol Genet Metab. 2010;99:26–33.

Website resources

1. *J.E. Wraith, P. Lee, A. Vellodi, M.A. Cleary, U. Ramaswami, Edmund Jessop. Guidelines for the Investigation and Management of Infantile Pompe disease (2 August 2006) www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4137654*

2. *P.B. Deegan,T.M. Cox, S Waldek, R Lachmann, Uma Ramaswami, Edmund Jessop. Guidelines for the Investigation and Management of Late Onset Acid Maltase Deficiency (Type II Glycogen Storage Disease / Pompe Disease) (Version 3 August 2007). http://www.specialisedservices.nhs.uk/library/23/Guidelines_for_Late_Onset_Pompe_Disease.pdf*

3. *Department of Health and Ageing, Australia. Guidelines for the treatment of infantile-onset Pompe disease through the life saving drugs program .* www.health.gov.au/internet/.../Infantile-Onset%20Pompe%20disease.doc

MUCOPOLYSACCHARIDOSIS TYPE I

INTRODUCTION

Mucopolysaccharidosis Type I (MPS I) is a recessively inherited, progressive lysosomal storage disorder due to the deficiency of an enzyme known as α-L-iduronidase. The disease causes widespread intracellular accumulation of the glycosaminoglycans (GAG) in tissues throughout the body. Tissues which are affected include skeleton, cartilage, liver, spleen, ligaments, joints, heart valves, airways, corneas and in some forms, the brain.[1]

Patients with MPS I are classified into three clinical syndromes based on their symptoms and the severity of their symptoms – Hurler, Hurler-Scheie and Scheie. Hurler syndrome is the most severe clinical phenotype; Hurler-Scheie syndrome is an intermediate clinical phenotype; and Scheie syndrome is a milder clinical phenotype.[1,2]

Hurler syndrome (MPS IH) is characterized by facial and skeletal deformities, cardiac disease, respiratory difficulties and mental retardation/ regression. In Scheie syndrome (MPS IS), joint stiffness, aortic valve disease and corneal clouding are the leading symptoms. Patients with Scheie syndrome are of normal intelligence and may have a near normal life-span. Hurler-Scheie syndrome (MPS IH-S) is an intermediate clinical phenotype and clinical features include short stature, coarse facies, corneal clouding, joint stiffness, deafness, valvular heart disease and there is usually little or no intellectual dysfunction.[1,2] MPS I is seen in all populations at a frequency of approximately 1:100,000 for the severe form and 1:500,000 for the attenuated form.[3]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY

The treatment of MPS I has mostly been symptomatic, involving orthopaedic, otolaryngological, cardiac, ophthalmological and neurosurgical interventions. Bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT) has been used successfully in patients with MPS IH and has been shown to maintain intellectual function in many patients. While such transplants greatly improve many of the symptoms of MPS I, significant skeletal problems still develop.[4,5]

In 2003, enzyme replacement therapy (ERT) with Chinese hamster ovary cell derived recombinant human α-L-iduronidase (Laronidase, Genzyme), was approved by both the European Union and the US Food and Drug Administration for long term treatment of patients with MPS I. Laronidase has been approved by National Pharmaceutical Control Bureau for treatment of MPS I in Malaysia.

In clinical studies, Laronidase has been shown to improve respiratory function, distance walked in 6 minutes, range of movements of joints, sleep disordered breathing and result in a reduction of urinary GAGs. Some tissues such as bone respond poorly to ERT. No benefit to the brain or nervous system has been demonstrated.[6-10] Therefore, BMT/HSCT will still be the treatment of choice for patients with MPS IH. This procedure should be performed within the first years of life to prevent irreversible damage to the brain; however, ERT may also be of importance for young patients with MPS IH, as it may improve general lung and heart function, making BMT/HSCT easier to tolerate.[5]

In view of the very high cost of treatment, wide variation in the extent of ERT benefit, and the risk and inconvenience associated with the need for frequent intravenous injections; guidelines are necessary for the selection of patients for treatment with the newly available intervention.

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY (ERT)

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of MPS I

The diagnosis of MPS I must have been established by the demonstration of specific deficiency of α-L-Iduronidase measured in lymphocytes or skin fibroblasts. The diagnosis can also be confirmed by the presence of mutations in the α-L-Iduronidase gene known to result in severe deficiency of enzyme activity.

3. Severity of disease

a. Patient has little or no cognitive impairment (IQ >70).

b. Patient should have a minimal level of disease severity in order to be considered for ERT. At least one or more of the following should be present :-

i. 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

ii. Respiratory Function Tests

Patients with FVC less than 80% of predicted value for height

iii. Cardiac

Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 56% (Normal Range 56-78%) OR a reduction in fractional shortening to <25% (normal range 2546%)

iv. 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

Patients with little or no cognitive impairment (MPS IS or I H-S) who fail to meet above criteria should be followed up in a systematic way with annual assessments designed to detect deterioration in their clinical condition. In this way they may be identified as suitable for treatment with ERT at a later date.

As Laronidase has only been shown to improve the non-neurological features of MPS I, there is no indication for long term treatment in MPS IH patients who have not had or are not planning to have a bone marrow transplant. BMT/HSCT transplant remains the treatment of choice for MPS IH.

4. Option of BMT/HSCT

All patients who are less than 2 years old and have normal IQ [>70] should be offered work up for BMT/HSCT if there is suitable donor.

5. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. Patients with another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy would not be considered eligible for treatment with ERT.

2. The presence of severe or irreversible end organ damage that is not likely to improve with ERT.

3. Patients with evidence of significant learning difficulties and/or progressive neuropsychological deterioration.

4. Refusal of the patients or caretakers to comply with the following:-

    a. To be compliant with the lifelong therapy, as recommended by the ERT committee, currently in the form of weekly intravenous infusion.

    b. To comply with the requirement to undergo regular follow up, evaluation and, monitoring procedures as recommended by the ERT committee, for the purpose of evaluating treatment efficacy and complication of the disease.

DRUG DOSAGE

Recommended dose regimen for Loranidase is 100U/kg/week via intravenous infusion.

CONSENT FORMS

Patients or their parents/ guardians are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

MONITORING OF THERAPY

Patient who is on subsidized ERT are monitored at regular intervals by the Technical Committee on ERT, basing on the data that are to be collected by the treating doctor **(see Appendix E)**.

WITHDRAWAL OF THERAPY

Subsidized ERT treatment could be withdrawn in any of the following situations:-

a. If the patient develops progressive neurological decline.

b. If the patient fails to comply with the therapy, follow up, evaluation and assessment procedure as recommended by the ERT guidelines.

c. If the patient develops another unrelated life threatening diseases/ conditions or severe diseases/condition that is likely to shorten his/her life span and life quality, in which he/she will not gain benefit from ERT for MPS I disease.

d. If the patient develops a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

e. If the patient develops irreversible or severe life threatening complications of MPS I that will not benefit from further ERT. For example: cardiac failure secondary to severe mitral regurgitation.

REFERENCES

1. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 136. Available at www.ommbid.com.

2. Muenzer J. The mucopolysaccharidoses: a heterogeneous group of disorders with variable pediatric presentations. J Pediatr.2004;144:S27–34.

3. Lowry RB, Applegarth DA, Toone JR, MacDonald E, Thunem NY. An update on the frequency of mucopolysaccharide syndromes in British Columbia. Hum Genet. 1990;85:389–90.

4. Braunlin EA, Stauffer NR, Peters CH, Bass JL, Berry JM, Hopwood JJ, Krivit W. Usefulness of bone marrow transplantation in the Hurler syndrome. Am J Cardiol. 2003;92:882–6.

5. Cox-Brinkman J, Boelens JJ, Wraith JE. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. Bone Marrow Transplant. 2006;38:17–21.

6. Wraith EJ, Hopwood JJ, Fuller M, Meikle PJ, Brooks DA. Laronidase treatment of mucopolysaccharidosis I. BioDrugs.2005;19:1–7.

7. Coppa GV, Buzzega D, Zampini L, Maccari F, Galeazzi T, Pederzoli F, Gabrielli O, Volpi N. Effect of 6 years of enzyme replacement therapy on plasma and urine glycosaminoglycans in attenuated MPS I patients. Glycobiology. 2010 Oct;20(10):1259-73

8. Tylki-Szymanska A, Marucha J, Jurecka A, Syczewska M, Czartoryska B. Efficacy of recombinant human alpha-L-iduronidase (laronidase) on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients. J Inherit Metab Dis. 2010 Apr;33(2):151-7

9. Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Sidman M, Kakkis ED, Cox GF. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics. 2009 Jan;123(1):229-40.

10. Wraith JE. The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. Expert Opin Pharmacother. 2005 Mar;6(3):489-506.

Website resources

1. J.E. Wraith, A. Vellodi, M.A. Cleary, U. Ramaswami, C. Lavery Edmund Jessop. Guidelines for the Investigation and Management of Mucopolysaccharidosis type I. www.specialisedservices.nhs.uk/.../Guidelines_for_Mucopolysaccharidosis_Type_I.pdf

2. Department of Health and Ageing, Australia. Guidelines for the treatment of Mucopolysaccharidosis type I (MPS I) disease through life saving drugs programe. www.health.gov.au/internet/main/publishing.nsf/Content/.../MPS%20I.doc

MUCOPOLYSACCHARIDOSIS TYPE II

INTRODUCTION

Mucopolysaccharidosis Type II (MPS II, Hunter disease) is caused by a deficiency of the lysosomal enzyme iduronate-2-sulphatase, which catalyzes a step in the stepwise degradation of the glycosaminoglycans, heparin sulphate (HS) and dermatan sulphate (DS). The enzyme deficiency will lead to progressive accumulation of partially degraded HS and DS in the lysosomes of cells in almost all tissues and organs. Tissues which are markedly affected include the liver and spleen and, to a lesser extent, skin, bone, cartilage, ligaments, heart valves, airways, meninges, and corneas.[1,2] Several surveys suggest MPS II has an incidence between 1:100,000 and 1:170,000 male births.[3,4]

MPS II is a rare X-linked disorder which typically affects the males but has also rarely been reported in females. The disease is progressive and eventually results in death, most commonly due to respiratory or/and cardiac failure. However, the severity varies and could range from the mild to severe. The severe form of MPS II is more common, has an early age of onset, usually between 1-4 years of age, and involves the central nervous system leading to intellectual impairment and progressive neurodegeneration. Other clinical features include coarse facies, growth retardation, joint stiffness, communicating hydrocephalus, chronic diarrhoea, sensorineural deafness, compression of the cervical cord, chronic respiratory disease, degeneration of the retina and cardiac valvular disease. The course is rapidly progressive and leads to death usually between 10 and 20 years of age.[1,2,5]

The attenuated form of MPS II has a later onset and has a slower rate of progression. There is little or no involvement of the central nervous system so intelligence is preserved. The somatic features are similar to, but milder than the severe form. Short stature, joint stiffness, early-onset osteoarthritis, carpal tunnel syndrome, cardiac valvular disease, cervical cord compression and sensorineural hearing loss are common features. Survival to the fifth or sixth decade occurs although deaths from the late teenage years have been reported.[1]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY (ERT)

Treatment of MPS II has generally been symptomatic, involving orthopaedic, otolaryngological, cardiac, respiratory and neurosurgical interventions. Unlike MPS I, Haematopietic stem cell transplant (HSCT) does not prevent neurodegeneration and is not recommended for the treatment of MPS II.[2,5]

In 2006, a recombinant form of human iduronate 2-sulfatase (idursulfase, Genzyme) has been approved in the United States and the European Union for the treatment of MPS II. Idursulfase has been approved by National Pharmaceutical Control Bureau for treatment of MPS I in Malaysia.

In clinical studies, idursulfase has been shown to improve respiratory function, distance walked in 6 minutes, , liver and spleen size and produce significant reductions in urinary GAGs. Idursulfase does not cross the blood-brain barrier and there is no evidence to support and no expectation that the neurological features will be improved by ERT.[5-10]

In view of the very high cost of treatment, wide variation in the extent of ERT benefit, and the risk and inconvenience associated with the need for frequent intravenous injections; guidelines are necessary for the selection of patients for this intervention.

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY (ERT)

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of MPS I

The patient has been confirmed to have the disease by the demonstration of absent or deficient Iduronate-2-Sulphatase activity in any of the following tissues/body fluid: serum, leucocytes and fibroblast. The diagnosis can also be confirmed by the presence of iduronate-2-sulphatase gene mutations known to result in severe deficiency of enzyme activity.

3. Severity of disease

a. Patient has little or no cognitive impairment (IQ >70).

b. Patient should have a minimal level of disease severity in order to be considered for ERT. At least one or more of the following should be present:-

i. 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

ii. Respiratory Function Tests

Patients with FVC less than 80% of predicted value for height

iii. Cardiac

Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 56% (Normal Range 56-78%) OR a reduction in fractional shortening to <25% (normal range 2546%)

iv. 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

Patients with little or no cognitive impairment who fail to meet above criteria should be followed up in a systematic way with annual assessments designed to detect deterioration in their clinical condition. In this way they may be identified as suitable for treatment with ERT at a later date.

Uncertainty around neurological involvement

The Committee recognizes that it is often difficult to distinguish between the severe and attenuated forms of MPS II early in life. Where the clinical assessment suggests mild/early neurological involvement, and potential but not conclusive severe CNS form of MPS II, the Committee may consider a trial of treatment, with frequent review of MRI and neuropsychological assessments, to be performed by a qualified neuropsychologist. The identification of evidence of neurological impairment will lead to the withdrawal of therapy. The Committee are aware that this will be a very difficult process for families and recommends the discussion of these issues prior to the commencement of therapy.

4. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. Patients with another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy would not be considered eligible for treatment with ERT.

2. The presence of severe or irreversible end organ damage that is not likely to improve with ERT.

3. Patients with evidence of significant learning difficulties and/or progressive neuropsychological deterioration.

4. Refusal of the patients or caretakers to comply with the following:-

    a. To comply with the lifelong weekly intravenous infusion therapy as recommended by the ERT committee'.

    b. To comply with the requirement to undergo regular follow up, evaluation and, monitoring procedures as recommended by the ERT committee, for the purpose of evaluating treatment efficacy and complication of the disease.

DRUG DOSAGE

Recommended dose regimen for idursulfase is 0.5 mg/kg weekly via intravenous infusion.

CONSENT FORMS

Patients or their parents/ guardians are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

MONITORING OF THERAPY

Patient who is on subsidized ERT are monitored at regular intervals by the Technical Committee on ERT, basing on the data that are to be collected by the treating doctor **(see Appendix E)**.

WITHDRAWAL OF THERAPY

Subsidized ERT treatment could be withdrawn in any of the following situations: -

a. If the patient develops progressive neurological decline. This would indicate that the child has the severe form of Hunter disease

b. b.If the patient fails to comply with the therapy, follow up, evaluation and assessment procedure as recommended by the ERT guidelines.

c. c.If the patient develops another unrelated life threatening diseases/ conditions or severe diseases/condition that is likely to shorten his/her life span and life quality, in which he/she will not gain benefit from ERT for MPS II disease.

d. d.If the patient develops a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

e. e.If the patient develops irreversible or severe life threatening complications of MPS II that will not benefit from further ERT. For example: cardiac failure secondary to severe mitral regurgitation.

REFERENCES

1. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 136. Available at www.ommbid.com.

2. Wraith JE, Scarpa M, Beck M, Bodamer OA, De Meirleir L, Guffon N, Meldgaard Lund A, Malm G, Van der Ploeg AT, Zeman J. Mucopolysaccharidosis type II (Hunter syndrome): a clinical review and recommendations for treatment in the era of enzyme replacement therapy. Eur J Pediatr. 2008;167(3):267–77.

3. Baehner F, Schmiedeskamp C, Krummenauer F, Miebach E, Bajbouj M, Whybra C, Kohlschutter A, Kampmann C, Beck M. Cumulative incidence rates of the mucopolysaccharidoses in Germany. J Inherit Metab Dis. 2005;28:1011–7.

4. Nelson J, Crowhurst J, Carey B, Greed L. Incidence of the mucopolysaccharidoses in Western Australia. Am J Med Genet A. 2003;123A(3):310–3.

5. Muenzer J, Beck M, Eng CM, Escolar ML, Giugliani R, Guffon NH, Harmatz P, Kamin W, Kampmann C, Koseoglu ST, Link B, Martin RA, Molter DW, Muñoz Rojas MV, Ogilvie JW, Parini R, Ramaswami U, Scarpa M, Schwartz IV, Wood RE, Wraith E. Multidisciplinary management of Hunter syndrome. Pediatrics. 2009;124(6):e1228–39.

6. Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, Vellodi A, Martin R, Ramaswami U, Gucsavas-Calikoglu M, Vijayaraghavan S, Wendt S, Puga AC, Ulbrich B, Shinawi M, Cleary M, Piper D, Conway AM, Kimura A. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med.2006;8:465–73

7. Schulze-Frenking G, Jones SA, Roberts J, Beck M, Wraith JE. Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II. J Inherit Metab Dis. 2011;34:203–8. Wraith JE, Beck M, Giugliani R, Clarke J, Martin R, Muenzer J., HOS Investigators. Initial report from the Hunter Outcome Survey. Genet Med. 2008;10:508–16.

8. Muenzer J, Gucsavas-Calikoglu M, McCandless SE, et al. A phase 1/11 clinical trial of enzyme replacement therapy in mucopolysaccharidosis 1/(Hunter syndrome). Mol Genet Metab 1997;90:329-37

9. Manara R, Rampazzo A, Cananzi M, Salviati L, Mardari R, Drigo P, Tomanin R, Gasparotto N, Priante E, Scarpa M. Hunter syndrome in an 11-year old girl on enzyme replacement therapy with idursulfase: brain magnetic resonance imaging features and evolution. J Inherit Metab Dis. 2010

Website resources

1. Department of Health and Ageing, Australia. Guidelines for the treatment of MucopolysacharidosisType II (MPS II) disease through life saving drugs programe.

   www.health.gov.au/internet/main/publishing.nsf/.../lsdp.../MPS%20II.doc

3. A. Vellodi, J.E. Wraith, M.A. Cleary, U. Ramaswami, C. Lavery, Edmund Jessop. Guidelines for the Investigation and Management of Mucopolysaccharidosis type II.

   www.specialisedservices.nhs.uk/.../Guidelines_for_Mucopolysaccharidosis_Type_II.pdf

MUCOPOLYSACCHARIDOSIS TYPE VI

INTRODUCTION

Mucopolysaccharidosis Type VI (MPS VI) or also known as Maroteaux–Lamy syndrome is an autosomal recessive lysosomal storage disorder (LSD) that results from a deficiency in the lysosomal enzyme, *N*-acetylgalactosamine-4-sulphatase (also known as arylsulphatase B). This enzyme deficiency leads to the intracellular accumulation and urinary excretion of undegraded/ partially degraded dermatan sulphate and chondroitin sulphate glycosaminoglycans.[1]

MPS VI patients can present with a spectrum of clinical phenotypes. The classical symptoms of MPS VI include short stature, hepatosplenomegaly, dysostosis multiplex, joint stiffness, corneal clouding, cardiac abnormalities, and facial dysmorphia. Severely affected patients suffer early onset symptoms with rapid disease progression, while patients at the attenuated end of the clinical spectrum have a later onset and variable clinical presentation. In the severe form of MPS VI, death usually occurs in the early teenage years due to respiratory and cardiac problems, while in patients with the attenuated form, lifespan can be up to 50 or more years in some cases. In contrast to many of the MPS disorders, MPS VI is not typically associated with progressive impairment of mental status, although physical limitations may impact learning and development. Birth prevalence is between 1 in 43,261 and 1 in 1,505,160 live births.[1,2]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY (ERT)

In the past, limited treatment options for MPS VI led many clinicians to adopt a palliative approach and focus primarily on management of individual disease complications such as physical therapy to minimize joint contractures and stiffness and improve muscle strength, spinal fusion for spinal cord compression or progressive kyphosis, hernia repair, tonsillectomy and adenoidectomy for airway obstruction or eustachian tube dysfunction.

Historically, HSCT had been the only specific therapy available for MPS VI. Successful HSCT has benefited a small number of patients with MPS VI. In 2006, enzyme replacement therapy (ERT) with Chinese hamster ovary cell derived recombinant human *N*-acetylgalactosamine-4-sulphatase (Recombinant Human Arylsulfatase B or rhASB; Galsulfase; Biomarin), was approved by both the European Union and the US Food and Drug Administration for long term treatment of patients with MPS VI. In clinical studies, Galsulfase has been shown to improve respiratory function, distance walked in 6 minutes, liver and spleen size and produce significant reductions in urinary GAGs,.

While ERT is effective, such chronic treatment places a burden on the individual patient, and is costly for society. Therefore, some guidance is judged to be necessary for the selection of patients for treatment.

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY (ERT)

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of MPS VI

The diagnosis of MPS I has been established by the demonstration of specific deficiency of *N*-acetylgalactosamine-4-sulphatase (arylsulphatase B) measured in lymphocytes or skin fibroblasts. The diagnosis can also be confirmed by the presence of *N*-acetylgalactosamine-4-sulphatase/ arylsulphatase B gene mutations known to result in severe deficiency of enzyme activity.

3. Severity of the disease

Patient should have a minimal level of disease severity in order to be considered for ERT. At least one or more of the following should be present:-

a. 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

b. Respiratory Function Tests

Patients with FVC less than 80% of predicted value for height

c. Cardiac

Myocardial dysfunction as indicated by a reduction in ejection fraction to less than 56% (Normal Range 56-78%) OR a reduction in fractional shortening to <25% (normal range 2546%)

d. 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

Patients who fail to meet above criteria should be followed up in a systematic way with annual assessments designed to detect deterioration in their clinical condition. In this way they may be identified as suitable for treatment with ERT at a later date.

Special circumstance

Hydrocephalus:

To date there is limited data on the response of hydrocephalus to enzyme replacement therapy. Each case will be considered on its merits. In general, enzyme replacement therapy would be recommended in addition to surgery rather than as an alternative to surgery.

Spinal cord compression:

Some patients receiving enzyme replacement therapy have developed spinal cord compression. Although each case will be considered on its merits, surgery remains the preferred treatment for this complication.

4. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. Patients with another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy would not be considered eligible for treatment with ERT.

2. The presence of severe or irreversible end organ damage that is not likely to improve with ERT.

3. Patients with evidence of significant learning difficulties.

4. Refusal of the patients or caretakers to comply with the following:-

   a. To comply with the lifelong weekly intravenous infusion therapy as recommended by the ERT guidelines.

   b. To comply with the requirement to undergo regular follow up, evaluation and, monitoring procedures as recommended by the ERT guidelines, for the purpose of evaluating treatment efficacy and complication of the disease.

DRUG DOSAGE

Recommended dose regimen for Galsulfase is 1mg/kg weekly via intravenous infusion.

CONSENT FORMS

Patients or their parents/ guardians are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

MONITORING OF THERAPY

Patient who is on subsidized ERT are monitored at regular intervals by the Technical Committee on ERT, basing on the data that are to be collected by the treating doctor **(see Appendix E)**.

WITHDRAWAL OF THERAPY

Subsidized ERT treatment could be withdrawn in any of the following situations: -

a. If the patient develops progressive neurological decline.

b. If the patient fails to comply with the therapy, follow up, evaluation and assessment procedure as recommended by the ERT guidelines.

c. If the patient develops another unrelated life threatening diseases/conditions or severe diseases/condition that is likely to shorten his/her life span and life quality, in which he/she will not gain benefit from ERT for MPS VI disease.

d. If the patient develops a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

e. If the patient develops irreversible or severe life threatening complications of MPS VI that will not benefit from further ERT. For example: cardiac failure secondary to severe mitral regurgitation.

REFERENCES

1. Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 136. Available at www.ommbid.com.

2. Valayannopoulos V, Nicely H, Harmatz P, Turbeville S. Mucopolysaccharidosis VI. Orphanet J Rare Dis. 2010 Apr 12;5:5. Review.

3. Turbeville S, Nicely H, Rizzo JD, Pedersen TL, Orchard PJ, Horwitz ME, Horwitz EM, Veys P, Bonfim C, Al-Seraihy A. Clinical outcomes following hematopoietic stem cell transplantation for the treatment of mucopolysaccharidosis VI. Mol Genet Metab. 2011 Feb;102(2):111-5.

4. Harmatz P. Enzyme replacement therapy with galsulfase for mucopolysaccharidosis VI: clinical facts and figures. Turk J Pediatr. 2010 Sep-Oct;52(5):443-9. Review

5. Lin HY, Chen MR, Chuang CK, Chen CP, Lin DS, Chien YH, Ke YY, Tsai FJ, Pan HP, Lin SJ, Hwu WL, Niu DM, Lee NC, Lin SP. Enzyme replacement therapy for mucopolysaccharidosis VI-experience in Taiwan. J Inherit Metab Dis. 2010 Oct 6. [Epub ahead of print]

6. Auclair D, Hopwood JJ, Brooks DA, Lemontt JF, Crawley AC: Replacement therapy in Mucopolysaccharidosis type VI: advantages of early onset of therapy. *Mol Genet Metab* 2003, **78:**163-174.

7. Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Miranda MC, *et al***.** Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr* 2006, 148**:**533-539.

8. Harmatz P, Giugliani R, Schwartz IV, Guffon N, Teles EL, Miranda MC, *et al*.: Long-term follow-up of endurance and safety outcomes during enzyme replacement therapy for mucopolysaccharidosis VI: Final results of three clinical studies of recombinant human N-acetylgalactosamine 4-sulfatase**.** *Mol Genet Metab* 2008, 94:469-475.

9. Harmatz P, Yu ZF, Giugliani R, Schwartz IV, Guffon N, Teles EL, *et al*. Enzyme replacement therapy for mucopolysaccharidosis VI: evaluation of long-term pulmonary function in patients treated with recombinant human N-acetylgalactosamine 4-sulfatase. *J Inherit Metab Dis* 2010, **33**(1)**:**51-60.

10. R Giugliani, P Harmatz, JE Wraith. Management Guidelines for Mucopolysaccharidosis VI. Pediatrics 2007;120(2) doi:10.1542/peds.2006-2184

Website resources

1. J.E. Wraith, A. Vellodi, M.A. Cleary, U. Ramaswami, C. Lavery, Edmund Jessop. Guidelines for the Investigation and Management of Mucopolysaccharidosis type VI. www.specialisedservices.nhs.uk/.../Guidelines_for_Mucopolysaccharidosis_Type_VI.pdf

2. Department of Health and Ageing, Australia. Guidelines for the treatment of Mucopolysaccharidosis Type VI (MPS VI) disease through life saving programme. *www.health.gov.au/internet/main/publishing.nsf/.../lsdp.../MPS%20VI.doc*

FABRY DISEASE

INTRODUCTION

Fabry Disease is an X-linked disorder caused by the deficiency of the lysosomal enzyme αGalactosidase A (α-Gal A). The deficiency of the enzyme causes accumulation of globotriaosylceramide (GL-3) and related glycolipids in tissues and body fluids. GL-3 accumulation affects many cell types, including vascular endothelium, various renal cell types, and epithelial and smooth-muscle cells of the cardiovascular and renal systems.[1]

The classic form, occurring in males with less than 1% α-Gal A enzyme activity, usually has its onset in childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias), the appearance of vascular cutaneous lesions (angiokeratomas), hypohidrosis, characteristic corneal and lenticular opacities, and proteinuria. Gradual deterioration of renal function to end-stage renal disease (ESRD) usually occurs in men in the third to fifth decade. In middle age, most males successfully treated for ESRD develop cardiovascular and/or cerebrovascular disease, a major cause of morbidity and mortality.[1,2]

Males with greater than 1% α-Gal A activity may have either (1) a cardiac variant phenotype that usually presents in the sixth to eighth decade with left ventricular hypertrophy, mitral insufficiency and/or cardiomyopathy, and proteinuria, but without ESRD; or (2) a renal variant phenotype associated with ESRD but without the skin lesions or pain.[1,2,3]

Heterozygous females typically have milder symptoms at a later age of onset than males. Rarely, they may be relatively asymptomatic throughout a normal life span or may have symptoms as severe as those observed in males with the classic phenotype.[4]

DISEASE MANAGEMENT AND ENZYME REPLACEMENT THERAPY (ERT)

Prior to the introduction of enzyme replacement therapy, treatment of Fabry Disease was symptomatic and included dialysis, renal transplantation, and neurotropic analgesics. ERT was evaluated in clinical trials during the late 1990s leading to the commercial availability of two enzyme formulations: agalsidase beta/Fabrazyme (Genzyme) and agalsidase alfa (Shire Human Genetic Therapies). Agalsidase alfa is produced using a genetically engineered human fibroblast cell line; whereas agalsidase beta is produced using a Chinese hamster ovary cell line. Biochemical comparison studies have shown that both preparations are structurally and functionally very similar. Fabrazyme has been approved by National Pharmaceutical Control Bureau for ERT of Fabry Disease in Malaysia.

Clinical studies have demonstrated that ERT may prevent irreversible end-organ damage in Fabry Disease from chronic GL-3 deposition. ERT has been shown to decrease pain and to stabilize renal function.[5-14]

ELIGIBILITY CRITERIA FOR ENZYME REPLACEMENT THERAPY (ERT)

1. Citizen of Malaysia

The patient must be a citizen of Malaysia. Permanent residents are not eligible.

2. Confirmed diagnosis of Fabry disease

a. In males, the diagnosis must have been established by the demonstration of specific deficiency of alpha galactosidase A measured in lymphocytes, plasma or cultured cells.sThe diagnosis can also be confirmed by the presence of alpha galactosidase A gene mutations known to result in severe deficiency of enzyme activity.

b. In females, DNA analysis is essential as enzymatic levels of the female heterozygote may lie within the normal range. In cases where DNA analysis is

non-conclusive examination of urine for globotriaosylceramide (GL-3) and cornea for verticillata may assist in the diagnosis.

3. Severity of disease

Patients must meet the criteria of at least one of the following four Fabry related diseases:-

a. Fabry-related renal disease

<u>All patients:</u>

Confirmation by renal biopsy is recommended to:

i. provide prognostic information;

ii. exclude other causes of nephropathy;

iii. demonstrate evidence of focal glomerular sclerosis or fibrosis greater, then that expected for age, once other causes of nephropathy have been excluded; and

iv. document significant histological changes related to Fabry disease.

Male Fabry patients:

i. proteinuria >300mg/24 hours with clinical evidence of progression; *or*

ii. abnormal albumin excretion rate (> 20µg/min) as determined by 2 separate samples, at least 24 hours apart; *or*

iii. albumin:creatinine ratio greater than upper limit of normal, in 2 separate samples, at least 24 hours apart.

Female Fabry patients:

i. proteinuria >300mg/24 hours with clinical evidence of progression.

b. Fabry-related cardiac disease

i. Left ventricular hypertrophy, as evidenced by cardiac MRI or echocardiogram data, in the absence of hypertension or other causes. If hypertension is present, it should be treated optimally for at least 6 months prior to the submission of an ERT application through this criterion.

ii. Significant life threatening arrhythmia or conduction defect.

iii. Valvular thickening/insufficiency.

c. Fabry-related ischaemic vascular disease

i. Stroke or transient ischaemic attacks (minumum 3 documented TIAs) at age less than 50 with no other cause identified.

ii. Documented progression of white matter microvascular disease with MRI with no other cause identified.

d. Fabry-related neuropathic pain

i. Uncontrolled chronic pain despite the use of maximum doses of analgesics and no other cuase identified.

4. Additional conditions as in Appendix A.

EXCLUSION CRITERIA

1. Patients with another life-threatening disease where prognosis is unlikely to be influenced by enzyme replacement therapy would not be considered eligible for treatment with ERT.

2. The presence of severe or irreversible end organ damage that is not likely to improve with ERT.

3. Patients with evidence of significant learning difficulties.

4. Refusal of the patients or caretakers to comply with the following:-

    a. Totcomply with the lifelong 2 weekly intravenous infusion therapy, as recommended by the ERT committee.

    b. To comply with the requirement to undergo regular follow up, evaluation and, monitoring procedures as recommended by the ERT guidelines, for the purpose of evaluating treatment efficacy and complication of the disease.

DRUG DOSAGE

Recommended dose regimen for agalsidase beta is 1mg/kg intravenously every two weeks.

Adjunctive therapies: ERT must be supplemented by optimal treatment with analgesics, reno-protective, cardio-protective and vasculo-protective medications as indicated.

CONSENT FORMS

Patients or their parents/ guardians are required to sign a consent form prior to the start of the subsidized ERT, to be submitted at the time of application **(see Appendix B)**.

MONITORING OF THERAPY

Patient who is on subsidized ERT are monitored at regular intervals by the Technical Committee on ERT, basing on with the data that are to be collected by the treating doctor **(see Appendix F)**.

WITHDRAWAL OF THERAPY

Subsidized ERT treatment could be withdrawn in any of the following situations:

a. If the patient develops progressive neurological decline.

b. If the patient fails to comply with the therapy, follow up, evaluation and assessment procedure as recommended by the ERT guidelines.

c. If the patient develops another unrelated life threatening diseases/ conditions or severe diseases/condition that is likely to shorten his/her life span and life quality, in which he/she will not gain benefit from ERT for Fabry disease.

d. If the patient develops a life threatening complication, which would compromise the effectiveness or benefit from continued ERT, including severe infusion-related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate pre-medication and/or adjustment of infusion rates

e. If the patient develops irreversible or severe life threatening complications of Fabry Disease that will not benefit from further ERT.

REFERENCES

1. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, eds. *The Metabolic and Molecular Bases of Inherited Disease (OMMBID)*. New York: McGraw-Hill. Chap 150. Available at www.ommbid.com.

2. Ries M, Gupta S, Moore DF, Sachdev V, Quirk JM, Murray GJ, Rosing DR, Robinson C, Schaefer E, Gal A, Dambrosia JM, Garman SC, Brady RO, Schiffmann R. Pediatric Fabry disease. Pediatrics. 2005;115:e344–55.

3. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J. 2007;28:1228–35.

4. Deegan PB, Baehner AF, Barba Romero MA, Hughes DA, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet. 2006;43:347–52.

5. Hoffmann B, Beck M, Sunder-Plassmann G, Borsini W, Ricci R, Mehta A. Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy--a retrospective analysis from the Fabry Outcome Survey. Clin J Pain.2007a;23:535–42.

6. Hoffmann B, Schwarz M, Mehta A, Keshav S. Fabry Outcome Survey European Investigators; Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol.2007b;5:1447–53.

7. Hoffmann B, Garcia de Lorenzo A, Mehta A, Beck M, Widmer U, Ricci R. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). J Med Genet.2005;42:247–52.

8. Mignani R, Panichi V, Giudicissi A, Taccola D, Boscaro F, Feletti C, Moneti G, Cagnoli L. Enzyme replacement therapy with agalsidase beta in kidney transplant patients with Fabry disease: a pilot study. Kidney Int. 2004;65:1381–5.

9. Schiffmann R, Askari H, Timmons M, Robinson C, Benko W, Brady RO, Ries M. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol.2007;18:1576–83.

10. Schiffmann R, Kopp JB, Austin HA, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285:2743–9.

11. Schwarting A, Sunder-Plassmann G, Mehta A, Beck M. Fabry Disease: Perspectives from 5 Years of FOS. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Effect of enzyme replacement therapy with agalsidase alfa on renal function in patients with Fabry disease: data from FOS – the Fabry Outcome Survey.* Oxford: Oxford PharmaGenesis; 2006: Chapter 38.

12. Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, Desnick RJ, O'Callaghan M. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int.2002;62:1933–46.

13. Vedder AC, Linthorst GE, Houge G, Groener JE, Ormel EE, Bouma BJ, Aerts JM, Hirth A, Hollak CE. Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS ONE. 2007;2:e598.

14. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, Ertl G, Knoll A, Wanner C, Strotmann JM. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation. 2003;108:1299–301.

Website resources

1. Department of Health and Ageing, Australia. Guidelines for the treatment of Fabry disease through life saving drugs programe.

www.health.gov.au/internet/main/publishing.nsf/.../Fabry%20Disease1.doc

2. D.A.Hughes, U. Ramaswam, P Elliott, P.Deegan, P. Lee, S.Waldek, G Apperley, T.Cox and A.B.Mehta for the National Specialist Commissioning Advisory Group (NSCAG). Guidelines for the diagnosis and management of Anderson-Fabry Disease. www.dh.gov.uk › Home › Publications

3. Lorne A. Clarke, Joe T.R.Clarke, Sandra Sirrs, Michael L West, R. Mark Iwanochko, JohnR. Wherrett, Cheryl R. Greenberg, Alicia K.J. Chan, Robin Casey. Fabry Disease: Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy in Canada. www.garrod.ca/data/.../CanadianFabryGuidelinesNov05.pdf

APPENDIX

APPENDIX A

GENERAL CONDITIONS FOR ELIGIBILITY

GENERAL CONDITIONS FOR ELIGIBILITY

1. Patients to be considered for financial support from the Malaysian government (Ministry of Health) or its related health agencies (eg Ministry of Higher Education and Ministry of Defence) for ERT treatment must be willing to participate in the long term evaluation of the efficacy of treatment via periodic medical assessment as required by the ERT Guidelines.

2. If, depending on the natural course of the disease, there is no evidence of: (a) substantial clinical improvement in the patient, or (b) stabilization of the patient's condition as assessed not later than 12 months after commencing therapy with the subsidized drug, then the patient's continued eligibility for financial assistance under these arrangements will be reviewed.

3. Where the patient fails to comply adequately with the treatment or measures taken to evaluate the effectiveness of the treatment, financial assistance under these arrangements will be withdrawn.

APPENDIX B

BORANG PERSETUJUAN PESAKIT

BORANG PERSETUJUAN PESAKIT

NAMA PESAKIT: .....

NOMBOR KP: .....TARIKH LAHIR: .....

HOSPITAL: ..... NOMBOR PENDAFTARAN HOSPITAL: .....

Nama rawatan yang dicadangkan:

Enzyme replacement therapy (ERT) untuk penyakit: (pilih yang berkenaan)

Pompe [ ] Gaucher [ ] Fabry [ ] MPS I [ ] MPS II [ ] MPS VI [ ]

A. Kenyataan pengamal perubatan:

Saya telah menerangkan rawatan yang dicadangkan kepada pesakit. Secara khususnya, saya telah menerangkan isu-isu seperti berikut:

1. Kebaikan dan sasaran rawatan yang diingini: (pilih yang berkenaan)

    [ ] Penyakit otot jantung (*cardiomyopathy*) pulih

    [ ] Bebas daripada bantuan alat pernafasan invasif

    [ ] Penyakit otot skeletal menjadi stabil atau pulih

    [ ] Bengkak hati dan limpa susut ke tahap yang minimal

    [ ] Masalah kekurangan sel-sel darah pulih

    [ ] Penyakit buah pinggang menjadi stabil atau pulih

    [ ] Peningkatan jarak di dalam ujian *six-minute walk*

[ ] Peningkatan fungsi paru-paru (*increased forced vital capacity*)

[ ] Lain-lain: .....

2. Risiko rawatan yang mungkin terjadi:

- *Anaphylaxis*
- Kesan alergi seperti ruam, gatal dan deman yang berkaitan dengan infusi ubat
- Kegagalan dalam mencapai sasaran rawatan yang diingini

3. Prosedur rawatan akan dijalankan: (pilih yang berkenaan)

[ ] seminggu sekali

[ ] dua minggu sekali

Bertempat di Hospital .....

Selain rawatan ERT, pesakit mungkin memerlukan rawatan *multidisiplinary* yang lain seperti berikut:

.....

.....

.....

4. Ujian pemantauan:

- akan dijalankan secara berkala
- ianya bertujuan memantau keberkesanan rawatan

5. Rawatan mungkin ditarik balik atau ditamatkan jika:

- tidak hadir tanpa sebab untuk rawatan sebanyak 2 kali dalam tempoh 6 bulan
- tidak hadir tanpa sebab untuk ujian pemantauan sehingga menjejaskan penilaian keberkesanan rawatan
- tidak hadir tanpa sebab untuk rawatan *multidisiplinary* yang lain
- rawatan tidak mendatangkan kebaikan yang diingini
- terdapat tanda-tanda kemerosotan fungsi otak

Tandatangan: .....

Tarikh: .....

Nama: .....

Jawatan: .....

B. Kenyataan penterjemah (sekiranya berkenaan)

Saya telah menterjemahkan segala maklumat seperti di atas kepada pesakit ini dengan sedaya upaya saya dan dengan cara di mana saya percaya ianya dapat difahami oleh pesakit.

Tandatangan: .....

Nama: .....

Tarikh: .....

C. Kenyataan pesakit

Sila baca borang ini dengan teliti. Sila juga baca helaian pertama borang persetujuan ini yang telah menghuraikan segala kebaikan, risiko, prosedur rawatan dan pemantauan yang telah dicadangkan. Sekiranya anda ada apa-apa soalan, sila kemukakan kepada kami. Kami di sini untuk membantu anda.

1.	Saya telah membaca helaian pertama borang ini dan telah faham kebaikan serta risiko rawatan yang dicadangkan.	YA	TIDAK
2.	Saya bersetuju menjalani rawatan yang dicadangkan.	YA	TIDAK
3.	Saya telah dimaklumkan tentang prosedur rawatan yang perlu dipatuhi.	YA	TIDAK
4.	Saya telah dimaklumkan tentang prosedur pemantauan yang perlu dipatuhi.	YA	TIDAK
5.	Saya telahpun dimaklumkan bahawa rawatan akan ditarik balik jika saya gagal mematuhi prosedur rawatan dan pemantauan yang ditetapkan.	YA	TIDAK
6.	Saya telahpun dimaklumkan bahawa rawatan akan ditarik balik jika saya gagal mencapai kebaikan atau sasaran rawatan yang dikehendaki.	YA	TIDAK

Tandatangan: .....

Nama: .....

Tarikh: .....

(Untuk pesakit di bawah 18 tahun, ibubapa/penjaga akan mewakilinya untuk menandatangani borang persetujuaan ini)

D. Saksi

Seorang saksi perlu tandatangani di bawah ini sekiranya beliau telah menyaksikan pesakit menandatangan di atas.

Tandatangan: .....

Nama: .....

Tarikh: .....

Jawatan: .....

APPENDIX C

MONITORING REQUIREMENT AND DATA SUBMISSION FORM FOR GAUCHER DISEASE

MONITORING REQUIREMENTS AND DATA SUBMISSION FORM

FOR GAUCHER DISEASE

Baseline and monitoring requirement (Gaucher disease)

	Baseline	3 months	6 months	12 months	Subsequently	
					6 monthly	12-24 monthly
Hemoglobin	X	X	X	X	X	
Platelet Count	X	X	X	X	X	
Total white count	X					
Chitotriosidase	X	X	X	X	X	
Liver function	X					X
Coagulation profile	X					
Calcium/Phosphorus	X					X
Liver Volume (Volumetric MRI or CT)	X			X		X
Spleen Volume (Volumetric MRI or CT)	X			X		X
X-ray: AP view of entire femora and lateral view of spine	X			X[1]		X[1]
MRI (coronal; T1 & T2-weighted) of entire femora	X			X[1]		X[1]
DEXA: lumbar spine and non-dominant femoral neck	X			X		X
Chest X-ray	X			X		X
ECG/Echocardiogram	X			X		X
Quality of Life and Health- Related assessments: SF-36 Health Survey PedsQL™ Measurement Model	X			X		X

[1] if treated for bone involvement

ENZYME REPLACEMENT THERAPY PROGRAM FOR LSD

DATA SUBMISSION FORM (GAUCHER DISEASE)

Patient details:

Patient's name: .....

Date of birth: ..... IC Number: .....

Contact No:..... Gender: Male [ ] Female [ ]

Address: .....

Doctor's details:

Doctor's name: .....

Phone number:..... Fax number:.....

Hospital address: .....

Treatment details:

Has received ERT before: No [ ] Yes [ ]

If yes,

Date ERT started: .....

Product: .....

Dose: .....

Frequency: .....

Clinical data:

Confirmation of disease:

Enzyme Assay .....

Genotype .....

Histology .....

(Please attach a copy of the result for the initial submission)

Height: ..... cm (..... %)

Weight: ..... kg (..... %)

Head Circumference: ..... cm (..... %)

Haematology: (Please provide serial results)

Date					
Hb (g/L)					
Platelet count (10^9/L)					

History of blood transfusion? No [ ] Yes [ ] Date: .....

History of platelet transfusion? No [ ] Yes [ ] Date: .....

Visceral involvement:

Liver: **:** (measured in midclavicular line)

Span: ..... cm Below costal margin:..... cm Date: .....

Volume: .....cc Date: .....

Spleen:(measured in midclavicular line)

Span: ..... cm Below costal margin: ..... cm Date: .....

Volume: .....cc Date: .....

Splenectomy †Yes †No If yes, provide date: .....

Liver dysfunction: No [ ] Yes [ ] Please provide details .....

Abdominal discomfort: No [ ] Yes [ ]

Skeletal Involvement:

Skeletal MRI report attached: Yes [ ] No [ ]

Please provide information to describe the patient's experience with any of the following.

Severe bone crisis: .....

Destruction of joints: .....

Spontaneous fractures: .....

Chronic bone pain: .....

Disease biomarker:

Date					
Chitotriosidase nmol/mL/hr					

Quality of Life and Health- Related assessments report atached: Yes [ ] No [ ]

(SF-36 Health Survey/PedsQL™ Measurement Model)

Other Complications: .....

Other medical problems: .....

Current medications: .....

Compliant: Yes [ ] No [ ] Hypersensitivity: Yes [ ] No [ ]

Other comments: .....

****Please provide ciopies of sonography/MRI/other relevant reports/CD

APPENDIX D

MONITORING REQUIREMENT AND DATA SUBMISSION FORM FOR POMPE DISEASE

MONITORING REQUIREMENTS AND SUBMISSION FORM FOR POMPE DISEASE

Baseline and monitoring requirements (Infantile Pompe Disease)

	Baseline	1 month	2 months	3 months	6 months	12 months	After 12 months
Echocardiogram[1]	X	X	X	X	X	X	6 monthly
Electrocardiography	X	X	X	X	X	X	6 monthly
Chest x-ray	X				X	X	as required
Biochemical Tests (CK, AST, LDH, ALT,urine tetraglucoside)	X	X	X	X	X	X	6 monthly
Sleep study/ overnight oxygen saturation	X					X	as required
Respiratory assessment[2]	X	X	X	X	X	X	6 monthly
Developmental assessment	X			X	X	X	6 monthly
Gross Motor Function measure (GMF), Walton-Gardner Medwin Score	X			X	X	X	6 monthly
Swallowing assessment	X			X	X	X	6 monthly
Audiology	X					X	annually
CRIM status	X						
Antibody Levels						X	annually
Growth: height, weight and head circumference	X	X	X	X	X	X	6 monthly

[1]measuring left ventricular mass index (LVMI), fractional shortening and ejection fraction

[2]Respiratory rate, oxygen saturation on room air, requirement for non-invasive/ invasive respiratory support

Baseline and monitoring requirements (Late-Onset Pompe Disease)

	Baseline	1 month	3 months	6 months	12 months	After 12 months
6-minute Walk Test[1]	X	X	X	X	X	6 monthly
Arm function test	X	X	X	X	X	6 monthly
Walton-Gardner Medwin score	X	X	X	X	X	6 monthly
Time function tests[3]	X	X	X	X	X	6 monthly

[1]Guidelines for the Six-Minute Walk Test: Please refer Am J Respir Crit Care Med Vol 166. pp 111–117, 2002

[2]by speech therapist

[3]modified Gowers' maneuver, 10-meter walk, 4-stair climb.

ENZYME REPLACEMENT THERAPY PROGRAM FOR LSD

DATA SUBMISSION FORM (INFANTILE POMPE DISEASE)

Patient details:

Patient's name: .....

Date of birth: ..... IC Number: .....

Contact No: ..... Gender: Male [ ] Female [ ]

Address: .....

Doctor's details:

Doctor's name: .....

Phone number: ..... Fax number: .....

Hospital address: .....

Treatment details:

Has received ERT before: No [ ] Yes [ ]

If yes,

Date ERT started: .....

Product: .....

Dose: .....

Frequency: .....

Clinical data:

Confirmation of disease:

Enzyme Assay .....

Genotype .....

Histology .....

Height: ..... cm (.....%)

Weight: ..... kg (.....%)

Head Circumference: .....cm (.....%)

Respiratory:

Ventilation: No [ ] Non-invasive [ ] Invasive [ ] Details: .....

Tracheostomy: No [ ] Yes [ ]

Sleep study report attached: ↑Yes [ ] No [ ]

Obstructive episodes (number/hour): ..... Lowest saturation: .....

Number of desaturations <80%: .....

Blood gas - pCO2, pH, bicarbonate: .....

Apnoea Hypopnoea Index: .....

Cardiology:

Pediatric cardiology assessment attached:↑Yes [ ] No [ ]

Echocardiogram attached: Yes [ ] No [ ]

Date					
Left ventricular mass index					
Fractional shortening					
Ejection fraction					

Valvular Pathology: .....

Electrocardiography attached:↑Yes [ ] No [ ]

Chest x-ray attached:↑Yes [ ] No [ ]

Haematology/Biochemistry:

Date			
Haemoglobin (g/L)			
Platelets (10^9/L)			
Creatine Kinase (CK)			
Alanine Amino Transferase (ALT)			
Aspartate Amino Transferase (AST)			
Lactate Dehydrogenase (LDH)			

Developmental Assessement Report attached: Yes [ ] No [ ]

Gross Motor Function Measure Report attached: Yes [ ] No [ ]

Walton-Gardner Medwin Score Report attached: Yes [ ] No [ ]

Swallowing Assessment: .....

Swallowing Assessment test results attached: Yes [ ] No [ ]

Hearing Test:

Date: ..... NORMAL/ABNORMAL

If abnormal:

Sensorineural: Max loss-Left ear: ..... Right ear: .....

Shape audiogram: .....

Conductive: Max loss – Left ear:..... Right ear: .....

Shape audiogram: .....

Neurological Examination:

Date	R Upper Limb	L Upper Limb	R Lower Limb	L Lower Limb
Reflexes				
Tone				
Power (?/5)				
Plantar				

Neurological Evaluation Report attached: Yes [ ] No [ ]

Other Medical Problems:

.....

.....

Current medication: .....

Compliant: Yes [ ] No [ ]

Hypersensitivity: Yes [ ] No [ ]

Other comments: .....

****Please provide ciopies of sonography/echocardiography/MRI/other relevant reports/CD

ENZYME REPLACEMENT THERAPY PROGRAM FOR LSD

DATA SUBMISSION FORM (LATE ONSET POMPE DISEASE)

Patient details:

Patient's name: .....

Date of birth: ..... IC Number: .....

Contact No:..... Gender: Male [ ] Female [ ]

Address: .....

Doctor's details:

Doctor's name: .....

Phone number: .....Fax number:.....

Hospital address: .....

Treatment details:

Has received ERT before: No [ ] Yes [ ]

If yes,

Date ERT started: .....

Product: .....

Dose: .....

Frequency: .....

Clinical data:

Confirmation of disease:

Enzyme Assay .....

Genotype .....

Histology .....

(Please attach a copy of the result for the initial submission)

Height: ..... cm (.....%)

Weight: ..... kg (.....%)

BMI: .....

Respiratory:

Ventilation: No [ ] Non-invasive [ ] Invasive [ ] Details: .....

Tracheostomy: No [ ] Yes [ ]

Sleep study with a report of Apnoea Hypopnoea Index: Date .....

(No. / hour): ..... Lowest saturation .....%

No. desaturations <80%: .....

FVC: Date .....

(if old enough to co-operate): ..... (mls) .....(%for age and height);

FEV 1: ..... (mls) ..... (%for age and height)

6 minute walk test: ..... metres (if old enough)

Mean performance time for:

Modified Gowers' maneuver: ..... seconds

10-meter walk: ..... seconds

4-stair climb: ..... seconds

Arm function test report attached: Yes [ ] No [ ]

Range of Movement of Joints evaluation report attached: Yes [ ] No [ ]

Neurological Examination:

Date	R Upper Limb	L Upper Limb	R Lower Limb	L Lower Limb
Reflexes				
Tone				
Power (?/5)				
Plantar				

Neurological Evaluation Report attached: Yes [ ] No [ ]

Swallowing Assessment: .....

Swallowing Assessment test results attached: ↑Yes [ ] No [ ]

Hearing Test:

Date: ..... NORMAL/ABNORMAL

If abnormal:

Sensorineural: Max loss-Left ear: ..... Right ear: .....

Shape audiogram: .....

Conductive: Max loss – Left ear: ..... Right ear: .....

Shape audiogram: .....

Haematology/Biochemistry:

Date			
Haemoglobin (g/L)			
Platelets (10^9/L)			
Creatine Kinase (CK)			
Alanine Amino Transferase (ALT)			
Aspartate Amino Transferase (AST)			
Lactate Dehydrogenase (LDH)			

Walton-Gardner Medwin Score Report attached: Yes [ ] No [ ]

SF-36 Health Survey Report attached Yes [ ] No [ ]

Other Medical Problems:

.....

.....

Current medication:

.....

.....

Compliant: Yes [ ] No [ ]

Hypersensitivity: Yes [ ] No [ ]

Other comments: .....

****Please provide ciopies of sonography/echocardiography/MRI/other relevant reports/CD

APPENDIX E

MONITORING REQUIREMENT AND DATA SUBMISSION FORM FOR MUCOPOLYSACCHARIDOSIS DISEASE

MONITORING REQUIREMENTS AND SUBMISSION FORM

FOR MUCOPOLYSACCHARIDOSIS DISEASE

Baseline and monitoring requirement (MPS Disease)

	Baseline	6 mths	12 mths	6mthly	Annually	Biannually
Height	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Head Circumference	X	X	X	X	X	X
Hepatomegaly[1]	X	X	X		X	X
Splenomegaly[1]	X	X	X		X	X
Sleep Study/Over-night O_2 saturation	X		X		X	X
Pulmonary function test	X		X		X	X
Echocardiogram[2]	X	X	X		X	X
Ophthalmological Examination	X	X	X		X	X
Skeletal Survey	X					
MRI craniocervical junction/spine	X		X		X	X
Six minute walk test	X	X	X	X	X	X
IQ / Neuropsychological tests	X		X		X	X
Full Neurological Examination	X	X	X	X	X	X
Audiology	X		X		X	X
Urinary GAGs - quantitative	X	X	X		X	X
ROM of joints[3]	X	X	X		X	X
Quality of Life and Health- Related assessments: SF-36 Health SurveyPedsQL™ Measurement Model	X		X		X	X

[1]Ultrasound. Just clinical once normal.

[2] Including ejection fraction and fractional shortening

[3]Shoulder Flex/Ext & abduction; Elbow Flex/Ext; Wrist Flex/Ext; Hip Flex/Ext; Knee Flex/Ext; Ankle Flex/Ext and Hand clawing nil/mild/mod/severe

Guidelines for the Six-Minute Walk Test: Please refer Am J Respir Crit Care Med Vol 166. pp 111–117, 2002

DATA SUBMISSION FORM (MPS DISEASE)

Patient details:

Patient's name: .....

Date of birth: ..... IC Number: .....

Contact No: ..... Gender: Male [ ] Female [ ]

Address: .....

Diagnosis: MPS I [ ] MPSII [ ] MPS VI [ ]

Doctor's details:

Doctor's name: .....

Phone number: ..... Fax number: .....

Hospital address: .....

Treatment details:

Has received ERT before: No [ ] Yes [ ]

If yes,

Date ERT started: .....

Product: .....

Dose: .....

Frequency: .....

Clinical data:

Confirmation of disease:

Enzyme Assay .....

Genotype .....

Urine glycoamineglycans analyses .....

(Please attach a copy of the result for the initial submission)

Height: ..... cm (.....%)

Weight: ..... kg (.....%)

Head circumference: ..... cm (.....%)

Liver size:(measured in midclavicular line)

Span: .....cm Below costal margin: .....cm

Spleen size:(measured in midclavicular line)

Span: ..... cm Below costal margin: ..... cm

Sleep study with a report of Apnoea Hypopnoea Index: Date .....

(No. / hour): ..... Lowest saturation ..... %

No. desaturations <80%: .....

FVC: Date .....

(if old enough to co-operate): .....(mls) ..... (%for age and height);

FEV 1: .....(mls) ..... (%for age and height)

Echocardiogram: Ejection Fraction: .....% or Fraction Shortening: .....%

Left ventricular hypertrophy (thickness): ..... Date .....

Valvular pathology: .....

Valvular stenosis/regurgitation (grade): .....

Opthalmological examination:

Corneal clouding Yes /No; Date .....

If patient able to co-operate then measure intraocular pressure ..... mm Hg, and

ERG ..... Date .....

VEP..... Date .....

Psychometric Testing:

Bayley Scale of Infant Development or Griffiths Mental Development Scale

WIPPSI: Full Scale .....; Verbal.....; Performance ..... Date: .....

WISC: Full Scale .....; Verbal.....; Performance..... Date: .....

(Please attach report)

Skeletal Survey including flexion and extension view of neck: Attach report

6 minute walk test:..... metres (if old enough)

Range of Movement of Joints:

	Normal	**Left**	**Right**
FOOT Dorsiflexion	**+20**		
Plantar flexion	**45**		
Inversion	**30**		
Eversion	**25**		

KNEE Flexion	**120-130**		
Extension	**0**		
HIP Flexion	**115-125**		
Extension	**-15**		
Abduction	**45**		
Adduction	**20-30**		
Internal Rotation	**30-45**		
External Rotation	**30-45**		
WRIST Flexion	**90**		
Extension	**70**		
Ulnar deviation	**35**		
Radial deviation	**25**		
ELBOWS Flexion	**145**		
Extension	**0**		
Pronation	**90**		
Supination	**90**		
SHOULDER Flexion	**180**		
Extension	**0**		
Abduction	**180**		
Internal rotation	**65-90**		
External rotation	**90**		
NECK Flexion	**45**		
Extension	**45**		
Rotation	**60-75**		
Lateral flexion	**45-60**		

Carpal Tunnel Syndrome: Yes [ ] Suspicious [ ] No [ ]

If suspicious: result of nerve conduction studies: Normal [ ] Abnormal [ ]

Hearing Test:

Date: ..... NORMAL [ ] ABNORMAL [ ]

If abnormal:

Sensorineural:

Max loss - Left ear: ..... Right ear: ..... Shape audiogram: .....

Conductive:

Max loss – Left ear: ..... Right ear: ..... Shape audiogram: .....

Neurological Examination:

Date	R Upper Limb	L Upper Limb	R Lower Limb	L Lower Limb
Reflexes				
Tone				
Power (?/5)				
Plantar				

Urinary GAGs (quantitative): ..... **gm/mol creat;** Date .....

SF-36 Health Survey /PedsQL™ Measurement Model Report attached Yes [ ] No [ ]

Surgery, if any: (date/ Procedure) .....

.....

Other Medical Problems: (date of onset/Problem/active or inactive)

.....

.....

Other medication:

.....

Compliant: Yes [ ] No [ ] Hypersensitivity: Yes [ ] No [ ]

Other comments: .....

.....

**** Please provide ciopies of skeletal radiography/sonography/MRI/other relevant reports/CD/ photos

APPENDIX F

MONITORING REQUIREMENT AND DATA SUBMISSION FORM FOR FABRY DISEASE

MONITORING REQUIREMENTS AND SUBMISSION FORM FOR FABRY DISEASE

Baseline and monitoring requirement (Fabry Disease)

	Baseline	6 monthly	12 - 24 monthly
Height/Weight	X	X	
Medical history[1]	X	X	
Physical examination[1]	X	X	
Blood pressure	X	X	
Serum Creatinine, blood urea and electrolytes	X	X	
Urinalysis	X	X	
24 hour urine for protein (or urine protein/creatinine ratio)	X	X	
GFR[2]	X	X	
Renal biopsy	X[3]		
Electrocardiogram	X	X	
Echocardiography	X		X
Eye examination	X		X
Audiology	X		X
MRI brain	X		**if required**
Pain, Quality of Life and Health-Related assessments: SF-36 Health Survey Brief Pain Inventory (Short Form) PedsQL™ Measurement Model	X	X	

[1]Clinical assessments focussed on the core Fabry related disease manifestations

[2]GFR can be estimated using equations such as the MDRD equation for adults and Schwartz formula for children

[3]If treated for renal indication

DATA SUBMISSION FORM (FABRY DISEASE)

Patient details:

Patient's name: .....

Date of birth: ..... IC Number: .....

Contact No:..... Gender: Male [ ] Female [ ]

Address .....

Doctor's details:

Doctor's name: .....

Phone number: ..... Fax number: .....

Hospital address: .....

Treatment details:

Has received ERT before: No [ ] Yes [ ]

If yes,

Date ERT started: .....

Product: .....

Dose: .....

Frequency: .....

Clinical data:

Confirmation of disease:

Enzyme Assay .....

Genotype .....

Histology.....

(Please attach a copy of the result for the initial submission)

Height: ..... cm (.....%)

Weight: ..... kg (.....%)

Blood pressure: Systolic: ..... Diastolic: .....

SF-36 Health Survey /PedsQL™ Measurement Model Report attached Yes [ ] No [ ]

Laboratory data *(Please provide serial results)*

Date				
Haemoglobin g/L				
Platelets $x10^9$/L				
White Cell Count $x10^9$/L				
Total Bilirubin µmol/L				
Alkaline Phosphatase u/L				
GGT u/L				
ALT u/L				
Total cholesterol mmol/L				
HDL-cholesterol				
LDL-cholesterol				
Triglyceride mmol/L				
Blood Urea mmol/L				
Plasma Creatinine µmol/L				
Proteinuria mg/24 hours				
Urine Alb:Cr ratio				
GFR (method) mL/min/1.73m²				

Cardiovascular findings

Hypertension: Yes: ..... No: ..... Date: .....

Echo:

Date: ..... Ventricular wall thickness: ..... mm

Other: .....

ECG:

Date: ..... Normal: ..... Abnormal: .....

PR interval: ..... mm

PQ interval (if available):

Other arrhythmia: .....

Stress test:

Date:..... Normal: ..... Abnormal: .....

Findings: .....

Cardiac MRI: Yes: ..... No: ..... Date: .....

Findings: .....

Cardiac Biopsy: Yes: ..... No: ..... Date: .....

Findings: .....

Electrophysiological Study: Yes: ..... No: ..... Date: .....

Findings:.....

History of arrythmia: Yes: ..... No: ..... Date of onset: .....

Type: .....

Treatment required: .....

History of acute myocardial infarction: Yes: .....No: ..... Date: .....

Investigations / Interventions: .....

Other cardiac event?: Yes: ..... No: ..... Date: .....

Findings: .....

Cerebrovascular findings

MRI date: ..... Location: .....

Findings: .....

Neurology

Clinical examination:

Sensory (Please tick)

Sensation	Normal	Abnormal	Sensory level (if abnormal)
Light touch			
Temperature			
Vibration			
Joint position sens			
Sweating			
Heat/cold tolerance			
Pain sensatio			

Other sensory abnormalities: .....

Motor examination/coordination

Test	Normal	Abnormal
Heel/toe		
Romberg		

Other gait/motor abnormalities: .....

Has this patient a history of transient ischemic attacks: Yes: ..... No: ..... Date: .....

Has this patient had a CVA: Yes: ..... No: ..... Date: .....

If yes, please provide details:

.....

Pain : Yes: ..... No: .....

If yes, Chronic: ..... Episodic: .....

Pain score: Brief Pain Inventory BPI– 9: .....

Vertigo : Yes: ..... No: .....

If yes, Chronic: ..... Episodic: .....

Hearing test:

Date: ..... Normal: ..... Abnormal: .....

Abnormalities : Left ear: .....

Right ear: .....

Renal findings

Dialysis : Yes: ..... No: ..... Date: .....

Renal transplant : Yes: .....No: ..... Date: .....

Other findings: .....

Lung function tests

	Result	Date
FEV1		
FVC		
VC		
FEF 50		
FEF 25-75		

Ophthalmic evaluation: .....

Gastrointestinal findings

Abdominal pain: Yes: .....No: .....

Diarrhoea: Yes: ..... No: ..... Details (include frequency):

Past medical history: .....

Previous medication: .....

Current medication: .....

Compliant: Yes [ ] No [ ] Hypersensitivity: Yes [ ] No [ ]

Other comments: .....

**** Please provide ciopies of skeletal radiography/sonography/MRI/other relevant reports/CD/ photos

APPENDIX G

SF-36 HEALTH SURVEY

SF-36 Health Survey

NAMA PESAKIT: …….....

NOMBOR KP: ……..... TARIKH LAHIR: …….....

HOSPITAL: …….....

NOMBOR PENDAFTARAN HOSPITAL: …….....

INSTRUCTIONS: This survey asks your views about your health. This information will help to keep track of how you feel and how well you are able to do your usual activities. Please answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. When you have completed, please return the questionnaire in the envelope provided.

1. In general, would you say your health is:

(circle one)

Excellent?	……..	1
Very good?	……	2
Good?	……	3
Fair?	……	4
Poor?	……	5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago.	……	1
Somewhat better than one year ago.	……	2

About the same as one year ago. ……. 3

Somewhat worse than one year ago. ……. 4

Much worse now than one year ago. ……. 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

Activities	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
Moderate activities, such as moving a table, pushing a, vacuum cleaner,bowling or playing golf	1	2	3
Lifting or carrying groceries	1	2	3
Climbing several flights of stairs	1	2	3
Climbing one flight of stairs	1	2	3
Bending, kneeling or stooping	1	2	3
Walking more than a mile [~1.5km]	1	2	3
Walking half a mile	1	2	3
Walking one hundred yards	1	2	3
Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Were limited in the kind of work or other activities	1	2
Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	Yes	No
Cut down on the amount of time you spent on work or other activities	1	2
Accomplished less than you would like	1	2
Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(circle one)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None	……	1
Very mild	……	2
Mild	……	3
Moderate	……	4
Severe	……	5
Very severe	……	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all	……	1
A little bit	……	2
Moderately	……	3
Quite a bit	……	4
Extremely	……	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	1	2	3	4	5	6
Have you been a very nervous person?	1	2	3	4	5	6
Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
Have you felt calm and peaceful?	1	2	3	4	5	6
Did you have a lot of energy?	1	2	3	4	5	6
Have you felt downhearted and low?	1	2	3	4	5	6
Did you feel worn out?	1	2	3	4	5	6
Have you been a happy person?	1	2	3	4	5	6
Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

(circle one)

All of the time …….. 1

Most of the time ……... 2

Some of the time ……... 3

A little of the time ……... 4

None of the time ……... 5

11. How TRUE or FALSE is each of the following statements to you?

(circle one number on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
I seem to get ill more easily than other people	1	2	3	4	5
I am as healthy as anybody I know	1	2	3	4	5
I expect my health to get worse	1	2	3	4	5
My health is excellent	1	2	3	4	5

APPENDIX H

GROSS MOTOR FUNCTION MEASURE (GMFM) SCORE SHEET

GROSS MOTOR FUNCTION MEASURE (GMFM) SCORE SHEET

(GMFM-88 and GMFM-66 scoring) Version 1.

Patient's Name: ……

Assessment Date: ……

Date of Birth: ……

Chronological Age: ……

Evaluator's Name: ……

GMFCS Level[1]: I [ ] II [ ] III [ ] IV [ ] V [ ]

Testing Conditions (eg, room, clothing, time, others present):

……

……

The GMFM is a standardized observational instrument designed and validated to measure change in gross motor function over time in children with cerebral palsy. The scoring key is meant to be a general guideline. However, most of the items have specific descriptors for each score. It is imperative that the guidelines contained in the manual be used for scoring each item.

SCORING KEY

0 = does not initiate

1 = initiates

2 = partially completes

3 = completes

NT = Not tested [used for the GMAE scoring*]

It is now important to differentiate a true score of "0" (child does not initiate) from an item which is Not Tested (NT) if you are interested in using the GMFM-66 Ability Estimator Software.

*The GMFM-66 Gross Motor Ability Estimator (GMAE) software is available with the GMFM manual (2002). The advantage of the software is the conversion of the ordinal scale into an interval scale. This will allow for a more accurate estimate of the child's ability and provide a measure that is equally responsive to change across the spectrum of ability levels. Items that are used in the calculation of the GMFM-66 score are shaded and identified with an asterisk (*). The GMFM-66 is only valid for use with children who have cerebral palsy.

[1] GMFCS level is a rating of severity of motor function. Definitions are found in Appendix I of the GMFM manual (2002).

Check (√) the appropriate score: if an item is not tested (NT), circle the item number in the right column

Item	A: LYING & ROLLING	SCORE				NT
1	SUP, HEAD IN MIDLINE: TURNS HEAD WITH EXTREMITIES SYMMETRICAL	0	1	2	3	1
*2	SUP: BRINGS HANDS TO MIDLINE, FINGERS ONE WITI H THE OTHER	0	1	2	3	2
3	SUP: LIFTS HEAD 45°	0	1	2	3	3
4	SUP: FLEXES R HIP AND KNEE THROUGH FULL RANGE	0	1	2	3	4
5	SUP: FLEXES L HIP AND KNEE THROUGH FULL RANGE	0	1	2	3	5
*6	SUP: REACHES OUT WITH R ARM, HAND CROSSES MIDLINE TOWARD TOY	0	1	2	3	6
*7	SUP: REACHES OUT WITH L ARM, HAND CROSSES MIDLINE TOWARD TOY	0	1	2	3	7
8	SUP: ROLLS TO PR OVER R SIDE	0	1	2	3	8
9	SUP: ROLLS TO PR OVER L SIDE	0	1	2	3	9
*10	PR: LIFTS HEAD UPRIGHT	0	1	2	3	10
11	PR ON FOREARMS: LIFTS HEAD UPRIGHT, ELBOWS EXT., CHEST RAISED	0	1	2	3	11
12	PR ON FOREARMS: WEIGHT ON R FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0	1	2	3	12
13	PR ON FOREARMS: WEIGHT ON L FOREARM, FULLY EXTENDS OPPOSITE ARM FORWARD	0	1	2	3	13
14	PR: ROLLS TO SUP OVER R SIDE	0	1	2	3	14
15	PR: ROLLS TO SUP OVER L SIDE	0	1	2	3	15
16	PR: PIVOTS TO R 90° USING EXTREMITIES	0	1	2	3	16
17	PR: PIVOTS TO L 90° USING EXTREMITIES	0	1	2	3	17
	TOTAL DIMENSION A					

Item	B: SITTING	SCORE				NT
*18	SUP, HANDS GRASPED BY EXAMINER: PULLS SELF TO SITTING WITH HEAD CONTROL	0	1	2	3	18
19	SUP: ROLLS TO R SIDE, ATTAINS SITTING	0	1	2	3	19
20	SUP: ROLLS TO L SIDE, ATTAINS SITTING	0	1	2	3	20
21	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD UPRIGHT, MAINTAINS 3 SECONDS	0	1	2	3	21
*22	SIT ON MAT, SUPPORTED AT THORAX BY THERAPIST: LIFTS HEAD MIDLINE, MAINTAINS 10 SECONDS	0	1	2	3	22
*23	SIT ON MAT, ARM(S) PROPPING: MAINTAINS, 5 SECONDS	0	1	2	3	23
*24	SIT ON MAT: MAINTAINS, ARMS FREE, 3 SECONDS	0	1	2	3	24
*25	SIT ON MAT WITH SMALL TOY IN FRONT: LEANS FORWARD, TOUCHES TOY, RE-ERECTS WITHOUT ARM PROPPING	0	1	2	3	25
*26	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S R SIDE, RETURNS TO START	0	1	2	3	26
*27	SIT ON MAT: TOUCHES TOY PLACED 45° BEHIND CHILD'S L SIDE, RETURNS TO START	0	1	2	3	27
28	R SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0	1	2	3	28
29	L SIDE SIT: MAINTAINS, ARMS FREE, 5 SECONDS	0	1	2	3	29
*30	SIT ON MAT: LOWERS TO PR WITH CONTROL	0	1	2	3	30
*31	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER R SIDE	0	1	2	3	31
*32	SIT ON MAT WITH FEET IN FRONT: ATTAINS 4 POINT OVER L SIDE	0	1	2	3	32
33	SIT ON MAT: PIVOTS 90°, WITHOUT ARMS ASSISTING	0	1	2	3	33
*34	SIT ON BENCH: MAINTAINS, ARMS AND FEET FREE, 10 SECONDS	0	1	2	3	34
*35	STD: ATTAINS SIT ON SMALL BENCH					35
*36	ON THE FLOOR: ATTAINS SIT ON SMALL BENCH	0	1	2	3	36
*37	ON THE FLOOR: ATTAINS SIT ON LARGE BENCH	0	0	2	3	37
	TOTAL DIMENSION B					

Item	C: CRAWLING & KNEELING	SCORE				NT
38	PR: CREEPS FORWARD 1.8m (6')	0	1	2	3	38
*39	4 POINT: MAINTAINS, WEIGHT ON HANDS AND KNEES, 10 SECONDS	0	1	2	3	39
*40	4 POINT: ATTAINS SIT ARMS FREE	0	1	2	3	40
*41	PR: ATTAINS 4 POINT, WEIGHT ON HANDS AND KNEES	0	1	2	3	41
*42	4 POINT: REACHES FORWARD WITH R ARM, HAND ABOVE SHOULDER LEVEL	0	1	2	3	42
*43	4 POINT: REACHES FORWARD WITH L ARM, HAND ABOVE SHOULDER LEVEL	0	1	2	3	43
*44	4 POINT: CRAWLS OR HITCHES FORWARD 1.8m (6')	0	1	2	3	44

*45	4 POINT: CRAWLS RECIPROCALLY FORWARD 1.8m (6')	0	1	2	3	45
*46	4 POINT: CRAWLS UP 4 STEPS ON HANDS AND KNEES/FEET	0	1	2	3	46
47	4 POINT: CRAWLS BACKWARDS DOWN 4 STEPS ON HANDS AND KNEES/FEET	0	1	2	3	47
*48	SIT ON MAT: ATTAINS HIGH KN USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS ..	0	1	2	3	48
49	HIGH KN: ATTAINS HALF KN ON R KNEE USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS	0	1	2	3	49
50	HIGH KN: ATTAINS HALF KN ON L KNEE USING ARMS, MAINTAINS, ARMS FREE, 10 SECONDS	0	1	2	3	50
*51	HIGH KN: KN WALKS FORWARD 10 STEPS, ARMS FREE	0	1	2	3	51
	TOTAL DIMENSION C					

Item D: STANDING SCORE NT

*52	ON THE FLOOR: PULLS TO STD AT LARGE BENCH	0	1	2	3	52
*53	STD: MAINTAINS, ARMS FREE, 3 SECONDS	0	1	2	3	53
*54	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND, LIFTS R FOOT, 3 SECONDS	0	1	2	3	54
*55	STD: HOLDING ON TO LARGE BENCH WITH ONE HAND, LIFTS L FOOT, 3 SECONDS	0	1	2	3	55
*56	STD: MAINTAINS, ARMS FREE, 20 SECONDS	0	1	2	3	56
*57	STD: LIFTS L FOOT, ARMS FREE, 10 SECONDS	0	1	2	3	57
*58	STD: LIFTS R FOOT, ARMS FREE, 10 SECONDS	0	1	2	3	58
*59	SIT ON SMALL BENCH: ATTAINS STD WITHOUT USING ARMS	0	1	2	3	59
*60	HIGH KN: ATTAINS STD THROUGH HALF KN ON R KNEE, WITHOUT USING ARMS	0	1	2	3	60
*61	HIGH KN: ATTAINS STD THROUGH HALF KN ON L KNEE, WITHOUT USING ARMS	0	1	2	3	61
*62	STD: LOWERS TO SIT ON FLOOR WITH CONTROL, ARMS FREE	0	1	2	3	62
*63	STD: ATTAINS SQUAT, ARMS FREE	0	1	2	3	63
*64	STD: PICKS UP OBJECT FROM FLOOR, ARMS FREE, RETURNS TO STAND	0	1	2	3	64
	TOTAL DIMENSION D					

Item	E: WALKING, RUNNING & JUMPING	SCORE				NT
*65	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO R.	0	1	2	3	65
*66	STD, 2 HANDS ON LARGE BENCH: CRUISES 5 STEPS TO L	0	1	2	3	66
*67	STD, 2 HANDS HELD: WALKS FORWARD 10 STEPS	0	1	2	3	67
*68	STD, 1 HAND HELD: WALKS FORWARD 10 STEPS	0	1	2	3	68
*69	STD: WALKS FORWARD 10 STEPS	0	1	2	3	69
*70	STD: WALKS FORWARD 10 STEPS, STOPS, TURNS 180°, RETURNS	0	1	2	3	70
*71	STD: WALKS BACKWARD 10 STEPS	0	1	2	3	71
*72	STD: WALKS FORWARD 10 STEPS, CARRYING A LARGE OBJECT WITH 2 HANDS	0	1	2	3	72
*73	STD: WALKS FORWARD 10 CONSECUTIVE STEPS BETWEEN PARALLEL LINES 20cm (8") APART	0	1	2	3	73
*74	STD: WALKS FORWARD 10 CONSECUTIVE STEPS ON A STRAIGHT LINE 2cm (3/4") WIDE	0	1	2	3	74
*75	STD: STEPS OVER STICK AT KNEE LEVEL, R FOOT LEADING	0	1	2	3	75
*76	STD: STEPS OVER STICK AT KNEE LEVEL, L FOOT LEADING	0	1	2	3	76
*77	STD: RUNS 4.5m (15'), STOPS & RETURNS	0	1	2	3	77
*78	STD: KICKS BALL WITH R FOOT	0	1	2	3	78
*79	STD: KICKS BALL WITH L FOOT	0	1	2	3	79
*80	STD: JUMPS 30cm (12") HIGH, BOTH FEET SIMULTANEOUSLY	0	1	2	3	80
*81	STD: JUMPS FORWARD 30 cm (12"), BOTH FEET SIMULTANEOUSLY	0	1	2	3	81
*82	STD ON R FOOT: HOPS ON R FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE					82
*83	STD ON L FOOT: HOPS ON L FOOT 10 TIMES WITHIN A 60cm (24") CIRCLE	0	1	2	3	83
*84	STD, HOLDING 1 RAIL: WALKS UP 4 STEPS, HOLDING 1 RAIL, ALTERNATING FEET	0	0	2	3	84
*85	STD, HOLDING 1 RAIL: WALKS DOWN 4 STEPS, HOLDING 1 RAIL, ALTERNATING FEET	0	1	2	3	85
*86	STD: WALKS UP 4 STEPS, ALTERNATING FEET	0	1	2	3	86
*87	STD: WALKS DOWN 4 STEPS, ALTERNATING FEET					87
*88	STD ON 15cm (6") STEP: JUMPS OFF, BOTH FEET SIMULTANEOUSLY	0	1	2	3	88
	TOTAL DIMENSION E					

Was this assessment indicative of this child's "regular" performance? YES[ ] NO[ ] COMMENTS:

.....

.....

.....

.....

.....

GMFM RAW SUMMARY SCORE

DIMENSION	CALCULATION OF DIMENSION % SCORES	GOAL AREA (indicated with √ check)
A. Lying & Rolling	Total Dimension A / 51 = _____ x 100% = _____ %	A.[ ]
B. Sitting	Total Dimension B / 60 = _____ x100% = _____ %	B.[ ]
C. Crawling & Kneeling	Total Dimension C / 42 = _____x100% = _____%	C.[ ]
D. Standing	Total Dimension D / 39 = _____ ´x100% = _____ %	D.[ ]
E. Walking, Running & Jumping	Total Dimension E / 72 = _____ x´100% =_____ %	E.[ ]

TOTAL SCORE = $\frac{\%A + \%B + \%C + \%D + \%E}{\text{Total \# of Dimensions}}$

= $\frac{+ \quad + \quad + \quad +}{5}$

= $\frac{\_\_\_\_\_}{5}$

= _____%

GOAL TOTAL SCORE = $\frac{\text{Sum of \% scores for each dimension identified as a goal area}}{\text{\# of Goal areas}}$

= %

APPENDIX I

BRIEF PAIN INVENTORY (SHORT FORM)

Brief Pain Inventory (Short Form)

Patient's Name: ……

Patient's IC: ……

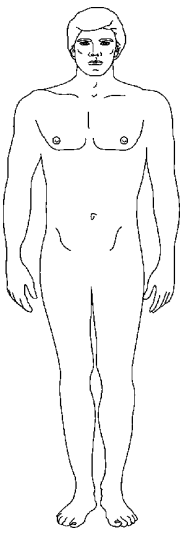
Date completed: ……

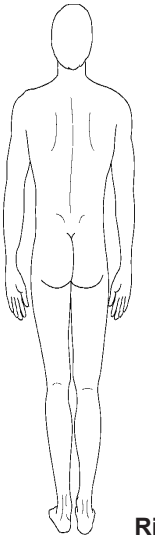
1. **Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?**

   Yes [ ] No [ ]

2. **On the diagram, shade in the areas where you feel pain. Put an "X" on the area that hurts the most.**

Front **Back**





Right **Left** **Left** **Right**

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No Pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells you how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

……

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No Relief Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely Interfere

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interfere

APPENDIX J

MRC SCALE FOR ASSESSMENT OF MUSCLE POWER

MRC SCALE FOR ASSESSMENT OF MUSCLE POWER

Each muscle group is graded as follows:

0 - no movement

1 - flicker is perceptible in the muscle

2 - movement only if gravity eliminated

3 - can move limb against gravity

4 - can move against gravity & some resistance exerted by examiner

5 - normal power

MODIFIED WALTER GARDNER MEDWIN SCORE

Grade 0 = Pre-Clinical. All activities.

Grade 1 = Walks normally. Unable to run freely.

Grade 2 = Detectable defect in posture or gait. Climbs stairs without using banister.

Grade 3 = Detectable defect in posture or gait. Climbs stairs only with banisters.

Grade 4 = Walks without assistance. Unable to climb stairs.

Grade 5 = Walks normally. Unable to rise from chair.

Grade 6 = Walks only with callipers or other aids.

Grade 7 = Unable to walk. Sits erect in a chair. Able to roll wheelchair and eat and drink normally.

Grade 8 = Sits unsupported in a chair. Unable to roll wheelchair or unable to drink from a glass unassisted.

Grade 9 = Unable to sit erect without support or unable to eat or drink without assistance.

Grade 10 = Confined to bed. Requires help for all activities.

ARM FUNCTION TEST

Grade 1 = Starting with arms at sides, the patient is capable to abduct the arms in a full circle until the handbacks touch above the head.

Grade 2 = Can raise arms above only by flexing the elbow (i.e., shortening the circumference of the movement) or using accessory muscles.

Grade 3 = Cannot raise hands above head but can raise an 8 oz. glass/cup of water to mouth (using both hands if necessary). When raising glass to mouth, the patient may not lower his head to reach the glass.

Grade 4 = Can raise hands to mouth but cannot raise an 8 oz. glass/cup of water to mouth.

Nothing = Cannot raise hands to mouth at all.

DRAFTING COMMITTEE

ADVISOR

Y.Bhg Dato' Dr Azmi Shapie
Director
Medical Development Division
Ministry of Health

AUTHORS

Dr Keng Wee Teik
Consultant Clinical Geneticist
Kuala Lumpur Hospital

Professor Dr Thong Meow Keong
Consultant Clinical Geneticist
University Malaya Medical Centre

Dr Ngu Lock Hock
Consultant Clinical Geneticist
Kuala Lumpur Hospital

Associate Professor Zarina Abd Latif
Consultant Clinical Geneticist
National University of Malaysia Medical Centre

Dr Rowani Mohd Rawi
Consultant Clinical Geneticist
Hospital University Science Malaysia

SECRETARIAT

Dr Noor Aziah Zainal Abidin
Senior Principal Assistant Director
O & G /Pediatric Services Division
Medical Development Division
Ministry of Health

Dr Jafanita Jamaludin
Principal Assistant Director
O & G /Pediatric Services Division
Medical Development Division
Ministry of Health

ACKNOWLEDGEMENT

Medical Services Development Section would like to express our gratitude and appreciation to :-

Y.Bhg. Datuk Dr. Noor Hisham bin Abdullah, Deputy Director General of Health (Medical) and Y.Bhg. Dato' Dr. Azmi bin Shapie, Director of Medical Development Division, Ministry of Health Malaysia for their continuing support and services rendered;

All members of the committee for their contributions in drawing up the guideline;

And last but not least to all those who provided valuable input and feedback to make this publication a success.

Medical Development Division

Block E1, Parcel E, Federal Government Administrative Centre,
62590 Putrajaya, Malaysia.
(T) 603-8883 1047 (F) 603-8883 1427

Kementerian Kesihatan Malaysia
(Ministry of Health

http://www.moh.gov.my