Health Policy and Technology 8 (2019) 14–23

Contents lists available at ScienceDirect

Health Policy and Technology

journal homepage: www.elsevier.com/locate/hlpt

Enzymatic replacement therapy for lysosomal storage disorders: Drug evaluations review in Spain

Josep Darbà[a,*], Meritxell Ascanio[b]

[a] Department of Economics, Universitat de Barcelona, Diagonal 696, Barcelona 08034, Spain
[b] BCN Health Economics & Outcomes Research S.L., Barcelona, Spain

ARTICLE INFO

Article history:
Available online 15 February 2019

Keywords:
Lysosomal storage disorders
Mucopolysaccharidosis
Gaucher disease
Pompe disease
Fabry disease
Enzymatic replacement therapy

ABSTRACT

Introduction: In the European Union companies only need to demonstrate that the risk-benefit balance of the new drug is favourable to obtain the authorization to sell new drugs. Hence a comparison with available treatments, a cost-effectiveness analysis and the place in the therapy of the new drug are not required. Therefore, it is necessary to carry out these analyses in an additional study. In Spain there is no national government agency, which conducts a centralized evaluation and makes decisions on funding and are the Pharmacy and Therapeutics committees that take mandatory decisions for the entire region.
Objectives: To identify all drug assessments and health technology assessment reports of the enzymatic replacement treatments for the four LSD considered in this study, including Mucopolysaccharidosis (MPS), Gaucher, Fabry and Pompe disease at the national, regional and hospital level; and to summarize the efficacy in terms of outcome measures, adverse events, economic impact and final recommendations and indicate potential improvements.
Methods: 19 reviews at the regional and hospital level and one therapeutic positioning report at national level for MPS were considered for this.
Results: In general, the drugs evaluated in LSD have proved to be effective in the most frequent clinical forms of disease. However, there are clinical phenotypes that still do not have available an effective treatment.
Conclusions: It is expected that new therapies, such as intrathecal therapies or gene therapy could be evaluated in the different types of LSD demonstrating positive effects, especially in the previous phenotypes.

Introduction

More than 50 rare metabolic disorders caused by the accumulation of non-degraded substrates in lysosomes due to an enzymatic defect are considered lysosomal storage diseases (LSDs) [1]. The specific LSDs considered in this review are mucopolysaccharidosis (MPS) [2,3], Gaucher disease [4,5], Pompe disease [6,7] and Fabry disease [8,9] which involve the accumulation of glycosaminoglycans, glucocerebrosides, glycogen and sphingolipids, respectively. Although most of the above mentioned diseases are autosomal recessively inherited, a fraction of them, such as Fabry disease and MPS type II, follow an X-linked recessive inheritance. Current treatment of LSDs in Spain is mostly centred on enzymatic replacement therapy (ERT).

In order to authorize the sale of a new drug in the European Economic Area (EEA), pharmaceutical companies are not required to provide evidence of the cost-effectiveness or place in the treatment of the drug [10]. A positive resolution can be obtained from national institutions or from the European Medicines Agency (EMA) through the risk-benefit balance of the therapy studied [11,12].

This being the case, and due to the fact that most of the drugs that are available in Spain are funded by the public health service, further studies need to be developed to determine the drug's place in therapy and cost-effectiveness [13].

Health institutions and Pharmacy and Therapeutics Committees (PTCs) in distinct regions of Spain carry out drug evaluations and decision-making at the regional level. The results are described in Health Technology Assessment (HTA) reports containing specific recommendations, which may or may not be followed by hospital and prescribers [14].

The PTCs specifically evaluate those drugs that are dispensed by the hospital pharmacy service or are administered directly to patients. The used drugs are selected by means of phamacoeconomic, efficacy, efficiency and safety relevance in comparison to the

* Corresponding author.
E-mail address: darba@ub.edu (J. Darbà).

https://doi.org/10.1016/j.hlpt.2019.02.004
2211-8837/

Table 1
Drugs assessed for the treatment of LSDs.

Name of the drug	Active substance	Pharmaceutical laboratory	Authorization date	Drug assessment reports
VIMIZIM® 1 mg/ml concentrate for solution for infusion	**Elosulfase alfa**	Biomarin Europe Limited	23-03-15	2016 – AEMPS
CEREZYME® (200;400) u powder for concentrate for solution for infusion	**Imiglucerase**	Genzyme Europe, Bv	01-06-98	2013 – CAMUH 2011 – CAMUH
VPRIV® 400 u powder for concentrate for solution for infusion	**Velaglucerase**	Shire Pharmaceuticals Ireland Limited	28-10-10	2011 – CAMUH
ZAVESCA® 100 mg, hard capsules	**Miglustat**	Actelion Registration Limited	18-03-03	2011 – CAMUH 2004 – HU Virgen del Rocío
ALDURAZYME®, 100 U/ml concentrate for solution for infusion	**Laronidase**	Genzyme Europe, Bv	24-06-03	2010 – Genesis group 2010 – CAMUH 2009 – AIAQS 2005 – HU Virgen del Rocío
REPLAGAL® 1 mg/ml concentrate for solution for infusion	**Agalsidase alfa**	Shire Human Genetic Therapies Ab	11-02-02	2012 – CAMUH 2008 – Hospital Morales Meseguer
FABRAZYME® (5; 35) mg powder concentrate for solution for infusion	**Agalsidase beta**	Genzyme Europe, Bv	31-08-01	2012 – CAMUH 2008 – Hospital Morales Meseguer
MYOZYME® 50 mg powder concentrate for solution for infusion	**Alglucosidase alfa**	Genzyme Europe, Bv	26-04-06	2012 – AETSA 2011 – CAMUH
ELAPRASE® 2 mg/ml concentrate for solution for infusion	**Idursulfase**	Shire Human Genetic Therapies Ab	08-02-07	2010 – CAMUH 2009 – AIAQS
NAGLAZYME® 1 mg/ml concentrate for solution for infusion	**Galsulfase**	Biomarin Europe Ltd	19-06-06	2010 – CAMUH 2009 – AIAQS

AEMPS Spanish agency of medicines and health products, *CAMUH* Committee for the Evaluation of Medicines for Hospital Utilization, *HU* Universitary Hospital, *AIAQS* Agency of information, evaluation and quality in health, *AETSA* andalucian agency of evaluation of health technology.

alternative drugs in the market and included in the hospital formulary [15].

Additionally, the Spanish Agency of Medicines and Health Products (AEMPS), which is associated to the national health ministry implements baseline evaluations regarding effectiveness, appropriate use and efficiency of the therapeutics according to legislation and carries out budget management and standardization at a national level. This information is displayed in Therapeutic Positioning Reports (TPR).

This study has two different objectives: (1) to identify all drug assessments and health technology assessment (HTA) reports of the current treatment for the four LSD considered in this study, including Mucopolysaccharidosis (MPS), Gaucher disease, Fabry disease and Pompe disease at the national, regional and hospital level; (2) to summarize the efficacy in terms of outcome measures, adverse events, economic impact and final report recommendations and indicate potential improvements.

Material and methods

Health technology assessments (HTA) and therapeutic positioning reports (TPR) published since 2004 were obtained from two different sources, GENESIS [16], a group of evaluation of novelties, standardization and research in drug selection, belonging to the Spanish Society of Hospital Pharmacy, and AEMPS [17], the Spanish Agency of Medicines and Health Products, respectively. A database was constructed in order to analyse and summarize parameters of interest by means of an indirect comparison.

The reports included in this analysis assess the current ERT for treatment of LSD except for one report assessing substrate reduction therapy (SRT) for Gaucher type I disease. The final selected reports correspond to a total of 20 national therapeutic positioning reports and reviews at the regional and hospital level. Specifically, 8 for MPS [18–24], 5 for Gaucher disease [25–28], 4 for Fabry disease [29–31] and 2 for Pompe disease [32,33].

The following parameters were extracted from the reports: agency or hospital where the report has been written, drug name, active ingredient, drug presentations, posology and administration form, pharmaceutical company that commercializes the drug, price, report publication date, evaluated indication, Anatomical Therapeutic Chemical classification (ATC) code, Randomized controlled trial (RTC) methodology, RCTs comparators, primary outcomes measures, secondary outcomes measures, efficacy measures results, adverse events, report conclusions and recommendations.

Results

The reports included in this analysis assess the current treatment of LSD. These correspond to 20 reviews at the regional and hospital level (Table 1).

Review of ERT evaluated in MPS

1) Elosulfase alfa (VIMIZIM®)

Elosulfase alfa has been evaluated as an ERT for the long term in patients diagnosed with MPS type IV A in patients of all ages (Table 2). Considering the efficacy and safety results and according to the report conclusions, the treatment of MPS type IV A with elosulfase alfa has proved to improve the functional capacity, based on the distance walked in the six-minute walking test in comparison with placebo, over a period of 24 weeks. Elosulfase alfa is generally well-tolerated among patients although it is important to control reactions related with infusion, anaphylactic reactions and development of antibodies against treatment.

Table 2
Parameter summary regarding elosulfase alfa for the treatment of MPS.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of mucopolysaccharidosis (MPS) type IV A in patients of all ages	**Posology** 2 mg/kg of body weight, administered once per week during infusion of 4 h **Administration form** Intravenous infusion	**Efficacy** • Distance walked in the six-minute walk test (TM6M) • Other measures: Number of steps walked up in 3 min (3MSC), Reduction of GAG in urine, functional respiratory tests and quality of life **Safety** Headache, nausea, vomiting, dyspnea, pyrexia, dizziness, chills and abdominal pain, development of antibodies against treatment **Cost** NA	Treatment of MPS type IV A with elosulfase alfa has demonstrated to improve the functional capacity, based on the distance walked in the TM6M in comparison with placebo, over a period of 24 weeks. Elosulfase alfa is generally well-tolerated among patients although it is important to control reactions related with infusion, anaphylactic reactions and development of antibodies against treatment.	It is recommended to control periodically the possible presence of antibodies anti-elosulfase alfa to corroborate if they are affecting the therapeutic efficacy, especially in those patients with lack of response. Moreover, treatment with elosulfase alfa should be revaluated when: Patients do not respond according to mobility/respiratory/cardiovascular parameters and quality of life. Absence of improvement in TM6M after 1-year treatment and/or progression of bone affection that leads to the need of wheelchair in those patients in whom treatment has been initiated by criteria of impairment of mobility. In case of recurrent anaphylactic reaction, not easily controllable with usual medication.

The therapeutic positioning recommendations suggest controlling periodically the possible presence of antibodies anti-elosulfase alfa to corroborate if they are affecting the therapeutic efficacy. Moreover, treatment with elosulfase alfa should be re-evaluated when: (1) patients do not respond according to mobility, respiratory and cardiovascular parameters and quality of life; (2) absence of improvement in six-minute walking test after 1-year treatment and/or progression of bone affection that leads to the need of wheelchair in those patients in whom treatment has been initiated by criteria of impairment mobility; (3) in case of recurrent anaphylactic reaction, not easily controllable with usual medication.

2) Laronidase (ALDURAZYME®)

Laronidase, an ERT, has been assessed for the long term in patients diagnosed with MPS type I (Table 3). According to the report conclusions and considering the efficacy and safety results, laronidase has shown to improve the respiratory function and physical capacity in comparison with placebo, over a period of 26 weeks. Moreover, the efficacy outcomes suggest that patients treated with laronidase present a decrease in hepatic volume and urinary glycosaminoglycans (GAG) concentration. These efficacy results are estimated to remain stable in the long term.

The therapeutic positioning recommendations suggest treatment with laronidase in patients who are: (1) <2 years with normal cognitive function and attenuated phenotype; (2) <2 years with normal cognitive function and severe physical impairment, as a previous treatment to HSCT; (3) <2 years with cognitive impairment; (4) >2 years without cognitive impairment; (5) >2 years with cognitive impairment, as palliative treatment.

3) Galsulfase (NAGLAZYME®)

Galsulfase has been evaluated as ERT for the long term in patients diagnosed with MPS type IV (Table 4). According to the efficacy and safety results and considering the report conclusions, galsulfase has proved to increase the resistance of patients based on the measures of the distance walked in 12-minute walking test and the number of steps walked up in 3 min in comparison with placebo. Moreover, the efficacy outcomes suggest a significant decrease in urinary GAG concentration in patients treated with galsulfase and an improvement of pain and joint stiffness based on quality of life parameters.

The therapeutic positioning recommendations suggest treatment with galsulfase as an alternative therapeutic option to conventional treatment of MPS type IV. Given the safety profile of galsulfase, it is recommended to control patients during infusion due to the possible onset of anaphylactic reactions.

4) Idursulfase (ELAPRASE®)

Idursulfase has been assessed as an ERT for the long term in patients diagnosed with MPS type II (Table 5). Bearing the efficacy and safety results in mind and in accordance with the report conclusions, idursulfase has shown to enhance the resistance and the respiratory capacity of patients based on the combined variable analysed in comparison with placebo. Besides, the efficacy outcomes indicate that produces a significant reduction of the GAG concentration in urine, as well as contributes to decrease organomegaly.

The therapeutic positioning recommendations suggest treatment with idursulfase as an alternative therapeutic option to conventional treatment of MPS type II.

Review of ERT evaluated in Gaucher disease

1) Imiglucerase (CEREZYME®)

Imiglucerase, an ERT, has been evaluated for the long term in patients diagnosed with type I Gaucher disease. Imiglucerase is also approved for treatment of type III Gaucher disease in patients who present non-neurologic manifestations that are clinically significant (Table 6). According to the efficacy and safety results and taking the report conclusions into consideration, imiglucerase has proved comparable results in terms of efficacy with regard to alglucerase, by increasing haemoglobin concentration and platelet count as well as reducing hepatic and splenic volumes. These efficacy outcomes are estimated to be stable in the long term. Furthermore, different studies suggest that the clinical response obtained

Table 3
Parameter summary regarding laronidase for the treatment of MPS.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of mucopolysaccharidosis (MPS) type I	**Posology** 100UI/kg of body weight, administered once per week during infusion of 3–4 h **Administration form** Intravenous infusion	**Efficacy** • Distance walked in the six-minute walk test (TM6M) • Forced vital capacity (FVC) -% of predicted • Other measures: Hepatomegaly, GAG concentration in urine, apnea/hypoapnea and joint mobility **Safety** Reactions related to infusion, cough, diarrhea, vomiting, fever, abdominal, development of antibodies against treatment **Cost** Annual treatment cost	Treatment of MPS type I with laronidase has demonstrated to improve the respiratory function and physical capacity in comparison with placebo, over a period of 26 weeks. Moreover, the efficacy outcomes suggest that patients treated with laronidase present a decrease in hepatic volume and urinary GAG concentration. These efficacy results are estimated to remain stable in the long term, except for the variable FVC. The most frequent adverse events attributed to laronidase are reactions associated with the drug administration and development of antibodies. Finally, the annual cost of treatment with laronidase is estimated at 153.660 - 576.342 € (body weight 18–80 kg), EUR 2010.	Treatment with laronidase is recommended in patients who: <2 years with normal cognitive function and attenuated phenotype <2 years with normal cognitive function and severe physical impairment, as a previous treatment to HSCT <2 years with cognitive impairment >2 years without cognitive impairment >2 years with cognitive impairment, as palliative treatment Finally, it is recommended to evaluate clinical response every 6 months and interruption of treatment should be considered in case of neurologic affection, whereas must be definitely interrupted when an increment of GAG in urine is >2*normal superior limit of this parameter or in case of osteoarticular/cardiac impairment.

GAG Glycosaminoglycan, *HSCT* hematopoietic stem cell transplant.

Table 4
Parameter summary regarding galsulfase for the treatment of MPS.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of mucopolysaccharidosis (MPS) type VI	**Posology** 1 mg/kg of body weight, administered every week during infusion of 4 h **Administration form** Intravenous infusion	**Efficacy** • Distance walked in 12 min walk test (TM12M) • Other measures: Number of steps walked up in 3 min (3MSC), urinary excretion of GAG concentration, pain and joint stiffness and respiratory/cardiac/visual function **Safety** Pyrexia, arthralgia and headache, abdominal pain, earaches, vomiting, development of antibodies against treatment **Cost** Annual treatment cost	Treatment of MPS type VI with galsulfase has demonstrated to improve the resistance of patients based on the measures of TM12M and 3MSC in comparison with placebo, over a period of 24 weeks. Moreover, the efficacy outcomes suggest a significant decrease in urinary GAG concentration in patients treated with galsulfase and an improvement of pain and joint stiffness based on quality of life parameters. The most frequent adverse events attributed to galsulfase are reactions associated with the drug administration and development of antibodies. Finally, the annual cost of treatment with galsulfase is estimated at 234.000 - 1.248.000 € (body weight 18–80 kg), EUR 2011.	Treatment with galsulfase is recommended as an alternative therapeutic option to conventional treatment of MPS type VI. Given the safety profile of galsulfase, it is recommended to control patients during infusion due to the possible onset of anaphylactoid reactions.

GAG Glycosaminoglycan.

from this treatment is not different from that obtained in patients with Gaucher type III.

The therapeutic positioning recommendations suggest treatment with imiglucerase in paediatric population with diagnostic of disease at this age, except in Gaucher type II disease.

2) Velaglucerase (VPRIV®)

Velaglucerase has been assessed as ERT for the long term in patients diagnosed with type I Gaucher (Table 7). In accordance with the efficacy and safety results and bearing the report conclusions in mind, velaglucerase has shown comparable re-

Table 5
Parameter summary regarding idursulfase for the treatment of MPS.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of mucopolysaccharidosis (MPS) type II	**Posology** 0,5 mg/kg of body weight, administered every week during infusion of 1–3 h **Administration form** Intravenous infusion	**Efficacy** • Combined variable (TM6M-FVC): sum of ranges of the change of the score of the six-minute walk test (TM6M) and the % of predicted Forced vital capacity (FVC) • Other measures: TM6M, FVC -% of predicted, excretion of GAG in urine, splenomegaly, articular mobility and left ventricular mass **Safety** Fever, headache, cough, pharyngitis, upper respiratory infections, nasal congestion, nausea and vomiting, abdominal pain, diarrhea and development of antibodies **Cost** Annual treatment cost	Treatment of MPS type II with idursulfase has demonstrated to improve the resistance and the respiratory capacity of patients based on the combined variable analyzed in comparison with placebo, over a period of 53 weeks. Moreover, the efficacy outcomes indicate that produces a significant reduction of the GAG concentration in urine, as well as contributes to decrease organomegaly. The most frequent adverse events attributed to idursulfase are reactions associated with the drug administration and development of antibodies. Finally, the annual cost of treatment with idursulfase is estimated at 292.000–1.022.000 € (body weight 18–80 kg), EUR 2010.	Treatment with idursulfase is recommended as an alternative therapeutic option to conventional treatment of MPS type II.

GAG Glycosaminoglycan.

Table 6
Parameter summary regarding imiglucerase for the treatment of Gaucher disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of type I Gaucher. Imiglucerase is also approved for treatment of type III Gaucher disease in patients who present non-neurologic manifestations clinically significant (anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly)	**Posology** 60 units/kg, administered every 2 weeks **Administration form** Intravenous infusion	**Efficacy** Platelet count, hemoglobin concentration, hepatomegaly and splenomegaly **Safety** Headache, rhinopharyngitis, bone pain, arthralgia, pyrexia, dizziness and development of antibodies **Cost** Annual treatment cost	Treatment of type I Gaucher disease with imiglucerase has demonstrated comparable results in terms of efficacy with regard to alglucerase, by increasing hemoglobin concentration and platelet count as well as reducing hepatic and splenic volumes, over a period of 9 months. These efficacy outcomes are estimated to be stable in the long term. Moreover, different studies suggest that the clinical response obtained from this treatment is not different from that obtained in patients with Gaucher type III. The safety profile of imiglucerase is comparable to velaglucerase, while it is estimated to induce less antibodies in comparison with alglucerase. Finally, the annual cost of treatment with imiglucerase is estimated at 27.947–279.469 € (body weight 5–50 kg), EUR 2013.	Treatment with imiglucerase is recommended in treatment of pediatric population with diagnostic of disease at this age, except in Gauche type II disease.

sults in terms of efficacy with regard to imiglucerase, by increasing haemoglobin concentration and platelet count as well as reducing hepatic and splenic volumes. These efficacy outcomes are estimated to be stable in the long term even if the dose is reduced a 50%.

The therapeutic positioning recommendations suggest that given the similar efficacy and safety profile of velaglucerase and imiglucerase, the selection of treatment between both drug formulations should take into account efficiency criteria.

3) Miglustat (ZAVESCA®)

Miglustat has been evaluated as a SRT for the long term under exceptional conditions in patients diagnosed with mild or moderate type I Gaucher disease who cannot or do not wish to receive ERT. Miglustat is also approved for paediatric and adult patients with Niemann–Pick type C disease (Table 8). Considering the efficacy and safety results and according to the report conclusions, miglustat as a maintenance therapy has only shown slight changes in organomegaly and hematologic parameters after an evaluation of 6 and 12 months. Moreover, it was found that the change of treatment from imiglucerase or miglustat + imiglucerase to miglustat as monotherapy resulted in a reduction of the platelet count. These results indicate that miglustat may be less effective than treatment with ERT.

The therapeutic positioning recommendations suggest the use of miglustat as a first choice drug in the following cases: (1) naive patients when ERT is contraindicated due to hypersensitivity or impossibility of intravenous use; (2) refractory patients or intoler-

Table 7
Parameter summary regarding velaglucerase for the treatment of Gaucher disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of type I Gaucher	**Posology** 60 units/kg, administered every 2 weeks **Administration form** Intravenous infusion	**Efficacy** • Change in hemoglobin concentration from baseline to week 41 • Change in hemoglobin concentration from baseline to month 12 • Other measures: Platelet count, hepatomegaly and splenomegaly, biochemical markers (CCL 18 and chitotriosidase concentration), quality of life (SF-36) **Safety** Headache, rhinopharyngitis, bone pain, arthralgia, pyrexia, dizziness and development of antibodies **Cost** Annual treatment cost	Treatment of type I Gaucher disease with velaglucerase has demonstrated comparable results in terms of efficacy with regard to imiglucerase, by increasing hemoglobin concentration and platelet count as well as reducing hepatic and splenic volumes, over a period of 9 months. This efficacy outcomes are estimated to be stable in the long term even if the dose is reduced a 50%. Velaglucerase presents a comparable safety profile to imiglucerase, although is estimated to induce less antibodies, in comparison with imiglucerase. This profile is estimated to be kept in the long term. Finally, the annual cost of treatment with velaglucerase is estimated at 174.001–464.004 € (body weight 30–80 kg), EUR 2011.	Given the similar efficacy and safety profile of velaglucerase and imiglucerase, the selection of treatment between both drug formulations should take into account efficiency criteria.

Table 8
Parameter summary regarding miglustat for the treatment of Gaucher disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Substrate reduction therapy (SRT) for the long term under exceptional conditions in patients with confirmed diagnostic of mild or moderate type I Gaucher disease who cannot or do not wish to receive Enzyme replacement therapy (ERT). Miglustat is also approved for pediatric and adult patients with Niemann-Pick disease type C.	**Posology** 100 mg administered three times per day. Dose can be reduced to 100 mg once or twice per day in case of diarrhea **Administration form** Oral route	**Efficacy** Platelet count, change in hemoglobin concentration, hepatomegaly, splenomegaly and quitotriosidase activity **Safety** Diarrhea, weight loss, flatulence, abdominal pain, tremor, headache, nausea and dizziness **Cost** Annual treatment cost	Treatment of type I Gaucher disease with miglustat as a maintenance therapy has only demonstrated slight changes in organomegaly and hematologic parameters after an evaluation of 6 and 12 months. Moreover, it was found that the change of treatment from imiglucerase or miglustat+imiglucerase to miglustat as monotherapy resulted in a reduction of the platelet count. These results indicate that miglustat may be less effective than treatment with ERT. The most frequent adverse events attributed to miglustat are gastrointestinal disorders and even neurologic events can appear (neuropathy). Finally, the annual cost of treatment with miglustat is estimated at 78.420 €, EUR 2011.	The use of miglustat is recommended as a first-choice drug in the following cases: Naive patients when ERT is contraindicated due to hypersensitivity or impossibility of intravenous use Refractory patients or intolerant to ERT Patients well-controlled in previous treatment with ERT, in whom it is decided to change treatment to miglustat as monotherapy due to the improvements in quality of life associated with the oral treatment. By contrast, miglustat is not recommended in patients with severe disease. Finally, the combined use of ERT + miglustat is not recommended either.

ant to ERT; (3) patients well-controlled in previous treatment with ERT, in whom it is decided to change treatment to miglustat as monotherapy due to the improvements in quality of life associated with the oral treatment.

Review of ERT evaluated in Fabry disease

1) Agalsidase alfa (REPLAGAL®)

Agalsidase, an ERT; has been evaluated alfa for the long term in patients diagnosed with Fabry disease (Table 9). According to the efficacy and safety results and considering the report conclusions, agalsidase alfa has shown to reduce the neuropathic pain of maximum intensity and also the cardiac deposits of globotriaosylceramide (GL3) in comparison with placebo. It has been found also a reduction in left ventricular hypertrophy. Moreover, it has been found that agalsidase alfa slightly differs in terms of efficacy from agalsidase beta, considering that both have proved to stabilize disease progression, especially with regards to the renal function.

The therapeutic positioning recommendations suggest that given the similar efficacy and safety profile of agalsidase alfa and agalsidase beta, the selection of treatment between both drug formulations should take into account efficiency criteria.

2) Agalsidase beta (FABRAZYME®)

Table 9
Parameter summary regarding agalsidase alfa for the treatment of Fabry disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of Fabry disease	**Posology** 0,2 mg/kg of body weight, administered in alternate weeks during infusion of 40 min **Administration form** Intravenous infusion	**Efficacy** • Neuropathic pain of maximum intensity without special medication for pain according with the Brief Pain Inventory (BPI) questionnaire • Cardiac GL3 levels • Other measures: severity of pain, quality of life, renal function from the BPI questionnaire, GL3 concentrations in plasma, urinary and renal biopsies, cardiac conduction, mass and left ventricular function **Safety** Headache, flu-like symptoms, back pain, paresthesia, pain, neuralgia, nausea, hyperkinesia, abdominal pain, diarrhea, diaphoresis, pharyngitis and development of antibodies **Cost** Annual treatment cost	Treatment of Fabry disease with agalsidase alfa has demonstrated to reduce the neuropathic pain of maximum intensity and also the cardiac deposits of GL3 in comparison with placebo, over a period of 24 weeks. It has been found also a reduction in left ventricular hypertrophy. Moreover, it has been found that agalsidase alfa slightly differs in terms of efficacy from agalsidase beta, considering that both have demonstrated to stabilize disease progression, especially with regards to the renal function. The most frequent adverse events attributed to agalsidase alfa are reactions associated with the drug administration and development of antibodies against treatment. Finally, the annual cost of treatment with agalsidase alfa (body weight 30–70 kg) is estimated at 77.644–155.289 €, EUR 2012.	Given the similar efficacy and safety profile of agalsidase alfa and agalsidase beta, the selection of treatment between both drug formulations should take into account efficiency criteria.

Table 10
Parameter summary regarding agalsidase beta for the treatment of Fabry disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of Fabry disease	**Posology** 1 mg/kg of body weight, administered every 2 weeks during infusion of 4 h **Administration form** Intravenous infusion	**Efficacy** • Proportion of patients free of GL3 deposits in capillary endothelium of kidneys • Time until first clinically relevant event (renal, cardiovascular, cerebrovascular or death) • Other measures: GL3 deposits in kidney, heart and skin, change of GL3 concentration in kidney and urine, change in score of pain from questionnaire McGill, serum creatinine, proteinuria, albumin and creatinine ratio in urine…etc. **Safety** Fever, chills, pyrexia and cold sensation, headache, paresthesia, nausea, vomiting, pyrexia and development of antibodies **Cost** Annual treatment cost	Treatment of Fabry disease with agalsidase beta has demonstrated to clear the GL3 deposits in capillary endothelium of kidneys as well as to reduce these levels in heart and skin in comparison with placebo, over a period of 20 weeks. It has been found also a reduction in left ventricular hypertrophy. Moreover, therapy with agalsidase beta slows progression of clinical results of renal/cardiac/ cerebrovascular complications and death, based on a long term analysis of 30–36 months. The most frequent adverse events attributed to agalsidase beta are reactions associated with the drug administration and development of antibodies against treatment (higher incidence than with agalsidase alfa). Finally, the annual cost of treatment with agalsidase beta (body weight 30–70 kg) is estimated at 77.654–155.308 €, EUR 2012.	Given the similar efficacy and safety profile of agalsidase alfa and agalsidase beta, the selection of treatment between both drug formulations should take into account efficiency criteria.

Agalsidase beta has been evaluated as ERT for the long term in patients diagnosed with Fabry disease (Table 10). Considering the efficacy and safety results and according to the report conclusions, agalsidase beta has proved to clear the GL3 deposits in capillary endothelium of kidneys as well as to reduce these levels in heart and skin in comparison with placebo. A reduction in left ventricular hypertrophy has also been found. In addition, therapy with agalsidase beta slows progression of clinical results of renal, cardiac and cerebrovascular complications and death, based on a long term analysis of 30–36 months.

The therapeutic positioning recommendations suggest that given the similar efficacy and safety profile of agalsidase beta and agalsidase alfa, the selection of treatment between both drug formulations should take into account efficiency criteria.

Table 11
Parameter summary regarding alglucosidase alfa for the treatment of Pompe disease.

Indication	Posology and administration	Parameters evaluated	Therapeutic positioning	
			Conclusions	Recommendations
Enzyme replacement therapy (ERT) for the long term in patients with confirmed diagnostic of Pompe disease in adult patients and pediatric population	**Posology** 20 mg/kg of body weight, administered once every 2 weeks **Administration form** Intravenous infusion	**Efficacy** • Distance walked in the six-minute walk test (TM6M) • Forced vital capacity (FVC) -% of predicted • Other measures: score in the quantitative muscle testing of arms and legs (% of predicted), maximum inspiratory pressure (% of predicted), maximum expiratory pressure (% of predicted), Physical Component Summary (PCS) of the Short Form-36 Health Survey (SF-36) **Safety** Falls, nasopharyngitis, headaches, reactions associated with perfusion, hypoacusis, diarrhea, arthritis, pain at limbs and development of antibodies **Cost** Annual treatment cost	Treatment of late-onset Pompe disease with alglucosidase alfa has demonstrated to improve with a modest efficacy the functional capacity and to stabilize lung function, based on the variables of TM6M and FVC in comparison with placebo, over a period of 78 weeks. Moreover, the efficacy outcomes suggest that this drug is more effective in the subgroups of patients with mild or moderate disease (defined as distance walked in TM6M at the beginning of treatment of $\geq$ 300 m and/or predicted FVC of at least 55%). It is worth mentioning that the maximum benefit of treatment has been observed during the first 26 weeks and afterwards the efficacy is stabilized. Alglucosidase alfa is generally well-tolerated, although anaphylactic reactions potentially mortal can appear. Finally, the annual cost of treatment with alglucosidase alfa (body weight 70 kg) is estimated at 366.912 €, EUR 2014.	Given the efficacy profile of alglucosidase alfa, it is estimated that the objective of treatment is prevention of loss tissue and muscular function. Therefore, patients in advanced stages of disease who present an irreversible affection of fibres and muscular tissues and with that a limited repair capability of the impaired tissues, they cannot have benefit from treatment with alglucosidase alfa. Moreover, the safety profile of alglucosidase alfa should be evaluated in the long term in order to control the possible anaphylactic reactions potentially mortal.

Review of ERT evaluated in Pompe disease

1) Alglucosidase alfa (MYOZYME®)

Alglucosidase alfa has been evaluated as ERT for the long term in adult and paediatric patients diagnosed with Pompe disease (Table 11). Taking into account the efficacy and safety results and considering the report conclusions, alglucosidase alfa has shown to improve with a modest efficacy the functional capacity. Alglucosidase alfa has also proved to stabilize lung function, based on the variables of six-minute walking test and FVC in comparison with placebo, over a period of 78 weeks. Besides, the efficacy outcomes suggest that this drug is more effective in the subgroups of patients with mild or moderate disease. It is worth mentioning that the maximum benefit of treatment has been observed during the first 26 weeks and afterwards the efficacy is stabilized.

The therapeutic positioning recommendations suggest that given the efficacy profile of alglucosidase alfa, it is estimated that the objective of treatment is prevention of loss tissue and muscular function. Therefore, patients in advanced stages of disease who present an irreversible affection of fibres and muscular tissues and with a limited repair capability of the impaired tissues cannot have benefit from treatment with alglucosidase alfa. Moreover, the safety profile of alglucosidase alfa should be evaluated in the long term in order to control the possible anaphylactic reactions potentially mortal.

Discussion

In order to enhance decision-making and accurate recommendations and indications, future drug assessments should be able to present further evidence regarding cost-effectiveness and place in treatment. To do so, new studies should be carried out and should include direct comparisons regarding alternative current therapies and more significant or clinically relevant outcome measures. Real world data studies regarding the use of therapeutics would add value to reports and would be useful in terms of recommendations updates.

Further, in order to speed up access to new drugs, new alternatives are being explored by the EU. The adaptive pathway reduces the access time of the orphan drug by approving it for a specific patient subgroup with a high unmet medical need and after that the indication is widened to a larger patient population [34]. Moreover, HTA reports are involved early in the process. Thus, the development of new and improved disease registries that can produce robust evidence is highly needed.

Conclusions

The evaluation reports of ERT have drawn conclusions about its efficacy in treatment for the four different LSD considered in this study. However, it is difficult to determine exactly its clinical effect, considering that LSD diseases are related to a progressive organ and tissue involvement that causes heterogeneous clinical symptoms.

In patients with MPS, galsulfase, laronidase and idursulfase have shown to improve the resistance and respiratory capacity and the last two, to reduce the GAG concentration in urine and organomegaly in the short term. Less robust data has been found for elosulfase alfa, whose benefit is based on the six-minute walking test results.

In patients with Gaucher disease type I, imiglucerase and velaglucerase have shown increasing haemoglobin concentration and platelet count as well as reducing hepatic and splenic volumes in the short and long term. Miglustat has only proved slight changes in organomegaly and hematologic parameters as well as a minor efficacy in comparison with ERT.

In patients with Fabry disease, agalsidase alfa and beta have shown similar efficacy in reduction of the cardiac deposits of GL3 and the left ventricular hypertrophy and stabilization of renal function, in the short term. Agalsidase beta also reduces the GL3 levels in kidney and skin and can slow the progression to renal, cardiac and cerebrovascular complications and death, based on a long-term analysis [22].

In patients with late-onset Pompe disease, alglucosidase alfa has proved to improve the functional capacity and to stabilize lung function with modest efficacy. An analysis per subgroups indicates there is a higher efficacy in patients with mild or moderate disease.

Regarding the safety profile of the ERT evaluated in LSD, the main adverse events are reactions associated with the administration of the drug and the development of antibodies against treatment. In the case of SRT, adverse reactions are more related to gastrointestinal disorders and neurologic events.

Regarding the economic impact of the evaluated drugs, it is estimated these are very expensive treatments, highlighting that idursulfase and galsulfase are two of the most expensive drugs. Taking into consideration the high cost of these treatments, in addition to a lack of evidence on the impact in quality of life and evolving of neurologic disease, it would be necessary to define the conditions of indication of these drugs, based on a group of experts.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Author statements

JD analysed and interpreted the drug assessment reports regarding the enzymatic replacement therapy considered in this study and was involved in drafting the manuscript and revising it critically for important intellectual content and gave final approval of the version to be published. MA analysed and interpreted the drug assessment reports regarding the enzymatic replacement therapy considered in this study and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Annu Rev Med 2015;66:471–86.
[2] Dalmau J, Guillén E, Pérez J, Couce ML, González L, Aldamíz L. Guía para el manejo de las MPS. Madrid, Spain: Ergon; 2015.
[3] Aguirre Rodríguez FJ, Aldámiz-Echevarría Azuara L, Dalmau Serra J, et al. Guía clínica de la mucopolisacaridosis tipo i (MPS i). Barcelona, Spain: Mayo; 2014.
[4] Giraldo P, Pocoví M. Guía de actuación en pacientes con enfermedad de Gaucher. Zaragoza, Spain: FEETEG; 2011.
[5] Baldellou A, Dalmau J, Sanjurjo P. Guía clínica para el diagnóstico, tratamiento y seguimiento de la enfermedad de Gaucher en la infancia. *Acta Pediatr* Esp 2006;64:175–80.
[6] Pascual-Pascual SI, Nascimento A, Fernández-Llamazares CM, et al. Guía clínica de la enfermedad de Pompe infantil. Rev Neurol 2016;63(6):269–79.
[7] Barba-Romero MA, Barrot E, Bautista-Lorite J, et al. Guía clínica de la enfermedad de Pompe de inicio tardío. Rev Neurol 2012;54:497–507.
[8] García de Lorenzo A. Consensus for the study and treatment of Fabry disease. GETER foundation. Med Clin (Barc) 2011;137(4):178–83.
[9] Grupo para el Estudio y Tratamiento de la Enfermedad de Fabry (GETEF). Guía clínica para el Estudio y Tratamiento de la Enfermedad de Fabry. Enfermedades raras 2005.
[10] European Medicines Agency (EMA). European Medicines Agency (EMA)–About us 2018 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/08/WC500211862.pdf.
[11] European Parliament Council of the European Union. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Text with EEA relevance). Offic J L 2004;136.
[12] AEMPS. Cómo se regulan los medicamentos y productos sanitarios en España; 2017. How are medicines and health products regulated in Spain? https://www.aemps.gob.es/publicaciones/publica/regulacion_med-PS/v2/docs/reg_med-PS-v2-light.pdf.
[13] Álvarez JS. Utilidad terapéutica y social de los medicamentos: ¿cómo evaluarla y cuantificarla?. Therapeutic and social usefulness of medicines: how can it be evaluated and quantified? Medicina Clínica 2009;132(3).
[14] GENESIS Grup. Normativas sobre selección de medicamentos y Comissiones de Farmacia y Terapéutica en comunidades autónomas [Regulation for medicine selection and FTCs in autonomous communities] https://gruposdetrabajo.sefh.es/genesis/index.php?option=com_content&view=article&id=51&Itemid=30.
[15] Lozano-Blázquez A, Calvo-Pita C, Carbajales-Álvarez M, Suárez-Gil P, Martínez–Martínez F, Calleja-Hernández MÁ. Drug assessment by a Pharmacy and Therapeutics committee: from drug selection criteria to use in clinical practice. Dovepress 2011:10.
[16] GENESIS website. http://gruposdetrabajo.sefh.es/genesis/genesis/Enlaces/InformesHosp_abc.htm.
[17] AEMPS website. https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/home.htm.
[18] Real JM, Palomo P, García-Jiménez MCGenesis Group. Laronidasa en Mucopolisacaridosis tipo I 2010 http://www.sefh.es/sefhgrupotrabajo/gt-acceso-genesis.php?file=Laronidasa_HUMS_10_2010.doc.
[19] AIAQS. Tratamiento de sustitución enzimática en pacientes con mucopolisacaridosis I, II y VI 2009 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2011/pdf/mucopolisacaridosis_enzim_pcsns09_aiaqs2011.pdf.
[20] CAMUH. Galsulfasa (Naglazyme®) per al tractament de la mucopolisacaridosi VI 2010 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2010/pdf/galsulfasa_mucopolisacaridosivi_aatrm2010ca.pdf.
[21] CAMUH. Idursulfasa (Elaprase®) per al tractament de la mucopolisacaridosi II 2010 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2010/pdf/idursulfasa_mucopolisacaridosi_aatrm2010ca.pdf.
[22] CAMUH. Laronidasa (Aldurazyme®) per al tractament de la mucopolisacaridosi I 2010 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2010/pdf/laronidasa_mucopolisacaridosi_aatrm2010ca.pdf.
[23] Hospital Virgen del Rocío. Informe sobre laronidasa en el tratamiento de mucopolisacaridosis I 2005 http://gruposdetrabajo.sefh.es/genesis/genesis/Documents/laronidasa_huvr_10_05.doc.
[24] AEMPS. Informe de Posicionamiento Terapéutico de elosulfasa alfa (Vimizim®) 2016 https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-elosulfasa-alfa-Vimizim-Mucopolisacaridosis.pdf.
[25] CAMUH. Imiglucerasa en pacients amb malaltia de Gaucher tipus III. 2013 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2013/pdf/imiglucerasa_gaucher_aiaqs2013ca.pdf.
[26] CAMUH. Tractament de substitució enzimàtica per a pacients amb malaltia de Gaucher tipus I 2011 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2011/pdf/tse_gaucher_imivelaglucerasa_aiaqs2011ca.pdf.
[27] CAMUH. Miglustat (Zavesca®) per a pacients amb malaltia de Gaucher tipus I 2018 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2011/pdf/miglustat_gaucher_aiaqs2011ca.pdf.
[28] Hospital Virgen del Rocío. Informe sobre miglustat en el tratamiento de la enfermedad de Gaucher tipo I. (2004). gruposdetrabajo.sefh.es/genesis/genesis/Documents/miglustat_hvr_05_04.doc.
[29] CAMUH. Agalsidasa alfa (Replagal®) i agalsidasa beta (Fabrazyme®) per al tractament de pacients amb malaltia de Fabry 2012 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2012/pdf/agalsidasa_alfa_beta_fabry_aiaqs2012.pdf.
[30] Hospital Morales Meseguer. Agalsidasa alfa y beta en la Enfermedad de Fabry 2008 http://gruposdetrabajo.sefh.es/genesis/genesis/Documents/Agalsidasa_HMM_1208.doc.

[31] Schiffmann R, Ries M, Timmons M, Flaherty JT, Brady RO. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. Nephrol Dial Transplant 2006;21:345–54.
[32] AETSA. Alglucosidasa alfa (Myozyme®) en enfermedad de Pompe de comienzo tardío 2012 http://www.juntadeandalucia.es/salud/servicios/contenidos/nuevaaetsa/up/AETSA_3_2012_Alglucosidasa_Pompe.pdf.
[33] CAMUH. Alglucosidasa alfa (Myozyme®) per al tractament de pacients amb formes tardanes de la malaltia de Pompe 2011 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2011/pdf/alglucosidasa_alfa_pompe_aiaqs2011ca.pdf.
[34] Adaptive Pathways. European Medicines Agency 2016 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp.