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Force Majeure: Therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease ☆

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ABSTRACT

Gaucher disease is the first lysosomal disorder for which clinically effective enzyme replacement therapy has been introduced. Lifelong treatment with imiglucerase, the recombinant glucocerebrosidase manufactured by the Genzyme Corporation (MA, USA), is administered intravenously — usually at biweekly intervals. An acute shortage of imiglucerase (to 20% of prior global supply) has occurred as a result of viral contamination of the production facility; production was halted, and a full supply of imiglucerase is not anticipated until January 2010. An urgent meeting of physicians, researchers, and patients was convened through the agency of the European Working Group for Gaucher Disease; this was instigated by patients internationally represented by the European Gaucher Alliance. Here we present a position statement based on the findings of the group, with key recommendations about identification and monitoring of at-risk patients threatened by the abrupt withdrawal of treatment, the equitable distribution of residual imiglucerase — and access to alternative treatments including those that have completed phase III clinical trials but have not yet been licensed.

Abbreviations: CEAP, Cerezyme Emergency Access Program; ECAP, European Cerezyme Access Program; EGA, European Gaucher Alliance; EMEA, European Medicines Agency; ERT, enzyme replacement therapy; EWGGD, European Working Group on Gaucher Disease; ESGLD, European Study Group on Lysosomal Diseases; FDA, Food and Drug Administration; GD, Gaucher disease; h-GCD, human cell-derived glucocerebrosidase (velaglucerase); ICGG, International Collaborative Gaucher Group; MPS II, mucopolysaccharidosis type II, Hunter disease; NP-C disease, Niemann-Pick disease type C; pr-GCD, plant-cell derived human glucocerebrosidase (taliglucerase); SRT, substrate reduction therapy.

☆ A position statement by the European Working Group on Gaucher Disease (EWGGD) and European Gaucher Alliance (EGA).

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Introduction

Gaucher disease is one of the most frequent lysosomal storage disorders in man. The disorder is caused by deficient activity of the enzyme glucocerebrosidase (EC 321.45) [1,2], for which therapeutic augmentation has proved to be highly effective. Gaucher disease is clinically heterogeneous [3,4]. Often classified operationally into three principal subtypes, the condition mainly affects the macrophage system [5]. Visceromegaly and cytopenias as well as disabling bone disease characterize type I disease. In contrast, manifestations in the central nervous system define the neuronopathic forms of Gaucher disease: type II disease, the acute and rapidly fatal form and type III disease with a more attenuated neurological course [5].

Treatment with enzyme replacement therapy (ERT) was initially developed using placentas as a resource and later using recombinant technology [6–8]. This enzyme, imiglucerase, manufactured by Genzyme Corp, MA, USA, has become available in 1994 and currently more than 1700 patients are being treated in Europe, parts of the Middle East and North Africa. ERT requires an apparent lifelong treatment with regular infusions. This therapy has shown to be extremely beneficial, resulting in normalization of blood counts, reductions in spleen and liver sizes, and improvement in bone symptoms [6–8]. So far ERT with imiglucerase is the only registered enzyme. Two new enzyme preparations are at the final stages of development programs: velaglucerase (h-GCB, Shire Human genetic Therapies, MA, USA) and taliglucerase (pr-GCD, Protalix Biotherapeutics, Carmiel, Israel [9,10]). Substrate reduction therapy (miglustat, Actelion therapeutics) is an oral treatment registered for Gaucher disease and indicated for mild to moderately affected adult patients for whom enzyme replacement therapy is not suitable (EMEA) or not a therapeutic option (FDA) [11].

In June 2009, Genzyme identified a virus (vesivirus 2117) in one of six bioreactors at the Allston manufacturing facility. The consequence of this infection is that it impairs the viability of the non-human Chinese Hamster Ovary (CHO) cells used to produce imiglucerase. Genzyme reported that this virus is not known to cause disease in humans. To clear the infection and restore full production rapidly, Genzyme temporarily suspended the manufacture of imiglucerase — a cessation that has caused a severe shortage of imiglucerase worldwide. At the end of June, the EMEA informed physicians in Europe of a temporary shortage of imiglucerase, which was expected to last for only a few weeks and with a reduction of supply to approximately 60% of normal [12]. This estimate was based on the assumption that most imiglucerase hypothecated to "work-in-process" (WIP) at the time of that their plant was shutdown would become available for distribution. However, by early August, it became clear that 80% of this WIP material would not to be released for further processing. Two lots were eventually found to be safe for further use, resulting in a worldwide availability of only 20% of the original amount of enzyme until the end of the year.

Given this *force majeure*, only a minority of patients with Gaucher disease can continue to receive treatment. The clinical implications of a temporary interruption of treatment are not easy to predict. Gaucher disease is heterogeneous; some patients have rapidly progressive disease, especially in childhood, while others may remain stable without treatment for decades. The consequences of treatment interruptions have only been documented in small groups of patients [13–18]. In summary, some of these patients remained stable up to 47 months, but progression of the disease at variable rates has also been reported. In many adult patients, interruption of therapy did not cause immediate reversal of the achieved therapeutic effects (i.e., within weeks). Perhaps the most important overall conclusion is that clinical deterioration may or may not occur when enzyme therapy is interrupted but on the basis of current knowledge, which patient will suffer a deterioration, if any, and to what extent, cannot be predicted.

In the United States, a Cerezyme Stakeholders Working Group consisting of physicians, patients, and Genzyme representatives was installed in response to this emergency. The group set out guidelines for the protection of the most vulnerable patients [19]. In addition, it should be noted that in early July, the FDA has contacted both Shire and Protalix about the possibility of initiating a treatment protocol for use of their phase III drugs at the time of imiglucerase shortage, and accordingly, two new protocols have been approved (NCT00954460 and NCT00962260, respectively).

Table 1
Revised recommendations for Cerezyme (EMEA questions and answers document [20] issued on August 14, 2009).

For Cerezyme, priority is given to infants, children and adolescents, and adults with severe, life-threatening disease progression:
A. Infants, children, and adolescents should receive Cerezyme at a reduced dose or at a reduced infusion frequency. However, no patient should be treated at a dose lower than 15 U/kg body weight every 2 weeks, or alternative treatment should be considered.
B. Adult patients with severe, life-threatening disease progression should receive Cerezyme at a reduced dose or at a reduced infusion frequency. However, no patient should be treated at a dose lower than 15 U/kg every 4 weeks, or alternative treatment should be considered.
C. In adult patients without severe, life-threatening disease progression, alternative treatment such as miglustat should be considered or treatment should be interrupted.
D. Adults who demonstrate progression to severe, life-threatening disease should re-initiate treatment with Cerezyme.

To protect the interests of Gaucher patients most at risk from complications, in Europe, the EMEA released guidelines at the end of June and revised these by mid-August. These guidelines are shown in Table 1 [20]. Although the distribution of vulnerable patients is not equal among the different European and affiliated countries, Genzyme initially had to decide to allocate 20% of previously ordered enzyme to each of these countries. The European and affiliated countries are summarized in Table 2. Following the EMEA guidance and management by Genzyme, concerns arose within the Gaucher community as to the equity of distribution, identification of patients at risk and their monitoring — as well as the potential access to alternative and emerging treatments. To address these concerns, a professional meeting of stakeholders in Europe was organized rapidly, the results of which are reported here.

Methods

Under the initiative of the European Gaucher Alliance (EGA), representing the interests of patients with Gaucher disease in Europe and several affiliated nations, including Israel, expert physicians, patient representatives, and laboratory experts met under the auspices of the European Working Group on Gaucher Disease (EWGGD, a daughter of the European Study Group on Lysosomal Diseases (ESGLD)). Pharmaceutical companies (Genzyme, Protalix, Shire, and Actelion) were

Table 2
Clusters of countries that comprise the European area, North Africa, and the Middle East.

Included Countries
Nordic–Benelux:
• Benelux: Netherlands, Belgium, Luxembourg
• Nordics: Sweden, Norway, Finland, Denmark, Iceland
UK–Ireland
France: includes North Africa (Algeria, Morocco, Tunisia)
Central Europe:
• Germany, Switzerland
• North Central Europe: Poland, Estonia, Lithuania, Latvia
• South Central Europe: Austria, Hungary, Czech Republic, Croatia, Slovakia, Slovenia
• Other Eastern European countries are included in Eurasian region
South Europe: Italy, Spain, Portugal, Greece, Israel, Turkey, and Middle East

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invited during a separate session to present their view on the crisis. The meeting was convened independently at Bad Honnef, Germany, on September 10, 2009, prior to the meeting of the ESGLD and supported in part by the ASIM (Arbeitsgemeinschaft für angeborene Stoffwechselstörungen in der Inneren Medizin), the German Working Group on Inborn Metabolic Errors in Metabolism in Adults.

Key representatives of pharmaceutical companies were invited to clarify their position in relation to the crisis of supply. The following issues were considered in depth:

Imiglucerase supply: what is the current status of treatment continuation and interruption in Europe an affiliated countries?
EMEA guidelines: how can the EMEA guidelines be translated into clinical practice, including the definition of severe, life-threatening disease progression in adults and what would be the lowest acceptable dose for those at risk?
Harmonization: how can equitable distribution of imiglucerase for all patients in this area be achieved?
Monitoring: how would patients be monitored on low-dose/alternative treatments or during cessation?
Use of miglustat: what is the therapeutic position of miglustat in this crisis?
Access to unlicensed treatments: since the companies Protalix and Shire inform us about opportunities for expanded access use of their enzymes (taliglucerase and velaglucerase, respectively) before licensing, how can this be managed and by what means can consolidated applications for patients with urgent need be made?

Results and discussion

Imiglucerase supply

What is the current status of treatment continuation and interruption?

According to recent data from the Gaucher Registry, Europe and affiliated countries (see Table 2) represent more than 35% of all patients treated with imiglucerase worldwide. All participants were asked to collect and present data on the number of patients treated with imiglucerase before the shortage and the composition of this population with respect to number of children and type III patients. Also the number of patients who were forced to reduce their dose significantly or had to interrupt treatment was recorded. Table 3 summarizes the data from this inventory, which include the numbers provided for each of the countries represented during the meeting. According to data from the International Collaborative Group on Gaucher Disease (ICGG), this table represents 85% of patients treated in these regions. All participants were asked to clarify the emerging therapeutic position in their country of domain.

In *France*, The Comité d'Evaluation du Traitement de la maladie de Gaucher (CETG) has translated the current EMEA criteria into a French recommendation. Monthly meetings of this committee are scheduled. More than 100 physicians are involved, and an independent national registry has been set up. Of the 240 patients previously on imiglucerase treatment, 163 interrupt treatment, while 73 patients reduce their dose and 4 patients remain on the original dose. Use of miglustat is proposed or discussed for 21 patients. There is no current need for additional imiglucerase in France to support patients at high risk, but it is felt that about 20 patients will be eligible for inclusion in an expanded access program for alternative therapeutic enzymes close to registration (involved companies Shire Human Genetic Therapies, USA, and Protalix, Israel).

In *Israel*, It is estimated that approximately 250 patients are on ERT and 50 patients are considered to be in the high-risk group. These are children (age<18 years), pregnant women and type III patients≥18 years (only 2 patients). The high-risk group receives imiglucerase as before. Others enter a 3-month drug interruption with complete blood count (CBC) done at baseline and at 3 months. Patients unwilling to stop ERT or experiencing acute medical problems are offered a switch-over protocol to taliglucerase (pr-GCD). It is emphasized that also for open-access protocols, the local institutional review board (IRB) has to be consulted. There has been a request for Shire's enzyme (velaglucerase).

In the *Czech Republic*, 31 Gaucher patients are known. Of those, 23 were treated with ERT including one type III patient. Five patients were treated with miglustat. Presently, 2 children and the type III patients are at unchanged dose. Three type I GD patients have switched to miglustat, and in the remaining 17, the dose of the enzyme was reduced to 15 mg/kg per month. Current stocks of imiglucerase will allow treatment at the reduced dose for about

Table 3
Distribution of types and ages of Gaucher disease patients among European and affiliated countries and current status of imiglucerase supply based upon information by the local physician or researcher.

	Total number of living Gaucher disease patients	On ERT	On SRT	Children[a]	Type III	Drug interruption or significant dose reduction	Data provided by[b]
France	530	240	25	39	10	240	NB
Israel	>800	250[c]	0	30	2	200	AZ
Czech Republic	31	23	5	2	1	17	MH
Italy	unknown	224[c]	4	39	18	71	BB, MR
Spain	324	170	40	25	10	140	PG
Greece	99	51[c]	3	11	6	unknown	HM
Germany	300	250[c]	unknown	40	10	200	EM
Poland		54	0	13	17	20	ATS
Portugal		80[c]	4	2	0	80	MCSM
United Kingdom		232	<20	39	unknown	200	PD, TC
The Netherlands		59	4	8	4	46	CH, LD
Hungary	25	23	unknown	4	unknown	19	[d]
Eastern European Countries[e]	Unknown	77	unknown	33		44	SF[e]
		1732		271	78	1277	

[a] Type III patients are mainly children, but not all.
[b] Initials of names are as indicated in author list.
[c] Number of treated patients is an estimation.
[d] This was kindly received by e-mail from Prof. L. Marodi.
[e] These numbers refer to patients within the European Cerezyme Access Program (ECAP) who receive their therapy through charitable supply of imiglucerase by Genzyme. Data were provided by Selena Freisens from Genzyme.

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3 weeks, after that the treatment will be interrupted. There is a centralized coordination for the distribution in the Czech Republic.

In *Italy*, there are a total of 224 imiglucerase-treated patients of whom 39 are children. Eighteen patients have type III GD. In some Italian regions, large stocks of enzyme are available for the next months and local re-distribution is discussed. Treatment has been interrupted in 70 patients, none of whom are children or have severe life-threatening comorbidity. Notwithstanding, of these 70 patients, some have active bone disease.

In *Greece*, there are 99 patients known to have Gaucher disease. Of these, 82 are type I, 11 type II, and 6 are type III. Fifty-one patients have been receiving ERT, but there is no exact information on how many patients have interrupted treatment or had their therapy reduced significantly. Nonetheless it is believed that none of the children will have dose restrictions. Three patients currently receive treatment with miglustat.

In *Spain* 170 patients are on treatment with imiglucerase and 40 receive miglustat. Twenty-five of the 170 patients are children, and 10 patients are type III patients. Current stocks of imiglucerase are minimal. Rules have been formulated by a national task force for guaranteeing access to imiglucerase for the most severely affected patients, but 140 patients have had their dose reduced or have interrupted therapy. Recommendations for monitoring have been formulated; accordingly, check-ups every 2 months in the respective local hospitals are planned.

In the *United Kingdom and Ireland*, 232 patients are treated with enzyme replacement therapy. Among these, 39 are children. Patients receiving treatment by home infusions have diminishing and variable stocks. Currently, most adult type I patients are on dose reduction or have stopped therapy. Given that the UK is a region where enzyme dosages have historically tended to be conservative, about 20 adult patients receive an unchanged dose or a dose reduced by about 50%. Patients have been offered miglustat. There is a restricted need to allocate additional drug to support high-risk patients at the moment. Although for a number of patients, use of either velaglucerase or taliglucerase is an option that will be vigorously pursued, access to non-licensed drugs raises logistical problems, since many patients receive treatment at home and the degree of supervision ethically required for administering an unlicensed agent would preclude delivery of the drug in the domicillary environment.

In *Germany*, there are about 250 patients on ERT, including 30 type I children who are currently receiving imiglucerase reduced to 50% of their original dose. Ten type III children continue on a 50%–100% dose according to age and three type III adults have switched to low dose in combination with miglustat. Some adult cases with complications remain on ERT, but a further reduction or interruption is expected in 200 patients during the coming months. A substantial number of these patients had recent bone complications and disease progression following prior dose reductions.

In *Poland*, a total of 54 patients receive imiglucerase. A large proportion of these patients (17 of the 54) are children with type III disease. Because of extra stock, resulting from dose reductions and savings, most patients can remain on treatment at a reduced dose. Type III children can maintain their original dose. There is a centralized coordination for the distribution in Poland.

In *Portugal*, there are 80 type I GD patients on therapy with imiglucerase of 110 diagnosed patients. Four patients receive miglustat. Very few patients have type II, and no patients have type III disease. Two type I children need to be treated immediately and are currently not receiving enzyme. Allocation of enzyme to Portugal is needed, since there is no residual stock available. There is a committee for the centralized coordinated distribution of imiglucerase.

In *Netherlands*, of 59 patients on imiglucerase treatment, 8 children (4 type III) were maintained at a 50% reduced dose as well as 5 adults identified to belong to the high-risk group. The remaining 46 patients have either interrupted treatment or had a significant dose reduction. Oral therapy with miglustat is initiated in 2–3 patients. It is felt that for a number of patients, use of either velaglucerase or taliglucerase can be an option.

Eastern European Countries. The Eastern European Cerezyme Access Program is a charitable initiative by Genzyme, to supply free imiglucerase to patients with GD in these countries. Most of these countries lack financial resources to reimburse therapy, although some governments can pay for a limited amount of patients. Here, 77 patients with generally more severe disease compared to patients in the Western European countries, including 33 children, are receiving imiglucerase therapy. The patients are particularly vulnerable because of the relatively high proportion of severely affected individuals, the high number of children, the shorter duration of therapy, and the incapability to access alternative treatments. During discussions with the supervising ECAP board, extra imiglucerase has become available from postponed earlier shipments, which allows all children to be treated at 50% of their initial dose and all adults at 15 U/kg every other week until December.

In summary, the current inventory shows that most patients who are expected to be at the immediate risk to experience complications from treatment interruption will remain on imiglucerase treatment, albeit at a reduced dose. On the other hand, Table 3 clearly shows that out of >1700 patients on ERT, around 80% will experience a substantial dose reduction or cessation of therapy. It was felt during meeting that around 15%–20% of these patients might become at risk for complications and that alternative treatments should be explored.

EMEA guidelines

How can the EMEA guidelines be translated into clinical practice, including the definition of severe, life-threatening disease progression in adults and what would be the lowest acceptable dose for those at risk?

As indicated above, EMEA provided guidelines for the definition of the most vulnerable patients (Table 2). These guidelines were discussed. Although there was general agreement that priority should be given to infants, children and adolescents, and adults with severe, life-threatening disease progression, the definition of the latter group of patients is insufficient for clinical practice. Also, the recommendations for dose reduction are not optimal; a dose of 15 U/kg per 2 weeks for infants, children, and adolescents may be sufficient for the less affected, but certainly not for the more severely affected patients. Also, the proposed 15 U/kg every 4 weeks for adults makes no sense. There is only evidence for some efficacy in the case of such dose administered at high frequency, i.e., 1.15 U/kg three times a week [21]. To adopt this historic protocol in the current situation is unpractical and this monthly dose at a 2- or 4-week interval is probably not effective. It was thus proposed to maintain infants, children, and adolescents at 50% of their dose and adults at high risk at a minimum of 15 U/kg every 2 weeks, either covered by local supplies or through an application for treatment from an emergency supply of imiglucerase pooled from diverse sources (see below).

In a plenary session, the group then discussed the criteria for being at “high risk” for the development of complications from Gaucher disease. These criteria are summarized in Table 4.

Harmonization

How can equitable distribution of imiglucerase for all patients in this area be achieved?

There was agreement at the meeting that equity was not guaranteed by an equal distribution of 20% of previously ordered enzyme to each of the countries/country clusters. It was also acknowledged that Genzyme could not require to direct a more justifiable distribution. The inequity is based upon the following

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Table 4
Criteria that identify patients at high risk for the development of progressive disease or complications.

A. Infants, children, adolescents	
B. Adult patients (either type I or III) with:	– Exacerbation of disease while on dose reduction/dose interruption – Platelet count <20.000/μl – Thrombocytopenia and bleeding – Symptomatic anemia – Severe comorbidity requiring imiglucerase treatment, such as: 1. Need for chemotherapy 2. Condition that puts a patient at risk for bleeding, e.g., cirrhosis, major surgery, that cannot be postponed for 3–6 months 3. Lung disease caused by Gaucher cell infiltration 4. New acute bone event during last 12 months
C. Pregnant women with symptomatic Gaucher disease	

differences between countries: (1) numbers of children, (2) numbers of type III patients, (3) dosing — some countries prescribing higher doses than others, for ostensibly equally affected patients.

It was agreed that re-allocation based upon medical emergency rather than historic use should be installed to warrant access to uninterrupted therapy for the patients who are considered most vulnerable. For this purpose, an independent pool of imiglucerase should be created, consisting of approximately 20% of the total amount for Europe and affiliated countries. A group of physicians was commissioned under the auspices of the EWGGD, to consider applications for those patients. For logistical reasons, a prerequisite to the granting of an application is that import of imiglucerase should be feasible within 1 month. An application form can be downloaded at www.amc.nl/cetp, www.ESGLD.org or www.gaucher.org.uk. To facilitate the smooth operation of this body and as far as possible ensure consistent standards of evaluation, it was agreed to employ a similar infrastructure to Genzyme's European Cerezyme Access Programme (ECAP) for this purpose, but to keep the supervision and central organization independent. Further details to this program can be found at the abovementioned Web sites.

On meeting senior representatives of the Genzyme Corporation, the group discussed how Genzyme could further assist European patients and those whose interests were subtended by the EGA. Genzyme indicated that logistical support could be organized as well as re-allocation before distribution has taken place (Genzyme noted that they are not able to re-allocate based on clinical needs, as this information is not available to them). Existing stocks in several countries, however, cannot be re-distributed by Genzyme. It was also discussed whether the imiglucerase vials, reserved for the phase III program of the new oral small molecule (GENZ-112638), could be released for normal use during the shortage. In this trial, non-inferiority will be investigated in a 2:1 randomized trial of GENZ-112638 versus imiglucerase as control arm; the trial will include patients who are mild to moderately affected and have stable disease. Both the FDA and EMEA had expressed great concerns about postponing this study — a view clearly shared by Genzyme. In view of the urgency of the issue, an emergency pool to treat the most severely affected patients was created as described above. It was considered that this would expedite the further enrolment of patients into the trial and obviate delay.

Monitoring

How would patients be monitored on low-dose/alternative treatments or during cessation?

Recommendations for monitoring during imiglucerase reduction or cessation of enzyme replacement therapy and during the recovery period were made by the group. Although some physicians were convinced that monitoring every month was not indicated in most patients, others felt that the more frequent monitoring would help to understand the implications of treatment interruptions and perhaps to identify patients at risk for progression at an early stage. The following guidelines were agreed:

- clinical examination and history at least every 3 months,
- complete blood count at least every 3 months, and
- plasma sample for biomarker analysis such as chitotriosidase.

For the assessment of chitotriosidase, it was recommended to employ local laboratory facilities for early evaluations, using percentage increase from baseline as a possible indication of deterioration. For an analysis of absolute values in the entire group, the stored plasma sample can afterwards be assayed at a central facility to correct for differences between laboratories.

Results of all follow-up studies need to be carefully recorded, and all were encouraged to submit these data to the Gaucher Registry of the International Collaborative Gaucher Group (ICGG) and/or national registries.

Use of miglustat

What is the therapeutic position of miglustat in this crisis?

Miglustat (Zavesca) has been licensed for use in type I Gaucher patients in the United States, the European Union, and other countries; in the European Union, it is also licensed for the treatment of Niemann-Pick type C disease patients. The indication in Gaucher disease is granted to patients with mild and moderate forms of the disease, for whom enzyme replacement therapy is unsuitable [11]. Theoretically, this definition would, after discontinuation of the drug imiglucerase, be applicable for many patients in the European area (see Table 3). It was pointed out by Actelion that the supply of miglustat can fully match possible needs for those European patients who are no longer able to receive enzyme therapy. Actelion also indicated that no data from current or other studies could give evidence for a role of miglustat in forms of the disease other than mild and moderate. Recent data on long-term maintenance with miglustat in patients who had been switched from previous enzyme therapy have been reported from Spain in the ZAGAL study [22]. This and other studies consider the impact of miglustat on bone manifestations of Gaucher disease [23]. While there are currently no plans to have expanded access in order to provide miglustat in countries where it is not approved, Actelion will bear the costs of treatment in those countries where miglustat is licensed, but currently not reimbursed. This will be the case until reimbursement has been granted or the shortage of imiglucerase has ended.

Access to unlicensed treatments

Since the companies Protalix and Shire inform us about opportunities for expanded access use of their enzymes (taliglucerase and velaglucerase, respectively) before licensing, how can this be managed and by what means can consolidated applications for patients with urgent need be made?

The company Protalix indicated that their product taliglucerase alfa, a recombinant form of human glucocerebrosidase produced in plants cells culture, is now available for hundreds of patients. It was stated that in 2010 Protalix will have the capacity to supply drug for more than 1000 patients and capacity for over 2500 patients by the end of 2010. The fast large-scale availability of taliglucerase alfa appears as a consequence of the unique production process of Protalix. Drug approval applications for taliglucerase alfa are in progress in various countries.

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For use as a compassionate use compound, the physicians in the individual countries would be required to approach their local authorities and to specifically approach Protalix with a request letter. In Germany and the UK, where this compassionate product release mechanism is about to be initiated, it is estimated that the time from the request to local delivery of the enzyme for infusion would be around 6 weeks based on the local regulatory timelines. Based on the phase III clinical study, which have been recently concluded, the initial registration application of the product has been submitted to the FDA. Fast-track approval has been granted as well as Orphan drug designation by the FDA. Practically, the company has to be contacted for use of the drug on a "compassionate use" or "named patient" basis, where permission by the local authorities will be granted. The patient will have to sign a consent form in order to receive the drug, which will be provided for a minimum of 9 months at no costs until marketing approval. It should be noted that at the present time, the treatment could only be available for adult patients aged >18 years, yet, pregnancy is not contraindicated.

The company Shire Human Genetic Therapies (HGT) estimates that it can provide uninterrupted treatment of velaglucerase alfa, their human-cell-derived glucocerebrosidase, for 300 to 600 type I Gaucher patients worldwide in 2009. Shire HGT has accelerated its manufacturing timelines and expects to be able to add several hundred more patients worldwide in 2010. The total number of patients who can be treated is dependent on patient weight, as well as the administered dose as recommended by the treating physician. Shire recently announced positive results from all three of its phase III studies, the submission of its New Drug Application to the US Food and Drug Administration, and the availability of velaglucerase alfa in the US through a treatment protocol. The company has requested an expedited review of its velaglucerase alfa Paediatric Investigational Plan and Marketing Authorisation Application (MAA) from the European Medicines Agency. To respond to the global supply shortage, Shire HGT has initiated processes for pre-approval access in a number of countries in the European Union and elsewhere. The company had a very positive recent experience with pre-approval access programs for Elaprase, their recombinant human-cell-derived idursulfase for the treatment of MPS II. Shire HGT is committed to providing patients started on velaglucerase alfa with uninterrupted treatment through the periods of MAA review, pricing and reimbursement timelines, and beyond. Requests for "compassionate use" or "named patient" use of velaglucerase alfa should be directed to Shire HGT's local medical directors. While this enzyme can be given to children, at the present time, pregnancy is an exclusion criterion.

As to access to the new small molecule compound, GENZ-112638, by the company Genzyme, the American authorities (FDA) have reinforced the importance of completing the proposed phase III trials and therefore will not approve the request for a compassionate use program. The current studies, which compare the use of GENZ-112638 with the conventional use of imiglucerase, will be extended. Enrolment of the patients within this study will require the normal approved process of a randomized clinical trial (RCT). There is currently no early access program in place for this agent.

Conclusions

The *force majeure* leading to an acute lack of imiglucerase therapy for the chronic treatment of Gaucher disease patients is unprecedented and has shocked the entire Gaucher community. The possibility of such an event has hitherto not been imagined by either physicians or patients — but nonetheless, the episode vividly illustrates the vulnerability of sophisticated biotechnology as well as the need for safety measures (stocks of products and/or effective alternatives). In the early aftermath of this crisis, the FDA and EMEA have played very different roles. For similar situations in the future, it is strongly recommended that expert physicians and patient organizations are consulted before guidelines are issued. During the EWGGD/EGA meeting, it was acknowledged that sufficient imiglucerase was available to maintain treatment, albeit at lower dose, for most infants, children, adolescents, and critically affected patients. Less severely affected patients with stable disease would probably not experience important clinical consequences during a treatment interruption of 3–6 months. Miglustat could be an option in those patients as well, depending on local prescription policies. For patients in need of enzyme treatment as defined in this article, the willingness of Protalix and Shire to make their products available is encouraging. Both enzymes are close to registration. Finally, this unfortunate event has emphasized the role for an independent working group for Gaucher disease, the EWGGD, as well as the EGA in providing advice as well as consenting to a compassionate re-allocation of imiglucerase. This EWGGD/EGA consortium will also further consider how the disaster can best be used as an opportunity to study the course of Gaucher disease after unplanned dose reduction or interruption.

Disclosures

Carla E.M. Hollak received reimbursement of expenses and small honoraria for lectures from Genzyme Corporation, Shire HGT, and Actelion. All honoraria are donated to the *Gaucher Stichting*, a national foundation that supports research in the field of lysosomal storage disorders.

Stephan vom Dahl received research grants, reimbursement of expenses, consulting fees, and honoraria for lectures from Genzyme Corporation, Actelion Pharmaceuticals, and Shire Human Genetic Therapies.

Johannes M.F.G. Aerts received reimbursement of expenses and small honoraria for lectures and teaching courses from Genzyme Corporation, Shire HGT, and Actelion. All honoraria are donated to the Gaucher Stichting, a national foundation that supports research in the field of lysosomal storage disorders. Nadia Belmatoug received grants for research form Genzyme, Shire HGT, and Actelion. These grants were provided to the association APRIMI.

Bruno Bembi received reimbursement of expenses and small honoraria for lectures on lysosomal disorders treatment, including Gaucher disease, from Genzyme Corporation and Actelion.

Yossi Cohen, Tanja Collin-Histed, and Jeremy Manuel are members of the EGA. The EGA have received unrestricted grants from the Genzyme Corporation, Shire Human Genetic Therapies, and Protalix Biotherapeutics. It is EGA policy not to accept grants of more that 30% of its annual budget from any one pharmaceutical company.

Patrick Deegan received speaking fees from Genzyme, Shire HGT, and Actelion.

Laura van Dussen has nothing to disclose.

Pilar Giraldo has received small fees from Shire and Actelion for lectures and sponsored events. All honoraria are donated to the Spanish National Gaucher Foundation, which supports research in the field of lysosomal storage disorders.

Eugen Mengel has received speakers fees from Genzyme, Actelion, and Shire as well as research grants from Genzyme and Actelion.

Helen Michelakakis has received honoraria from Actelion, Genzyme, and Biomarin.

Martin Hrebicek has nothing to disclose.

Rosella Parini has nothing to disclose.

Jörg Reinke has received speakers fees from Actelion and Shire.

Maja di Rocco received speaker's fees from Genzyme and Actelion.

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Anna Tylki-Szymanska received honoraria from Genzyme for lectures.

Ari Zimran receives consulting fees from Shire HGT and from Protalix Biotherapeutics; he has stock options with Protalix and receives research reimbursement of expenses and occasional honoraria for lectures from Genzyme Corporation. Genzyme also provides a grant to the Gaucher Clinic to support its participation in the Gaucher Registry (ICGG).

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