

CADTH COMMON DRUG REVIEW

Patient Group Input Submissions

MIGALASTAT (GALAFOLD)

(Amicus Therapeutics)

Indication: Fabry Disease

CADTH received patient input for this review from:
Canadian Fabry Association with Canadian Organization for Rare Disorders

On or before June 26, 2017

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While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

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1. About Your Patient Group

The Canadian Organization for Rare Disorders is registered charity that provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. COD provides education and resources to patient groups to enable them to better meet their members' needs.

The Canadian Fabry Association (CFA) aims to inspire hope and improve the quality of life for all those affected by Fabry Disease through the support of research, public education, advocacy and awareness.

2. Information Gathering

The summary patient perspectives submitted here were collated from patient feedback collected through a combination of methods: written individual testimonials, semi-structured interviews, and an internet survey developed by the Canadian Organization for Rare Disorders in collaboration the Canadian Fabry Association (CFA). The testimonials and interviews were used primarily to elicit patient experiences and perspectives for developing the survey and providing a context for data interpretation and validation. The survey consisted of open-ended questions, rating scales, and forced-choice options. The individual participants were recruited by CFA and the survey was distributed through the CFA database and posted on the CFA website with request for secondary distribution to other patients and relatives. There were English and French versions of the survey. They were active on Survey Monkey from 23 May to 15 June 2016.

The survey was sent to the Fabry Australia Organization, National Fabry Disease Foundation (United States) as well as one patient in Belgium, and two patients in Norway, all currently being treated with migalstatat.

This submission is based on two testimonials, four interviews, and 84 survey responses. All interviews and testimonials were provided by patients living with Fabry disease. In terms of the survey respondents, nearly three-fourths (74%) were persons diagnosed with Fabry disease who qualified for enzyme-replacement therapy (ERT), about one-tenth (11%) were diagnosed with Fabry but were not qualified for ERT, another one-tenth (11%) were caregivers of someone with Fabry disease, and the remaining 4% were patient advocates or clinicians. Among respondents, 39% were males, 58% females, and the remaining chose not to respond. The median age of the person with Fabry disease was 53 years; the youngest was 20 years old and the oldest reported was 99 years of age. Many respondents included in their response information about more than one family member, including parents, grandparents, aunts, uncles, siblings, and young children also diagnosed with Fabry disease. Overall, 90% of respondents reside in Canada, 7% in the USA, and the remainder either "elsewhere" or "not declared." In terms of Canadian residence, one-third (32%) live in Ontario, one-fifth (20%) in British Columbia, 15% in Nova Scotia, one-tenth (10%) in Quebec, and 2% - 3% in each of Saskatchewan, Manitoba, or New Brunswick.

3. Disease Experience

Respondents were asked to describe "how the disease impacts" their daily lives or those of their caregivers. Many described their current status as well as their experience prior to ERT and/or the impact on older relatives. Most respondents said that Fabry had a significant impact on their physical condition, ability to carry out daily activities, and their emotional well-being. The symptom that was most often cited was pain (specifically in their hands and feet), often described as sharp, severe, and excruciating pain. Patients also said they suffered from symptoms that impaired their ability to carry out daily activities, especially fatigue or lack of energy. Most also were affected by the inability to tolerate heat or cold, gastrointestinal problems, and cognitive impairment (lack of concentration, poor memory, and difficulty learning). These symptoms led to consequences including serious impact on school performance, inability to undertake certain jobs or to perform to expectations, reduced social life, and challenges with fulfilling daily tasks of living. Not surprising, respondents also cited employment, social and financial issues. Finally, respondents said they experienced emotion issues, including depression and mood swings.

"I have had to learn to live with constant pain, ringing in my ears, bowel issues while still maintaining a full-time career." "I was diagnosed with Fabry since the age of 11 yr olds [sic]. Symptoms include excruciating pain in hands and feet, gastro-intestinal symptoms, enlarged heart, and mild stroke." "It has limited employment through battling fatigue, swelling, cognitive functions and

sensitivity to heat/cold.... Not being able to be on my feet, limited choices of work... Emotionally devastating as nothing to take away pain.”

There were, somewhat surprisingly, numerous descriptions about the impact of Fabry on females. Until recently, Fabry (an X-linked condition) was considered a “male” disease with females regarded as asymptomatic carriers. “I was initially diagnosed as a carrier.... My heart valve damage and heart disease from Fabry disease qualified me for ERT.... I had chronic diarrhea (20 + BM per day - couldn't walk to work without stopping at washrooms) that severely limited my ability to exercise and socialize.” “I was lucky to have a heart transplant in 2012 or I'd be dead.” “When I had my daughter, we had to fight to get her tested at birth for Fabry disease because female are 'just carriers'. I had a TIA at 27. I have kidney disease. I spent 9 days in hospital this year and that doesn't include ER trips.” “I had difficulty concentrating and memorizing... I was making mistakes at work.... Stomach aches and acroparesthesias prevented me from doing social activities.... My biggest disappointment was not having had the energy to take care of my son at 100% of my abilities.”

Respondents also described the impact of the disease on the family, often across generations. “My brother went into kidney failure in mid 20's, fractured both hips during grand mal seizure... kidney transplant lasted 10 + years, then had a stroke, had kidney failure again, had heart failure and open heart surgery to replace damaged valves... had stroke during heart surgery- did not survive... He died at 46.” “My father and uncle suffered unbearably throughout their lives.... They both died in their 40's leaving their wives with children to raise on their own.... Many medical emergencies occurred.”

“I, two of my children, and at least one grandchild have Fabry disease. My son has been suffering since he was 8 years old. He's had a valve replacement and a kidney transplant... My daughter has severe digestive difficulties and I have an enlarged heart, causing A-fib and CHF. My third daughter doesn't have the gene, but has donated a kidney to her brother.” “Living with both a spouse and a daughter with Fabry has created many rifts due to the way it causes mood swings and depression.”

Parents also suffer from the guilt of passing Fabry to their children. “I had to watch my two sons grow up suffering the hands and feet pain, 3 day bouts of pain and fever, not being able to participate in any school sports (it would trigger pain), hardly any social life at all, etc. I did not experience the same physical symptoms as my sons, but, I lived with the pain and guilt feelings of watching them grow up suffering themselves.”

Not surprisingly, some couples chose not to have children. “My husband and I chose to not have children as we did not want anyone to suffer as my brother had.” “[I]t makes me not want to have children - even if I chose to have only sons, what if I die young and leave my wife to raise young children on her own?”

4. Experiences With Currently Available Treatments

Among 90 respondents, about three-fourths (73%) had received ERT. Among these, 97% were still taking ERT. About 7% reported they have been on therapy for less than one year, while 50% said they had been on therapy for 1 to 10 years, and 40% had been on ERT for more than 10 years. About two-fifths reported they were on Fabrazyme and the other three-fifths on Replagal. There were no significant differences between the two groups on any of the questions.

Interviews and open-ended comments support the benefits of ERT in terms of symptom management or reduction, organ protection, energy, ability to work, socialize, carry out daily activities, and overall quality of life. Almost all spoke to the increase in energy and reduction in pain in their extremities. Some felt they had reversed previous cardiovascular problems and, overall, credited ERT with allowing them to return to work and to lead near-normal lives.

“I have had two strokes, but with the therapy have not had any more.” “I used to, and sometimes still do feel limited to the amount of physical activity I can handle. With my infusions I get every two weeks I feel physically more capable of taking on daily tasks and enjoying life. I have been receiving the infusions for several years now. Not sure how my health would be if I never received them.” “I am eternally grateful for ERT... and the quality of life I now have. I am able to work as a physiotherapist in our local hospital because my disease is controlled.”

To collect quantitative data to supplement the qualitative responses, we provided a list of symptoms and outcomes associated with ERT and asked respondents to choose the option that best described their personal experience: “severe or frequent in past but not now”; “somewhat in past but not now”; “never”; “somewhat now”; “severe or frequent now.” Overall, the responses show a pattern of

symptom reduction and organ protection with ERT but a significant proportion of respondents have continued to experience some symptoms (heat and cold intolerance, fatigue, GI issues, and heart-related issues) and reduced quality of life.

Patients, almost all of who were on ERT, reported currently experiencing symptoms related to Fabry disease, moderately and even severely or frequently. About two-thirds reported experiencing heat or cold intolerance, with one-third saying it was “severe or frequent” another one-third saying it bothers them “somewhat.” Only one-fifth (19%) said they had experienced this problem in the past but not now. A similar pattern of responses was found for heart-related problems (including high blood pressure). More than one-fourth (28%) said they suffer these symptoms frequently or severely, while nearly half (47%) said they experience heart problems “somewhat.” Only 10% of respondents said that previous heart-related issues were no longer experienced.

The responses were similar for “fatigue, lethargy, or weakness” with three-fourths reporting some experience of these symptoms. About one-fourth saying the symptoms are severe or frequent while half said they were somewhat problematic; only one-fifth said they are no longer experiencing these symptoms. Similar responses were noted for experience of “gastrointestinal problems, including diarrhea or constipation”, with one-fifth (18%) saying these were severe or frequent and 45% saying they experienced these to some degree; again one-fifth say previous severe or moderate GI problems are no longer experienced.

The reduction of acute or chronic pain is slightly more positive, with only 15% reporting frequent or severe pain and slightly less than two-fifths (38%) reporting some experiences of pain; importantly, about 30% say previous experiences of pain were resolved. In terms of kidney-related problems, about one-fourth said they were experiencing some or severe problems related to kidney functioning, while about one-tenth said previous issues were no longer experienced. It is important to note that about two-thirds said they had never experienced kidney-related problems (which is usually present only at advanced stages of disease progression). We can summarize the experiences of “excessive sweating”, “ringing in ears”, “skin lesions or rash”, “depression or bad mood”, and “nervous system problems including numbness or tingling” as following similar patterns, with about 60% saying each of these symptoms was experienced to some or severe degree and about 10% to 15% reporting they were no longer experiencing these symptoms.

Finally, in terms of changes in quality of life (which may or may not be directly related to ERT), about one-fifth reported severe issues with work, school or family life; nearly two-fifths said there is some impact. Similarly, more than one-fifth (22%) said they experience severe financial impact and nearly one-half said that there is at least some financial impact, with 12% to 15% saying these are no longer issues.

Interviews and open-ended responses provide important insights on these findings. First, patients do believe that ERT is helping to control symptoms and disease progression, including major organ failure and early death, compared to their lives prior to ERT and to the experiences of parents and older relatives. Second, ERT has not totally resolved the symptoms and for a majority of persons; the experience of some symptoms remains severe or frequent, especially heat/cold intolerance, fatigue, GI issues, pain, and heart-related problems. Third, ERT treatment is perceived as by some patients and families as disruptive and even difficult, based on the amount of time required, frequency of treatment, and venous entry. Fourth, patients are unsure about the long-term impact of ERT in avoiding serious events, including stroke, heart-related and kidney-related problems. On-going experiences of symptoms increase the uncertainty as to the protection.

“I often miss work to get to appointments regarding my Fabry disease, as most are 3 hours away from me. As a family, we must plan every other weekend around my treatment time.” “My overall health seems to be well managed, though the thought of sudden death from my Hypertrophic cardiomyopathy is always at the back of my mind, causing much anxiety.”

Finally, there may be some patients who believe that ERT is not working for them based on their mutation. “There are 14 living members of my family with Fabry disease.... My mother has many heart issues and lives in pain every day. My brother has had strokes, heart problems, gastro issues and lives with severe pain every day. I have similar problems, TIAs heart issues, pain and gastro. My son (16) is always in pain and gastro issues. There is some proof that ERT does not work for our mutation.”

5. Improved Outcomes

There are many levels of answers to the question of “what outcomes patients would want from a new therapy.” We chose to collate responses to this question from the other questions posed in the interviews or surveys, rather than ask the question directly. While patients suggested they would ideally want a cure that is risk-free and permanent, they realistically want a therapy that is as effective

as possible in slowing progression, reducing symptoms and avoiding organ damage, with few or no side effects. “I hope it will help...different part[s] of my body (kidneys, heart etc.) to keep it functioning normally.”

Several patients referred to ERT as “life-saving” because it has slowed progression of disease and allowed them to live years longer than did their parents and grandparents. Patients responded that ERT helps manage their most difficult symptoms, even if these are not totally resolved. They reported they currently live with much less pain, fatigue, intolerance of heat or cold, GI problems, and risk of stroke. However, they also described the infusions as highly disruptive to daily living so they would want a therapy that does not take hours to administer, does not require regular trips to a special clinic, does not require special storage or handling, and is easily transported so they can travel for work or pleasure.

They also indicated that a more ideal therapy would have fewer side effects. “I hope it reduces the number of side affects that those who have Fabry currently have due to infusion. In addition, it will significantly add to quality of life/time due to the [current] need to rearrange one's day, travel, work schedule, etc. around the timely infusions.”

A number of respondents felt that it would be more effective to have a treatment which allows the enzyme to “remain longer in the body at a stable level”, either through more frequent dosing or a slow-release therapy. Patients also wanted an alternative to infusion. “...my personal fear is in regards to the infusion wear and tear on my veins and damage caused to them with the infusion needles.” I believe it is excellent [to have an alternative to infusion]. Children and adults alike no longer dreading needles, less anxiety. This makes us free to live as much as normal as we can be, not having to take the time off from work or school.” Even those on home infusion expressed the need for a less burdensome therapy. “It would be wonderful to just be able to take a pill for treatment and not have to worry about delivery, storage and infusion times, as long as it was affordable and easy to take it would make life so much more simple!”

Respondents also suggested that an oral therapy could increase compliance and perhaps reduce costs (“not needing a special infusion nurse”). Overall, patients suggested that if another drug became available, competition might reduce costs for both the new therapy as well as the existing ERTs.

6. Experience With Drug Under Review

Overall, eight patients reported experience with Galafold (migalastat), either through clinical trial, extended clinical trial, or compassionate access (some patients said they did not know the difference among these pathways). All had previously been on infusion ERT, ranging between one and ten years. The length of time reported on Galafold varied from a few months to more than two years. All reported they were still taking Galafold.

All recipients reported positive benefits with Galafold in comparison to infusion ERT. These advantages were the convenience of administration and management of the drug as well as better symptom management and potentially long-term organ protection. “Migalastat has changed my life.” “I have been taking migalastat for several years and I am aware of the benefits medically.... My symptoms have decreased by 90%.” Some specifically spoke about the increase in energy and mental functioning, and consequently daily living and quality of life. “It gives me more energy and more concentration.” According to one patient, “I have energy to take care of my son and do my job. I have the ability to go to university, because I have more concentration and I remember! I complete my certificate in administration on June 11, 2017. I participate in social activities without being afraid of stomachache or the like. My confidence in myself and my esteem have increased. I get up in the morning and I know I slept. I have energy.”

Others spoke of the convenience of a pill over the infusion schedule. “It is the most convenient drug for Fabry when it comes to administering it and it has a far less disrupting effect on your daily life routines thus a better quality of life as a patient. With Migalastat (Galafold) I have less time away from work due to my treatment than before on ERT.”

In terms of side effects, patients reported experiencing few or no side effects. “I don't think their [sic] is any bad [e]ffect.” “The only side effect I ever experienced is a slight rumbling feeling in the stomach a bit like feeling hunger.” One patient reported experiencing vaginitis, which was resolved with medication. “So I take two tablets of ‘CANESORAL,’ twice a week. But that's all. I would not stop the mlgalastat for this side effect. This situation does not bother me.”

All respondents were asked about their level of awareness of migalastat (Galafold). Overall, the level of awareness appears to be fairly low. About one-fourth said they “not at all” aware of the new oral therapy, while about three-fifths (60%) said they were

“somewhat” aware but varied in terms of how it was used or for whom it was indicated. Less than one-fifth (15%) said they were well aware of the therapy and how it was used. They were provided with a very brief description of the therapy, the indicated use for certain amenable mutations, and the clinical evidence, to date. They were all asked to indicate how important they thought it would be to have the oral therapy Galafold as a treatment option, regardless of whether it was indicated for them personally. The response was overwhelmingly positive, with 95% rating it as “very important” to have an oral drug and only 1% saying it was “not important” and 1% as “neither important or not.” The open-ended comments spoke to the potential freedom from infusions, more effective therapy and fewer side effects.

“ERT is very intrusive into one's life. Like dialysis, it is a necessary evil.” “Oral therapy gives patients one less additional challenge, easier on children, less time in a hospital setting, less invasive, and shows to have less adverse reactions.” “...hope it will benefit my family mutation for my son's sake. He refuses ERT due to his severe fear of needles.” “[An oral drug]..will give Fabry patients more freedom, power over their life and agenda. ...it gives them a chance to have a regular work schedule,” “This will definitely alleviate problems with absence of work. As this will also help with loss of income.” “...it will not work for my family's mutation but I think it will be great for those who it will work for. It will give them more freedom and hopefully less side effects.” “As it is your own enzyme production that suddenly gets active I hope it will be more effective throughout the whole body.”

In summary, there is a considerable interest in an oral therapy as an alternative to infusion. Most have heard about it but were not fully knowledgeable about the use or results. Nevertheless, almost all patients felt very strongly that an oral alternative was important and should be available.

7. Companion Diagnostic Test

As noted in the treatment guidelines, only specific GLA mutations, resulting in misfolded enzymes, are amenable to treatment with migalastat. In Canada, this may correspond to only 20% of Fabry patients; most families representing the largest patient cohort in Nova Scotia do not have amenable mutations. It is our understanding that the standard genetic testing that is done routinely for all Fabry patients is sufficient to determine whether the mutation is amenable so no additional testing is required. It is also our understanding that the manufacturer (Amicus) is continually updating the list of amenable mutations so there is theoretically no additional cost to the healthcare system to determine eligibility.

8. Anything Else?

We do not see the purpose of asking how much money has been contributed by any entity that may have an interest in this population or drug. There is no context for how this money is contributed, used, or managed. Moreover, there is no context for how much this accounts for overall revenue or other resources. Finally, if it really makes no difference, why is it being asked?

Appendix (A): Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No outside help was provided. CODR did the background research, conducted the interviews, prepared the survey, analyzed the data, and prepared the submission in collaboration with the Canadian Fabry Association.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

See above.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Sanofi Genzyme			X	
Shire			X	
Amicus	X			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger

Position: President & CEO

Patient Group: Canadian Organization for Rare Disorders

Date: 26 June 2017

Appendix (B): Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

CORD did the background research, conducted the interviews, prepared the survey, analyzed the data, and prepared the submission in collaboration with the Canadian Fabry Association.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

CORD (see above).

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Sanofi Genzyme				X
Shire				X
Amicus		X		
Protalix	X			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Julia Alton

Position: Executive Director

Patient Group: Canadian Fabry Association

Date: June 25, 2017