CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

pegunigalsidase alfa

Chiesi Canada Corp.

Indication: Long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase).

March 31, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: [redacted]
Indication: <Enter Response here>
Name of Patient Group: Canadian Fabry Association
Author of Submission: David

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

www.fabrycanada.com

2. Information Gathering

Personal experience

3. Disease Experience

Patient personal experience

4. Experiences With Currently Available Treatments

<Enter Response Here> I have been on [redacted] enzyme replacement therapy (ERT) for several years (see below), and I've noticed the GI issues have become substantially less frequent. In high school and college I could more or less rely on at least one episode a week, and to last several hours, but in recent years on treatment the frequency has dropped to probably once or twice a month, if not less, still randomly, and also the episodes tend to last less time, maybe an hour or two on average

My heat and cold tolerance don't seem to have changed much; as I've been told, no ERT for Fabry disease has really helped with those symptoms.

Kidney and cardiovascular health have been generally well maintained. This requires some testing to track, but kidney function hasn't declined substantially in the tests. Heart MRI and echocardiograms have shown slow progression of LVH, which is about what's expected based on other ERTs so far and is encouraging to me .

Brain MRIs have shown some small white matter lesions but the progression still seems slow

One vital aspect for me is that I've had no side effects or complications of [redacted]. Other ERTs for Fabry disease are known to cause allergic reactions and immune responses, which can be treated. But I've never experienced any of these or other side effects. The only downside is needed to have an enzyme infusion every two weeks, which for me is a small price to pay to keep disease progression slow and hopefully allow me to lead a long and relatively healthy life.

5. Improved Outcomes

<Enter Response Here> For me, if the disease can't be cured, slowing the progression of the symptoms substantially is still a good overall outcome. Not having the GI issues I've described, keeping kidney health good, and slowing or stopping cardiac issues are key. Not having to worry about if I'm going to be feeling okay to go to work or go out and do things in the world, having less of a spectre of heart issues and stroke risk hang over me would also be good. I'd also rather have to spend a few hours every couple

weeks getting treatments than possibly a few hours once or more a week in gastrointestinal pain, being afraid that eating will just make it worse or last longer, or even trigger an episode.

6. Experience With Drug Under Review

<Enter Response Here>I started on [redacted] in the US, in Dallas Texas, on a study for it, during a dosage determination phase in 2016. It was open ;label so I know I've been receiving treatment for several years. Previous to that I was on a chaperone drug trial, which is only helpful for specific mutations of the disease. I was on that for two years and didn't notice any change for better or worse, and after about 2 years and several kidney biopsies, the study sponsor learned my mutation didn't work with that treatment, at which point I was able to join the [redacted] trial. Of what I call the “experienced symptoms”, that is the easily noticeable symptoms that don't require testing, the GI issues improved more on [redacted] than the previous treatment. It's hard to determine how much the heat and cold tolerance and hypohidrosis changed as I'd already molded a fair amount of my lifestyle to minimize exposure to heat and cold that would impact me.

At the time, I lived in Los Angeles CA, so had to travel every two weeks to Dallas. The treatments were slow, taking up to 8 hours for infusion, and these combined factors made being on the study a challenge for me. Every other weekend I had to travel and spend time at the hospital, basically giving up a whole weekend. But my day to day life improved if for other reason than the lessend frequency of GI issues. The treatments themselves caused no other issues and had no side effects.

Over time we were able to switch to home infusions and the infusion time went down to only 60-90 minutes with a 60 minute post-infusion observation period. Without travel, and with a short infusion time, things became even easier. A nurse would visit for a few hours on a weekend morning when I would have planned to be home relaxing anyway, so the overall interference of treatment with my life lessened greatly.

After moving to Canada, I started on the study in the US and would travel every other weekend to Washington state and get treatments there. This was somewhat inconvenient but I learned to make the most of the trips by planning other things around them. I'd spend a few hours in Washington including other errands or fun things to do and then come home.

After the study concluded in the US, my doctor in Vancouver was able to get special permission to administer the drug locally, and the company donated the drug, so I've been going to VGH every two weeks for treatments. This is a minor inconvenience to drive to the hospital, sometimes wait for the pharmacy to prepare the drug and get o the infusion clinic, but it's a comfortable clinic with good, caring staff who do their best. It takes a few hours every other weekend so it minimally impacts my life otherwise.

- 7. Companion Diagnostic Test

<Enter Response Here>For me, this includes blood and urine tests, echocardiograms, and if possible MRI of brain and heart. The latter were part of the study and haven't been continued regularly since so may not be needed any more. Taking [redacted] doesn't include any more or different testing than other treatments for Fabry Disease

8. Anything Else? From what I've read and learned over the course of the study and continued treatment since, [redacted] does the same thing other ERTs for Fabry Disease, just better. Less risk of side effects, and what I've read about indicates it has longer activity in the body. I'd like to see if possibly become a monthly treatment instead of bi-weekly, but this may be on the drug manufacturer to study and determine if it's a viable approach. But moving to less frequent treatments, possibly at a higher dose if needed, would make the treatment as a whole even better.

<Enter Response Here>

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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, I did not.

5. 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.

No.

6. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
N/A				

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:
Position:
Patient Group:
Date:

CADTH

Patient Input

Name of Drug: pegunigalsidase alfa
Indication:
Name of Patient Group: Canadian Fabry Association
Author of Submission: Julia Alton

1. About Your Patient Group

The Canadian Fabry Association educated all those impacted by Fabry Disease and empowers patients to make the best-informed decisions so they can have the best health outcomes and quality of life.

<Enter Response Here>

2. Information Gathering

Information gathering was collated from patient feedback collected though individual testimonials and semi-structured interviews to learn their lived experience.

3. Disease Experience

Fabry Disease impacts nearly every aspect of a person's life. It is a multi-systemic condition and causes chronic pain, fatigue, heat intolerance, gastrointestinal issues, kidney disease, heart problems, and an increased risk of stroke, often starting in childhood. Many patients face misdiagnosis and emotional struggles**,** leading to anxiety, depression, and feelings of isolation. Daily life, including work, school, and relationships can be challenging.

4. Experiences With Currently Available Treatments

Two enzyme replacement therapies (ERT's) agalsidase alfa (REPLAGAL])and agalsidase beta (FABRAZYME), and one chaperone therapy migalastat (GALAFOLD), are currently available in Canada. These Fabry specific treatments have all impacted patients lives drastically and positively. During interviews and in patient conversations, collectively patients reported to have more energy, less episodes of pain crisis, less GI pain, and an ability to carry out everyday life activities. Overall patients reported a reduction in their symptoms and felt that being on therapy helps to control symptoms and diseases progression, including major organ involvement/failure compared to their lives prior to treatment. The impact this has is greatly correlated to a persons overall mental health which can be equally as important as our mental health.

Infusion related reactions and adverse drug antibodies continue to be a concern for some patients who are receiving ERT. Nausea, fatigue, chills, and fever are experienced in some patients during and after their infusions.

5. Improved Outcomes

An improved outcome would be less frequent infusions as they can be onerous on a person's life. Another improved outcome would be to improve infusion related reactions and antibodies for those patients that experience them. There is a need for an additional ERT that reduces the development of ADA's for patients who can't tolerate current ERT's. Lastly, therapies are needed that can further slow progression and provide prolonged and consistent symptom control in patients who are experiencing worsening disease on currently available therapies.

6. Experience With Drug Under Review

During a patient interview the patient reported “I am feeling great, and this has been very encouraging to me, I noticeably feel better, and have less severe symptoms, my GI pain has almost been resolved, and I haven’t experienced any complications or side effects during or after the [redacted] infusion.

In conversations with patients, collectively they feel an overall sense of wellness, improved energy levels, improved sleep, less pain, and when the pain is present it is not as severe. Patients reported that cardiac and renal symptoms have remained stable.

Patients received the drug under review in a clinical trial. One patient started [redacted] in the United States and continued receiving therapy in Canada. All patients felt strongly that additional ERT’s are needed to better meet the needs of each individual patient. Fabry disease comes with a vast presentation, and it is crucial to have precise treatment options to address the symptoms patients present. Doing this provides the best outcome and quality of life that we all deserve.

7. Companion Diagnostic Test

- **N/A**

8. Anything Else?

It is crucial that we address the unmet needs so Fabry patients in Canada can live their best and full life. There is a need for additional ERT’s that reduce the development of ADA’s and IRR’s. In the BALANCE clinical trial, data suggests favorable safety and tolerability and demonstrated that [redacted] has a good immunogenicity profile. There is no cure at this time for Fabry patients, but this life-saving therapy drastically improves patients’ quality of life, and health outcomes so that they can live better, stronger, healthier, and happier lives. Throughout interviews and patient conversations, it is reported that this is exactly what [redacted] is bringing to patients.

Thank you for hearing our patient voice.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.

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.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi				x
Takeda				x
Amicus			x	
Chiesi			x	
Sangamo		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: March 12, 2025

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0872-000
Generic Drug Name (Brand Name): pegunigalsidase
Indication: Fabry disease
Name of Clinician Group: Canadian Fabry Disease Initiative (CFDI)
Author of Submission: Drs. Anna Lehman, Aneal Khan, Sandra Sirrs, Michael West on behalf on CFDI

1. About Your Clinician Group

We are physicians with decades of experience and expertise in the treatment of Fabry disease. We are all investigators of the Canadian Fabry Disease Initiative (http://www.the-cfdi.ca/), a prospective Canadian disease registry that has enrolled over 740 patients with this rare disorder – this is the majority of patients in Canada.

2. Information Gathering

The information presented here was gathered by review of published, peer-reviewed studies on Fabry disease, from CFDI registry data, and from professional expertise.

3. Current Treatments and Treatment Goals

Fabry disease is a pan-ethnic disease that can affect an individual with any ancestry; the majority of patients in Canada have ancestral backgrounds different from populations with founder mutations. It is an X-linked disease and a single causative mutation, which can be a de novo occurrence, can occur in all groups including Indigenous populations.

Fabry disease is treated in Canada according to regularly updated Canadian guidelines issued by the scientific committee of the CFDI. These guidelines are accessible at the website of the Garrod Association (https://www.garrod.ca/guidelines-and-resources). There is no cure for Fabry disease. Management includes multi-modal approaches to optimize outcomes, including lifestyle changes, adjunctive medications, cardiac conduction support and interventions, and disease-modifying therapies. Numerous studies have documented reduced life expectancy in untreated patients.

Adjunctive management

Because the small blood vessels, especially those in the brain, heart, and kidneys, are a major site of disease pathogenesis, much attention is directed toward optimizing vascular health. Patients are encouraged to abstain from smoking, excess alcohol, and unhealthy foods such as trans fats, sugar, and nitrites. They are prescribed regular exercise of at least 150 minutes of moderate to vigorous aerobic exercise per week, adjusted as needed for cardiac status. They are encouraged to maintain a normal

waist circumference and body mass index. Patients with Fabry disease in Canada are routinely monitored for dyslipidemia, hypertension, and diabetes mellitus in order detect and treat these amplifying co-morbidities promptly and according to guideline-defined “high risk” targets. They are also monitored for direct complications of Fabry disease, particularly with respect to kidney and heart disease. If these develop, adjunctive medications may be prescribed, such as ACE or SGLT2 inhibitors for proteinuria, or these drugs plus mineralocorticoid receptor antagonists and beta blockers for cardiomyopathy. Pacemakers or implantable cardioverter defibrillators can be life-saving for patients who have developed life-threatening arrhythmia secondary to cardiac fibrosis from Fabry disease. Adjunctive management can help optimize care when combined with disease-specific treatment. The disease modifying effects of adjunctive therapies in Fabry disease are unknown and all outcomes studies in Fabry disease are confounded by the use of adjunctive treatments.

Disease-specific drugs

There are two classes of medication targeted to the specific pathophysiology of Fabry disease. They are currently considered non-inferior to one another based on a head-to-head trial (Hughes et al, 2017) although differences in the characteristics of patients enrolled in the clinical trials of the different classes limit the generalizability of this designation. Deficiency of alpha galactosidase in the lysosome leads to incomplete recycling of cell membrane components (globotriaosylceramide or Gb3), which in turn poisons the cell, especially those in the kidney, heart, small nerve fibers, and small blood vessels. Two recombinant forms of alpha galactosidase are currently on the market and generally reimbursed by drug plans across Canada: agalsidase beta and agalsidase alfa. By infusing replacement enzyme every two weeks, a portion of functionality is restored to the lysosome. The second class of medication available in Canada is a pharmacologic chaperone that binds to certain mutant versions of alpha galactosidase and increase enzymatic activity through stabilization. Only 35% of Fabry patients in Canada are candidates for this type of treatment as determined by response in an in vitro assay, so-called amenability; in Canada, fewer than 20% of treated patients take the only medication in this class, migalastat (CFDI 2024 data). The most common variant in Canada, called A143P, is not amenable to this chaperone class of therapy, but the second most frequent variant, N215S, is amenable (Theberge, et al., 2024). The third most common variant in Canada (c.640-801G>A), present in most Fabry patients of Taiwanese descent, is not amenable. Chaperone treatment comes in the form of a tablet taken orally every other day and is therefore generally preferred by eligible patients. It is well tolerated with no serious drug-related adverse effects of note identified yet, over the first 6 years of marketing.

Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017;54:288–296.

Guideline-directed indications for initiation of disease-modifying therapy

The Canadian Fabry disease guidelines include clear criteria for initiating therapy according to a chief aim to begin treatment as soon as evidence of renal or cardiac damage begins to accrue and cross pre-defined thresholds. These criteria are available to all on the Garrod Association website. Treatment initiated based on diagnosis alone could lead to years of overtreatment potentially, particular in women with milder variants, such as c.640-801G>A. Currently, provincial drug plans use the CFDI to adjudicate individual cases to determine if criteria have been met or not. The CFDI committee provides their recommendation to the physician who then supplies the approval to the funder. While CFDI approval to start drug is not mandatory in all provinces, data analysis supports the role of treatment when patients show disease-specific signs and symptoms rather than treating all patients simply based on a genetic test result. The CFDI guidelines have thus supported the use of an expert review committee to avoid unnecessary treatment and direct resources to the patients that are most likely to benefit.

Effectiveness of current treatment

Both enzyme replacement therapy (ERT) and chaperone therapy have been shown to stabilize renal function, as measured by estimated glomerular filtration rate, and stabilize left ventricular enlargement, a pathological finding correlated to adverse cardiac events. There is evidence that disease trajectory of progression is less steep in treated than in untreated or late-treated patients. As well, both ERT and chaperone therapy have been shown to reduce the frequency of Fabry disease clinical events (cardiac, renal, stroke and deaths). There is also recent evidence suggesting that enzyme replacement therapy with agalsidase beta results in decreased stroke incidence. (Burlina A *et al* Mol Genet Metab 2025)

Feldt-Rasmussen et al. Long-term efficacy and safety of migalastat treatment in Fabry disease: 30-month results from the open-label extension of the randomized, phase 3 ATTRACT study. Molecular genetics and metabolism. 2020 Sep 1;131(1-2):219-28.

Ramaswami et al., Cardio- Renal Outcomes With Long- Term Agalsidase Alfa Enzyme Replacement Therapy: A 10- Year Fabry Outcome Survey (FOS) Analysis. Drug Design Development and Therapy, 13(0), 3705-3715 - October 2019

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

While reducing or delaying dialysis and heart failure are major treatment goals for patients with Fabry disease, there are other disease manifestations that have been proven much more difficult to target with drugs, including abdominal pain, neuropathic pain, stroke, and mental health problems. In addition, cardiac disease continues to progress despite the altered trajectory. There continue to be high rates of atrial fibrillation and other arrhythmia, heart failure, and chest pain. ERT faces fundamental limitations as a treatment strategy, including the large portion of drug that is taken up by the wrong organ, the liver with the kidneys receiving only 10% of the dose and the heart receives even less at 7%. While ERT does not cross the blood-brain barrier, it does impact the vascular endothelial barrier. Dosing intravenously every two weeks is burdensome for patients, and as the ERT plasma half life is around 2 hours, this dosing interval means that the enzyme is not circulating for the majority of the time in between treatments. Patients that have difficult intravenous access can sometimes require repeated attempt to obtain access and this can become more difficult over time. Reducing the need for the high frequency of intravenous infusions is considered a target for future therapies. For males with severe deficiency especially, there is a risk of developing IgG antibodies that neutralize the drug, reducing efficacy. In a few men with extremely high titres of neutralizing antibodies, ERT has been stopped as totally ineffective. Unfortunately, these patients have no other proven option for treatment. Migalastat has a major limitation in that many patients, particularly patients with the most severe forms of the disease not making any enzyme, do not respond to this treatment at all. The high cost of these treatments has likely been a factor explaining the dearth of research into combining these therapies, which theoretically could be complimentary to one another. Therefore, there remains an large unmet need in terms of clinical efficacy and to reduce the frequency of enzyme infusions needed.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Pegunigalsidase is another recombinant enzyme replacement therapy, similar to the others, except pegylated. The pegylation modification was hypothesized to result in longer availability for action as well as better masking from anti-drug immune responses. It is intended as a stand-alone disease-modifying therapy that could be used either first-line or as an alternative to current ERT. Reasons for switching could include change in reimbursement such that the other products are no longer available or recurrent immune responses to the other products. In addition, the dosing of pegunigalsidase is 1 mg/kg, the same as agalsidase beta and 5X the dose of agalsidase alfa. There is emerging evidence suggesting severely affected young males may benefit more from the higher dosed ERT. Hence, some of the more severely affected males in Canada who have been treated with agalsidase alfa (0.2 mg/kg) have been switched to agalsidase beta (1 mg/kg) (personal experience, Dr. Lehman, Dr. Khan). A switch study going from agalsidase alfa to pegunigalsidase found similar improvements in plasma lyso-Gb3 biomarker as well as eGFR slope. There has not been a dosing study comparing agalsidase alfa at 0.2 mg/kg to a higher dose of pegunigalsidase alfa 1 mg/kg. Furthermore, while the oral drug, migalastat, has a threshold for approval of 5% increase in enzyme activity, the actual increase in enzyme activity is not disclosed by the manufacturer for each mutation – it is possible the increase may not represent the same benefit in a severely affected patient as 1 mg/kg of enzyme therapy. Therefore, for Canadian patients, there is only 1 choice available at the 1 mg/kg enzyme dose. The use of pegunigalsidase represents another product that could be used at 1 mg/kg if needed.

Pegunigalsidase alfa has been shown to be non-inferior to agalsidase beta in a one year head-to-head trial of patients with deteriorating renal function. Both products are dosed at 1 mg/kg. In that trial, the rate of neutralizing antibodies in pegunigalsidase alfa patients (15%) trended lower than in agalsidase beta patients (26%) and there was a lower rate of infusion related reactions in the pegunigalsidase group which did reach statistical significance. However, due to differences in techniques of measuring immunogenicity, data are insufficient at this time to determine if the immunogenicity of pegunigalsidase is actually lower than agalsidase beta. There is a need for products of lower immunogenicity for those patients (usually males with the classical phenotype) who may have reduced response to existing ERTs because of high levels of neutralizing antibodies. It is not yet known if pegunigalsidase will fill this need.

At the present label with dosing every 2 weeks, pegunigalsidase is not expected to significantly change the Fabry disease treatment paradigm. A study is underway looking at dosing every 4 weeks which may represent and advantage for some patients. (Holida *et al*. J Inherit Metab Dis. 2024;1–17. doi: 10.1002/jimd.12795) For example, in patients on home infusions in a remote setting, or those with difficult venous access who do not tolerate frequent iv use, there may be a role for dosing every 4 weeks instead of every 2 weeks. This reduced frequency of dosing would certainly be popular with patients and redcue the burden of treatment.

Linhart et al. Safety and efficacy of pegunigalsidase alfa in patients with Fabry disease who were previously treated with agalsidase alfa: results from BRIDGE, a phase 3 open-label study. Orphanet Journal of Rare Diseases. 2023 Oct 21;18(1):332.

Lenders M and Brand E. Comment to: Head-to-head trial of pegunigalsidase alfa versus aglasidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study – determination of immunogenicity. J Med Genet. 2024;61:531-33.

Riccio et al., Clin Genet. 2023 Mar;103(3):371-376.

Wallace et al. Heat-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: Results from the 2- year randomised phase III BALANCE study. J Med Genet. 2024;51:520-530.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

This drug would not change the established patterns of practice for treatment of Fabry disease patients in Canada. The CFDI guideline committee already annually reviews published evidence, and evidence from CFDI, to adjust treatment initiation criteria to balance the risks of undertreatment against overtreatment. Current initiation criteria require a confirmed diagnosis of Fabry disease based on an unequivocal combination of DNA, enzyme, phenotypic, and biomarker evidence. Then, there must be clear evidence of stroke, renal or cardiac disease consistant with Fabry disease. Rarely, other organ involvement may lead to treatment initiation criteria being met, such as severe neuropathic pain not controlled with multiple oral medications. Canada has a well-established network of expert clinics treating Fabry disease, making it unlikely that many patients are followed by non-specialists. The vast majority of diagnoses are straightforward, with patient access to specialized testing and care in most provinces, and the vast majority of treatment initiation decisions are straightforward. Most patients in Canada are diagnosed because an affected family member was diagnosed making it fairly easy to make a diagnosis using blood enzyme levels and DNA testing. Patients may also be identified through symptomatic presentations such as severe pain, stroke, cardiomyopathy or chronic kidney disease. There is only 1 gene known to cause Fabry disease and diagnostic testing is considered a routine process with a low chance of misdiagnosis. There is oversight provided by CFDI, which also provides a venue for adjudication of complex, nonconforming cases. The addition of this drug in Canada would provide an alternative form of ERT at the 1 mg/kg dose but would not be expected to impact the indications for treatment. It may prove to be useful for some adult males with high titre neutralizing antidrug antibodies (ADA) that are limiting

response to therapy. While less *in vitro* binding of ADA to pegunigalsidase alfa has been shown, there are no *in vivo* data yet to support this hypothesis.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Because Fabry disease is a very slowly progressive disease, which is expected to continue to progress, albeit at a slow rate, even on treatment, it is not possible to precisely measure a "treatment response" in individual patients. The best measure of treatment response in an individual currently available is plasma lyso-Gb3, but this is not easily accessible in most provinces. Also, it may be less informative in females and in those patients with late onset disease variants. Other measures like left ventricular mass index and eGFR can vary considerably due to other factors making them not precise enough. If frank disease progression is observed, one may check for neutralizing anti-drug antibodies, but generally a decision is rarely made to stop treatment because the disease progressed. Most patients with Fabry disease are managed through specialized treatment centres in their province or neighboring province. Specialists in Fabry disease monitor for disease-related outcomes, initiating and stopping therapy and end of life support. Biomarker testing, with urine Gb3 or plasma lyso-Gb3 on clinical grounds is not available as an in-house test in any province. The CFDI registry supports a research-based analysis of urine Gb3 and plasma lyso-Gb3 accessible to centres that enroll patients in the CFDI without cost. In many centres, sponsored testing of these biomarkers is used.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Guideline-directed reasons to stop are currently patient preference, severe drug intolerance, treatment futility or very short life expectancy.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

We strongly recommend management by a specialist with experience in Fabry disease or supervision under this type of specialist. We also strongly recommend that the application for disease modifying drug approval be reviewed by an expert committee, such as the CFDI or equivalent, before patients are started on therapy. The specialist may have a background in genetics, inherited metabolic diseases, nephrology, or cardiology. Most patients eventually require additional involvement from multiple specialists (eg., cardiac electrophysiologists, pain specialists, neurologists, transplant teams, etc.).

Pegunigalsidase alfa has been safely and successfully given in Canada to patients enrolled in phase III studies in their home by a visiting nurse. Ideally this would continue if this agent is licensed by Health Canada. Routine administration every 2 weeks in a hospital setting is more expensive and less convenient for patients. Intravenous use in a specialty clinic would also be possible if the home infusion was not acceptable or available.

6. Additional Information

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

We received no outside input or assistance for the completion of the submission.

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

We received no outside input or assistance for the completion of the submission.

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. Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Anna Lehman
Position: Medical Director, Adult Metabolic Diseases Clinic, Vancouver General Hospital; Investigator of CFDI
Date: 08-02-2025

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

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Sanofi*				X
Takeda*				X
Chiesi*			X	
Amicus*				X

***amounts include contributions to CFDI**

Declaration for Clinician 2

Name: Dr. Aneal Khan
Position: Medical Director, M.A.G.I.C. Clinic in Calgary (Metabolics and Genetics in Canada)
Date: 09-02-2025

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

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Sanofi	X Consulting fees, Travel Expenses			X Research grants
Takeda	X Consulting fees, Travel Expenses			X Research grants
Chiesi	None			
Amicus	X Consulting fees, Travel Expenses			X Research grants

*** Place an X in the appropriate dollar range cells for each company.**

Declaration for Clinician 3

Name: Dr. Sandra Sirrs
Position: Medical lead – rare diseases, Provincial Health Services Authority, BC Ministry of Health
Date: 10-02-2025

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Dr. Sirrs has nothing to disclose

Declaration for Clinician 4

Name: Dr Michael L West
Position: nephrologist, professor, Department of Medicine, Dalhousie University, QE II Health Sciences Centre, Halifax NS; Chair, Steering Committee, CFDI Registry
Date: 16-02-2025

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

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Chiesi		**X Consulting fees; speaker honorarium**		
Amicus				**X Research grant; consulting fees, speaker honorarium**
Sanofi				**X Research grant; speaker honorarium**
Takeda				**X Research grant; speaker honorarium**
Octant	**X Consulting fees**			
Glafabra	**X Stock options**			

*** Place an X in the appropriate dollar range cells for each company.**