Common Drug Review
Patient Group Input Submissions

elosulfase alfa (Vimizim) for Mucopolysaccharidosis IVA (Morquio A syndrome)

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
The Isaac Foundation for MPS Treatment and Research/ The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (The Canadian MPS Society) — permission granted to post.

CADTH received patient group input for this review on or before November 20, 2015

Disclaimer: The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

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

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 personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

The Isaac Foundation for MPS Treatment and Research/ The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (The Canadian MPS Society)

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	VIMIZIM – (Elosulfase alfa) – MPS IVA - Morquio A Syndrome
Name of the patient group	The Isaac Foundation for MPS Treatment and Research/ The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (The Canadian MPS Society)
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1.1 Submitting Organization

The Isaac Foundation's mission is to fund innovative research projects that aim to find a cure for MPS, a rare, debilitating, and devastating disease. We provide support for families of individuals suffering from MPS and advocate on their behalf to ensure government funding for expensive, life-sustaining treatments are covered by the health care system.

Founded in 1984, The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (The Canadian MPS Society) is committed to providing support to individuals and families affected with MPS and related diseases, educating medical professionals and the general public about MPS, and raising funds for research so that one day there will be cures for all types of MPS and related diseases.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

The Isaac Foundation

1. BIOMARIN PHARMACEUTICALS: The Isaac Foundation has received sponsorship funds from Biomarin Pharmaceuticals over the course of the past 6 years. Sponsorship has been granted to our Annual GALA FOR A CURE, an event designed to raise funds to find a cure for MPS diseases. Biomarin has been a sponsor of this event since its inception 6 years ago.

2. SHIRE PHARMACEUTICALS: The Isaac Foundation has received sponsorship funds from Shire Pharmaceuticals for various events over the past two years. These sponsorship grants go directly to our MPS II Research program, with all dollars raised funding research projects that aim to find a cure for MPS II (Hunter Syndrome).

3. JANSSEN PHARMACEUTICALS: Janssen Pharmaceuticals, a division of Johnson and Johnson, began supporting our GALA FOR A CURE in 2013 and 2014, and has committed to supporting our event again in 2015. All money provided by Janssen goes directly toward funding research projects aimed at finding a cure for MPS.

The Canadian MPS Society

The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (Canadian MPS Society) provides support to individuals and families affected by MPS. They also provide education to medical professionals and the general public about MPS and raise funds for research. The Society receives unrestricted grants and event sponsorships from Genzyme Canada, Shire Canada, and Biomarin Pharmaceuticals. It declared no conflict of interest in the preparation of this submission.

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

The Isaac Foundation and the Canadian MPS Society has no conflict of interest to declare with respect to anyone playing a significant role in compiling this submission. All work, interviews, and drafting of this submission was supported and completed by our organizations alone.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

Information for Section 2 was obtained using one-to-one conversations with a number of patients using the current therapy, as well as parents of patients on therapy. Online surveys were used and both organizations were able to connect with many of the patients that participated in the clinical trial through these surveys. Personal information was also used, as our organizations help and support numerous families suffering from Morquio A Syndrome. We also have referenced printed sources, published articles, available clinical trial data, and discussed the condition and experiences using the new therapy with the lead investigator responsible for the VIMIZIM clinical trial here in Canada.

2.2 Impact of Condition on Patients

Morquio A Syndrome is a disease that has numerous life-altering and very progressive symptoms. These symptoms include but are not limited to bone and joint disease, heart and airway disease, progressive stiffening of the joints, corneal clouding, hearing loss, and decreased endurance.

All patients that were interviewed for this submission reported that Morquio A Syndrome affects all aspects of their lives. One patient noted, ***"Morquio affects all parts of my life. Every movement has to be thought about to try to minimize pain. From rolling over in bed, to standing up at the kitchen sink to getting into a vehicle all requires forethought."***

A parent of two affected individuals expressed similar experiences dealing with the disease: ***"They are very tiny, which creates a world of issues all in itself, but the amount of energy required to do everyday things is remarkable and exhausting. They cannot do what an average person can do in a day without becoming very tired and sore. The fatigue they feel in their legs and joints is incredibly painful and not always manageable with pain medication. They require regular rest times and time to just find the energy to finish their day. Even just getting dressed is exhausting and doing something as simple as walking up our stairs in our two story home requires a lot of effort."***

"My joints are all affected and because of this I have progressively had to rely on a wheelchair for mobility. Obviously there are limits associated with using a wheelchair that I must deal with. Even grocery shopping is a difficult thing when you have to consider how to carry (the groceries) to the van in the snow in a wheelchair." – Patient Interview

Morquio A Syndrome is a very progressive disease, and all patients suffering from the condition that were interviewed reported numerous activities that they could not do that used to be a "normal" part of their life. Examples of lost abilities include bike riding, ice skating, walking on a beach or trail, dressing themselves, and grocery shopping.

The aspects of this condition that are most important to control are endurance and bone and joint disease. These two symptoms seem to play a crucial role in the quality of life of affected individuals. Improved endurance has an impact on all facets of life and endurance is a good measurement on how well a patient's body is performing. From heart to bones to pulmonary function, increased endurance indicates that those systems are working better. With respect to bone and joint disease, the stabilizing or improving of this aspect of the disease would lead to a better quality of life, reduced reliance of mobility devices, and the potential for pain reduction in all affected joints.

Those surveyed commented that due to their symptoms, they have difficulty with self-care (for many, it's impossible to reach the back of their heads), holding objects, and doing things like opening doors due to decreased wrist strength. They are reliant on others for assistance. One mother of two affected children said, ***"They just can't do what an average person does. Even taking a shower takes 45 minutes and is exhausting. Never mind going for a walk – just putting on their shoes to do that is a huge challenge. They don't have the dexterity to tie their laces and watching them try to get up off the floor can be heartbreaking."***

All respondents have difficulty walking long distances and climbing stairs, which means they are often excluded from sporting, school and/or social activities with their peers or even family members (some reported that they have to avoid certain relatives' homes as they cannot manage to get up and down

their stairs). Due to social isolation and the stigma associated with using wheelchairs, those affected reported challenges with self-esteem and difficulty in forming relationships.

All respondents have had to give up activities that they enjoyed before the symptoms of MPS IV A increased to the point that they were no longer able to participate: some of the children loved to play baseball but cannot catch a ball anymore; some used to love playing mini-stick hockey, but cannot get up off the floor to play anymore; some enjoyed dance classes until they could not keep up; others have given up riding their bikes (one mother commented that her 11-year-old son loved riding his bike so much that when he could no longer manage that on his own, he tried with training wheels, but eventually had to give it up altogether. He also had to give up swimming, even though he had previously been on his school's swim team); and some have given up cooking and baking as it's become too difficult to reach shelves or lift pans. Even preparing simple snacks is impossible for some of the individuals surveyed.

All patients and caregivers interviewed expressed a desire to see the disease stabilized or the progression of the disease slowed down or halted. ***"The most important thing from a mom's perspective is the slowing of the progression of this disease. We are told from diagnosis the disease is progressive and degenerative until the eventual death of our children. There is now hope with the prognosis of slowing this progression and giving our children a more productive and a better quality of life."***

2.3 Patients' Experiences With Current Therapy

Before Vimizim was approved by Health Canada, patients suffering from Morquio A Syndrome have had no access to treatment (unless they took part in the clinical trials). Prior to Vimizim, treating the disease was done by managing symptoms as they appeared. This has led affected individuals to undergo numerous surgical interventions, with more severe effects being seen as the disease progressed. In Canada, 21 patients have participated in the clinical trial, and the patients that I interviewed have all seen dramatic improvements in their condition and general quality of life.

One caregiver noted the impact she has seen on her children while participating in the clinical trial for Vimizim: ***"Since starting on Vimizim the boys have certainly had much more energy and endurance for doing everyday things. They are taking much less pain medications and have had a noticeable decrease in the amount of corrective orthopaedic surgeries. Their lung function tests are improved and the amount of times the boys have had lung related issues has been almost non-existent since starting this trial."***

A consistent theme that showed in all interviews was how stable patients were since undergoing treatment with Vimizim. All reported a marked stabilizing of the condition, which is remarkable for such a progressive disease. One patient remarked what stability really meant to him, and why such stability was important to his quality of life: ***"I think with determination and Vimizim – I would say that I am mostly stable and somewhat improved in some areas. Some might think that "Stable" is not a big thing, but for me it is HUGE. To understand what that means to me you have to understand my situation a bit better. In the period leading up to being invited to participate in the study – I had noticed a steady decrease. Being in my 30's I was getting old for Morquio. It is degenerative. I had noticed the wear and tear on my joints beginning to show. I had a steady increase of pain in my joints and more problems were what I needed to expect. I went to doctors about the problems as they began to show up – things like my elbow, my shoulder, and the break down of my neck fusion. Each looked at my x-rays or MRI and saw how far the disease had progressed and did not want to proceed unless the***

pain became unbearable – the concern was that they could make it worse and if a bone shattered I might lose everything." The symptoms he discusses have been stabilized and no medical interventions were needed.

Current treatment with Vimizim is very effective in controlling aspects of this disease. Recent clinical trial data made available by Biomarin Pharmaceuticals showed a dramatic increase in endurance for patients participating in the clinical trial. This increase in endurance has the potential to manifest improvements into all aspects of disease progression. Endurance is a good indicator on how well the body is working, and any such increase works to improve overall quality of life. Other publications that have delved further into the Clinical Trial data also show efficacy for patients, even when walk test data is removed from the equation ***(C.J. Hendriksz, et al., Multi-domain impact of elosufase alfa in Morquio A syndrome in the pivotal phase III trial, Mol. Genet. Metab. (2014))***

In addition, patients have reported a noticeable drop in medical interventions since beginning treatment through the clinical trial. One caregiver reported that her son had been a candidate for a major operation on his knee and leg bones, a surgery that was expected due to the progression of the disease over a number of years. After some time on the clinical trial, the orthopaedic surgeon now believes that the surgery can be pushed into the future, or may not be needed at all. While he was not able to conclude that Vimizim was the reason that the long-planned surgery didn't need to take place, he did note that the only thing to change for the patient was his participation in the clinical trial. He noted significant stabilization in the knee and leg bones and expressed his belief to the caregiver that the enzyme replacement therapy was the reason.

"We have certainly had so many positive aspects it's really hard to find any negative aspects to this therapy. The possibility of the boys have a better quality of life and living longer is really all we hope for and everything else is a bonus." – Caregiver Interview

However, treatment using enzyme replacement therapy (ERT) for this condition does not come without some level of hardships. While none of the patients interviewed experienced any adverse reactions during their infusions or afterward, Biomarin Pharmaceuticals does indicate on their labeling that anaphylaxis, or a severe life threatening reaction, can occur during the infusion process.

Primarily, the hardships reported during interviews centered on location and travel time associated with receiving infusions. Many patients have to travel multiple hours to and from infusion sites, which makes the process take the better part of one or two days. Added travel to an already tiring infusion process creates an exhaustion level for patients that is difficult to recover from. All patients and their caregivers express a keen desire to have home-infusions. This will cut travel time for infusions down to zero, allows families to better schedule their lives around infusion timelines, and allow patients and caregivers the ability to lead a more normal life. Caregivers expressed a desire to return to the work force full time, and patients expressed a desire to miss less schooling. Home infusions would allow that for all involved.

2.4 Impact on Caregivers

Caregivers face significant challenges caring for patients with Morquio A Syndrome. First and foremost, the stress managing a loved one's progressive disease is unquantifiable, and as many supports as possible should be put in place to help all caregivers of patients suffering from Morquio A Syndrome.

Patients suffering from Morquio A Syndrome require significant medical interventions, long hospital stays, many surgical procedures, and repeated appointments with a host of specialists. These visits,

operations, and appointments cannot be done alone, and caregivers sacrifice a lot of their own time to ensure patients receive company and support during these visits.

While such sacrifice from caregivers is difficult to imagine, it doesn't come without its own rewards for them. One mother expressed both the challenges and the reward in her patient interview: ***"There have always been hardships in having children affected with this disease. The many surgeries, the financial strain of finding equipment for the boys' mobility, the home renovations and van conversions, the emotional stress of having children with so many medical needs has been hard on our family but have also proven to bring us all closer together as a family."***

Many caregivers must leave the workplace for all or a portion of the workweek in order to care for their loved ones battling this disease. With ERT infusions, this may still be the case due to the current need to infuse in a hospital setting. This leaves parents and partners of those affected bringing their loved ones into infusion centres for the day or two-day long treatment (depending on travel time).

All respondents to our survey cited missed work, difficulty finding suitable work or the inability to work full-time as a major stressor. Every single person surveyed reported financial, emotional and relationship stress. Some of the financial stress came from costly home renovations and costly devices and equipment, but much of it came from the employment challenges previously mentioned. Parents commented that their caregiving roles are emotionally and physically draining, and that they are always ***"on."*** One mother compared caring for her adolescent daughter to caring for a toddler, as constant attention is required. One mother commented that she is always ***"waiting for the phone to ring"*** when her child is at school and that she has suffered from panic attacks during and following her son's surgeries due to worries about the high anesthesia risk for those with MPS IV A.

Parents also cited that the demands of navigating the medical, educational and social services systems are exhausting. The extra layer of complexity when planning, scheduling (and executing) their and their children's lives is extremely time-consuming. The impact on siblings was also reported across the board, with many parents feeling their unaffected children's lives are affected by the overall adaptations and sacrifices required due to MPS IV A in the family.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information for Section 2 was obtained using one-to-one conversations with a number of patients using the current therapy, as well as parents of patients on therapy. Personal information was also used, as our organization helps and supports numerous families suffering from Morquio A Syndrome. We also have referenced printed sources, published articles, available clinical trial data, and discussed the condition and experiences using the new therapy with the lead investigator responsible for the VIMIZIM clinical trial here in Canada.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

It is expected that the lives of patients will be improved significantly by this new drug. First and foremost, and much like other enzyme replacement therapies being used for MPS related diseases, stabilization of the disease is expected to occur in all individuals, regardless of when treatment begins. Clinical trial data also points to increased endurance and a decrease in overall GAG accumulation in the

urine of Morquio A Syndrome patients. The decrease in this GAG accumulation indicates a lower storage of these GAGs in the bones, tissue, organs, and muscles of patients. Accumulation of these GAGs results in the clinical symptoms that individuals experience and a reduction in the body would indicate a slowing-down of the disease progression.

Currently, there are no other treatments available for patients so there is a tremendous unmet need for this ERT. The adverse effects that were experienced in the clinical trial setting were very minor compared to the benefit that this treatment offered patients. The opportunity to see improvement in endurance, bone and joint disease, and heart and pulmonary function far outweighs the relatively minor allergic reaction that can sometimes occur during the infusion process. In addition, such reactions during infusion are rare and easily managed by slowing down the infusion process or halting it until the reaction has been corrected and maintained.

Any improvement in this condition can have a profound effect on the quality of life for patients suffering from this disease. All such improvements lead to fewer hospital visits, fewer medical interventions, and fewer doctors' appointments. The results of that lead to less time off work, less time away from school, and more time together as a family. All of these benefits are unquantifiable from a socio-economic perspective, but are incredibly important to the well-being of patients and their families.

a) Based on patients' experiences with the new drug as part of a clinical trial:
All of the patients that were interviewed and on the clinical trial for Vimizim reported improvements in endurance and stabilization in their condition since they began therapy. There were no comments regarding negative effects of the drug on their conditions. One patient summed up the following about their experience on this new drug: ***"Vimizim has helped me have more energy and has kept my condition stable over the past 3 years. I certainly look forward to being able to live my life in much better shape than I expected before I started Vimizim because at that time I had no help, no treatment. Now that I am on Vimizim, when I have a minor setback, I feel confident that it will level out again. It has given me hope that my condition will continue to be stable with my current lifestyle for years to come."***

All of the reported adverse effects were thought to be acceptable for patients receiving this therapy, especially since this is the only treatment available for Morquio A Syndrome. The benefits of treatment reported include increases in weight, strength, height (some have grown several cms. during the past several months), and overall energy levels. Those surveyed said their breathing is better (one mom said her ***daughter "no longer has to gasp for breath"***), their snoring has decreased (one young man no longer requires biPAP overnight) and ear and upper respiratory infections have decreased substantially.

"The drug has changed my outlook on long-term health a lot, I used to think I had an expiry date – one that in my 30's I was getting closer and closer to. Now I don't think of the disease that way – more something that I have to deal with on a day-by-day basis. Overall it has had a truly positive effect on my well-being." – Patient Interview
Those on treatment report waking up feeling better rested, being able to get through the day with a more positive attitude and without naps (which previously were common). Mobility, which is as previously mentioned the most important indicator of quality of life in those with MPS IV A, has increased dramatically while on treatment. The young boy who had given up swimming can now swim back and forth across the pool while his mom watches proudly. One young woman on treatment can walk double the length she could when she started the trial. Stair climbing has gotten easier. One girl on the trial could previously only walk up 2-3 stairs and generally had to be carried. Now, she can manage

30-40 stairs at a time. Several respondents commented that they can now go places they previously couldn't, like long grocery stores aisles and relatives' homes that were previously inaccessible. One young woman who drives said her increased mobility means she doesn't always need to transport her wheelchair in and out of her vehicle as she can now manage short errands without a mobility aid. This has had a huge impact in her ability to lead a more normal, independent life.

Overall, those on treatment have seen their disease symptoms stabilize and they overwhelmingly report better mental health due to knowing their disease is no longer taking its natural course.

The impact of this treatment on the patients and families battling Morquio A Syndrome cannot be understated. All patients discussed the improved quality of life they have experienced since treatment began for them. Older patients on the clinical trial stated their wish was to have had access to this therapy earlier in life, so that some symptoms could have been diminished or avoided altogether. In addition, caregivers expressed the joy and hope that this treatment provides their family, while others talked about the future more than they would have prior to beginning treatment. This was a common theme amongst interviewees, and is summed up nicely by this caregiver: ***"We are hopeful now with this new therapy that we can enjoy many more years together. We all have a new found hope for the future."***

Section 4 — Additional Information

It is our hope that patient input and this comparison are considered and included during this next review. Our organizations, as well as the patients and families consulted during the last review, felt that our input was not taken into consideration. In essence, there was frustration that our input was sought after and then ignored when crafting the previous recommendation. These frustrations were shared with Mr. Brent Fraser at the Ontario Ministry of Health before he took on his new role at CADTH. We were assured that the process was changing and evolving. We expressed our hope that patient input would take on more significance moving forward.

As such, in addition to our patient stories included in the above sections, we are including the following additional information put together by both The Isaac Foundation and the Canadian MPS Society. This section was put together by both The Isaac Foundation and the Canadian MPS Society and compares the rationale for the DO NOT LIST recommendation with the document created by NICE (National Institute for Health and Care Excellence) in the UK.

Recently, NICE recommended full reimbursement for patients throughout the UK. The comparison between the two documents couldn't be starker. Whereas the CDR team has not consulted the experts that deal with this disease on a daily basis, NICE sought evidence and advice from a wide range of people involved with Morquio A Syndrome and with Vimizim. Where CDR couldn't be certain what the clinical significance of some outcomes were with respect to the clinical trial, NICE worked to clarify and understand. The CDR Clinical report mentions the use of their "clinical expert" 19 times, each time in the singular. The NICE report talks at length about the many experts they consulted. In the end, this makes a difference and it's important for our patients, families, and for The Isaac Foundation and The Canadian MPS Society to ensure the inaccurate and lack of expert opinion in the initial CDR is brought to the forefront of this new process.

Quick Snapshot:

Canada: Approximately 70-100 patients
CDR Recommendation = Do Not List
Clinical Experts Consulted = 1
Clinical Experts That Have Treated and Used Vimizim Consulted = 0

UK: Approximately 88 patients
NICE Recommendation – Reimbursement for All Patients
Clinical Experts Consulted = Multiple, across specialties
Clinical Experts that Have treated and Used Vimizim Consulted = Multiple, across specialties

CDR Denial Rationale Compared to Real-World Evidence and Information
CDR Reason 1

- While one double-blind, phase 3, placebo-controlled randomized controlled trial (RCT) (MOR- 004; N = 177) demonstrated that treatment with elosulfase alfa was statistically superior to placebo for improvement in six minute walking distance (adjusted LS mean difference: 22.5 m; 95% CI, 4 to 41 m), the clinical relevance of this finding is uncertain.

This rationale is ludicrous – if the "clinical relevance of this finding is uncertain", why has the CDR team not taken the time to solve that uncertainty? Rather than dismissing such statistically significant and important findings of a controlled clinical trial, the CDR committee should have taken steps to fully understand the relevance of such findings. It is possible to speak with the clinical experts that deal with this disease on a daily basis, the practitioners who have had patients enrolled in the clinical trials here in Canada and around the world, patient organizations, and patients themselves to help shed light on what these findings truly mean. Instead, the CDR committee decided to consult one person – a person who has never treated this disease and has never seen the impact that Vimizim has had on patients.

The NICE committee in the UK did such investigations regarding the clinical significance of the 6-minute walk test. Their conclusion was that the walk test was an appropriate measure of clinical efficacy of Vimizim and that results of such increase in walking distance should not be underestimated. To wit:

- The Committee concluded that, as a proxy outcome that provides a broad measure of overall functioning, **the 6MWT was broadly appropriate and useful in giving some indication of the real-life benefits of treatment experienced by patients.**
- The Committee discussed the endpoints assessed in the clinical trials. It understood that the primary outcome in the randomized clinical trials, **the 6-minute walk test (6MWT), is a surrogate outcome that provides a broad measure of overall functioning, including musculoskeletal health, cardiovascular and respiratory aspects, pain and fatigue.**
- The Committee noted that the improvement in 6MWT with elosulfase alfa was statistically significant compared with placebo (see sections 4.6 to 4.8). **It heard that the 6MWT has been used successfully in other MPS disorders, and is used in clinical practice to monitor progress in people with MPS IVA**. Patient experts noted that improvements in 6MWT scores during clinical trials reflected improvements in other aspects of their condition and their quality of life, and emphasized that the ability to move around (for example, at school) is an important part of everyday life.
- Clinical experts noted in their submissions that the surrogate and composite measures used in trials were not satisfactory but were the only available options. A patient expert noted in their submission that the improvement in quality of life associated with elosulfase alfa might be greater than the

increase in 6MWT, and noted that even a small improvement in endurance could make a substantial difference to the quality of life of a person with MPS IVA.
- Patient expert submissions highlighted that a small improvement in mobility can make the difference between needing to adapt their whole house for a wheelchair and being able to walk around the home independently, or allow visits to shops or friends' houses that are not wheelchair accessible.

Within the literature, the efficacy of Vimizim was noted using the results of the 6MWT, but also confirmed to be efficacious even without that data. In the peer-reviewed publication "Multi-domain impact of elosulfase alfa in Morquio A syndrome in the pivotal phase III trial", the efficacy without the 6MWT is noted: "The results of the O'Brien analyses showed improved efficacy (lower P-values) of elosulfase alfa qw as more variables were added, indicating that changes in each of these variables contribute to its efficacy**. The results remained statistically significant without 6MWT or height z score included in the O'Brien analysis. These findings suggest that the efficacy of elosulfase alfa is not only driven by its impact on 6MWT distance."**

CDR Reason 2
- Treatment with elosulfase alfa has not been shown to improve other clinical endpoints, including reducing pain, fatigue, disease progression, or the need for surgical intervention.

Again, this rationale for imposing a Do Not List recommendation for the drug is misleading and not based on sound experience from patients or practicing clinicians. The Clinical trial was not designed to look at these clinical endpoints, as is the case with all other rare disease clinical trials. Therefore, the clinical trial did not note improvement in the areas the CDR committee were looking for. However, there have been numerous peer-reviewed studies that were published after the clinical trial ran its course and could have been looked at by the CDR team as they sought direction on Vimizim. Again, the NICE committee in the UK used relevant experience from clinical experts, patient organizations, and real-world experience with patients to comment the following in their recommendation to reimburse Vimizim countrywide:
- The Committee discussed the clinical benefits associated with elosulfase alfa as experienced by patients. It heard from the patient experts that, with treatment, patients can expect the disease to stabilize and also to get better. **The clinical experts stated that most people treated with elosulfase alfa experienced clinical improvements beyond what could be attributed to a placebo effect, including improved endurance, pulmonary function, anthropometrics, wheelchair dependency and quality of life. The patient experts also described positive effects on sleep, pain, energy levels and fatigue, dexterity and ability to complete everyday activities.** However, these benefits were not known at the onset of the clinical trials for elosulfase alfa, so the trials were not designed to capture them.

- In general, the **patient experts considered that treatment offered substantial benefits to people with the condition, with some going from being non-ambulant, unable to speak and having a short life expectancy to being in stable health, able to speak again and resume university studies**.

- **The Committee heard that young people who started treatment maintained their ability to walk and continued to grow. In addition, treatment improved pulmonary function**, so reducing the frequency and severity of chest infections and allowing a normal recovery from common respiratory illnesses.

- The patient experts also highlighted the quicker recovery from physical exertion with elosulfase alfa, which saved energy for other day-to-day activities. Based on the patient testimonies, the Committee concluded that elosulfase alfa improved various abilities and aspects of health compromised by the disease, and that the patients' experience with treatment had been largely positive, with health and quality of life improving significantly in some patients.

- The Committee understood that MPS IVa is a complex and highly heterogeneous disorder, and evidence on the natural history of the condition is still evolving. It heard that, at the outset of the clinical trials for elosulfase alfa, the clinical community believed that MPS IVa was purely a skeletal disorder, and this was also supported by the literature. The general belief at the time was that enzyme replacement therapy would not treat musculoskeletal symptoms. However, the clinical experience during the trials was unexpectedly positive, and remarkable improvement was seen in some patients, including those who had established skeletal disease for many years. It became apparent that the skeletal features, although important, were only part of a multi-system disorder, and that non-skeletal features, including cardiac and respiratory complications, contribute heavily to the burden of illness

CDR Reason 3

- There was no statistically significant difference between elosulfase and placebo for improvement in the endurance of mucopolysaccharidosis (MPS) IVA patients, as measured by the three-minute stair climb test (3MSCT) (adjusted LS mean difference: 1.1 stairs/min; 95% CI, –2.1 to 4.4 stairs/min).

On the surface, this statement is accurate. However, the CDR report neglects to note that this data was a secondary efficacy measurement and the trial data and, by extension, approval throughout the developed world, didn't hinge on the data collecting using this test. As, well, it wasn't taken into consideration that the 3-minute stair climb test at each institution was difficult to perform. For instance, at the Hospital for Sick Children, many of the patients enrolled in the Clinical Trial were able to walk the entirety of the 8 floors during their walk test. They reached the maximum height available to them before the time was completed but still had the ability to continue the climbing. These types of events, which took place in many centres, impacted the measurable goal considerably.

The NICE report acknowledges this appropriately, while the CDR report does not address it at all. Directly from the NICE report:

- The results of MOR-004 suggested that elosulfase alfa 2 mg/kg/week provided improvements in endurance, pulmonary function, anthropometrics and quality of life compared with placebo at week 24. Statistical significance was not reached, although the company noted that the study was not powered to detect differences in secondary or tertiary outcomes.

Within the published literature, which are readily available to the CDR teams, the problems with the 3-minute stair climb test (3MSCT) were noted, and with possible explanations for the lack of efficacy data collected using this test. For instance, Katherine A. Lyseng-Williamson notes in her paper entitled **"Elosulfase Alfa: A Review of Its Use in Patients with Mucopolysaccharidosis Type IVA (Morquio A Syndrome)"** that "Changes in the 3MSCT (secondary efficacy outcome) and tertiary outcomes did not differ significantly between elosulfase alfa and placebo in the 24 week trial. The **lack of a significant BGD in the 3MSCT may be because: this outcome is not suitable for use in patients with MPS IVA due to their baseline ambulatory difficulties; the duration of the trial was not long enough to show a difference…**"