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CADTH COMMON DRUG REVIEW

Patient Input

inotersen (Tegsedi)
Akcea Therapeutics Inc.
Indication: Hereditary transthyretin amyloidosis

CADTH received patient input from:
Hereditary Amyloidosis Canada

March 15, 2019

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Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Tegsedi (inotersen)** **Treatment of stage 1 or 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)**
Name of the Patient Group	**Hereditary Amyloidosis Canada**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
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1. About Your Patient Group

Hereditary Amyloidosis Canada (HAC) is dedicated to supporting the needs of patients, caregivers and families affected by hereditary ATTR amyloidosis. The group was formed to unite the hATTR amyloidosis community across Canada, and to help make connections between patients, caregivers and healthcare providers in both Canada and globally. HAC's mandate is to provide the hATTR amyloidosis community with direct access to information about the disease, the pathway to diagnosis and treatment, and up-to-date clinical trial information, in order to improve patient outcomes. HAC also supports the hATTR community to advocate for what they need to live their best lives with this rare and devastating disease. www.madhattr.ca

2. Information Gathering

The information was gathered through both an online survey and telephone interviews. All of the data was contributed anonymously.

Hereditary Amyloidosis Canada developed and designed a 10-minute, 18-question online survey that was disseminated in English and French. Recruitment was undertaken by HAC and other members of the hATTR community through social media and other online platforms, as well as direct email to physicians, patients and caregivers. The online survey was open between February 11th and March 1st, 2019. There were 25 respondents in total (13 hATTR patients, 10 hATTR caregivers/family members, 1 patient with another form of amyloidosis and 1 unidentified). The respondents were from Canada (16), USA (6), UK (1), Australia (1) and unknown (1).

The telephone interviews were all conducted by Anne Marie Carr, between January 21st and February 14th, 2019. There were 7 people interviewed (6 patients, 1 caregiver), all of whom had experience on Tegsedi. As there were no clinical trials for Tegsedi done in Canada, only one of the people interviewed was Canadian.

3. Disease Experience

Most people reported that the time to a hATTR amyloidosis diagnosis was between 1 and 5 years from the when the patient first sought medical care for their symptoms. Some reported that diagnosis was quicker (a few weeks to under a year), but many of these patients were aware that hATTR amyloidosis ran in their families. A number of patients reported seeing various specialists and being misdiagnosed, including a few patients who knew of other relatives who had been diagnosed with the disease.

> *"3 years after seeing many different physicians i.e. cardiologist, respirologist, 2 separate angiograms, stress tests, etc. Most of the physicians that I saw were not very knowledgeable regarding hATTR and I was misdiagnosed."*

Most people reported that the disease limited their ability to perform daily tasks such as food shopping, meal preparation, eating, housework and maintenance, personal care/bathing, etc. Some patients reported that their symptoms (neuropathy, severe diarrhea, extreme fatigue) limited their ability to work, and some reported having to leave their jobs. Others reported refraining from participating in leisure activities and social/family events due to their symptoms. Some also noted that their loved ones ultimately became fully dependent on family members and outside support for their care and survival.

> *"My mother's well-being, independence, and physical abilities were impacted gravely. Her body slowly shut down as her heart, digestive tract, and nervous systems all became "polluted" by this monster of a disease. She lost all her appetite and had trouble eating. In the end, she was given a feeding tube, she had an ileostomy as her large intestine had to be removed, and she had a tube in her urethra as she could no longer get out of bed to urinate. This was very hard on the family and on her. Her mind was 100% sharp right to her last breath. Her biggest complaint was that she felt overwhelmingly fatigued. Mom was at home for most of her disease and fully dependent on family for help. She spent the last year in Complex Care as her needs were so great."*

Significant deterioration in the patient's quality of life contributing to emotional distress was reported by the majority of patients and caregivers in the survey. Many responded that their lives are consumed by managing their disease, or by caring for their loved one with the disease. Many noted that the quality of life of the patient becomes very poor leading to feelings of uselessness, hopelessness and depression. Caregivers and family members also reported an impact on their mental health, causing stress, depression, anxiety and fear for the future when others in the family have been diagnosed.

> *"Quality of life as a patient, suffice to say, I am a shadow of my former self. Anything that requires fine motor skills is a challenge. Any physical activity has become almost impossible. The bathroom issues are another saga. Whenever I am out, the first thing I need to find is the washroom. Due to the autonomic conditions, even a few second delay ends in disaster. Blood pressure tanks. Dizziness upon standing. Uncooperative limbs climbing a flight of stairs or going downstairs. So, quality of life is impaired drastically due to this illness. We desperately need some treatment to assist making us feel somewhat human again."*

The majority of patients and caregivers noted that the most critical need for symptom control is slowing the progression or reversal of peripheral neuropathy (pain, numbness, sleep issues) and autonomic neuropathy affecting the gastrointestinal system (severe diarrhea, vomiting, choking) and blood pressure. Fewer patients and caregivers mentioned cardiac symptoms or the need for control of symptoms like heart palpitations, congestive heart failure, fatigue or shortness of breath.

When asked to what extent the person diagnosed with hATTR had problems or difficulties with a range of symptoms, the vast majority of patients reported being most severely impacted – and regularly incapacitated – by symptoms caused by nerve damage, including tingling, numbness and burning pain. A significant percentage of patients reported being severely affected by GI symptoms and cardiac symptoms, such as fatigue and shortness of breath. Patients noted being the least affected by symptoms related to kidney disfunction, brain disfunction and eye problems.

- **Nerve damage: tingling, numbness, burning pain, carpal tunnel, weakness** – **88%** report experiencing "severe" to "incapacitating" symptoms, with **36%** experiencing incapacitating symptoms regularly
- **Cardiac: leg swelling, fatigue, shortness of breath, dizziness** – **60%** report experiencing "severe" to "incapacitating" symptoms, with **24%** experiencing incapacitating symptoms regularly
- **GI: diarrhea, nausea, constipation, urinary tract infections** – **48%** of patients report experiencing "severe" to "incapacitating" symptoms, with **16%** experiencing incapacitating symptoms regularly
- **Sexual dysfunctions, sweating, dizziness upon standing, weight loss** – **44%** of patients report experiencing severe to incapacitating symptoms, with **24%** experiencing incapacitating symptoms regularly
- **Cardiac: palpitations, arrhythmia, chest pain** – **40%** of patients report experiencing severe to incapacitating symptoms, with **12%** regularly experiencing incapacitating symptoms
- **Kidney dysfunction** – **72%** of patients report experiencing no or minor symptoms, whereas **16%** of patients report experiencing severe to incapacitating symptoms
- **Eye: glaucoma, pupil abnormalities, blurred vision, detached retina** – **72%** of patients report experiencing no or minor symptoms, with **8%** experiencing incapacitating symptoms regularly
- **Brain dysfunction: dementia, movement control, headaches, seizures** – **68%** of patients report experiencing no or minor symptoms, with **24%** reporting severe symptoms, but none that are regularly incapacitating

4. Experiences With Currently Available Treatments

More than half of the people surveyed said they/the patient had received or were currently receiving treatment specifically for hATTR amyloidosis, and 9 said they had not received or were not currently receiving treatment for hATTR. These responses underscore the significant unmet need for disease-specific treatment options.

Most patients reported that they had received treatment for their disease – many mentioned diflunisal (NSAID), but only two patients among those treated with the drug felt it was effective. About one-third of patients had not received any treatments at all and one person reported having had a liver transplant because no treatments were available at the time. A few patients said they had been prescribed treatments for symptoms including water retention and explosive diarrhea. Two patients mentioned having been treated with revusiran which has since been discontinued.

Among the patients treated with diflunisal, most noted that they continued to experience symptoms and saw their disease progress, and a few had to discontinue treatment due to side-effects. Conversely, two patients on diflunisal felt that the drug slowed their disease by suppressing the development of amyloid proteins.

Most patients treated with diflunisal reported not experiencing any side effects, however a few mentioned increased bowl /stomach issues, reduced kidney function, and interactions with other drugs. One respondent said that the side-effects to withdrawing the only dug for the disease (presumably revusiran) are rapid onset of peripheral neuropathy and the continued deterioration of the heart.

Some patients noted having "extreme difficulty" accessing treatment in Canada, which they found to be "distressing, tiring, time-consuming and extremely expensive." Financial barriers to accessing treatment were mentioned by one third of respondents, including the cost of travel to the nearest clinic in Canada or the U.S. for treatment which resulted in time off work. Patients also mentioned that treatments for hATTR which were approved in the U.S. and in Europe were either not approved or not funded in Canada, and therefore out of reach due to the high cost of treatment and travel to get it. A few patients mentioned having difficulty accessing diflunisal due to supply issues.

Six patients experienced difficulty swallowing diflunisal, with some frequently choking on the pills, while most patients on treatment did not report any difficulties.

5. Improved Outcomes

According to the survey results, providing neuropathy symptom relief (primarily from pain) was the most significant improvement people hoped Tegsedi would be able to provide to the health of patients with hATTR – 72% of people included this in their response. This was followed by an improved quality of life and slowing the progression of the disease. One caregiver responded *"This would be amazing. They could lead a normal life. My dad right now without treatment is a vegetable not able to do anything."*

Assuming that the desired improvements were provided through Tegsedi, respondents were asked how their daily lives as patients/caregivers would be different. People mentioned the ability to go for a walk, no longer having a fear of leaving the house (often because there is no washroom close by), being able to help around the house (i.e. cutting the grass, shoveling snow), getting a good sleep, being less exhausted and suffering from less anxiety/depression.

Again, assuming that the desired improvements were provided through Tegsedi, respondents were then asked how their quality of life as patients/caregivers would be different. People noted overall that their quality of life would return to normal – they would have less/no pain, have full feeling in their hands/feet, be able to return to work, be able to travel, have a healthy appetite, be able to plan for the future, have a positive outlook on life and once again feeling like a part of the family.

6. Experience With Drug Under Review

Six patients and one caregiver who had experience with Tegsedi were interviewed by telephone. Two out of the six respondents (patients) have been on Tegsedi for over four years. Two out of the six have been on Tegsedi for approximately nine months and the two others just started Tegsedi in February, 2019.

Four out of the six respondents indicated they have been able to access Tegsedi through a clinical trial (one of whom has transitioned over to private insurance). The other two indicated they have access through a compassionate program set up by the drug company.

When asked what Tegsedi has meant to their quality of life, two out of the six respondents indicated a significant improvement. Not surprisingly, both of these individuals had been on the drug for over four years. For the two who just started Tegsedi, it was too early to tell what impact the drug has had. It's also worth noting that three individuals had tried diflunisal prior to going on Tegsedi (one of whom had also tried revusiran).

By way of comparison to other treatments, the three respondents that had previously tried other therapies were asked to describe the benefits and disadvantages experienced with Tegsedi. One person indicted that their neuropathy had remained fairly stable under Tegsedi (unlike revusiran, when they went from no neuropathy to too much). That individual noted no disadvantages with Tegsedi. The second person indicated that their neuropathy is better, their eyes feel better, they don't have dizziness anymore and while their autonomic problems are still there, those issues are also improved. That individual also noted no disadvantages from Tegsedi. The third person noted *"a slight improvement in my GI issues and in my polyneuropathy. The only disadvantage has been nuisance level. Weekly injections and lab visits are no fun, but not terrible."*

Again, by way of comparison to other treatments, the three respondents that had previously tried other therapies were asked if Tegsedi has been easier to use. Two people said diflunisal was easier to use, but that it did not seem to stop the development of symptoms for hATTR. One person said both Tegsedi and diflunisal have been easy to use, while another saw Tegsedi and revusiran as comparable.

In terms of how the benefits of Tegsedi have impacted the quality of life of patients, the survey results indicate an increase in hope for the future, a clearing of symptoms and more energy. One person said *"It's been a miracle as indicated by how I feel, how I perform athletically, my echocardiogram results and my cardiac MRI results."*

In terms of how the disadvantages of Tegsedi have impacted the quality of life of patients, only one person noted anything negative; namely, needing to schedule weekly injection and lab visits, and having to plan travel around these appointments.

When asked about what side effects people have experienced on Tegsedi, brief redness/soreness at the injection site was mentioned by five of the six respondents (one person indicated no side effects). In every case, the respondents have been able to tolerate and manage the redness/soreness experienced with little issue. Other side effects noted were chills/flu like symptoms immediately after injection (one person), headaches and bruising at the injection site.

7. Anything Else?

All of the survey respondents agreed that it was Very Important that hATTR patients have the option to access Tegsedi in a timely manner, if it is appropriate for them.

Respondents were also asked what it would mean for those affected by hATTR to have access to Tegsedi. The overwhelming response was hope - hope for a better life, hope that they thought they would never have and ideally hope for a normal and long life. The ability to once again enjoy life, including both a better quality of life and quantity of additional years, was also mentioned. A couple of people described Tegsedi as *"a lifeline"*. Other responses focused on choice (having a viable treatment option for patients), eliminating pain and fatigue and a return to being a productive member of society.

Without publicly funded access to this drug, patients sit with a death sentence. Given the organs that are involved, we know after many years of suffering progressively that this disease will slowly, but surely, kill patients. Access to Tegsedi means hope, and that's not too much to ask for hATTR patients and their families.

Appendix: 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

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.

   Yes, we worked with Impetus Digital to design, collect and analyze the survey results.

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
None				

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: Anne Marie Carr
Position: Founder
Patient Group: Hereditary Amyloidosis Canada
Date: March 13, 2019