Ontario
Ministry of Health and Long-Term Care

Ontario Public Drug Programs
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Submission of Patient Evidence

Please send completed submission and/or any additional relevant information to the Ontario Public Drug Programs, Patient Evidence Submission, 5700 Yonge Street, 3rd Floor, Toronto ON M2M 4K5, fax to 416 327-8123 or email to PatientSubmission.OPDP@ontario.ca.

Section I - Author Information

Date *(yyyy/mm/dd)*	Drug and Indication
2018-12-12	Drug: Edaravone Indication: Amyotrophic lateral sclerosis (CDR)

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Section II - Conflict of Interest Declaration

The author and the patient group must declare any potential conflicts of interest that may influence or have the appearance of influencing the information submitted. Examples of conflicts of interest include, but are not limited to, financial support from the pharmaceutical industry *(such as educational/research grants, honoraria, gifts, and salary)*, as well as affiliations or personal/commercial relationships with drug manufacturers or other interest groups.

The following companies have sponsored the ALS Canada Research Forum scientific conference with financial contributions of less than $10,000 each: AB Science, Cytokinetics (annual contribution over each of the last 2 years), Innovative Medicines Canada and MT Pharma.

Section III - Impact of the Disease/Condition

What symptoms and problems do patients have as a result of the disease/condition? How does the condition affect day-to-day life? For example, are there activities that patients are not able to do as a result of the condition?

See Appendix for response

Treatment outcomes that matter most to patients

What are the most important aspects of the condition that patients would like to see addressed by treatments?
In terms of treatment efficacy and side effects, what are patients getting from the existing treatments and what would patients like new treatments to do differently?
Are there other practical implications to be considered in determining the value of a treatment? For example, how do treatments impact patients' or caregivers' daily routine or lifestyle?
In addition to the drug cost, are there other financial implications to patients or caregivers *(e.g. traveling cost, time away from work, drug disposal issues, drug administration supplies)*?

See Appendix for response

Information from patients who have used this drug

For patients who have used this drug as part of a clinical trial or from a manufacturer's compassionate supply or have purchased it through other means (private insurance or paid out of pocket).

What positive and negative impacts does the drug have on the condition?
Which symptoms is the drug best or worst at treating *(advantages and disadvantages)*?
What difference does the drug make to patients' long-term health and wellbeing?
What are the side effects of the drug, which ones are patients prepared to put up with, and which ones do they find unacceptable?
How does the drug compared with other available treatments in terms of efficacy, side effects and other practical implications *(e.g. administration, time, costs)*?

See Appendix for response

Confirmation of Authorship:

☒ I declare that I am the sole author of this submission and confirm that no other parties had input into the submission.

Signature 

Date *(yyyy/mm/dd)* 2018-12-12

APPENDIX: SUBMISSION FROM THE ALS SOCIETY OF CANADA

DECEMBER 12, 2018 – Drug: edaravone; indication: Amyotrophic lateral sclerosis

SECTION III: IMPACT OF THE DISEASE/CONDITION

ALS is a terminal disease that gradually paralyzes people because the brain is no longer able to communicate with the muscles of the body that we are typically able to move at will. Over time, as the brain's connection with the muscles of the body breaks down, someone living with ALS will lose the ability to walk, talk, eat, swallow, and eventually breathe.

Every year, ALS kills approximately 1,000 Canadians and a similar number are diagnosed. There are currently about 3,000 people living with ALS in Canada, approximately 1,000 of which live in Ontario. The causes are unknown and 80% of people with ALS die within two to five years of being diagnosed. There is no cure and only one other treatment option is available (riluzole). **Edaravone is only the second ALS treatment** to be approved by Health Canada and **the first in nearly 20 years.**

The impact of the disease on people and their families – emotionally, financially, and psychologically – is tremendous. In June 2018, ALS Canada conducted a survey of 575 people across Canada including people living with ALS (hereby referred to as patients) as well as their caregivers and people who lost a loved to ALS. In the results, one respondent noted that *"**ALS changes everything**"* and ***"took over my life,"*** another described living with ALS as "***running full speed on a treadmill but still moving backwards,"*** and a third described it as ***"[s]lowly being imprisoned in a non-functioning body."***

People living with ALS experience a wide variety of symptoms, which progress over time as they become increasingly paralyzed. Patients, their families, and caregivers must constantly adjust to additional losses in motor function. As one patient shared, ***"Every day I find something else I cannot do and I mourn the loss."*** Several other respondents noted in the June 2018 survey that one of the daily impacts of ALS is the **increased time and effort** that it takes to do things that were once simple.

As ALS causes motor neurons to stop communicating with the muscles in the body, muscles begin to atrophy from disuse. Consequently, **muscle fatigue and discomfort** are ever-present, with 96% of patients surveyed in June 2018 experiencing decreased muscle tone, which affects daily life for patients and caregivers: "***I cannot lift my arms above my chest, so [that makes it difficult to do] all hygiene, showering, dressing, [and my] hair."*** The disease's effect on muscles resulted in 70% of patient respondents needing assistance with mobility, which 66% of caregivers noted has significantly affected or completely changed their lives. The physical requirements of providing assistance is challenging for many caregivers.

Many people living with ALS also struggle with **pain.** In the June 2018 survey, 42% of patients reported they sometimes experience pain, another 18% experience pain daily, and another 10% experience pain multiple times per day. The physical symptoms brought on by ALS also negatively affect sleep, with 73% of patient respondents experiencing **insomnia** caused by discomfort. Patients also experienced headaches, stomach problems and itchiness. **Losing control of one's bladder or bowels** is also a difficult but common experience for 52% of patients. As a result, patients often require assistance with self-care. Out of 175 patient respondents in June 2018, 58% had **trouble breathing**, and 58% experienced **choking** episodes. Nearly half of patients (48%) reported experiencing **reduced food intake and weight loss**.

These symptoms have a significant impact on their lives. One patient expressed that they are ***"losing autonomy bit by bit. Humiliated in public by the drooling and inability to eat properly and drink."***

Patients also require varied degrees of assistance from caregivers and medical workers to eat or drink properly, prepare food, or use a feeding tube. This affects the lives of caregivers, with 59% stating in the June 2018 survey that their day-to-day lives were significantly negatively affected or completely changed. One caregiver noted that ***"[f]amily dinners changed and I had a hard time eating at the table enjoying a delicious meal while he was fed through a tube. His empty chair at the dinner table was an emptiness like no other – even though he was just in the other room."***

As ALS progresses, people have greater **difficulty communicating,** with 67% of patients in the June 2018 survey indicating they have difficulty forming words or projecting their voice. This is a significant challenge for many patients, with one indicating that they "***can't smile, sing, laugh or tell jokes***." To address this, 45% of those respondents received assistance to speak and 50% received assistance to type or write, which significantly affected the daily lives of both patients and caregivers. One caregiver noted that "***never hearing my mom's voice again was heartbreaking."***

The physical symptoms of ALS have significant **impacts on emotions and mood** of both the patient and the caregiver. Feelings of apathy or depressive behaviour were experienced by 69% of patients in the June 2018 survey. **Isolation** from family and friends and loss of independence greatly impact people diagnosed with ALS. One Ontarian living with ALS noted that ***"[i]t has been 6 months since I hugged anyone."***

Caregivers' mental health is also affected, with some developing anxiety and depression or finding *it* ***"so hard on the family to watch [our loved one] deteriorate."*** The lack of options for treatment made some caregivers feel ***"helpless"*** and ***"hopeless"*** and the ***"[l]evel of psychological distress was palpable… financial and psychological impact and burden are unbelievable with a diagnosis of ALS."***

A diagnosis of ALS and the realities of living with the disease profoundly affect people's day-to-day lives. Of those surveyed, 54% of patients and 80% of caregivers reported that family life is significantly negatively affected or completely changed. Much of this is due to the intense and sustained efforts of providing care during the course of ALS. Work or school life was also significantly affected: [translation] ***"I am less physically strong so I get tired more quickly and in my job as a police officer had to be re-assigned to a light-duty office worker."***

ALS also significantly affects **finances**. The average cost of ALS to a family is between $150,000-$250,000.[1] In the June 2018 survey, the financial situations of 49% of patients and 54% of caregivers were significantly negatively affected or completely changed. One patient described the impact: ***"I am in more debt [than] I care to admit and that's just from having to buy medical equipment. Not accounting for home modifications and transportation methods [and g]as for appointments that are out of town."*** Many patients and caregivers are unable to work in order to cope with the demands of the disease, while others have to adjust their work schedule or hours. One caregiver respondent stated that ***"Assistance that was provided under OHIP was not in the realm of enough. Even when she was in a hospital we had PSWs to help. [Twenty-four] hours of assistance was needed, both hospitals she was in didn't have enough people to provide the overwhelming level of care that was needed. It was extremely expensive."***

[1] Gladman, M., Dharamshi, C., and Zinman, L., Economic burden of amyotrophic lateral sclerosis: A Canadian study of out-of-pocket expenses, *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2014 Sep;15(5-6):426-32. doi: 10.3109/21678421.2014.932382. Please note that the out-of-pocket expenses cited in this paper include lost income from patients/caregivers having to quit/leave their jobs.

When recently asked by ALS Canada (December 2018) how day-to-day life has been affected by ALS, a patient in Ontario shared the following:

> ***I went from being an active, fit and always busy man in the prime of my life to sitting in a lift chair all day. Everything I loved to do involved my hands and they are what I lost first. My 8 year old daughter and I were inseparable and always hanging out and doing hobbies. My work made me proud and I had worked hard to climb the ladder, I was the guy that everyone came to [but] now I can't even have a conversation with them and visits frustrate and wear me out. There is always somebody in the house, I am only alone when I am sleeping and even then my wife uses a monitor in case I need assistance. My wife has taken on everything and I have to watch her break down and try to juggle it all. My daughter wants the old me back and misses the way life used to be. I am a shell of the person I used to be but my mind has stayed the same allowing me to experience every loss and change but also allowing my mental strength and determination to push me through this monster.***

TREATMENT OUTCOMES THAT MATTER MOST TO PATIENTS:

The ALS community shared that they highly desire treatments that will slow disease progression or delay symptom onset. They would like to see a treatment that would enable them to maintain mobility and independence, give them more time with their family and friends, continue their professional or school lives, work on their hobbies, and feel like themselves.

In the June 2018 survey, patient respondents identified mobility, communication, muscle weakness, stiffness and atrophy, swallowing, and nerve pain as important aspects to be addressed through treatment. When asked what it would mean to them if edaravone were able to delay the progression of ALS, several words reappeared many times among respondents: *"**more time**," "**everything**," "**priceless**"* and *"**the world**."* Slower progression of ALS would enable them to *"**sustain some independence**" and "**continue to lead a fulfilling life.**"*

Caregivers noted they would like to see improvements in all symptoms of ALS, often focusing on the ones that affected their loved ones. For one caregiver whose loved one's disease had progressed, ***"[i]t would have meant a great deal if it could have slowed the progression. Everything was so rapid, there was no time to plan in advance and every accommodation was quickly out-stripped by need."*** One caregiver responded that it would mean "***more family and community time, Christmas, birthdays, camping, helping others with ALS… more hugs and I love yous … more time to treasure**."* Another caregiver noted that slower progression ***"would have allowed my father a little more time between losses of mobility to accept and grieve the loss of his independence."***

When asked what delayed onset of disease symptoms would mean for them, patients responded that it would *"**reduce depression and anxiety**," and allow for them to "**still have [the] ability to experience and enjoy the everyday activities that are so important to quality of life**."* Respondents also noted that delayed onset would result in *"**less financial hardship**,"* and help them *"**stay at home longer.**"* For some, it would mean they *"**have longer to live a normal life**."* For others it would mean *"**more self-reliance; delayed need for more invasive treatments; delayed increasing disability**,"* and they would *"**feel like there was a point to staying alive**."*

Currently, the only other medication that has received market authorization from Health Canada to extend survival for those with ALS is riluzole. But due to the lack of drugs that modify the disease or delay its progression, responses from the June 2018 survey suggest that many patients are accessing a

variety of experimental or off-label medications from outside Canada because there are no other options available.

In the June 2018 survey, of those who described their experiences with riluzole, some patients noted their mood improved and they had more energy. One noted it is easy to take, while others said they had not seen any improvements. Patients also report some negative experiences with riluzole. One patient noted it caused cramps; two others noted it made them feel sick; one patient discontinued its use due to high levels of liver enzymes, and another found it caused heartburn which later subsided.

In terms of the host of other medications many patients take to manage ALS symptoms, many in the June 2018 survey reported experiencing emotional and physical benefits, including that they *"**help with secondary control of sadness and anxiety of coping with the disease**."* However, some felt there was no relief to their disease symptoms, as one patient noted: *"**there is really nothing that has worked effectively to control the symptoms without causing another symptom**."*

Out of 163 patient respondents in the June 2018 survey, 55% somewhat disagreed, disagreed or strongly disagreed with the statement "**My current treatments are able to control my ALS symptoms**" while 22% neither agreed nor disagreed and 23% somewhat agreed/agreed/strongly agreed. When asked to explain their responses, patients noted that *"**because they do not slow down the progression of the disease, the symptoms of ALS only increase**,"* that *"**the disease continues to do its damage**"* and that they are *"**still wasting away**."* Others noted that specific symptoms have not improved on their current treatments or that they weren't sure that their current treatments were helping, noting that it was *"**hard to determine what effect a treatment is having as you don't know how you would have progressed without**."*

Regarding experienced side effects, one respondent in the June 2018 survey noted a lot of sleepiness from their "**cocktail**" of medications. Others noted diarrhea, constipation, fatigue, and mood changes; no improvements in fasciculations; tinnitus; erectile dysfunction; headaches; extreme dry mouth and double vision resulting from the different medications they took. Another noted that they are taking the maximum daily doses of some drugs and continue to have muscle spasms; however, if they increase the doses, they become too sleepy. It is also important to note that some medication is also difficult to swallow for ALS patients.

INFORMATION FOR PATIENTS WHO HAVE USED THIS DRUG:

Among survey respondents in June 2018, 26 patient respondents and 20 caregivers had experience with edaravone. At the time of the survey, Radicava (edaravone) was not yet approved by Health Canada and it was most common for patients to access the generic form of the drug – or potentially the Japanese brand version, Radicut. As such, this submission uses the term "edaravone" throughout.

Of those, 69% somewhat agreed/agreed/strongly agreed that it "**better controlled ALS symptoms than any other treatment used**" while 23% neither agreed nor disagreed with this statement and 8% somewhat disagreed/disagreed/strongly disagreed.

When asked whether edaravone "**improved daily life compared to other treatments,**" over half (57%) agreed/strongly agreed while 30% neither agreed nor disagreed and a small percentage (12%) disagreed/strongly disagreed. When caregivers were asked whether it improved their day-to-day lives, there was almost an even split (52% agreed, and 47% did not).

Recently (December 2018), a patient in Ontario accessing edaravone through the Mitsubishi Tanabe Pharma Corporation edaravone supply program (a modified version of Health Canada's Special Access

Program) shared that the treatment gave them "**more energy**" and that "**I have not experienced a major progression change since I started it [breathing, walking].**" Another Ontario patient accessing edaravone in the same way indicated they have noticed a "**slow down with the tremors**," while another shared they "**haven't noticed any physical changes but it's definitely helping with my mental state…**"

Edaravone has also brought tremendous hope to the community, hope "**that these…disabling symptoms could be slowed or diminished."** As shared by another patient in December 2018:

> ***ALS is a death sentence. Waiting and watching your body lose its ability to be controlled is emotionally and physically draining. People need hope in their lives and edaravone could be that seed of hope. Hope is needed to [live] a more fulfilled life.***

In June 2018, of the 26 patients who reported using edaravone, 85% said they experienced no side effects, and 12 of 17 of caregivers (70.6%) reported that they saw no side effects in their loved one. A number of respondents noted that it was often difficult to determine whether some symptoms of ALS (e.g., weakness, changes from walking gait, etc.) were side effects of edaravone or not. **Skin inflammation or rash** was reported by a small number of patients, as were **redness, swelling, bruising, pressure and pain** at the infusion site. When asked in the June 2018 survey, the majority of patients indicated they would be willing to tolerate these side effects if edaravone were to delay the progression of their ALS. However, only a small number were willing to tolerate side effects related to their respiratory ability (12% were willing to tolerate respiratory disorder and 10% were willing to tolerate respiratory failure and hypoxia).

Edaravone is administered through an IV for 10 days, followed by 14 days without, and then the cycle begins again and continues indefinitely. When asked whether they were willing to tolerate the infusion schedule the majority (75%) of patients in the June 2018 survey stated that they were. Some noted that anything that decreases the impact of the disease – or stops it altogether – was "**worth it**." However, other patients noted that the treatment is time-consuming, they live far away from health facilities, or they are "**stuck at home for the infusions**." Others shared that they don't have enough energy for such a schedule and that they have "**no money [and] no transportation**."

Of those patients receiving edaravone treatment in June 2018, most (58%) received infusions at home, while the remaining received infusions at either the hospital, or a combination of the hospital and outpatient clinic, and at home. But due to fatigue and potentially far distances to travel to a clinic or hospital, many patients and caregivers indicated that having edaravone infusions administered by nurses through home care was preferred. Several caregivers highlighted the difficulty in accessing nurses to administer the infusion and the distance traveled to do so. Some patients noted in the survey that obtaining the infusions is "**very inconvenient**" and expensive, leading some to pay for private infusions.

Many cited cost as a significant factor in treatment administration. For a private home care company to administer edaravone in Ontario, the price can be upwards of $125 per treatment (and treatments are required every 25 days). One caregiver noted that it was "**hard to administer, costly to administer, [and] time consuming to administer**." Additionally, one patient noted that "**the only negative experience I have had is the cost of the medication because I can no longer work full time.**"

In addition to the medication, supplies are necessary that are not always provided free of charge from clinics: "**[e]very day requires a new line, an infusion bag, two vials of edaravone, sterile wipes for the line, four flush syringes, the actual sterile needle and a flush of heparin. We haul a couple of boxes of supplies every week... Then, of course, there's also a box where the used needles are kept. …This is no small project!**"

For those not taking edaravone, a large percentage (81%) responded that if offered to them, they would try edaravone, with some patients highlighting that they "**would do anything that would help with this disease.**" One patient commented: "**[t]his disease is debilitating and fatal … anything I could do to slow this progression down so I can spend more time with my children would be amazing.**" Some patients responded that they would want more information about the treatment before taking it, including consultations with their neurologist. Other patients noted that their disease has progressed, and they did not expect that edaravone would help them or that their neurologist did not think it would help.

Edaravone is the first drug in nearly 20 years to receive Health Canada approval. We support timely access to ensure Ontarians living with ALS get the care they need.