

CADTH COMMON DRUG REVIEW

Patient Input

SACUBITRIL/VALSARTAN (Entresto)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Heart failure, NYHA Class II or III

CADTH received patient input from:

The HeartLife Foundation

May 20, 2020

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Name of the Drug and Indication	Entresto (Sacubitril/Valsartan) - Heart failure, NYHA Class II or III
Name of the Patient Group	The HeartLife Foundation
Author of the Submission	[REDACTED]
Name of the Primary Contact for This Submission	[REDACTED]
Email	[REDACTED]
Telephone Number	[REDACTED]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

The HeartLife Foundation is Canada's first – and only – national patient-led heart failure organization. We are a Canadian Federal Charity aimed at raising public awareness of heart failure, engaging patients, families, and caregivers to provide education and support, facilitate access to the latest research, innovations, and treatments, and advocate better care for all.

Our Mission: We aim to empower patient voices to stimulate dialogue, advance understanding of patient needs, improve access to treatments and research, raise heart failure awareness, and improve patient care in Canada. Our organization collaborates with partners in healthcare, government, and industry to establish a strong, critical voice for heart failure patients in Canada.

Founded by Dr. Jillianne Code, a two-time heart transplant recipient, and Mr. Marc Bains, a heart failure survivor and transplant, we have a network of over 1000 patient and carers across the country. As a volunteer run organization, The HeartLife Foundation works with 15-20 patient and carer champions to administer service programs, support groups, workshop events, public awareness campaigns and government relations activities. In collaboration with Dr. Sean Virani, one of Canada's leading heart failure specialists, thought leaders, and promoter of patient and family centred care, we endeavour to ensure that there is an open dialog including patients as partners with healthcare providers, government, and industry across Canada.

Website: www.heartlife.ca

Facebook: www.facebook.com/heartlifecanada

Twitter: www.twitter.com/heartlifecanada

Instagram: www.instagram.com/heartlifecanada

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Patient perspective information was gathered by The HeartLife Foundation through one on one interviews in which we discussed the lived experience of Canadians with Heart Failure (HF), virtual workshops with peers, an in-person roundtable, and literature searches from peer reviewed publications.

Lived Experience Interviews

The HeartLife Foundation conducted three lived experience interviews with patients and cares in Canada. Interviews were conducted with patients and family carers aged 35-62 and represented a current heart failure patient, a family carer, and a post heart transplant recipient. All interviewees had experience with the medication.

In-Person Roundtable

The purpose of the roundtable was to gain insight into the challenges facing Canadians directly affected by heart failure. The roundtable included 17 patients and carers from 8 Provinces aged 34-67. Specific objectives of the roundtable included: 1. Discuss patient/caregiver first-hand experiences, outcomes and identify gaps in the care continuum and 2. Discover aspects of care that are most valued to patients and caregivers and determine if these aspects are being met. The roundtable was held in May 2019. Please note, roundtable findings were previously used in a submission and are relevant to this particular submission.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Heart Failure in Context

An estimated 600,000 people are currently living with heart failure in Canada (Heart & Stroke Foundation, 2016). In their 2016 Report on the health of Canadians, the Heart & Stroke Foundation estimates that 50,000 Canadians are diagnosed with heart failure each year and this number is on the rise. Heart failure costs the Canadian healthcare system more than \$2.8 Billion dollars per year – with the majority of those dollars being spent on acute care. Research has shown that effective treatment improves clinical outcomes, prevents hospitalizations, increases patient self-efficacy for managing their condition, and overall quality of life. Despite these findings, there continues to be significant gaps in criteria to prescribe innovative and proven therapies in an acute setting. Early adoption of proven treatments is paramount in helping patients self-manage their condition and live the quality of life they deserve.

Lives of patients with heart failure and their family carers dramatically change upon diagnoses of heart failure. The word 'failure' has a negative connotation and immediately changes an individual's perspective. Individuals with heart failure experience a wide range of physical, social and emotional challenges. Individual can be born with the disease, develop it throughout their adult lives, or be diagnosed in their later years. Symptoms of heart failure vary among patients. It is a condition that requires daily monitoring, adherence and vigilance on the part of the patient in order to control the delicate balance of symptoms. These symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema and bloating. Many patients also have palpitations and arrhythmia as a result of the underlying etiology of the cause of their heart failure. Heart Failure has no cure and, if not treated in timely fashion it become progressively worse over time. Heart Failure is commonly associated with a variety of comorbidities, anxiety, depression, a decline in cognitive ability, and can have a negative impact on mental health.

Lived Experience Interviews

Although heart failure cannot be cured, patients and carers have the opportunity to live a good quality of life if the disease is effectively managed. In a timely manner. The right treatment plan along with support can help patients feel better and live longer.

NYHA Class II

While in NYHA Class II, symptoms could be mild to moderate most days which means that laying down to sleep requires one or two pillows to help you be able to breathe at night while sleeping. Sleep is often restless, and disturbed, but if congestion is controlled well with medication, fluid restriction, and a low sodium diet, resting is possible. A daily nap is not unusual in these stages. In terms of daily activity, with mild to moderate symptoms, doing basic house hold chores and working in a non-strenuous job is manageable – as long as the patient is careful to adhere to the daily regimen of medications, diet, fluid restriction, and ensure that they get the rest they need. Weekends are often spent napping and resting. With exposure to others in the workplace, many heart failure patients are quick to catch seasonal colds and flus, which can easily exacerbate and even worsen heart failure symptoms potentially leading to hospitalization. In addition, with any physical activity, patients in this class will often have to take frequent breaks, will tire easily, become short of breath on exertion, and have to be careful to avoid extreme weather conditions (hot/cold). Many patients find regular exercise challenging, and demoralizing, and often walking on flat surfaces for short distances is all they can manage. Symptoms change daily.

Patient Experience Aged 56: *I am 56 years old and I live with a congenital heart defect. I was operated on at the age of 7 when the physicians repaired a coarctation of the aorta. My parents and I were told that I was "fixed". I led a very active young adult life into my thirties with many ups and downs, two live births of children, one at 29 and the next at 34 years of age. Fast forward to turning 40 when the troubles all truly began for me. I found myself winded while doing any activity, tired all the time, legs and arms heavy. I worked part time but I found I was unable to do much more then work, come home and sleep, go back to work. At this time, a very good friend of mine suggested one day when I was complaining about the fact I was so tired and winded, "that it could it be your heart." Famous last words! Within the ensuing 15 years, I have had many tests, many medications and four ablations. I got a call from my GP's office while on vacation the summer of 2015, they had done testing and sent the results to my GPs office, who were following up with a phone call with me as they were concerned about the results. I knew what they were going to say before they said it! My heart arrhythmias were back, my ejection fraction was low. Life again was on hold. **(Please note, this Interview was conducted for a previous submission. We believe it is relevant for this submission).***

NYHA Class III

Patients in NYHA Class III, are at higher and – if they can tolerate it – the most ‘optimal’ or recommended dosages of current medications including. Because symptoms are more difficult to control because of the increasing weakening or damage to the heart muscle as a result of the underlying disease causing the heart failure, patients are even more limited. Breathing at night is often congested, leaving patients with an increase in their diuretics thus increasing the frequency urination, leading to even more interrupted, and often sleepless nights. If a patient can sleep, it is often with at least two pillows. Standard treatment also dictates an increase in beta-blockers which artificially slow the heart rate of patients, leading to further feeling of fatigue, resulting in an increased likelihood of depressive episodes. Many patients have trouble tolerating beta blockers and are often not on the optimal dosage because of this intolerance – placing they am increased risk of poor outcomes. Patients in this class are often fitted with an Internal Cardioverter Defibrillator (sometimes with a pacemaker) and have an ejection fraction (EF) of less than 30%, have low blood pressure (as a result of the combination of medication and as a function of the disease).

Patient Experience Aged 33: *I was diagnosed with heart failure at the age of 18. In my perspective, I wasn't even an adult. I was in shock. I thought heart issues only effected the elderly. When I received my initial diagnosis I was entering university, playing football, and enjoying a normal life. Thinking about it now, I had no reason to believe my heart was failing. My ejection fraction, which I came to understand was an important metric, ranged from 5%-20% throughout my journey. At first, I was depressed. I was sad that my life had stopped while my peers moved forward. After the initial impact was overcome, I decided I wanted to pursue a normal life. whatever a new normal was. It was integral for myself and my family to manage my HF and live a good quality of life. It was easier said than done. Although I am post-transplant, HF and the journey I went through continues to affect my day-to-day life. Don't get me wrong, the medications, surgeries and amazing teams propelled me to move forward and continue to live. That being said, I am still unable to work at my desired career, exercise regularly, and take part in activities I love. I have had to find a 'new normal' for life, one which I am grateful to have.*

Patient Experience Aged 44: *It is difficult to try and I tell all the details of my story. I could discuss about how for most of my adult life I have suffered, how at 28 heart failure literally squeezed the life out of my body, how I struggled to breathe with what felt like a vice around my chest. That despite a stroke, multiple ICD shocks, a left ventricular assist device, severe GI bleeding, countless transfusions, 13 months on the transplant list, a heart transplant, 8 days in a coma with multi organ failure, delirium, and having to learn to feed myself and walk again – that I refused to die. In the world of chronic illness, people often speak of finding your 'new normal'. Those who are in it now, will understand what I mean. But even if you have never been there I think you can probably imagine what it might be like to have something so profound happen to you that you need to readjust your horizon. Constantly needing to find a 'new normal'. 2 years after my second transplant, three years after my first transplant, 14 years after my diagnosis I still wonder at the logic of this statement. What does that even mean? What is normal, anyway? ***(Please note, this interview was conducted for a previous submission. We believe it is relevant for this submission).****

Impact on Carers

Caregivers play an integral role in the heart failure care continuum. The challenges of heart failure on caregivers and family members cannot be understated. Caregivers provide support, guidance, attend appointments, track medications, monitor symptoms, and are often the first point of contact with the

healthcare team. The lives of caregivers can be as unpredictable as the patient. They have to make drastic life changes and sacrifices to meet the demanding needs of this devastating illness. Some family carers take time from work, change or miss social events, and make personal sacrifices for their loved ones. As a patient progresses through each stage of the disease, the physical and psychological trauma is felt by the patient with heart failure but equally so by the family carer. Effective treatment options combined with the right plan improve the quality of life for both patients and family carers. A caregiver gives his account of what life is like as family living with heart failure.

Family Carer Experience:

*Caregiver Experience Aged 52: Our lives were essentially flipped upside down. It was difficult to hear that our son’s heart was failing and there was nothing we could do about it. Little did we know; the most difficult times were ahead. Heart failure was to become a family disease. As a family it was important to understand what heart failure was, the symptoms associated with it, the potential treatments, outcomes and how we could live a new normal. There were periods where different family members had to take time off work, adjust daily schedules and even cancel family trips. We were in this together. Although self-management for our son was important, we still were cognisant of the meals we cooked, the places we went, and the activities we participated in. Something as simple as walking a trail could be the most difficult thing in the world for a patient living with heart failure. All that to say, as family carers it was imperative to maintain our quality of life for both our mental and physical health. As with many patients, we find new ways to lead ‘normal’ lives, often slowing down or doing things a little differently. **(Please note, this Interview was conducted for a previous submission We believe it is relevant for this submission).***

Roundtable Findings:

The purpose of the roundtable session was to: gain insight into the key challenges facing Canadians directly affected by heart failure, prioritize the challenges, and identify the top three health care challenges and gaps to address. Representation of patients and carers included: BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Newfoundland and Labrador. As you will note below, equal access to medication was paramount for patients and carers.

Responses were consolidated to the following key challenges and prioritized green (1st), yellow (2nd), red (3rd)

Diagnosis – time to diagnosis / misdiagnosis ✓✓✓
Equal access to care – medications, rehab, digital records etc. ✓✓✓✓✓✓✓✓
Multidisciplinary care ✓✓✓✓✓✓✓✓✓✓
Life after heart failure – quality of life ✓✓✓
Transition from diagnosis to home ✓✓
Transparency of processes – e.g. how do I get a copy of my records? ✓✓
Education and self-management – expectations, post-surgery ✓✓✓✓
Mental health support – patients & caregivers ✓✓✓✓✓✓✓✓✓✓

The top 3 identified priorities, as voted on by the patient & caregiver participants, were:

1. Equal Access to Care – medication / rehab / digital records
2. Multidisciplinary Care
3. Mental Health Support – patients & caregivers

4. Experiences with Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

As long as patients have access to qualified care providers with an understanding of the latest developments in heart failure treatments, most often identified by the Canadian Cardiovascular Society and Canadian Heart Failure Society guidelines adopted across the country, then placing patients on optimal therapy is a matter of following the guidelines.

That being said, there is often a challenge with access to medications. The Canadian Drug Expert Committee has already recommended that sacubitril/valsartan be listed for the treatment of heart failure (HF) with reduced ejection fraction in patients with New York Heart Association (NYHA) class II or III HF to reduce the incidence of cardiovascular (CV) death and HF hospitalization. Given the positive outcomes, there is no reason why the current request should not be approved. For heart failure patients, years, months and even days on proven therapies can be the difference between a good quality of life, hospitalization, and or even death.

The Paradigm HF Trial showed positive outcomes in key end-points: a reduction in re-hospitalization when compared with patients treated with standard therapy and a reduction in overall mortality. Additionally, individuals equated the new therapy with better management and indicated a better a quality of life. If approved, the new indication for Entresto will reduce the burden on the health care system and more importantly improve the quality of life for patients and carers.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

When considering and evaluating new therapies, patients and caregivers examine both quantitative and qualitative outcomes. Heart failure is the leading cause of hospitalisation for those over the age of 65 and represents a significant clinical and economic burden (Azad, N., & Lemay, G. 2014). Hospital visits due to heart failure have gone up every year for the past several years, with 60,000 reported in 2013–2014 according to the Canadian Institute for Health Information. In Canada, heart disease is the second leading cause of death after cancer, and a leading cause of hospitalization.

Virtual Workshop Findings

A significant number of our patient-members take or have taken Entresto and are quite vocal about the success they have found with it – especially around quality of life and the reduction in rehospitalization. As our membership has grown it is ever more prevalent that disparities exist among our patients with respect to pharmacologic treatments (among others). Improving access to Entresto is high on our agenda. Because of the pandemic, our members are extremely concerned about a number of things: 1) How they are to maintain their health with limited access to specialist physicians as they are redeployed across acute care settings? 2) What should patients do if they find themselves decompensating given this limited access and fear of being an increased burden? And 3) if they find themselves in need of going to the hospital, they question whether they should go at all out of fear of getting infected with COVID-19. Even more concerning, a patient potentially making the decision NOT to go to the hospital resulting in acute decompensation resulting in permanent harm.

Especially given the time that we are in – the risk of hospitalization (and death) of heart failure patients has increased exponentially both from COVID-19 infection, but even more so through the downstream effects this pandemic is already having cardiac care as noted in the evolving COVID-19 literature. These risks must be mitigated and enabling early access to Entresto is one way to ensure that the needs of Canadians with heart failure are met and lives are saved.

6. Experience with Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies' patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Multiple interviewees and workshop attendees have/had experience with Entresto. All indicated an improvement of quality of life soon after therapy was initiated. Overwhelmingly, patients indicated that earlier use of the medication would have been welcomed.

Below is an excerpt from our patient interview exhibiting the benefits of Entresto:

Patient Experience Aged 56: Sure enough, at my cardiologist appointment the following week, back on the list for an ablation. May 2016 saw a failed ablation attempt, a medication change, dosage update, and a feeling that this was how I was going to live. In heart failure, with little energy. I had been on Ramipril and bisoprolol now for a while and I was convinced that my body was not liking the combination. I attended two conferences where the doctors were talking about this “miracle” drug, that they were seeing such positive results with people with heart failure. I listened, I wrote notes, I looked it up myself. I asked my cardiologist about it. I wanted a change, I argued for a change, I asked why could I not get a change. After all the testing was done again, and my doctor told me that my ejection fraction was up and I was no longer in active heart failure and I should be glad of that and not want to fix what isn’t broken, I said “BUT it is broken, I feel like horrible.” I am winded doing nothing but going upstairs, I sweat profusely sometimes having to change my clothes in the middle of the day, and I am tired all the time! I backed up my arguments with statistics and anecdotal evidence. In the end, he agreed to let me try it. I stopped my old medication and started the new one. Honestly, by day two, I felt better. Less winded, less sweaty, no shortness of breath. I am still feeling better, much better, physically, psychologically and soulfully even in this time of medical crisis. ***(Please note, this Interview was conducted for a previous submission and we believe it is relevant)***

The following key points are an excerpt from the CADTH Canadian Drug Expert Committee Final Recommendation on sacubitril/valsartan and should be taken into account when making a decision on the new indication:

- Sacubitril/valsartan demonstrated a statistically significant improvement over enalapril in all cause mortality (17% versus 20%, respectively; HR 0.84; 95% CI, 0.76 to 0.93).
- There were fewer CV-related deaths in the sacubitril/valsartan versus enalapril groups (13% versus 17%, respectively; HR 0.80; 95% CI, 0.71 to 0.89), including fewer sudden deaths (6.0% versus 7.4%) and pump failures (3.5% versus 4.4%).
- The differences in CV mortality or first HF hospitalization were statistically significant for sacubitril/valsartan (22%) compared with enalapril (27%) (HR 0.80; 95% CI, 0.73 to 0.87).

Online Literature

The Pioneer-HF study found that the time-averaged reduction in the NT-proBNP concentration was significantly greater in those prescribed sacubitril–valsartan. Among patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure, the initiation of sacubitril–valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy (N Engl J Med 2019; 380:539-548)

Based on information from the European Society of Cardiology, compared with enalapril, treatment with sacubitril/valsartan led to a significantly greater decline in hsTnT and sST2 (Figure 1) that paralleled the decline in NT-proBNP reported previously.⁶ This effect on hsTnT was significant by 4 weeks with a 16% greater reduction in hsTnT (P < 0.001) with sacubitril/valsartan. Similarly, a 9% greater reduction in sST2 with sacubitril/valsartan was evident already by 1 week (European Journal of Heart Failure 2019 doi:10.1002/ejhf.1531).

We believe it is important that you approve the manufacturers request (as stated on the CADTH website) “that initiation of sacubitril/valsartan may be considered in patients stabilized from a heart failure

hospitalization without prior exposure to angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).”

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.
 - a. Nothing to declare. This submission was developed and prepared solely by The HeartLife Foundation.

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.
 - a. Nothing to declare. This submission was developed and prepared solely by The HeartLife Foundation.

1. 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
AstraZeneca Canada Inc.			X	
Boehringer Ingelheim Canada				X
Medtronic Canada				X
Servier Canada			X	
Novartis Canada			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: Marc Bains
 Position: Co-Founder
 Patient Group: The HeartLife Foundation
 Date: April 18, 2020

References:

Azad, N., & Lemay, G. (2014). Management of chronic heart failure in the older population. *Journal of Geriatric Cardiology: JGC*, 11(4), 329-37

Statistics Canada. Table 102-0561 – The ten leading causes of death, 2012. CANSIM (death database) [Internet]. Ottawa (ON): Statistics Canada; 2015 Dec 10 [cited 2016 Sep 14]. Available from: www.statcan.gc.ca/pub/82-625-x/2015001/article/14296-eng.htm

Canadian Institute for Health Information. Inpatient Hospitalizations, Surgeries and Childbirth indicators in 2013–2014 [Internet]. Ottawa (ON): Canadian Institute for Health Information; 2015 Mar 5 [cited 2016 Sep 14]. Available from: <https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC2805&media=0>

Heart & Stroke Foundation. (2016). 2016 Heart and Stroke Foundation Report on the Health of Canadians. Ottawa, ON.

The New England Journal of Medicine. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. Feb 7, 2019. *N Engl J Med* 2019; 380:539-548

European Journal of Heart Failure 2019 doi:10.1002/ejhf.1531.