



CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

AVAPRITINIB (TBC)
(Medison Pharma Canada Inc.)

Indication: for the treatment of adult patients with Advanced Systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

May 7, 2024

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

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Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: avapritinib (Ayvakit)

Indication: for the treatment of adult patients with Advanced Systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Name of Patient Group: The Leukemia & Lymphoma Society of Canada (LLSC)

Author of Submission: Colleen McMillan, Advocacy Lead, LLSC

1. About Your Patient Group

The Leukemia & Lymphoma Society of Canada - bloodcancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- Funding research from bench to bedside.
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy

2. Information Gathering

As Mastocytosis is a rare disorder, LLSC reached out to clinicians across Canada in an effort to connect with patients and caregivers with personal experience with Mastocytosis to inform this submission. LLSC was able to conduct four one-on-one interviews with three patients and one caregiver who have experience with Mastocytosis.

- One patient interviewee has Advanced (aggressive) Systemic Mastocytosis and is currently being treated with the drug under review
- One patient interviewee has Indolent Systemic Mastocytosis
- One caregiver interviewee was a caregiver for her father who had Advanced (aggressive) Systemic Mastocytosis and had experience with the drug under review
- One patient interviewee was unsure of their specific subtype of Systemic Mastocytosis.

3. Disease Experience

DIAGNOSIS:

Mastocytosis is a rare disorder. Due to the varying symptoms and cutaneous manifestation, in some cases, diagnosis of Mastocytosis can take years. It can often be misdiagnosed upon physical exam alone, both by patients themselves and medical professionals alike.

One caregiver shared her father's road to diagnosis:

"In 2018 my father was having this rash. We thought it was allergies because he was allergic to things like eggs and oatmeal when he was younger, but the doctor sent us to a dermatologist and she thought it might be something like Grover's disease, which is common in seniors. I thought, okay, but he's got this rash that seems to be growing on him and nobody could give us a direct answer. In 2020, my dad moved in with me and he still had the rash and was complaining of the itching, so I took him to my doctor right away and got referred to a dermatologist. As soon as that doctor looked at it, he sent us to another dermatologist and right away soon as he saw it, he said this is Mastocytosis I think. This isn't right. Then we thought, this is a blood disorder? Oh no! Because he had had it for a couple of years then and it had grown. And he's 92 years old at this point. Then they went into his hip and did a biopsy of the bone marrow and officially diagnosed it as Mastocytosis."

A patient detailed the bumps in the road of her 5-year long battle to find her diagnosis:

"When I when I was 18, I saw two little red dots on my arm. Over the next two years, my legs and arms were completely covered. I showed it to my walk-in doctor and they sent me to a dermatologist. The dermatologist gave me cortisone cream and sent me on my way. The cream in fact, made it much worse. It felt like it was on fire and swelled up even more. I was irritated all over. It was burning like, internally. I saw two more dermatologists, both had no idea what it was, which led me to a naturopath. They told me I had celiac disease and an allergy to corn and to stay away from those. The other doctors I saw were all walk-in or emerge doctors because there weren't any family doctors here so I stopped searching and said, forget it, I can't find help. I don't know what's happening to me. My grandmother ended up setting up an appointment with a rare disease doctor and wanted to see if she could do anything about it. The doctor cut a spot off of my back and had sent it into the Cancer Research centre and I was finally told that I had mastocytosis. That was in 2022. At age 23 I got the confirmation that it was cancer. After five years."

DISEASE IMPACT:

The symptoms of Mastocytosis are notorious for their unpredictability, casting a shadow of uncertainty over patients' lives. From mild skin irritations like itching, flushing, and hives to debilitating bouts of severe abdominal pain, excruciating body aches, and relentless diarrhea, the spectrum of manifestations is vast and unnerving.

This erratic nature not only wreaks havoc on the body but also takes a toll on the mind, leaving patients constantly on edge, never knowing when or how severely Mastocytosis will strike next. The looming threat of potentially life-threatening anaphylactic shock adds an extra layer of fear, perpetuating a sense of vulnerability and unpredictability that can profoundly impact patients' mental well-being.

Patients endure a sense of powerlessness as they contend with relentless itchiness and unsightly lesions and hives, which can appear anywhere from their face to their extremities, causing extreme discomfort and visible distress. Faced with limited treatment options, patients and caregivers often feel a profound sense of hopelessness, and caregivers struggle to alleviate their loved ones' suffering.

Patients may also experience severe eye dryness and extensive pain in their bones, joints, connective tissues, and muscles. The constant fear of sudden, life-threatening anaphylactic reactions lurking around every corner creates extreme anxiety, making it nearly impossible for patients and caregivers alike to experience any semblance of a normal, high-quality life.

One patient stated, "It can pop up on different parts of your body different days. That unpredictability. That's unsettling."

Patients vividly described their skin symptoms, including spots, rashes, itching, and hives, shedding light on the varied manifestations and challenges of living with Mastocytosis:

"Most of the spots are not raised, they're flat against your skin. Most of them are brown or a salmon pink/brown color of varying sizes. Most of them are on the top of my arms. I have them on the lower part of my arms too and throughout my body. On my torso and upper legs, and around my hips and buttocks. From time to time they get really itchy. It usually takes something to trigger them, it could be anything. Whether it's being scratched, or certain types of fabrics, it can be heat and cold. They definitely really respond to heat and cold.

I get a lot of hives and they're big and really itchy, so it's very, very uncomfortable and it's really hard to get the itch and hives settled and under control. Now I'm on higher doses of antihistamines and that is helping but it doesn't solve the problem and I'm definitely getting more spots more regularly. It's definitely getting worse."

"It feels almost itchy from the inside out and it's an itch that you can't get rid of. A burning itch. A deep itch that you just can't reach. You can't reach it. You can't make it not itchy. And of course, you go to your regular sort of topical things like calamine lotion or things to try and settle it. Sometimes I'll put on like a cool cloth, but sometimes I just can't get rid of it until it decides to settle down so it's very uncomfortable."

"I go by a door frame, and I want to itch my entire back against it"

"The discoloration or the blotches. I tease everyone that I'm a leopard because I'd have blotches all over everywhere."

"The more spots I get, I get more and different symptoms".

"I find heat very therapeutic. I use a heating pad on my back sometimes and I have a heated mattress pad. Sometimes I'll put it on just long enough to warm it up so that it's soothing and it kind of makes me feel like I can relax, but I have to turn it off quickly because if I'm on it too long, I'll instantly get hives from the heat. I will get hives at night. I'll wake up with them sometimes and it's a mystery to me. Did I just get too warm in bed?" I don't know exactly what's causing them at night."

Mastocytosis patients endure high levels of body pain.

Patients we spoke to were unable to identify the source of the pain and said they're unsure what causes this pain in their bones, joints, connective tissues, and muscles, but described it as debilitating. Those we interviewed found traditional pain medication insufficient, leaving them to seek alternative methods to mitigate their pain. The relentless pain these patients are experiencing profoundly disrupts their quality of life and impedes their ability to participate in the activities of daily living.

"I get cramps inside the bone. They're not cramps exactly, but the only way I can relieve that is by taking a hot shower. Just as hot as I can stand. I think it expands the bone a little and that helps. I think it's a pressure going on inside. I have severe body pain. It's also in my legs, in my shins. It's similar to a muscle cramp but it hurts a lot more. The pain stretches. I haven't found anything that's stopped the pain. Pain medication doesn't help. It doesn't even touch it. Nothing will."

"I'm feeling a lot of pain. On a regular basis. I've had pain for quite a few years. Pain that concerns me and that limits my mobility. I don't feel that I'm nearly as active as I used to be because of it. I feel that it really limits me and I don't want to be one of those people who is not mobile, especially at a young age. I feel like it's bone pain. I feel like it's joint pain. I feel like it's probably connective tissue and I feel like it's maybe tendons, I feel like it's everything, muscles. Before I knew that I had Mastocytosis I used to wonder, do I have fibromyalgia? I used to think that to myself. I never really kept going to the doctor and saying, oh, I'm in pain, I'm in pain, you know. Because the few times I did mention it, we've done some exploratory type X rays or things like that and it really didn't show a lot, so I'm just like, well, I just have to live with the pain."

Sleep disturbances pose a significant challenge for individuals with Mastocytosis.

Compounded by the fatigue induced by their illness itself and/or the medications they may be taking to mitigate their symptoms, patients find themselves trapped in a cycle of exhaustion. Their rest is disrupted by relentless body pain and intolerable itchiness, preventing them from achieving quality sleep. They're often woken up mid-sleep, if they're able to fall asleep at all, by these unbearable affects of Mastocytosis. Sleep deprivation further exacerbates their struggle to feel physically and mentally well.

"Sleep is horrible. Even though I'm so tired, I only sleep for a couple hours because then something will bother me, like my pain or itchiness."

"I get hives at night. I wake up with them and the itch interrupts my sleep. So does the pain. Sometimes I wake up because of the pain and sometimes I can't even fall asleep because of it. It's both. And it's often. And it's been going on for quite a few years now. I used to be a really good sleeper. I would get a good sleep and I would feel rested and that's not the case anymore. I feel like I'm waking up a lot. Whether it's pain or being itchy, or a combination of the two, I find that it's definitely increasing for me. It's getting more and more disruptive."

One patient expanded on the effects of fatigue:

"I don't have any idea if (Mastocytosis) treatment would help, but I've been feeling really tired, and I get tired easily. It could be directly related to, just my system constantly fighting this, or it could be a combination of

that and my sleep disruption. I'm really finding the tiredness and the brain fog is an issue for me. I don't know how much of it is directly related to the mast cell overproduction or the fact that my histamine levels are high, and my body is constantly fighting to balance that. But I do find that I just feel really tired."

Some additional symptoms noted by interviewees include fever, brain fog, enlarged liver, enlarged spleen, and low platelet levels. One patient has undergone multiple lymph node removals and tests due to their persistent growth.

Another patient expanded on some other symptoms that she continues to experience:

"There are some other things that I've been experiencing, like my eyes have been bothering me for probably two or three years. Really extra itchy and dry. I've been using eye drops, but they're red almost all the time. I also get a lot of flushing. I'm always red. Always. People are always asking me if I have a sunburn. There is definitely brain fog also and it causes me memory loss. Work takes me a lot. I have to concentrate very hard. I find that I have a hard time focusing and remembering things compared to what I used to."

All of the challenges that accompany Mastocytosis including pain, itchiness, fatigue and cognitive impairment/"brain fog", among others, collectively impact patients' ability to sustain employment while battling their illness.

Patients described how Mastocytosis has affected their ability to continue with work:

"I worked for about three years after I was diagnosed, and I was just grinding. I'd get up at 6am and I'd get home at 6pm and I'd be so exhausted that I'd go to bed, not even have dinner. Then I had to get out. The doctor declared me as disabled and said I shouldn't be working anymore."

"I've had to take days off work a few times. Not very often, but I really feel if it continues in this way and if these symptoms continue to increase, I will have to and that is a concern because I really can't afford to do that and I really do not want to be who is looking at disability or something like that in the future. I don't want to be in that category. I'd really rather do what I can to slow this down and find a way of there is one to suppress it or to live and feel more normal and healthy. I don't want to be a person who is ill or unwell or taking time off work or going on disability or something like that. I don't want that to be my future. I worry about those things. With the pain I feel and the symptoms I have, I start to worry about those things. You know, if it gets worse, what am I going to do?"

The impact of Mastocytosis extends beyond physical comfort and disrupts patients' ability to continue doing the things they enjoy with the people they love.

Despite their desire to participate in fun, enjoyable activities, even the simplest activities or tasks of daily living can be a challenge for these individuals.

"I'll do as much as I can around the house until I get tired. I try to help out but I can't do a lot. I'll try to get out to mow the lawn but then my son will have to take over after I get about 1/3 of it done."

“I’m not really up to doing a lot of things. I used to curl. I can’t curl anymore. Occasionally I’ll try to go for a bike ride but that’s very tiring. I also have a segue so I use that sometimes to walk with my wife but that gets tough standing up all the time too, my legs get sore. I try to get out as much as I can but it’s limited.”

The constraints imposed on patients’ activity by the symptoms of Mastocytosis not only weigh heavily on the patients themselves but also impose a significant burden on their caregivers.

Patients struggle with the fear and concern of becoming a burden to their families or loved ones, while caregivers find themselves having to assume additional responsibilities to provide essential care and support for the patient.

“My son and my wife absolutely have to help me out with daily living. They’re my caregivers I should say. They worry but I think they are a lot better than at the original prognosis. It’s still a little stressful but I think they’re managing quite well, and I’ve been trying to keep my spirits up too. I keep my spirits up most when I’m around other people. I don’t want anybody to know how sick I am or anything like that so I kind of guard against anybody seeing a lot of it.”

“I fear that the day is coming when I will need a caregiver. I don’t up to this point, but I do fear that because there are days that I stand up in the morning and I’m having a lot more pain than before and it’s like, wow. I don’t want that. It’s scary. It scares me.”

“At the beginning he was able to shower himself. We had to have a stairlift put in and I would go down and check on him and make sure he was OK. He never cooked for himself. He used to love to bake. I didn’t take any other help with caring for him until the final months. Hospice said it’s enough now because I was sleeping on the floor beside him and really not sleeping, helping him if he had to get up in the middle night to go to the bathroom and stuff like that, so for the last month or two we had people help with him at night so I could sleep but I had no problem washing him, doing all that. It was actually good because I bathed him, and I would put the creams and things on his skin and I could watch and could tell the doctor where there was a new spot here or there or where it had dissipated. I could speak to it.”

One patient commented on the burden of regular blood testing that is required due to his Mastocytosis diagnosis:

“I have to go to see my hematologist once a month and do blood tests as well. I’m quite a pincushion, especially when we first started. I think because of how hard it is on all the organs and everything, the liver. They had me do blood tests every day for a week, and then once a week, and then once every two weeks, once every three weeks, and then once-a-month, and I’m still on the once-a-month schedule.”

Life threatening, unexpected anaphylactic shock reactions can occur in individuals with Mastocytosis.

Mastocytosis is characterized by an abnormal accumulation of mast cells in various tissues of the body. These mast cells contain histamine which is released in response to allergen triggers, for example, certain foods or medications. When a person with Mastocytosis encounters a trigger, it can lead to anaphylactic

shock. In severe cases anaphylactic shock can progress rapidly and be life threatening if not treated promptly with epinephrine.

Due to the increased number of mast cells in the bodies of Mastocytosis patients they are at a particularly high risk of experiencing anaphylactic shock. It is difficult for individuals with Mastocytosis to identify and avoid their specific triggers because they may develop new and sudden allergies at anytime leading to extreme anxiety and fear on the part of patients and their caregivers and a need to be prepared with an Epi-pen at all times.

“My doctor told me I should be taking antihistamines every day. That's the only treatment I've been on since my diagnosis is daily antihistamines. I wasn't followed until last year by an immunologist or somebody from hematology. When I started going to the immunologist, she put me on a higher dose of the daily antihistamine, cetirizine hydrochloride. I was on 10 milligrams a day. Last summer she put me on 20 milligrams twice a day. My tryptase levels indicated that's what I should be on from how I understand it. I needed higher doses of that to help manage some of the symptoms and the progression, and I do have an Epi-pen. When I found out I had this they said I should have one and prescribed it to me and I've had it ever since.”

4. Experiences With Currently Available Treatments

Currently, Canadian patients with Advanced Systemic Mastocytosis face a daunting reality: there are no readily accessible treatment options for their disease.

There is a great unmet need for treatment options for this patient population who are often suffering, untreated, with this multifaceted and challenging illness. Treatment options are currently inaccessible without special or compassionate access programs that are not always available.

One treatment option that may in some cases be accessed through compassionate or special access, midostaurin, has provided relief for some individuals but this can come at a cost for these patients as this treatment bears a significant burden of side effects. As access to midostaurin is obtained through special access programs this is also a hurdle and a contributor to a delay in starting treatment as this process can be lengthy, taking several weeks or months from application to initiation. While midostaurin has shown effectiveness in reducing symptoms such as diarrhea and itching, it doesn't eliminate all manifestations of Mastocytosis including hives, bone pain, fevers, and fatigue. Moreover, toxicities can induce adverse reactions, including severe nausea and vomiting, which can significantly impact the quality of daily life and the personal relationships of patients.

Despite these challenges, some patients have persevered through treatment, hoping for sustained benefits but others have no choice but to explore alternative therapies or clinical trials for other treatment options that may be more tolerable.

One patient shared an account of his experience while undergoing treatment with midostaurin. He delved into the various effects of this treatment starting with the physical repercussions.

“The nausea and vomiting are so severe. It got so toxic; I couldn't keep it down. We went on a cruise. I toughed it out. I think on a 10-day cruise I was able to hold down maybe 3 or 4 meals. I'd just get sick and throw the medication up. I know what colour it is on the inside, and once I get it out of my system, I'm okay. I would always get sick within about 2 and a half hours. I always took it with food but anywhere from 2-3 hours I knew it was coming. I was even taking anti-nausea pills as well and after the 2-3 hours I was still going to be sick. And it made me so tired. I was sleeping so much more. It kind of wrecks the whole day. You just have a lack of energy and are sleepy and you just don't feel good. For me the throwing up got so bad that I also started smoking cannabis. That seemed to be quite helpful at least reducing, not eliminating, but at least reducing some of the nausea and vomiting. I didn't have the cannabis on the cruise, so the sickness came right back. Sometimes it'd be hours and I'd be stuck in my room during that time and here at home I'm spending my time in the bathroom a lot of the time as well. Another major symptom was diarrhea. It's a very upsetting drug.”

This patient expanded on the need for his use of alternative treatment with cannabis products to get through the horrific physical side effects of nausea and vomiting caused by the toxicity of treatment on his body. Using a mixture of treatments, the patient has created a regimen that helps him to keep the medication in his system, as well as food:

“My GP lined me up with a cannabis doctor and when I take the right one, I actually feel hungry and then I can eat and take my medicine at the same time and that gives me the best shot of holding everything down, along with my nausea medicine as well, so that's how I've been doing it. That helps me hold the medicine and the food down.”

“I usually smoke the cannabis about 1/2 an hour before I take the anti-nausea medication because it seems like it takes the cannabis about 1/2 hour - 45 minutes to kick in. Then I'll take the anti-nausea medication about 1/2 hour before I take the midostaurin. After I get a small amount of food, let's say half, then I'll take the midostaurin, and then eat the other half and that seems to work quite well. So I'm trying to balance all of these things. The downside is then I can't drive. I get the beneficial effects of it which is great so I'll keep it up. Whatever works. When I was throwing up, I was throwing up blood and bleeding and everything, my wife said we've got to do something here, so we talked to my GP and he lined me up with this fantastic cannabis doctor and she's been fantastic.”

The impacts and side effects of currently accessible treatment can significantly impede a patient's ability to socialize and spend quality time with family and loved ones, and to actively engage in and enjoy daily life.

“Our kids were over, and we have two grandkids that I just love and adore and I just wasn't up to being around them and didn't have enough energy to be around them. I slept through most of their visit as well, so this treatment definitely stops those interactions with friends and family.”

“We've had to cancel so many trips, a cruise to Hawaii and a cruise around Panama.”

This patient is currently in a state of anxious anticipation, awaiting news on whether he has been accepted into a clinical trial for a new treatment option. The toxicity of his current treatment has taken a toll on his body, and after six years of enduring its effects, he finds himself unable to tolerate the medication any longer. With the uncertainty of how much longer he can endure this treatment,

the patient pins his hopes on being admitted to the clinical trial as a potential lifeline for his ongoing care.

“The medication is working. It's a tough drug to take and there isn't much that makes me sick, but this drug makes me sick. I thought I had a cast iron stomach and maybe that's why it's lasted 6 and half years. A lot of people don't keep taking it or only take one pill or two pills and can't take the full dose because it's a tough drug to be on. I understand that but I've weathered through, and I just hope that this other drug works out well. The reading I've done, on the studies they kind of alluded that it reaches a toxic level in your body and my doctor said I'm at the toxic limit now if I'm throwing up every day when I take it. It's doing its job to hold the KIT gene down and the mast cell concentration down, but it's just so toxic and I know my body is throwing up immediately to it because it knows it's toxic. By the grace of God everything will turn out well with this new drug.”-

Treatment for this disease requires a multidisciplinary approach to patient care that ideally involves dermatologists, allergists, hematologists, and other specialized team members to tailor treatments based on individual patient needs and the severity of the disease and its symptoms.

When patients are unable to access treatment options that meet their need for high level targeted treatment for Mastocytosis, they will try anything due to how disruptive their disease is to their quality of life and the fact that there are no effective treatment options available to treat their disease. These patients are often receiving no treatment at all, so they are relying on alternative therapeutic options, or over-the-counter treatment options in an effort to try to alleviate some of their significant symptom burden. Patients have no choice but to treat their immediate symptoms, rather than their underlying illness.

As previously mentioned, patients generally find that traditional pain medication is not strong enough to relieve the significant, debilitating body pain caused by Mastocytosis, but this is the only medication option they have so they will often choose to treat their pain with these medications, in vain.

“I'll take Tylenol or Tylenol Arthritis when I feel I really need it, but a lot of the time I'm just dealing with the pain. It doesn't provide a lot of relief. I would say it helps a little bit to take the edge off.”

With no medication options available to treat their menacing, persistent rashes, skin spots and hives, patients often resort to topical creams or over-the-counter lotions or allergy medicines.

“There was a compound cream that I would get. London drugs would make that, they'd send away to make it up. That gave him some relief, but it didn't dissipate it. It was everywhere, on his neck, his back, on his chest and his arms and legs, down the groin area, all over.”

“I was taking Benadryl, but my doctor suggested that I take Reactine instead. She has adjusted all my meds to try to reduce the affects, but I use topical creams as well for my rashes. I have tried things through my cannabis doctor too and it helps to some extent but not a large extent. THC and CBD creams which help with muscle fatigue. It doesn't help for the pain I have, but for the itching I put a very small amount on my body, and it reduces the feeling of prickly-ness, so that's very helpful but the itch, it's been horrible, and my skin is really horrible, I have these dark, dark splotches. I've got this splotchy mess all over my back.”

One patient also tried UV light therapy:

“UV light therapy. That’s what the doctor recommended for the Mastocytosis spots on my body. He said it can help suppress it or it can help stop the progression of it. So, I did do that as well. It was 2 or 3 times a week. That was a few years ago that I tried that.”

5. Improved Outcomes

Patients with Advanced Systemic Mastocytosis (ASM) rightfully deserve access to available, accessible treatment options. Unfortunately, the current landscape presents a stark reality: treatment options for ASM are severely limited, and traditional access pathways fail to provide accessible solutions for Canadian patients. This disparity underscores a critical gap in patient care, highlighting an urgent and unmet need within this vulnerable patient population.

Advanced Systemic Mastocytosis is a rare and aggressive form of Mastocytosis that can affect various organs throughout the body. It is a severe and progressive stage of this disease. In the advanced stage, mast cells infiltrate not only the skin but also internal organs such as the bone marrow, liver, spleen, GI tract, and lymph nodes. These widespread affects can lead to a range of debilitating symptoms and complications. Patients with ASM are also at increased risk of experiencing life threatening complications such as anaphylaxis, bleeding, and organ dysfunction.

One patient expressed her thoughts and fears about going untreated while waiting for new treatment options to become available:

“I don’t want be one of those people that it does progress and progress and if there was a way to stop that, obviously I would consider it because I don’t want to continue progressing.”

Patients require treatment options that are efficacious, with limited toxicities. Patients are currently going without treatment and physicians are understandably cautious about prescribing treatments that carry significant risks of harm, as these may exacerbate patients’ conditions and impose a heavier burden of side effects than the disease itself.

“My doctor told me that he didn’t really feel that I needed treatment at this point, but we will continue to monitor. He said that there may be new options coming available and they would definitely be a better option for me because he said, you have to weigh the pros and cons and the risks. He didn’t feel like the treatments available right now are worth the risk to me, however, if there was something else available that had less negatives or less risks of side effects, then I would probably be safer to start a treatment sooner. It might make more sense then.”

Patients need treatment options that are effective, with a lower side effect profile that will enable them to uphold a satisfactory quality of life. This encompasses not only physical well-being but also mental health, increasing the ability for patients to actively engage in activities and spend quality time with loved ones.

“I guess the most disappointing thing is missing out on time with friends and family. I'm just not up to seeing friends or family right because you know, when you're 50% most of the time and when people are here, it just makes it tough.”

“My doctor said that the nausea, how much that's affected me, is not something that is seen as much in the patients who are on this new treatment, so if we can get this new treatment it could hopefully help a lot of people.”

One interviewee shared what they feel are the Mastocytosis symptoms that are the most important for new treatment options to control:

“The top would for me would be the allergy type symptoms. The itch, the rash, and the hives. The pain for sure. Mostly because of the way it restricts my activities and it's very hard dealing with pain on a regular basis. And of course, the sleep disruption. And it's not my top priority, but visibly getting so many more spots. I would prefer to have that managed so that I don't get a whole bunch more lesions and that is hard because before it wasn't really on my face and neck, most of it was where I can just wear a shirt and I can cover it up, but it is traveling further down my arms, it's traveling further down my legs, and on top of my feet, and onto my face. I really would prefer if there was a way to stop that or slow that. It's not just really just for looks that I'm concerned about it, it's not just vanity, although that's part of it, because it is embarrassing. It is what people see, so that is a part of it, but also the more I get, the more symptoms I'm going to have, right? The more area where these spots occur is where these problems ate, the hives and the itch and it's obviously the accumulation of mast cells and that's not good for me. So, if we could stop it or slow it down, or reduce it with a treatment, I would absolutely be open to it.”

6. Experience With Drug Under Review

Mastocytosis, being a rare disease, presents challenges in gathering patient experiences. Gathering patient experiences with avapritinib treatment is even more challenging, due to the limited experience of Canadian patients.

We were able to connect with one patient with Aggressive ASM who is currently undergoing treatment with avapritinib as well as one caregiver of a patient with Aggressive ASM who underwent avapritinib therapy before he unfortunately passed.

Please see their experiences reflected separately, below:

CAREGIVER OF AN AGGRESSIVE SYSTEMIC MASTOCYTOSIS PATIENT ON AVAPRITINIB TREATMENT:

We had the opportunity to speak with the patient's daughter, who served as his immediate caregiver. Through this interaction, we gained insights into their shared journey with Mastocytosis and the effects of avapritinib treatment.

This caregiver explained that her father was able to access avapritinib treatment through a clinical trial. This patient was 92 years old at the time of his Mastocytosis diagnosis and was able to live an additional 3 years post-diagnosis with positive results and limited side effects while being treated with avapritinib.

“His doctor approached us with avapritinib and explained what it could do, and we said yeah let's give it a go. It was trial he was a part of, and they said that it could help people with this condition and asked if we would be willing to try. We said absolutely we'll will try anything, and we went ahead. He didn't go on it right away because it wasn't available. They applied for it, sent in his application and his condition and then he got accepted so it took a bit, it probably went into the next year, but he started the treatment, and he survived 3 years. Here he is 95 years old, celebrated 3 birthdays. And it didn't affect him in terms of any bad side effects. His quality of life was important, but the avapritinib was good. He was never nauseous, he continued to be a great eater, and he did have fatigue, but I think was just part of the whole package.”

When asked about the practicalities of treatment administration when it came to avapritinib, the caregiver expressed that managing the treatment regimen and attending medical appointments proved relatively straightforward and easy for both herself and her father.

“As for his medication I just gave it to him once in the morning and once at night. As for appointments, once he was set up with his hematologist, she basically took over his care. He didn't need to see the dermatologist anymore. He would see the hematologist about every 3 weeks. At the end she would call if it was too hard for him come in, but he was usually pretty good to get there. The doctor was only about 15 minutes away so that wasn't bad at all.”

The caregiver conveyed a deep sense of gratitude, acknowledging that avapritinib treatment provided her father with significant relief from his Mastocytosis symptoms, notably alleviating his persistent skin issues and intense itching. This improvement in symptoms contributed to an enhanced quality of life for her father, allowing him to experience a measure of comfort and well-being until the time of his passing.

“The thing that bothered him the most was the itch and each time we would go he'd complain about the hives, and he'd go back to his childhood. He was allergic to eggs and oatmeal. Once he started taking the avapritinib it helped, and I remember it was pretty quick. Given everything going on, problems with his eyes, this and that, that was what affected him the most was the itch, until he got that taken care of with avapritinib. The rash dissipated, and the itch dissipated, and his quality of life was better until the end.”

EXPERIENCE OF AN AGGRESSIVE SYSTEMIC MASTOCYTOSIS PATIENT CURRENTLY BEING TREATED WITH AVAPRITINIB:

This patient has been on avapritinib treatment for two years, profoundly grateful for the opportunity to access this treatment through compassionate care.

Avapritinib been transformative for her, significantly easing her symptoms and enabling her to reclaim her former vitality. Not only has it restored her physical health, but it has also alleviated the immense mental strain she experienced, stemming from the relentless symptom burden of ASM and the adverse effects of prior treatments.

Prior to starting treatment with avapritinib, this patient underwent two previous treatment regimens to treat her ASM. During chemotherapy treatment, this patient had to stay in a hospital away from home for 5 days at a time, each cycle, contributing to her mental and financial burden.

“First, I tried the Gleevec pill and had severe reactions. I was allergic to it and would throw up and had huge hives. Then we started my first round of cladribine chemotherapy. For five days I would stay at the hospital in Calgary and have two-hour treatments for the five days, then you go home, and you feel gross and disgusting and you have a little bit of like skin relief but not so much relief with the sweating and the sleeping or any of that. I was also on AISH at the time so I would have to apply to AISH and get approved to be away from home every time so there's that. Plus gas, and then food, but I wasn't really eating much at the time. So, five days in hospital then home until I could go for another treatment. I did that from 2016 to 2019. I had seven rounds and then my doctor didn't want to put me through anymore because it does cause bone marrow toxicity so she was pressed to try and find something different by the time we hit seven rounds - or 70 hours of treatment. And chemo took my teeth. I wouldn't have that if I took avapritinib before hand but I know that chemo took my teeth.”

The symptoms of ASM are truly unbearable, and the mental toll of grappling with this diagnosis, along with its relentless symptoms, can drive patients to question the purpose of enduring such torment without the hope of treatment or relief. This patient bravely revealed that at one stage of her journey, she reached a point so despairing that she attempted suicide. She emphatically stated that she is a living testament to the lifesaving potential of avapritinib

“In my opinion go straight to avapritinib in the first line. I honestly think it's going to change lives. Save lives. I know that it's life saving because it saved my life. So many people are at that stage where they don't have answers or a solution like this medication and they take their life. When I found out I had cancer I tried to kill myself. It has such a big impact on your mental status and health and everything and that's not the case anymore. I feel better. I can take the medication and be good for the day. There aren't many days where I'm sitting around being upset because I'm scared not knowing what comes next.”

“It's like it's daylight now for me, I open my eyes and it's not so gloomy anymore because of this medication. It's kind of hard to not be happy on this medication.”

This patient elaborated on her thoughts, feelings and experiences regarding the profound benefits of avapritinib treatment, describing it as a “night and day” transformation in every aspect of her life. She expresses profound gratitude for the impact avapritinib has had on her physical and mental well-being, daily functioning, social interactions, and overall sense of returning to her former self.

“On avapritinib I have more relief. It took the sting out of my skin. I don't cry when I sweat now. I don't even feel when I'm sweating anymore. Sweating used to feel like I was getting needles constantly. Like small pricks. My skin doesn't break out with tight waistbands anymore. Even sleeves, my arms used to get really red and swell up and my skin would peel. And my dots haven't come back, so I think that's over now, that aspect.”

“My tryptase level is either at one or non-existent, which high levels can be up around 200. It has definitely made a difference for me. I can't even believe it, I had bone thinning before any treatment and chemo didn't

really do much for that either but avapritinib seems to have lessened that pain. You can't get rid of it but now it's dull. It's manageable.”

“Avapritinib takes the sting out of my pain, it's just dull. I take the avapritinib and I'm just on my merry little way. It's targeting those “pings” and those rashes. I haven't had a rash for quite some time. Before, I mean anything could touch me and I'd just puff right up. I don't puff up anymore, my skin isn't reactive. I'd really have to try to make it react. Before, my doctor drew on my back with the end of a pen, and it puffed right up now it doesn't react. No red line, nothing.”

“I didn't like to wake up at all before this medication, I would wake up at noon, 2, 3, 4:00pm, now I'm up at 8:00 AM. Sometimes when I wake up I'm still a little slow but I take my medication get some liquid in and then I've got a full day of energy and I was diagnosed when I was 23 so this has been a decade in the making. Just be able to sit with myself and not be in all sorts of pain. I honestly think this is our next step for systemic mastocytosis.”

“Things would be completely different for people. They wouldn't be wandering around looking for over the counter stuff because it's the only thing that they felt would help. This stuff it is night and day for treatments. I mean it. Medicine has never agreed with me so when I found avapritinib and it worked out it was a shock. I'm not getting sick from it, I'm getting relief from it. Relief I didn't think I'd ever feel again. This needs to be available to everybody.”

“I wish I could tell other people with this disease to go talk to their doctor and ask for it because that's how life changing it is. There are parents that have kids that have it, and how relieving it could be for them. I can get up and I can be around people and not be moody because I'm sick or sore. I don't spend 90% of my day in the bathroom throwing everything up. It's made a difference in how I'm able to spend time with family and friends. I'm walking around and making jokes and having fun with friends again. I just wish I would have found it a little sooner but hey, it's here.”

“This treatment is completely night and day. Chemo kills everything. With avapritinib I'm not dealing with reacting to everything. I'm not on pins and needles anymore. I'm getting tattoos again. I just had a medic alert tattoo done.”

“I have had no issues with it, and if I can take it with no issues when I was at the state that couldn't even take Advil then this is less problematic than other things. Especially on the aggressive side of Mastocytosis because you've gone through all the other things like, try this, try that, you've really been through the ringer with what they're having you take. It's been a long haul. But now I've been on this for two years and I just feel normal again, so that's a big deal for me. I'm back to my old self, I can be back outside and walk around.”

7. Companion Diagnostic Test

As avapritinib is a targeted therapy specifically for Advanced Systemic Mastocytosis and is a highly selective inhibitor of the KIT D816V mutation, there is diagnostic testing required by a pathologist to identify patients who would benefit from this treatment.

However, this genetic test is integrated as a part of Next Generation Sequencing (NGS) panels, which are routinely administered to patients with hematological malignancies. In this case, the panel will identify mutations that may be associated with the mast cells using a bone marrow or gastrointestinal biopsy.

It can take up to 6-8 weeks to receive the results of this panel.

8. Anything Else?

In this exceedingly small patient population, there is a critically unmet need for viable treatment options.

Without treatment options currently available to Canadians through traditional pathways, avapritinib patients are consequently reliant on over-the-counter remedies and alternative therapies in an attempt to alleviate the symptoms of their condition, while their underlying illness remains untreated.

These patients are subjected to relentless suffering. Whether grappling with the incessant itch, enduring chronic pain, or wrestling with the mental anguish of navigating a disease that brings unpredictable symptoms, they find themselves in constant agony. This anguish affects every facet of their life, disrupting daily routines, affecting their ability to sleep and feel rested, and interfering with their capacity to spend time doing things they enjoy with friends and loved ones.

Advanced Systemic Mastocytosis may be able to achieve a significant response rate with durable responses regardless of whether they had received prior therapies. Responses are also rapid, with a median time to response of 2 months in trial.

Additionally, as Advanced Systemic Mastocytosis is an extremely rare condition, the budget impact of offering this treatment to Canadians may be low.

The individuals that we spoke with who have experienced avapritinib treatment for Mastocytosis has spoken to a treatment that alleviates symptom burden with limited side effects, if any.

The introduction of new, available treatment options can offer hope where there currently may be none. Hope for improved symptom management and a better quality of life for these patients, as well as their caregivers.

With advancements like targeted therapies emerging, there is hope for improved symptom management and overall quality of life for individuals living with Mastocytosis.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

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

No

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

No

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

Table 1: Financial Disclosures

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

Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Novartis			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: Colleen McMillan

Position: Advocacy Lead

Patient Group: The Leukemia & Lymphoma Society of Canada

Date: May 7, 2024

Avapritinib Patient Input

About Heal Canada

Heal Canada is a registered not-for-profit organization that aims to empower patients, improve healthcare outcomes, and advocate for equitable access to quality healthcare across Canada. We are committed to fostering a patient-centred healthcare system that prioritizes every individual's well-being, dignity, and rights through:

- Patient Empowerment
- Patient Education and Awareness
- Advocacy for Equity
- Collaboration and Partnerships with the highest ethical standards.

Methodology:

Online survey:

- On February 27 of this year, Heal Canada launched an online survey to assess different aspects of patients living with blood cancer. As of May 4, only one registered patient was diagnosed with systemic mastocytosis (SM); the subtype was indolent SM, so we didn't include it in the submission.

Patient Interview:

- We contacted the Mastocytosis Society Canada and The Mast Cell Disease Society to reach patients with advanced systemic mastocytosis without success.

Medical Literature:

For a more robust analysis, we mainly used publications from The Mast Cell Connect Registry (MCCR) for the submission (1). Some additional information will be integrated. The complete reference is at the end of the document.

Limitation:

Only 5-10% of patients diagnosed with SM have an advanced form (Fig1). So, the information available on indolent SM (ISM) is more robust due to the sample size compared to the advanced form. However, based on the MCCR data, the proportion of patients experiencing symptoms is similar or higher in advanced forms than ISM. Also, the severity of the symptoms and their impact on life are comparable or more critical in advanced forms

than ISM. So, the report will include all SMs, and discrimination between ISM and advanced SM will be provided when possible.

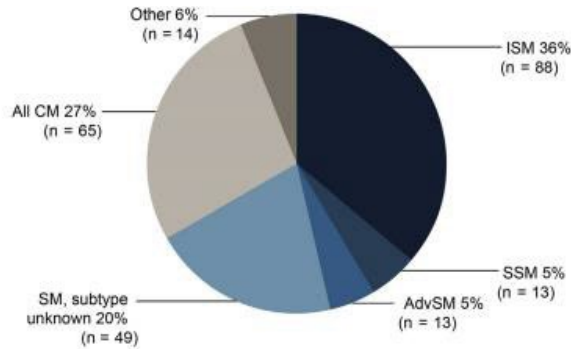


Fig. 1. Mast cell connect registry: participant-reported disease subtypes.

Diagnosis:

Systemic Mastocytosis (SM) is a rare disease with a complex and variable clinical presentation. These two elements combined explain the difficulty patients experience before getting a concrete diagnosis; for patients with advanced SM, an average of 3 years is observed between the onset of symptoms and the diagnosis MCCR (1). Frustration due to the general lack of knowledge regarding the diagnosis and treatment of SM is a major topic during the support discussion group. Even some patients can be referred to psychiatry. SM is often misdiagnosed as CMML or MDS.

Table 3 Mast cell connect registry: time from symptom onset to diagnosis					
	SM (n = 149) ^a	ISM (n = 80) ^a	SSM ^b (n = 13)	AdvSM ^b (n = 13)	CM (n = 61) ^a
Median (y) ^c	7	9	9	3	1
Mean (SD) ^c	12 (13)	12 (12)	12 (11)	11 (14)	7 (14)

Abbreviation: SD, standard deviation.

^a Number of participants who responded to this question.

^b The numbers of participants who reported a diagnosis of AdvSM or SSM are small; hence, results should not be considered representative of patients with AdvSM or SSM in general.

^c Derived from the following questions: At what age did the participant first begin experiencing symptoms of mastocytosis? At what age was the diagnosis of mastocytosis made?

Patients visited a median of 3 specialists before making a diagnosis (2), and nearly half consulted 3 to 6 physicians while seeking a diagnosis (3).

The specialties most often consulted are dermatology, allergy/immunology, hematology/oncology, internal physicians and general practitioners.

Based on recommendations, a bone marrow biopsy should be performed to confirm the diagnostic, but only 40% of responders recalled this assessment.

Symptoms and their impact on QoL:

The frequency and intensity of any given symptom can vary widely. Some patients are chronically disabled, whereas others may lead relatively normal lives (4).

However, the unpredictable onset of symptoms seems to be a major concern for all patients. This can be easily explained by the fact that a frequent proportion of patients identified these elements as a trigger: Heat (82%), Stress (81%), Temperature change (76%), Exercise (63%), Alcohol (54%), Medication (53%), Odors (48%), cold (40%), insect stings (35%), food (31%) and food additives (9%) (1,2). In a recent patient-reported outcome (TouchStone SM Patient Survey), 64% of patients reported avoiding leaving the house because of SM (8).

You will see in Table 4 the moderately to severe symptoms spectrum experienced by SM patients. You will notice that some more prevalent symptoms are more frequently observed in AdvSM vs SM in general:

- Systemic symptoms: Fatigue, and Pain.
- GI symptoms: Abdominal pain, Nausea and vomiting
- Mental Health-related symptoms: Difficulty concentrating and sleeping as well as anxiety and depression.

In the TouchStone study, the most bothersome SM-related symptoms are anaphylactic episodes, abdominal pain, diarrhea and fatigue (8). These symptoms are more present in Advanced SM than in ISM (1).

Table 4
Mast cell connect registry: frequency (%) of participants experiencing moderately to severely bothersome symptoms within the past year

	SM (n = 163)	ISM (n = 88)	SSM (n = 13)	AdvSM (n = 13)	CM (n = 65)
Systemic symptoms					
Fatigue/tiredness	72	72	62	85	42
Pain (other than abdominal)	56	57	46	62	31
Headache	42	48	38	23	32
Sweating	36	38	15	46	23
Swelling	35	38	15	38	18
Anaphylaxis	33	33	38	31	14
Difficulty breathing	28	32	46	31	22
Gastrointestinal symptoms					
Abdominal pain	54	55	46	69	48
Bloating	48	50	38	46	34
Diarrhea	45	42	46	46	25
Nausea	42	43	46	77	23
Flatulence	33	31	31	38	17
Vomiting	21	18	31	54	14
Skin symptoms					
Itching	47	45	85	54	51
Flushing	44	45	46	38	43
Skin changes	42	43	23	46	57
Other impacts					
Difficulty concentrating	60	59	62	85	43
Difficulty sleeping	55	56	46	69	35
Anxiety	41	40	31	62	45
Depression	33	34	15	54	20

The number of participants who reported a diagnosis of AdvSM or SSM is small; hence, results should not be considered representative of patients with AdvSM or SSM in general.

Impact on daily life and QoL

64% of patients have a moderate to extremely severe reduction in quality of life (3). Feelings of sadness, concern, lack of motivation, discouragement, frustration, or reduced capability were identified for approximately two-thirds of mastocytosis patients (6).

In Figure 2 of MCCR, we can observe that the disability experienced by patients due to symptoms occurred independent of diagnosis type.

More specifically in AdvSM,

- The disease limits work, daily and leisure activities in 92% of patients.
- 92% of patients are worried, are feeling irritable and have a form of depression.
- 85% of patients report that the disease has quite or very much impacted their family and social life.

In other references, it has been reported that more than 50% of AdvSM patients also reported worrying and feeling nervous.

We can find more information in the TouchStone study to assess if SM can impact work capabilities (8):

- 54% of respondents reported ever reducing their work hours
- 27% reported voluntarily quitting their job because of SM
- 16% reported being terminated from their job as a result of SM

66% of patients mentioned pain as the mean symptom interfering with work and patients who reported severe pain were more likely to note SM-related

changes to employment status(8). For example, 100% of patients who reported early retirement because of SM also reported severe pain over the past 4weeks (8).

The majority of adult SM patients report fear of “worsening disease” and fear of “disease progression”. (5,6)

Current treatments :

In this debilitating symptomatic disease, where the QoL is highly impacted by the fear of having a crisis due to omnipresent triggers, having better access to holistic care approaches is vital. Integrating relaxation techniques (meditation, yoga), proper diet, and good sleep hygiene is necessary. Diet and exercise can be complicated for SM patients because they can trigger a reaction. So, they need professional support.

As a treatment, SM patients want therapies that address the underlying disease rather than medications that manage only their symptoms. Current access is an issue, as a rare disease they need to advocate harder for better access to targeted therapy.

- They are frustrated by the absence of curative therapy (83%)(5)
- Fear of anaphylaxis triggered by prescribed medication (75%)(5)
- Fear of receiving an inappropriate treatment if unresponsive (70%)(6)
- Frustrated by general HCPs' lack of knowledge of current treatment consensus.
- Patients seem also to fear transplantation which seems to be proposed early in the process at non-expert centers (1).

They have a high level of polypharmacy. More than 50% of patients in the TouchStone survey reported using three or more OTC medications and three or more prescription medications (8). So, not surprising to read, in MCCR publication, that patients and caregivers are concerned about:

- Drug interactions
- Reaction to medication:
 - Patients may be triggered by nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid narcotics, making pain management challenging.
 - Some patients use compounding pharmacies to eliminate reactions to unnecessary fillers.
- Long-term effects of antihistamine use on cognition; adding a continuous intravenous delivery route elevates concerns.

What is interesting about avapritinib is that contrary to imatinib and midostaurin, selective inhibitor of KIT and PDGFRA with high potency for the KIT D816V mutation. This mutation is observed in ~95% of patients.

Avapritinib (9)

Avapritinib can offer an option to patients who do not have any real options. It is a therapy that addresses the underlying disease like they hope for. Also, it can offer an option for people who do not respond to their current medications.

- The efficacy is good with an ORR of 71% including 19% of CR/CRh
- The response is fast with a median time to response of 2.3 months and the response improves over time with a median time to CR/CRh at 7.4 months.
- The response seems durable with a median duration of response (DOR) was not reached.
- This medication demonstrates disease modifier properties with:
 - 89% of patients have a reduction of $\geq 50\%$ in bone marrow mast cell infiltration
 - 66% of patients have a reduction of reductions of KIT D816V variant allele fraction
 - 89% of patients have a reduction of serum tryptase
 - 70% of patients have a reduction of $\geq 35\%$ in spleen size
- Median OS was not reached (median follow-up 17.7 months).
- Avapritinib was effective in all AdvSM subtypes,
- Avapritinib was effective in all AdvSM regardless of the number/type of prior therapies or poor prognostic somatic mutations.
- Avapritinib was effective in all AdvSM in poor prognostic somatic mutations.
- Avapritinib significantly reduces symptom burden (mean change from baseline AdvSM-SAF TSS score)
- Avapritinib improves QoL (physical, role, emotional, cognitive and social domains)
- Avapritinib was safe and well-tolerated

Disclosure section:

- No help from outside the organization has been provided to support this submission.
- No help from outside the organization has been provided to collect or analyze the data used in this submission.

- See the list of pharmaceutical companies providing funding to support Heal Canada. None of these companies has a direct or indirect interest in the drug submission.
 - o Novartis
 - o SOBI

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- 8- Mesa A et al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: results of the TouchStone SM Patient Survey, *Cancer*, Oct 2022, 3691-3699
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CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0335

Generic Drug Name (Brand Name): avapritinib

Indication: For the treatment of adult patients with Advanced Systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Name of Clinician Group: Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Author of Submission: Dr. Tom Kouroukis

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Input was gathered by email.

3. Current Treatments and Treatment Goals

Treatments include cytoreductive therapies (e.g., imatinib, cladribine, cytarabine, azacitidine, hydroxyurea and fludarabine) plus mast cell stabilizers or inhibitors of release (e.g., antihistamines). Midostaurin is also an option, however this is not funded in Ontario.

Treatment goals are to control disease, quality of life, life expectancy and reduce transfusion dependence.

4. Treatment Gaps (unmet needs)

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

This indication is for a rare clinical scenario with poor outcomes and very symptomatic patients.

5. Place in Therapy

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

This can be used at any line of therapy. If this drug is approved, it would be used as first line.

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

This can be used in all patients with aggressive SM, given that the driver mutation is present in 95% of these patients.

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

Improvement in clinical symptoms, tryptase levels, spleen volume, bone marrow improvement. This can be assessed once a month or as needed.

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

Significant intolerance or overt disease progression.

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

Hematologists with experience in management of SM or other myeloproliferative neoplasms.

6. Additional Information

N/A

7. Conflict of Interest Declarations

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

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

OH (CCO) provided a secretariat function to the group.

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

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Tom Kouroukis

Position: Lead, OH (CCO) Hematology Cancer DAC

Date: 02-05-2024

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

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 2

Name: Dr. Pierre Villeneuve

Position: Member, OH (CCO) Hematology DAC

Date: 02-05-2024

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

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Add company name				
Add company name				
Add or remove rows as required				

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

x

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PC0335-000

Generic Drug Name (Brand Name): avapritinib (Ayvakit)

Indication: for the treatment of adult patients with Advanced Systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Name of Clinician Group: LLSC Clinician Network/MPN Canada Clinician Group

Author of Submission: Dr. Stephanie Lee

For inquiries, please contact: Colleen McMillan, Advocacy Lead, LLSC

1. About Your Clinician Group

A group of Canadian clinicians with experience with Advanced Systemic Mastocytosis.

Dr Stephanie Lee is the principal investigator of St Michael's Hospital Centre of Excellence in Systemic Mastocytosis, a designation given by the American Initiative in Mast Cell Diseases ([AIM](#)). AIM, led by Dr Jason Gotlib, is a consortium of centres of excellence and reference centres in North American dedicated to advancing the research, education, and treatment of systemic mastocytosis (SM) and related mast cell diseases. St Michael's Hospital is the only hospital in Canada with the Centre of Excellence designation based on the experience and expertise of our clinical and histopathological team.

The Canadian MPN group is a dedicated collaborative group of physicians across Canada. Our mission to enhance the care of patients with MPNS through harmonization of practice , facilitate cutting-edge research, and foster national collaboration . Our group is experienced in treating all MPNs including mastocytosis.

2. Information Gathering

The Leukemia Lymphoma Society of Canada (LLSC) and Dr. Stephanie Lee facilitated information gathering through a series of interviews and discussions with clinicians from various Canadian cancer centres, who have experience with Advanced Systemic Mastocytosis.

3. Current Treatments and Treatment Goals

The primary goals of treatment for patients with advanced systemic mastocytosis (SM) are to (1) improve health-related quality of life, (2) prevention of life-threatening anaphylaxis, (3) reverse end organ damage, (4) prolong survival

Anti-mediator therapies such as anti-histamines and leukotriene receptor antagonists are used to manage mast cell activation symptoms. Prevention of anaphylaxis is managed with therapies such as Omalizumab and venom immunotherapy as well as cyto-reduction. Cyto-reduction is the principal treatment for advanced SM, which improves

quality of life, reverses and prevents organ damage, and prolongs survival. Available cytoreductive options in Canada for advanced SM include midostaurin, cladribine, interferons (e.g. peginterferon alfa-2a) and imatinib. International guidelines and expert consensus recommend enrollment in clinical trial or a KIT inhibitor such as midostaurin or avapritinib in the front-line for advanced SM as well as cladribine can be considered when rapid debulking is required.

Midostaurin is an oral multikinase inhibitor approved for treatment of advanced SM in many countries including Canada, the United States and Europe. While midostaurin received Health Canada approval for SM, CADTH issued a negative recommendation so it did not get listed by any public plans and is not reimbursed across Canada. Except for some exceptional coverage through “patient d’exception” in Quebec, there are currently no compassionate programs for midostaurin in Canada. The annual out of pocket cost that must be incurred by patients can exceed \$100 000 CAD, rendering this medication accessible only to the few with extraordinary wealth.

Cladribine is not approved by Health Canada for SM but is used historically off-label for all variants of advanced SM and has been shown to have variable overall response rates and variable durations of response. In the modern clinical landscape, the principal way cladribine fits into the treatment paradigm is for rapid disease debulking, which may be needed when patients present very acutely at diagnosis. Infectious complications and myelosuppression are significant and frequent adverse events that extremely limits the long-term use of this medication especially in patients who are very frail, which is common at disease presentation.

Interferons (e.g. peginterferon alfa-2a) have been historically used off label in Canada for patients with advanced SM. In the current treatment landscape, it can be considered for (1) the rare patient with ASM with very slowly progressive disease, (2) patients with severe refractory bone pain that has not responded to other lines of treatment and (3) SM-AHN (typically when the AHN component requires treatment). Interferons are not an appropriate treatment for patients who present acutely and require immediate disease control to prevent life-threatening organ failure as response times are variable and can be very delayed (up to 12 months in some reports). In clinical practice, interferon is essentially never an adequate front-line treatment option for advanced SM.

Imatinib is approved by Health Canada for advanced SM in those without *KIT*D816V mutation or with unknown *KIT* mutational status; since > 90% of patients with SM have *KIT* D816V mutation, imatinib has a very limited role in the treatment of advanced SM.

There is a paucity of high-quality data on the role of allogenic hematopoietic stem cell transplant (allo-HSCT) in advanced SM but it is typically reserved for patients with aggressive/treatment refractory disease and those with SM-AHN with high risk AHN features (e.g. AML). Prior to transplant, most experts recommend that patients not proceed with transplant unless there is at least a partial response prior to transplant. KIT inhibitors are very effective treatments to bridge patients to allo-HSCT by reducing mast cell burden, improving organ function, reducing spleen size and improving patient fitness. The role of KIT inhibitors in the post-transplant setting has not been formally studied in prospective trials but many experts recommend using a KIT inhibitor in the post-transplant setting especially if there is evidence of minimal residual disease.

The ideal treatment should improve quality of life, improve survival, reverse organ damage, be easy to administer, be affordable, and not cause severe treatment adverse effects.

4. Treatment Gaps (unmet needs)

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

There is an enormous treatment gap in Canada for patients with advanced SM. KIT inhibitors are the standard of care and recommended by major international guidelines as front-line treatment from patients with advanced SM. While midostaurin is approved by Health Canada, CADTH unfortunately issued a negative recommendation. With the lack of compassionate programs in much of the country and the extreme financial toxicity of midostaurin, it is not a realistic treatment option in Canada. Taken together, most Canadian patients with advanced SM do not have access to first- or second-line treatment. This represents a significant care gap but also an equity issue as only patients who live near

academic centres with the opportunity to participate in clinical trials or those with financial security can access standard of care treatments in Canada.

5. Place in Therapy

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

In the current treatment paradigm of advanced SM, avapritinib would be used as front-line monotherapy.

Avapritinib will be the second treatment approved to address the underlying disease process with the caveat that the first approved treatment (i.e. midostaurin) is not a practical option for patients in Canada (outside of Quebec) and is not part of the current treatment paradigm for most patients.

Avapritinib would be used as front-line treatment as monotherapy with the exception of patients who (1) present very acutely and need rapid debulking with cladribine; in these cases, often a single cycle of cladribine could be offered for immediate disease control followed by monotherapy with avapritinib or (2) patients with a platelet count $< 50 \times 10^9/L$; in these cases, a short course of midostaurin or cladribine (if patient could not afford a short course of midostaurin) as initial cytoreduction to allow platelet count to recover to $> 50 \times 10^9/L$ then transition to avapritinib. This could be a strategy to minimize financial toxicity of midostaurin but lead to sufficient disease control to allow patients to safely start avapritinib.

Avapritinib would completely change the treatment landscape in Canada and allow patients access to therapy that is widely accepted internationally as the standard of care for front-line treatment for advanced SM. If avapritinib was funded, it would almost never be appropriate to expose a patient to the financial toxicity of the other available front-line treatment (i.e. midostaurin) with the exception of patients with platelet count $< 50 \times 10^9/L$ with the strategy outline above.

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

All subtypes of advanced SM are predicted to benefit from avapritinib monotherapy. All patients with advanced SM should be considered for treatment especially those with life-threatening organ damage and debilitating symptoms. There is no companion diagnostic test needed other than the investigations outlined in the 5th Edition of WHO diagnostic criteria.

Identifying which patients will have an optimal treatment response is not well defined. There is some data supporting that patients with complex molecular profiles and those with SM-AHN may be at elevated risk of treatment resistance and/or disease progression in the setting of KIT inhibitor monotherapy; however, this would certainly not preclude treatment with single agent avapritinib.

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

Response criteria used in clinical trials continue to be frequently modified to (1) best capture clinical benefit, (2) better define long-term outcomes in the TKI era and (3) standardize response evaluation across clinical trials so that efficacy of different drugs can be appropriately compared. Major response criteria that have been used in clinical trials and in clinical practice include the Valent criteria (plus its modified version), Mayo criteria, IMWG-MRT-ECNM criteria (plus its modified version) and more recently pure pathological criteria and ECNM-AIM criteria. Many patients will have a partial

response as per criteria above but will have tremendous clinical improvement after starting treatment and this isn't always captured by these criteria, which are designed predominantly for clinical trials.

Assessment of a clinically meaningful response requires integration of patients' goals of treatment with clinical and histopathological factors. From a clinical perspective, improvement in patient symptom score is a critical part of the response assessment. Avapritinib improves patients' symptom score which often translates to improved quality of life and patient fitness. These, of course, are important factors for all patients but are additionally important if the goal is to improve fitness to proceed with allo-HSCT as patients with advanced SM can present with severe cachexia and poor performance status.

From a laboratory perspective, normalization of CBC and reduction/absence of transfusion requirements not only improve patients' quality of life but also liberates them and their caregivers from the time and financial burden of constantly needing to travel for count checks and transfusions. In those with liver involvement, normalization of elevated liver enzymes, reduction in liver size, and reduction in need for diuretics and/or therapeutic paracentesis have similar benefits on quality of life and reduced burden on the patient, caregivers, and health care system. Patients also commonly have splenomegaly and avapritinib can reduce spleen size, which is a key treatment target prior to allo-HSCT. Routine monitoring of basal serum tryptase levels are also an important surrogate for disease response.

From a histopathological perspective, reduction in abnormal mast cell burden in bone marrow is a critical part of treatment response as well as treatment response to AHN component such as improvement in blast count and restoration of effective hematopoiesis.

From a molecular perspective, reduction in variant allele frequency of *KIT* variants is becoming an increasingly important marker for response to treatment though funding for this is not widely available in Canada.

Clinical and laboratory monitoring as summarized above should be done at every visit, which is more frequent at the initiation of treatment. Specific timepoints for histopathologic assessment of disease response is not well defined in the literature. Histopathological assessment should be done at three months after initiation of avapritinib treatment and then can be considered every 3 months thereafter for the first 12 cycles of therapy and/or if there is evidence of loss of response or disease progression (e.g., worsening cytopenias or -cytosis, increased peripheral blasts, increasing tryptase).

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

Factors that should prompt treatment discontinuation include (1) patients no longer getting clinical benefit from a symptom/quality of life perspective, (2) patients with platelet count below $50 \times 10^9/L$, (3) persistent severe treatment AEs that cannot be managed with dose interruptions or dose reductions and (4) evidence of progressive disease, either in the SM or AHN disease component (if present) or (5) patients who are pregnant.

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

International guidelines suggest patients with SM be treated by medical teams with expertise in diagnosis, treatment, and response assessment. For patients that live far from a centre with such experience, shared care model with local partners can be considered.

6. Additional Information

In the current clinical setting, we are not providing adequate care for patients with advanced SM in Canada. A positive CADTH approval for avapritinib will dramatically change the treatment landscape for patients in Canada and will finally allow us to provide standard of care treatments for all patients across Canada. The current literature shows the benefits of using targeted oral therapies for advanced SM over historical treatments. In many countries, patients have access to two front-line TKI therapies: avapritinib and midostaurin. Right now in Canada, most patients have access to neither. There is extremely limited compassionate access to midostaurin; in my large practice of patients with advanced SM, I have only ever had one patient who was able to afford a short course of midostaurin. Midostaurin is not a realistic part of the treatment paradigm due to its severe financial toxicity and we have a national obligation to provide affordable access to standard of care treatments for all Canadians, not just for patients with financial security or who are lucky to live near centres with clinical trials.

7. Conflict of Interest Declarations

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

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.
No
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.
No
3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Stephanie Lee

Position: Hematologist, Assistant Professor at the University of Toronto

Date: 23-04-2024

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

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Medison		X		
Novartis	X			
Add or remove rows as required				

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

Declaration for Clinician 2

Name: Dr. Shireen Sirhan

Position: Assistant professor McGill University -Jewish General Hospital

President – Canadian MPN Group

Date: 03-05-2024

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

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Novartis			X	
GSK		X		
Janssen		X		
DISC Medicine		X		

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

Declaration for Clinician 3

Name: Sasan Zandi , MD, PhD, FRCPC

Position: Assistant professor, University of Toronto

Medical director and Division head of hematopathology, St Michael's Hospital Department of Pathology

Date: 30-04-2024

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

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Medison	X			
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 4

Name: Dr. Brian Leber

Position: Professor of Medicine (Hematology) , McMaster University; Disease Site Group Head- Leukemia, Juravinski Cancer Centre/Hamilton Health Sciences

Date: 05-05-2024

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

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Novartis		X		
SOBI Pharma		X		
Add or remove rows as required				

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

Declaration for Clinician 5

Name: Dr. Lynda Foltz MD, FRCPC

Position: Hematologist

Date: 06-05-2024

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

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000
Novartis		X		
GSK		X		
Medison Pharma	X			

* Place an X in the appropriate dollar range cells for each companyDeclaration for Clinician 1

Declaration for Clinician 6

Name: Dr. Sonia Cerquozzi

Position:

Date: 06-05-2024

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

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	\$0 to \$5,000	\$5,001 to \$10,000	\$10,001 to \$50,000	In excess of \$50,000

* Place an X in the appropriate dollar range cells for each companyDeclaration for Clinician 1