Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Avapritinib (Ayvakyt)

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).

Sponsor: Medison Pharma Canada Inc.

Recommendation: Reimburse with Conditions

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that avapritinib be reimbursed for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

pERC recognized the rarity of AdvSM and the significant unmet need for additional treatment options given the poor prognosis and substantial morbidity of this disease. Evidence from 2 single-arm, open-label, multi-centre studies, phase II PATHFINDER and phase I EXPLORER, suggested that treatment with avapritinib may result in a clinically meaningful benefit in overall response rate (ORR) in patients with AdvSM. In total, 105 patients in the PATHFINDER and 21 patients in the EXPLORER trials received the Health Canada-approved dose. The ORR, the primary endpoint in the PATHFINDER trial, was [redacted] and met the prespecified end point (i.e., ORR exceeded the null hypothesis of 28%; June 23, 2020, data cut-off date). Responses appeared durable (median duration of response was not reached [95%CI, 37.1 months to not estimable]). The EXPLORER study was primarily a dose-finding trial and its results supported the findings from the PATHFINDER study. pERC considered the safety profile of avapritinib to be manageable, but noted the risk of intracranial bleeding and cognitive impairment which would require adequate monitoring and appropriate dose adjustments.

Patients identified a need for effective treatments that improve disease symptoms, have fewer adverse events, and improve quality of life. pERC considered that avapritinib may meet patients' needs for improved disease control and access to an additional treatment option. While no detrimental impact on health-related quality of life (HRQoL) or symptom severity was observed with avapritinib, no definitive conclusion could be reached due to the open-label and non-comparative nature of the analyses.

Despite uncertainty in the results of the indirect treatment comparisons due to methodological limitations, there was consistency in the direction of effects for overall survival (OS), ORR, complete remission (CR), and duration of treatment favoring avapritinib over relevant comparators (midostaurin and best available therapy [BAT]) in patients with AdvSM.

The results of CADTH's pharmacoeconomic alternative analyses remain highly uncertain and prone to bias whose direction and magnitude are both unknown due to limitations with the clinical evidence and the analytical approach used by the sponsor. The committee considered alternative analyses conducted by CADTH which estimated the cost-effectiveness of avapritinib relative to first line (1L) BAT (a weighted basket of treatments comprised of cladribine, peginterferon alfa-2a, and imatinib) in the 1L population and avapritinib relative to second-line or later (2L+) BAT (a weighted basket of treatments comprised of cladribine, peginterferon alfa-2a, imatinib and midostaurin) in the 2L+ population, based on data from the sponsor's Inverse Probability of Treatment Weighted (IPTW - weighted) analysis. Based on the sponsor's submitted price for avapritinib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) was estimated to be $435,876 per quality-adjusted life-year (QALY) gained compared with 1L BAT in the 1L population, and $660,217 per QALY gained compared with 2L+ BAT in the 2L+ population. A price reduction would be required for avapritinib to achieve an ICER of $50,000 per QALY, although due to the substantial uncertainty associated with the economic analysis, a greater price reduction may be required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with avapritinib should be reimbursed in adults aged 18 years or older who meet all the following criteria: 1.1 Documented diagnosis of ASM, SM-AHN, or MCL based on the WHO diagnostic criteria[a] 1.2 ECOG PS of 0 to 3.	Evidence from the PATHFINDER and EXPLORER trials suggested that avapritinib resulted in clinical beneficial responses in patients with these characteristics.	Multidisciplinary case conference (MCC) involving regional and/or provincial experts with expertise in the diagnosis and management of AdvSM may optimize utilization of avapritinib in the desired patient population.
2. Patients must not have any of the following: 2.1 Platelet count less than 50,000/μL or receiving platelet transfusion(s) 2.2 High risk of intracranial bleeding (as per clinician judgement) 2.3 Primary brain malignancy or metastasis	There is no evidence from the PATHFINDER and EXPLORER trials to support a benefit or safety of avapritinib treatment in patients with these characteristics, as they were not eligible to enrol into these trials.	The risk of intracranial bleeding is higher in patients with platelet counts < 50,000/ μ L. Measures to minimize the risk of intracranial bleeding may include platelet monitoring and interruption of therapy in patients developing severe thrombocytopenia (platelet count < 50,000/ μ L).
Discontinuation		
3. Avapritinib should be discontinued in patients for whom treatment is intolerable, or upon the occurrence of disease progression.	In the PATHFINDER and EXPLORER trials, patients who experienced disease progression, required initiation of alternate cytoreductive therapies, or experienced intolerable toxicity were discontinued from avapritinib.	—
Prescribing		
4. Avapritinib should be prescribed by medical teams with access to expertise in the diagnosis, treatment, and response evaluation of patients with AdvSM.	These conditions will ensure that avapritinib is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner	—
5. Avapritinib should not be reimbursed when used in combination with other systemic therapy for AdvSM.	There is no evidence from the PATHFINDER and EXPLORER trials to support the use of avapritinib in combination with other systemic therapies. Administration of palliative and supportive care for disease-related symptoms were permitted during the studies.	—
Pricing		
6. A reduction in price	The cost-effectiveness of avapritinib is highly uncertain. A robust CADTH base case could not be determined. The clinical evidence was highly uncertain and lacked face validity.	—

Reimbursement condition	Reason	Implementation guidance
	CADTH undertook reanalyses for the 1L and 2L+ populations by adopting different OS and PFS parametric distributions for avapritinib in the 1L population and removing midostaurin from 2L+ BAT treatment costs. The CADTH reanalyses were derived by making changes in model parameter values and assumptions, in consultation with clinical experts. These analyses indicated that at least 87% reduction in price is required to achieve an ICER of $50,000 per QALY.	
Feasibility of adoption		
7. The economic feasibility of adoption of avapritinib must be addressed	At the submitted price, the incremental budget impact of avapritinib is expected to be greater than $40 million in years 2 and 3.	—

1L = first line of therapy; 2L+ = second line of therapy or later; ASM = aggressive systemic mastocytosis; BAT = best available therapy; ICER = incremental cost-effectiveness ratio; MCL = mast cell leukemia; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; WHO = World Health Organization.

[a] Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013;121(13):2393-401.

Discussion Points

- pERC deliberated on avapritinib considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CDA-AMC Reimbursement Reviews. Reflecting on input from clinical experts and patients, pERC acknowledged the rarity and severity of AdvSM and the unmet need for additional effective treatment options. Furthermore, the committee noted the challenges with conducting randomized controlled trials (RCTs) in the target patient population. pERC discussed that the available efficacy and safety evidence was from noncomparative trials, and the GRADE assessment of the evidence was of 'very low' certainty. Weighing the limitations of the evidence against the significant unmet need in this patient target population, the committee concluded that the available evidence reasonably suggested that avapritinib has the potential to reduce morbidity and mortality associated with AdvSM.
- pERC discussed the poor prognosis for patients with AdvSM and the need for effective therapies alongside the uncertainty of the evidence. pERC agreed with clinical experts that the ORR and duration of response, observed in the PATHFINDER trial, appeared compelling, durable, and clinically meaningful for patients given the current lack of effective treatment options. The findings from the EXPLORER trial were consistent with the results from PATHFINDER; however, only 17 patients who provided ORR data had received the Health Canada-approved dose, which limited interpretation of the findings of this smaller cohort.
- pERC discussed the indirect treatment comparisons (ITCs) submitted by the sponsor, including 1 published unanchored matching-adjusted indirect comparison (MAIC) of avapritinib relative to midostaurin and 1 observational comparison comparing avapritinib with real-world midostaurin or BAT (a basket of treatments including cladribine, imatinib, and interferon, with or without midostaurin). The results suggested consistency in the direction of effect for response (ORR and CR), OS, and duration of treatment favoring avapritinib over midostaurin and BAT, although there were substantial limitations with the evidence. Limitations identified in the analyses included heterogeneity in the data sources and patient characteristics, missing or unmeasured prognostic factors and effect modifiers, small sample sizes, few events, imbalanced follow-up times, and immaturity of survival data. pERC noted there was significant uncertainty in the magnitude of the comparative benefit with avapritinib due to limitations of the available indirect comparisons.
- pERC discussed the safety profile observed with avapritinib. pERC noted that the non-randomized design of PATHFINDER and EXPLORER trials makes interpreting the safety events attributable to avapritinib challenging, since all patients received the same treatment. However, pERC agreed with the clinical experts that the incidence and severity of adverse events seemed overall manageable. The most common treatment-emergent adverse events (TEAEs) included edema, anemia, diarrhea, nausea, fatigue, vomiting, cognitive effects (most commonly memory impairment, cognitive disorder and confusional state), and thrombocytopenia. pERC noted the risk of intracranial bleeding and cognitive impairment which will require adequate monitoring and appropriate dose adjustments.

Background

Systemic mastocytosis (SM) is a heterogenous group of rare disorders caused by clonal, neoplastic proliferation of abnormal mast cells, that accumulate typically in bone marrow and other extracutaneous tissues. Symptoms of SM are related to the release of mast cell mediators and mast cell tissue infiltration which can vary widely from isolated symptoms to a constellation of symptoms, commonly including cutaneous involvement (e.g., skin flushing, pruritis, itching, hives, skin rash), wheezing and shortness of breath, dizziness, cardiovascular symptoms (e.g., rapid heart rate, chest pain, low blood pressure), gastrointestinal symptoms (e.g., diarrhea, nausea, vomiting, abdominal pain), fatigue, musculoskeletal symptoms (e.g., bone and/or muscle pain), and neuropsychiatric symptoms (e.g., headache, brain fog, cognitive dysfunction, anxiety, depression).

SM is classified into distinct subtypes in order of increasing disease burden: indolent SM and bone marrow mastocytosis, smoldering SM, aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Advanced SM (AdvSM) includes the disease variants of ASM, SM-AHN, and MCL. The prevalence rate of SM is estimated at 1 per 10,000 people of all ages. Based on estimates from Danish incidence and German prevalence of adults with AdvSM, the estimated AdvSM incidence rate in Canada is 0.06 cases per 100,000 adults and the prevalence rate is 5.2 cases per million adults. Median overall survival has been estimated at 41 months for ASM, 11 to 42 months for SM-AHN depending on the type of AHN, and 2 to 19.2 months for MCL.

Cytoreduction is the principal treatment for AdvSM, which may improve quality of life, reverse or prevent organ damage, and prolong survival. Current available cytoreductive options in Canada for AdvSM include midostaurin, cladribine, interferons (e.g. peginterferon alfa-2a) and imatinib. The 2024 National Comprehensive Cancer Network (NCCN) clinical practice guidelines, recommend enrollment in clinical trial, or V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) inhibitors, midostaurin or avapritinib, as first-line treatment for AdvSM. According to the clinical experts consulted for this review, there is a major treatment gap for patients with AdvSM in Canada. The off-label treatments currently available (cladribine and interferon) have low or unpredictable response rates, response of short duration, and may cause significant toxicity. Imatinib is suitable for a small minority of patients with AdvSM who do not have the KITD816V mutation or with unknown KIT mutational status. The targeted therapy, midostaurin, is approved for the treatment of AdvSM in Canada but is not publicly funded and therefore is inaccessible. Avapritinib was approved by Health Canada for the treatment of adult patients with AdvSM. AdvSM includes patients with ASM, SM-AHN, and MCL. Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 x 10^9/L. Avapritinib is a Type 1 kinase inhibitor. It is available as 25 mg, 50 mg, 100 mg and 200 mg oral tablets and the dosage recommended in the product monograph is 200 mg daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 open label, single arm clinical trials in adults with AdvSM; indirect evidence from 1 indirect treatment comparison and 1 observational comparison
- patients' perspectives gathered by 2 patient groups, Heal Canada and the Leukemia and Lymphoma Society of Canada (LLSC)
- input from cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with AdvSM
- input from 2 clinician groups, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee and the LLSC Clinician Network and Myeloproliferative Neoplasms Canada Clinician Group
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions, including Heal Canada and the LLSC. Heal Canada is a not-for-profit organization that aims to empower patients, provide patient education and awareness, improve healthcare outcomes, and advocate for equitable access to quality health care. LLSC is a national charitable organization dedicated to finding a cure and improving quality of life for people and their families affected by blood cancers through research, educational resources, services, and support. Heal Canada conducted an online survey of patients living with blood cancer (February to May 2024); however, no patient with AdvSM was recruited and no patient was identified to have had experience with avapritinib, so the submitted information was based on the Mast Cell Connect Registry (MCCR) data and its publications. LLSC conducted one-on-one interviews with 3 patients with SM (1 patient each, with AdvSM, indolent SM, and unknown SM subtype) and 1 caregiver whose father had AdvSM. One interviewed patient with ASM and a caregiver of a patient with ASM reported on experience with avapritinib. The caregiver reported her father's skin issues and itching dissipated and his quality of life improved while receiving avapritinib, with no major adverse effects. The patient who received avapritinib via compassionate care access, expressed its life-changing impact in alleviating symptom burden and mental strain due to the disease, with no observable adverse effects.

Both Heal Canada and LLSC reported SM to be a rare disease with a complex and variable clinical presentation which can lead to misdiagnosis or delays in diagnosis. Patients with AdvSM frequently reported symptoms of fatigue, concentration difficulties, body pain, sleep disturbances, nausea, vomiting, skin irritations (e.g., rashes, itching, hives), and anxiety and depression. The onset of symptoms is unpredictable, and may be triggered by temperature, stress, exercise, food, medication and other factors. Patients are at risk of life-threatening anaphylaxis due to SM. The frequency and intensity of symptoms can vary widely, with some patients chronically disabled while others may lead relatively normal lives.

There is a lack of accessible and effective treatments for patients with AdvSM in Canada. Patients seek better treatments that improve disease symptoms, have fewer adverse events, improve quality of life, allow the restoration of daily activities, and improve physical and mental wellbeing.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted for this review, there is a major treatment gap for patients with AdvSM in Canada. The off-label treatments currently available have low or unpredictable response rates, response of short duration, and may cause significant toxicity. The clinical experts stated that avapritinib would be used as first line monotherapy in patients with AdvSM, except for patients who present very acutely and need rapid debulking with cladribine or those with a platelet count less than 50×10^9/L. In these patients, avapritinib may be used second line, after debulking or once platelet counts had increased. The experts identified the patients most suitable for treatment are those who meet the WHO diagnostic criteria for AdvSM, who are treatment-naïve or who have received prior therapy for AdvSM. The experts anticipated that patients with all subtypes of AdvSM (ASM, SM-AHN, MCL) would benefit from treatment with avapritinib monotherapy.

According to the clinical experts consulted, assessment of a clinically meaningful response requires integration of patients' goals of treatment with clinical and histopathological factors. Improvement in a patient's symptoms is a critical part of the response assessment. Treatment response also requires a reduction in abnormal mast cell burden in bone marrow, and improvement in clinical signs of organ damage due to infiltration by neoplastic mast cells. This may include normalization of complete blood counts and liver function enzymes, reduction in spleen or liver volume, reduction or absence of transfusion requirements, and reduction in need for diuretics and/or therapeutic paracentesis.

As per the pivotal trials and input from the clinical experts, avapritinib should be discontinued if the patient is no longer getting clinical benefit from a symptom or quality of life perspective, in those who experience intracranial bleeding or have a platelet count less than 50×10^9/L, in patients with persistent severe treatment-related adverse events that cannot be managed with dose interruptions or dose reduction, if there is evidence of progressive disease of either the SM or AHN disease component, or if patients are pregnant.

Clinician Group Input

Two clinician groups provided input for this review, including Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (based on 2 clinicians) and the LLSC Clinician Network and Myeloproliferative Neoplasms Canada Clinician Group (based on 6 clinicians).

In general, the clinician group inputs were consistent with the input provided by the clinical experts consulted for this review. The clinician groups agreed that there is a significant unmet need for patients with AdvSM in Canada, who have poor outcomes and a high symptomatic burden. The experts anticipated that avapritinib would be used as first line monotherapy in Canada for adults with all subtypes of AdvSM. The clinician groups agreed that patients with AdvSM should be managed by hematologists or medical teams with expertise in diagnosis, treatment, and response evaluation. Input from clinician groups indicated that standardized response criteria are evolving and may be used in conjunction with evaluations of clinical benefit, including patient-reported symptoms and HRQoL. The clinician groups agreed that treatment with avapritinib should be discontinued among patients whose HRQoL is impacted by lack of clinical benefit, and those with a platelet count below 50 x 10^9/L, detectable disease progression, or significant adverse effects.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
Currently there is no standard of care for AdvSM. Comparators may include cladribine, interferon, imatinib, and midostaurin. Although midostaurin has been approved by Health Canada for AdvSM, it received a do not reimburse recommendation from CDA-AMC. How does the efficacy and safety of avapritinib compare to the above?	The clinical experts stated that cladribine is the most accessible therapy for AdvSM, and response rates are typically low and of short duration. Funding for interferon is limited and it is difficult to access this drug. Further, it is not an appropriate treatment for patients who present acutely and require immediate disease control to prevent life-threatening organ failure as it may take up to a year of treatment before the patient demonstrates any improvement. Imatinib is only appropriate for a small subset of patients with AdvSM who do not have the KITD816V mutation or with unknown KIT mutational status (<10%), and midostaurin is largely unavailable in Canada. pERC acknowledged the unmet need for effective therapies to treat patients with AdvSM. pERC noted that the evidence from the PATHFINDER and EXPLORER trials suggested that treatment with avapritinib may result in clinically meaningful benefit in overall response rate in patients with AdvSM. However, pERC noted that there was significant uncertainty in the magnitude of the comparative benefit with avapritinib compared to currently available treatments.
Generalizability	
Should patients currently on other systemic therapies be switched to avapritinib?	pERC agreed with the clinical experts that patients who have stable disease on an existing therapy would likely remain on that treatment, unless patients experience toxicity or signs of disease progression.

AdvSM = advanced systemic mastocytosis; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog.

Clinical Evidence

Systematic Review

Description of Studies

Two open label, single arm clinical trials provided data on the efficacy and safety of avapritinib in adults with AdvSM. Eligible patients were 18 years of age or older with an adjudicated diagnosis of either ASM, SM-AHN, or MCL according to the WHO diagnostic criteria. The phase I EXPLORER study enrolled 86 patients, including 69 patients with AdvSM, who received avapritinib in either the dose escalation phase (part 1) or the extension phase (part 2). In the dose escalation phase, patients received avapritinib 30 mg to 400 mg daily, and in the extension phase, the avapritinib starting dose was 300 mg or 200 mg daily. The phase II PATHFINDER study was ongoing at the time of this review and provided results for 62 patients at the first data cut (the planned interim analysis), and for 105 patients at a second data cut. Patients in the PATHFINDER study received an avapritinib starting dose of 200 mg daily. The key efficacy outcomes were overall response rate (ORR), overall survival (OS) and change in patient-reported symptom severity, measured using the Advanced Systemic Mastocytosis Symptom Assessment Form Total Symptom Score (AdvSM-SAF TSS).

The results presented are from the final data cut-off date of the EXPLORER trial (January 19, 2023) as well as the first data cut (23Jun2020) and second data cut (September 9, 2022) of the ongoing PATHFINDER study, which had a mean treatment duration of [redacted], respectively, in the safety population. The median OS follow up duration was [redacted] and 26.3 months in the EXPLORER (final data cut) and PATHFINDER first and second data cuts, respectively.

The mean age of patients enrolled was 65.0 years (standard deviation [SD] = 11.2) and 67.5 years (SD = 11.0) in the EXPLORER and PATHFINDER studies, respectively, including 41% and 45% of patients who were female, and 59% and 55% who were male. In the EXPLORER and PATHFINDER studies, respectively, the most common AdvSM subtype was SM-AHN (70% and 69%) followed by MCL (19% and 16%) and ASM (12% and 15%). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 (70% and 69%), with 20% and 23% of patients rated as having an ECOG score of 2, and 10% and 8% rated as having a score of 3, in the EXPLORER and PATHFINDER studies, respectively. In the EXPLORER study, 59% of patients had received prior antineoplastic therapy, compared with 68% of patients in the PATHFINDER study.

Efficacy Results

The ORR was the primary outcome in the PATHFINDER study and a secondary outcome in the EXPLORER study. Response was based on the centrally adjudicated modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria in the Response Assessment Committee response-evaluable (RAC-RE) population. In both studies, overall response was defined as patients with complete remission (CR), complete remission with partial recovery of peripheral blood counts (CRh), partial remission (PR) and clinical improvement (ClinI). The observed ORR was [redacted] in the EXPLORER study, 75.0% [redacted] in the first data cut of the PATHFINDER study, and [redacted] in the second data cut. According to the statistical analysis plans, the ORR was tested versus the 28% null value, which was the post hoc estimate of the ORR for midostaurin. In the EXPLORER study and first data cut of the PATHFINDER study, the P value was less than 0.0001 based on 1-sided test.

Overall survival was an exploratory outcome in the EXPLORER study and a secondary outcome in the PATHFINDER study, and was reported for the safety population. The median survival was not reached for either study, as [redacted] were alive at the end of the EXPLORER study, and [redacted] were alive at the second data cut of the PATHFINDER study. In the EXPLORER study, the Kaplan-Meier estimates for the proportion of patients alive at [redacted]. At the interim analysis of the PATHFINDER study, [redacted] of patients were alive at 6, 12 and 18 months, respectively. As of the PATHFINDER second data cut, the Kaplan-Meier estimate for OS was 79.0% (95% CI, 70.8% to 87.3%) at 2 years.

The AdvSM-SAF TSS captures the severity of 8 symptoms (abdominal pain, nausea, vomiting, diarrhea, spots, itching, flushing, and fatigue) and is scored from 0 (no symptoms) to 80 points (worst imaginable) based on the average daily score over the prior week. Using anchor-based methods, the estimated within-person minimum important difference (MID) was 9 to 14 points for the TSS. In the EXPLORER study, the AdvSM-SAF questionnaire was completed during part 2 only (safety population), with 40 patients (74%)

reporting a baseline score. At baseline, the mean TSS score was 19.1 points (SD = 12.2), with a mean change from baseline of [redacted] at cycle 11 day 1.

In the PATHFINDER study, 56 of 62 (90%) patients reported a baseline AdvSM-SAF TSS score at the first data cut, and [redacted] reported a score at the second data cut (safety population). For the first data cut, the baseline mean TSS score was 18.3 points (SD = 12.5, N = 56), with a mean change from baseline of -9.8 points (95% CI, -14.9 to -4.6, N = 22) at cycle 11 day 1. For the second data cut, the baseline TSS score was not reported and the mean change from baseline was [redacted] at cycle 11 day 1.

Among patients who met the overall response criteria, the median duration of response was [redacted] in the EXPLORER study (N = 44). The median duration of response was not reached by the second data cut of the PATHFINDER study (N = 60). At 24 months, [redacted] of responders in the EXPLORER study, and [redacted] of responders in the PATHFINDER study had maintained the response. At 36 months, the proportion of patients was [redacted] in EXPLORER and PATHFINDER studies, respectively. The median time to response was [redacted] in the EXPLORER study, 2.0 months (95% CI, 0.3 to 12.2) in the first data cut of the PATHFINDER study, and 2.2 months (95% CI, 0.3 to 15.0) in the second data cut.

Progression free survival (PFS) was an exploratory outcome in the EXPLORER study and a secondary outcome in the PATHFINDER study. In the EXPLORER study the median PFS was 49.0 months (95% CI 31.2, not estimable), and at 24 months the Kaplan-Meier PFS estimate was [redacted]. The median PFS had not been reached in the ongoing PATHFINDER study, which reported a 24-month PFS survival estimate of 76.5% (95% CI, 66.9% to 86.0%) in the second data cut.

Harms Results

All patients in the EXPLORER and PATHFINDER studies reported at least 1 adverse event. The most common adverse events were periorbital edema (69% and 41%), anemia (57% and 51%), diarrhea (49% and 31%), thrombocytopenia (41% and 43%) and peripheral edema (41% and 47%), in the EXPLORER and PATHFINDER (second data cut) studies, respectively.

Serious adverse events (SAEs) were reported [redacted] and [redacted] of patients, and [redacted] and [redacted] of patients stopped treatment due to adverse events in the EXPLORER and PATHFINDER (second data cut) studies, respectively. In the EXPLORER study, the most common SAEs were [redacted]. Limited information on specific adverse events was available for the PATHFINDER study. [redacted] in the EXPLORER study and [redacted] in the PATHFINDER study (second data cut) died due to adverse events.

Intracranial bleeding was identified as an adverse event of special interest by the sponsor and by the clinical experts who were consulted for this review. In the EXPLORER study [redacted] experienced intracranial bleeding. In the PATHFINDER study, 1 patient (1.6%) in the first data cut and 4 patients (3.7%) in the second data cut experienced intracranial bleeding.

Cognitive adverse events were common and were reported by [redacted] of patients in the EXPLORER and PATHFINDER studies, respectively. These events included [redacted].

Critical Appraisal

Both pivotal trials were open label, single arm studies, and thus provided no direct evidence on comparative efficacy or safety. The lack of controlled trials has implications for the overall strength and interpretability of the results. With single arm studies, there is an increased risk of bias in the estimation of treatment effects due to the potential for confounding related to natural history and prognostic factors. Moreover, the extent of any selection bias is difficult to ascertain. The clinical experts emphasized that AdvSM is a heterogeneous disease, and prognosis varies substantially based on the disease subtype and other factors. The primary outcome (ORR) and other response-related outcomes were analyzed in a subset of patients enrolled in the studies, not the entire population with AdvSM, which is another potential source of selection bias.

While the lack of a comparator group in the pivotal evidence limits the overall interpretation of the results, the feasibility of conducting a randomized controlled trial was low, given the rarity of AdvSM, and potential ethical issues were raised by the clinical experts consulted, due to the efficacy and safety of the available comparators.

The primary outcome was based on ORR according to the modified IWG-MRT-ECNM criteria. The clinical experts noted that response criteria used in clinical trials and in practice are evolving to best capture clinical benefit and to better define long term outcomes, given the availability of targeted therapies. While the clinical experts consulted agreed that the IWG criteria used in the trials were acceptable, there is no clear data to suggest which response criteria performs better in terms of predicting long-term outcomes like survival.

The pivotal trials were open label, whereby the investigator and the study participants were aware of their treatment status, potentially increasing the risk of detection bias and performance bias. As such, the open-label trial design limits the interpretability of the subjective study outcomes, such as AdvSM-SAF and adverse events, and may impact some components of the IWG-MRT-ECNM criteria. The AdvSM-SAF were further limited by the extent of missing data, with 26% and 10% of patients excluded from the analysis at baseline, and due to attrition, with 59% and 65% of patients with missing data at cycle 11 for the EXPLORER and PATHFINDER (first data cut) studies, respectively. In the PATHFINDER study the use of last observation carried forward imputation method for patients with missing data also may have biased the findings.

Most of the time-to-event outcomes were considered immature, as the median OS was not met for either study, and the median PFS and duration of response was not met for the PATHFINDER trial. Additionally, comparative OS and PFS cannot be adequately assessed in a single-arm trial because all patients receive the same treatment. The FDA Medical Review report states that the effect of avapritinib on OS cannot be interpreted due to the single-arm, open label design of the studies, which can return biased results.

With regards to external validity, the results predominantly reflect patients with SM-AHN with an ECOG performance score of 0 or 1 and who had received prior systemic therapy for AdvSM. In Canada, SM-AHN is the most common type of AdvSM, which is consistent with the studies. However clinical experts consulted noted that the proportion of patients with high ECOG performance scores was lower than expected in the trials, thus the study patients may be less ill than patients who may receive avapritinib in clinical practice. Both trials excluded patients with comorbidities such as seizure disorder, uncontrolled cardiovascular disease, reduced renal and hepatic function, and those at higher risk of intracranial bleeding, thus the safety and efficacy of avapritinib is these patients is unknown. Approximately three quarters of patients in the EXPLORER study did not receive the Health Canada recommended starting dose, which may impact the generalizability of the findings to clinical practice, particularly for safety, as the sponsor identified dose related toxicities.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus currently available therapies, the certainty of evidence for single-arm trials started at very low certainty.

For the GRADE assessments, findings from EXPLORER and PATHFINDER studies were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans.

Table 3: Summary of Findings for Avapritinib for Adults With AdvSM

Outcome and follow-up	Patients (studies), N	Effect	Certainty [a]	What happens
Overall Response: RAC-RE population[b]				
Proportion of patients with overall response[c] (95% CI) Follow-up: 39.8 or 10.2 months[d]	89 (2 single arm studies)	EXPLORER • [redacted] PATHFINDER (first data cut) • 750 per 1,000 [redacted][e]	Very low	The evidence is very uncertain about the effect of avapritinib on overall response when compared with any comparator.
Overall Survival: Safety population[b]				
Probability of being alive at 2 years (95% CI) Median OS follow-up: [redacted] months[f]	174 (2 single arm studies)	EXPLORER • [redacted] PATHFINDER (second data cut) • 79.0% (70.8% to 87.3%)	Very low[g]	The evidence is very uncertain about the effect of avapritinib on the probability of being alive at 2 years when compared with any comparator.
Probability of being alive at 4 years (95% CI) Median OS follow-up: [redacted] months	69 (1 single arm study)	EXPLORER • [redacted]	Very low	The evidence is very uncertain about the effect of avapritinib on the probability of being alive at 4 years when compared with any comparator.
Patient Reported Symptoms: Safety population[b]				
AdvSM-SAF TSS (0 [best] to 80 [worst]), within group mean change from baseline (95% CI) Follow-up: Cycle 11 day 1	44 (2 single arm studies)	EXPLORER • [redacted] PATHFINDER (first data cut) • -9.8 (-14.9 to -4.6)	Very low[h]	The evidence is very uncertain about the effect of avapritinib on patient reported symptoms (based on the AdvSM-TSS score) at 11 months when compared with any comparator.
Duration of response: RAC-RE population with Response[b]				
Probability of maintaining response at 2 years (95% CI) Follow-up: not reported	104 (2 single arm studies)	EXPLORER • [redacted] PATHFINDER (second data cut) • [redacted]	Very low	The evidence is very uncertain about the effect of avapritinib on the duration of response when compared with any comparator.
Time to response: RAC-RE population with Response[b]				
Median time to response, months (range) Follow-up: Not reported	104 (2 single arm studies)	EXPLORER • [redacted] PATHFINDER (second data cut) • 2.2 months (0.3 to 15.0)	Very low	The evidence is very uncertain about the effect of avapritinib on the time to response when compared with any comparator.
PFS: RAC-RE population[b]				
Probability of being alive without disease progression at 2 years (95% CI)	138 (2 single arm studies)	EXPLORER • [redacted]	Very low	The evidence is very uncertain about the effect of avapritinib on the probability of being alive

Outcome and follow-up	Patients (studies), N	Effect	Certainty [a]	What happens
Follow-up: [redacted] months[i]		PATHFINDER (second data cut) • 76.5% (66.9% to 86.0%)		without disease progression at 2 years when compared with any comparator.
Notable harms: Safety population[b]				
Proportion of patients with SAEs Follow-up: mean exposure duration of [redacted] months[j]	191 (2 single-arm trials)	EXPLORER • [redacted] PATHFINDER (second data cut) • [redacted]	Very low[k]	The evidence is very uncertain about the effect of avapritinib on SAEs when compared with any comparator.
Proportion of patients with intracranial bleeding Follow-up: mean exposure duration of [redacted] months[j]	191 (2 single-arm trials)	EXPLORER • [redacted] PATHFINDER (second data cut) • [redacted]	Very low[k]	The evidence is very uncertain about the effect of avapritinib on intracranial bleeding adverse events when compared with any comparator.
Proportion of patients with cognitive adverse events Follow-up: mean exposure duration of [redacted] months[j]	191 (2 single-arm trials)	EXPLORER • [redacted] PATHFINDER (second data cut) • [redacted]	Very low[k]	The evidence is very uncertain about the effect of avapritinib on cognitive adverse events when compared with any comparator.

AdvSM = advanced systemic mastocytosis; CI = confidence interval; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis International Working Group; NR = not reported; ORR = overall response rate; OS = overall survival; RAC-RE = response assessment committee-response evaluable; SAE = serious adverse event.

Note: All serious concerns with study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias are documented in the table footnotes.

[a] In the absence of a comparator group, conclusions about efficacy or safety relative to any comparator cannot be drawn and the certainty of evidence is started at very low. In addition, rated down all outcomes 1 level for serious study limitations. The efficacy results are based on small sample sizes of the studies and it is unclear if results would be replicable in a larger sample. Rated down all outcomes 1 level for indirectness as ≥70% patients in the EXPLORER study did not receive the recommended avapritinib starting dose of 200mg daily.

[b]The RAC-RE population included all patients with AdvSM who received at least 1 dose of avapritinib, were deemed evaluable per modified IWG-MRT-ECNM criteria at baseline as assessed by Study Steering Committee review and had 1 of the following conditions: had 2 or more complete postbaseline bone marrow assessments and had been on study for at least 6 cycles (6 x 28 days), or had an end of study visit. The Safety population included all patients who received at least 1 dose of avapritinib. For efficacy outcomes in the EXPLORER trial, the safety population only included patients with AdvSM (69 of 86 patients enrolled), but for adverse event outcomes, data from all patients were the reported, including 17 patients with indolent or smoldering SM. Results from the EXPLORER study were based on patients who received any starting dose of avapritinib (30 mg to 400 mg daily), the PATHFINDER first data cut included patients who received a starting dose of 100 mg (2 patients) or 200 mg daily (60 patients), and the second data cut included patients who received a starting dose of 200 mg daily (105 patients).

[c] Overall response was defined according to the modified IWG-MRT-ECNM criteria and included patients who experienced a best response of complete remission, complete remission with partial recovery of peripheral blood counts, partial remission, or clinical improvement.

[d] Median follow up was [redacted] for the EXPLORER study and 10.2 months for the planned interim analysis of the PATHFINDER study.

[e] As per the planned interim analysis of PATHFINDER study, the ORR was tested at a 1-sided alfa 0.00625, thus the 98.75% CI were listed.

[f] Median follow up for survival was [redacted] for EXPLORER and 26.3 months for the second data cut of the PATHFINDER study.

[g] Rated down 1 level due to risk of bias, as the second data cut of the PATHFINDER study was not a pre-planned interim analysis, according to the study protocol, and as such should be interpreted as supportive data.

[h] Rated down 2 levels for risk of bias due to missing data and open label design. Not all patients enrolled provided results at baseline (missing [redacted] of patients), with further attrition over time ([redacted] of patients missing from cycle 11 time point in EXPLORER and PATHFINDER, respectively). Use of last observation carried forward in

the PATHFINDER study may bias the results given the magnitude of missing data at cycle 11. The open-label study design and patients' and assessors' knowledge of assigned treatment may lead to biased estimates of subjective outcomes.

[i] Median follow up was [redacted] for the EXPLORER study and [redacted] for the second data cut of the PATHFINDER study.

[j] Mean avapritinib exposure duration was [redacted] in the final data cut of the EXPLORER trial, and [redacted] in the second data cut of the PATHFINDER study.

[k] Rated down 1 level due to risk of bias due to open-label study design. Patients' and assessors' knowledge of assigned treatment may lead to biased estimates of subjective outcomes and harms. Due to the lack of control group, the proportion of adverse events that are attributable to avapritinib versus the disease or other factors is unclear.

Source: Final Clinical Study Report for EXPLORER, Interim Clinical Study Report for PATHFINDER, PATHFINDER Clinical Summary document. Additional data supplied by the sponsor (June 17, 2024). Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted.

Indirect Comparisons

Description of Studies

The sponsor submitted 1 indirect treatment comparison and 1 observational comparison that evaluated the efficacy of avapritinib versus available treatments for patients with AdvSM. The indirect treatment comparison was based on a published matching-adjusted indirect comparison (MAIC) comparing avapritinib with midostaurin on OS, ORR, and CR. The individual patient-level data (IPD) observational comparison was based on inverse probability of treatment weighting (IPTW) methods comparing avapritinib with midostaurin, and with real-world best available therapy (BAT), on OS and duration of treatment.

Efficacy Results

Overall Survival

In the MAIC of avapritinib (pooled EXPLORER and PATHFINDER safety population) versus the pooled midostaurin cohort (pooled D2201 and A2213 full analysis set), the OS hazard ratio (HR) was 0.42 (95% CI, 0.25 to 0.71), favouring avapritinib. Follow-up in the MAIC for OS was median 22.9 months and median 7.0 months in the EXPLORER and PATHFINDER trials for avapritinib, respectively; follow-up duration was median 124 months and median 26 months in the A2213 and D2201 trials for midostaurin, respectively.

In the IPTW-weighted observational comparison of avapritinib first line therapy (PATHFINDER safety population) versus BAT first line therapy with follow-up of mean [redacted], respectively, OS HR was [redacted], favouring avapritinib first line therapy.

In the IPTW-weighted observational comparison of avapritinib second or later line therapy (PATHFINDER safety population) versus BAT second or later line therapy with follow-up of mean [redacted], respectively, OS HR was [redacted], favouring avapritinib second or later line therapy.

In the IPTW-weighted observational comparison of avapritinib first line therapy (PATHFINDER safety population) versus in the midostaurin first line therapy with follow-up of mean [redacted], OS HR was [redacted], favouring avapritinib first line therapy.

Duration of Treatment

In the IPTW-weighted observational comparison of avapritinib first line therapy (PATHFINDER safety population) versus BAT first line therapy with follow-up of median [redacted], respectively, the HR for duration of treatment was [redacted], favouring avapritinib first line therapy.

In the IPTW-weighted observational comparison of avapritinib second or later line therapy (PATHFINDER safety population) versus BAT second or later line therapy with follow-up of median [redacted], respectively, the HR for duration of treatment was [redacted], favouring avapritinib second or later line therapy.

In the IPTW-weighted observational comparison of avapritinib first line therapy (PATHFINDER safety population) versus in the midostaurin first line therapy with follow-up of median [redacted], OS HR was [redacted], favouring avapritinib first line therapy.

Overall Response Rate

In the MAIC of avapritinib (pooled EXPLORER and PATHFINDER RAC-RE population) versus the midostaurin cohort (D2201 primary efficacy population), the odds ratio for ORR was 4.06 (95% CI, 3.09 to 5.33), favouring avapritinib.

Complete Remission

In the MAIC of avapritinib (pooled EXPLORER and PATHFINDER RAC-RE population) versus midostaurin (D2201 primary efficacy population), complete remission was achieved by 10 of 79 patients (12.66%) and 1 of 89 patients (1.12%), respectively, for an odds ratio of 9.56 (95% CI, 0.97 to 93.81), favouring avapritinib.

Harms Results

No comparative safety data were available in the indirect evidence.

Critical Appraisal

In the indirect treatment comparison (MAIC), methods for study selection were poorly reported. No information was provided on details of the literature search, study selection process, and data extraction. No information including rationale was provided for not assessing the quality of the included studies. Across the included cohorts, trial start dates were heterogenous and notably older in the midostaurin trials (2005 and 2008 for the A2213 and D2201 trials, respectively) than in the avapritinib trials (2016 and 2018 for the EXPLORER and PATHFINDER trials, respectively). The MAIC reported limited details regarding patients enrolled in the trials. Across the studies, differences were observed in dosing of avapritinib (between EXPLORER and PATHFINDER) and response evaluation (criteria across the 4 trials), and no information on time point(s) used in evaluating response were provided for the trials. Prognostic factors associated with poor outcomes such as AdvSM subtypes of SM-AHN (particularly for type of myeloid neoplasm) and MCL, the *KIT* D816V variant allele frequency and type of gene mutation (e.g., SRSF2) were not included in the MAIC. The selection of prognostic factors used for matching was based on an arbitrary P value of below 0.1 from exploratory subgroup analyses that contained the same data used for assessment which is not consistent with recommended approaches in the NICE Decision Support Unit Technical Support Document 18. Information on patients who received prior systemic therapy in the midostaurin trials were not available. Patients in the avapritinib and midostaurin trials were matched on baseline imbalances that differed by outcome and by analysis populations. Similarities and differences between the populations of analyses were not detailed in the MAIC, making it challenging to determine comparability of treatment groups and interpretation of findings. Findings for OS and ORR after weighting resulted in reduced effective sample sizes to suggest incomplete overlap between the avapritinib and midostaurin populations and that results may be driven by a subset of the sample from the index trials that were not representative of the entire sample. The exclusion of data from the A2213 trial and exploratory nature of the response analysis increases the potential for prognostic imbalance and risk of type 1 error. In the MAIC, avapritinib 200 mg (the dose recommended by Health Canada for the indicated population) versus midostaurin were based on sensitivity analyses using the pooled EXPLORER and PATHFINDER RAC-RE population. There is uncertainty in these results at least in part due to the small sample sizes in the avapritinib 200 mg cohort (44 patients and 42 patients for OS and ORR, respectively) which is reflected in the wide CI that crosses the null for survival, and in findings which are driven by a reduced sample of the overall population.

No study protocol, statistical analysis protocol, or study report was provided for the observational comparison using IPTW analysis that was based on an updated data-cut of September 2022 for the PATHFINDER trial. Information presented for the methods of the observational comparison were limited to the sponsor-provided observational comparison report and publication based on earlier analyses (data cut-off date of April 2021), where several inconsistencies and gaps in information were found. Four subgroup analyses that were specified in the sponsor-submitted observational comparison report were reported in the publication but did not match those reported in the updated analyses. Sensitivity analyses of OS described in the sponsor's observational comparison report were not included in the submission. There were no sensitivity analyses reported to evaluate the potential impact of bias due to informative censoring on effect estimates in patients who were censored due to a new primary malignancy after the index date or due to avapritinib initiation in the BAT cohort. Patients in the avapritinib cohort were enrolled from March 2016 to April 2021 in the

EXPLORER and PATHFINDER trial, respectively. Real-world patients with AdvSM who received BAT were enrolled from January 2009 to October 2021 and included as controls. Contextual information such as standards of care at a specified time point and across time was not directly captured. For patients in the external control group who received BAT as first line therapy and then went on to receive avapritinib as second or later line therapy either by enrolling into a trial (in EXPLORER or PATHFINDER), or via compassionate program access, follow-up was censored at avapritinib initiation. No further information was detailed regarding how patients who received avapritinib in second line therapy were included and/or analyzed in the observational comparison. Follow-up duration was not specified for patients included from the PATHFINDER trial. The baseline period differed between the comparative cohorts (defined as the 8-week period up to the index date for avapritinib and the 12-week period up to the index date for BAT); no rationale was provided for the different time periods used to ascertain baseline characteristics. While AdvSM subtype was diagnosed based on the WHO criteria for all patients, the evaluation was confirmed by the response assessment committee for the avapritinib cohort and based on local clinician assessment for the BAT cohort; there may be a greater risk of bias among patients who were diagnosed in the BAT cohort due to the retrospective nature of chart review and lack of information on the assessors. Imbalances in covariates that were found to persist after IPTW-weighting (including imbalances which increased for some covariates) including region, ECOG PS scores, anemia, thrombocytopenia, leukocyte counts, and serum tryptase concentrations, suggested that there was lack of sufficient overlap between the cohorts (i.e., the cohorts may be meaningfully different). While findings for OS and duration of treatment were presented for both the safety and RAC-RE populations of analyses, imbalances in covariates differed for the safety and RAC-RE populations such that it was challenging to meaningfully assess how such differences may have translated to adjusted results (after IPTW-weighting) and the comparability of the adjusted results between the analyzed populations. An analysis in the overall sample (avapritinib from EXPLORER and PATHFINDER versus BAT from real-world patients regardless of lines of therapy) was not submitted by the sponsor for updated analyses (data cut of September 2022); rather, 3 analyses with longer follow-up were submitted that appeared to be subgroup or post-hoc analyses, given that the analysis comparing avapritinib with exclusively midostaurin were not prespecified in the sponsor's observational comparison report or the publication. The small sample sizes, both overall and reduced for the avapritinib cohort compared to the BAT cohort, makes it difficult to ensure prognostic matching was appropriate in the analyses. Median OS had not been reached in the avapritinib cohort in any line of therapy, indicating that OS data were immature. In the observational comparison, avapritinib 200 mg dose was a subgroup analysis of the PATHFINDER trial with small sample sizes. Variations in timing of assessments and follow-up of patients who received BAT in the real-world setting may not fully match patients who received avapritinib in the EXPLORER and PATHFINDER trials; given the absence of information on follow-up duration (other than at least 3 months of follow-up in the BAT cohort), and its potential to create prognostic imbalance between the avapritinib and BAT cohorts, there is an unknown direction and magnitude of impact on duration of treatment and survival. Several methods of imputations for missing data (e.g., ECOG PS score, serum tryptase) were at risk of underestimating disease severity among included patients, although the direction and magnitude of potential bias cannot be determined since the proportion of patients with missing data for the avapritinib cohort were not reported.

The findings from the indirect treatment and observational comparisons suggested a benefit (point estimate and lower and upper bounds of the confidence intervals suggested benefit) of avapritinib when indirectly compared to currently available treatments for ORR, duration of treatment, and OS. Due to the substantial limitations identified in the analyses there remains significant uncertainty in the magnitude of the benefit with avapritinib compared to currently available treatments. However, it appears unlikely that the benefit seen with avapritinib is solely explained by the noted limitations and sources of uncertainty of these comparisons. Therefore, while it is not possible to ascertain what the true effect is between the comparisons, it is likely to be in favour of avapritinib.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned Survival Model
Target population	Adult patients with advanced systemic mastocytosis (AdvSM) which includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), in the first-line (1L) and second-line or later (2L+).
Treatment	Avapritinib
Dose regimen	200 mg once daily until progression or unacceptable toxicity
Submitted price	Avapritinib: $1,343.36 per 25 mg, 50 mg, 100 mg, or 200 mg oral tablet
Submitted treatment cost	Avapritinib: $37,614.08 per 28-day cycle ($490,362.40 annually)
Comparators	• 1L best available therapy (BAT): a weighted basket of treatments comprised of cladribine, peginterferon alfa-2a, and imatinib • 2L+ BAT: a weighted basket of treatments comprised of cladribine, peginterferon alfa-2a, imatinib and midostaurin
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (1L population: 34 years; 2L+ population: 28 years)
Key data sources	IPTW-weighted analysis in which the effectiveness of avapritinib was informed by PATHFINDER (an open-label, single arm, Phase 2 clinical trial) and the effectiveness of BAT was informed by BLU-285-2405 (external control study of real-world patients treated with BAT)

Key limitations	• The comparative efficacy of avapritinib relative to BAT is highly uncertain. The results produced by the model are therefore uncertain and lack face validity due to multiple factors:
	  ○ The sponsor used an inverse probability treatment weighted (IPTW) approach to estimate comparative overall survival (OS) and time on treatment (ToT) for avapritinib and BAT. This approach was associated with substantial limitations that resulted in an inability to robustly estimate comparative efficacy.
	  ○ The model estimated progression-free survival (PFS) for avapritinib using data from a separate subpopulation of the trial than was used to estimate OS and ToT. PFS was assumed to equal ToT for patients receiving BAT, which was not aligned with CADTH's clinical expert input for how some treatments within BAT are administered.
	  ○ The evidence supporting the efficacy of BAT in the 2L+ population within Canada included midostaurin. Midostaurin is not an appropriate comparator in Canada, as determined by clinical expert input and drug plans. The estimated efficacy of BAT is therefore likely not reflective of Canadian practice.
	  ○ KM data for OS in the 1L population exceeded KM data for PFS which is clinically implausible as it predicts more patients are at risk of progression than are alive.
	  ○ Predicted OS in the 1L population exceeded clinical expert expectations. The sponsor's chosen extrapolation for OS in the 1L population predicts that 22% of patients remain alive at 90 years old, a result that lacks face validity.
	  ○ The sponsor's chosen extrapolations for OS and PFS for BAT resulted in the 2L+ population living longer (i.e., higher total LYs) and experiencing a better quality of life (i.e., higher total QALYs) than patients in the 1L population which lacked clinical plausibility as clinical expert input noted the risk of death generally increases as the number of lines of therapy received increases.

Component	Description
	• Comparator treatment costs lack face validity due to the inclusion of midostaurin in 2L+ BAT, variability in cladribine's dosage, mode of administration, and treatment length, and variability in access and use of peginterferon alfa-2a. • The estimated health state utility is highly uncertain largely owing to the sponsor's inappropriate pooling of utility values from the AML literature to derive the Progressive Disease health state utility value.
CADTH reanalysis results	• A CADTH base case could not be derived due to the limitations in comparative efficacy and cost. CADTH undertook an alternative set of analyses for the 1L and 2L+ populations, adopting different OS and PFS parametric distributions for avapritinib in the 1L population and removing midostaurin from 2L+ BAT treatment costs. • In the CADTH alternative analysis of the 1L population, avapritinib was more costly (incremental costs: $2,005,267) and more effective (incremental QALYs: 4.60) than 1L BAT, resulting in an ICER of $435,876 per QALY gained. • In the CADTH alternative analysis of the 2L+ population, avapritinib was more costly (incremental costs: $1,172,109) and more effective (incremental QALYs: 1.78) than 2L+ BAT, resulting in an ICER of $660,217 per QALY gained. • In both the sponsor's base case and the CADTH alternative analysis, a price reduction is required for avapritinib to be considered cost-effective at a WTP threshold of $50,000 per QALY gained. The magnitude of price reduction needed to reach cost-effectiveness could not be estimated.

1L = first line of therapy; 2L+ = second line of therapy or later; AE = adverse event; AML = acute myeloid leukemia; BAT = best available therapy; ICER = incremental cost-effectiveness ratio; IPTW = inverse probability of treatment weighting; KM = Kaplan Meier; LY = life-year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Note: 1L BAT is comprised of cladribine, peginterferon alfa-2a, and imatinib. 2L+ BAT is comprised of cladribine, peginterferon alfa-2a, imatinib, and midostaurin. When not specified, 'BAT' encompasses both 1L and 2L+ BAT.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: a misalignment of model inputs between the sponsor-submitted economic analysis and budget impact analysis, overestimating drug acquisition costs; the eligible population size is uncertain; the Non-Insured Health Benefits population was inappropriately calculated; the market uptake of avapritinib is uncertain.

CADTH revised the market shares attributed to the 2L+ market share and aligned treatment acquisition costs with CADTH's reanalysis of the sponsor's submitted cost-utility analysis for the 1L population (assuming $0 drug acquisition costs for midostaurin). The CADTH BIA base case suggests the 3-year budget impact of reimbursing avapritinib for the treatment of adult patients with AdvSM including ASM, SM-AHN, and MCL to be $149,033,058 (Year 1: $34,684,252; Year 2: $53,054,704; Year 3: $61,294,102).

The estimated budget impact is sensitive to the number of patients eligible for avapritinib and the price of avapritinib.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: September 11, 2024

Regrets:

2 expert committee members did not attend.

Conflicts of interest:

None