SMC2849

avapritinib film-coated tablets (Ayvakyt®)

Blueprint Medicines

05 June 2026

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

avapritinib (Ayvakyt®) is not recommended for use within NHSScotland.

Indication under review: As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

In a non-randomised phase II study, 73% of patients with response-evaluable ASM, SM-AHN or MCL who received avapritinib achieved an overall response.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Avapritinib is a type 1 tyrosine kinase inhibitor (TKI) with specific activity on the mutated KIT kinase (including mutations of the D816 codon) and of the structurally related platelet-derived growth factor receptor-alpha (PDGFRA). These tyrosine kinase proteins are found on the surface of mast cells and help control cell growth. In patients with advanced systemic mastocytosis (SM), these proteins can be abnormal (mutated) causing cells to multiply uncontrollably. The recommended starting dose of avapritinib for this indication is 200 mg orally once daily, which is also the maximum recommended dose. Treatment should be continued until disease progression or unacceptable toxicity. The dose should be adjusted based on safety and tolerability. See the Summary of Product Characteristics (SPC) for more details.[1-3]

1.2. Disease background

Mastocytosis is a spectrum of disorders characterised by abnormal growth and accumulation of mast cells.[4] Aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL) are three subtypes of advanced SM. Advanced SM are rare haematologic neoplasms primarily driven by a mutation in the KIT D816V gene. It is a severe and aggressive form of mastocytosis that can lead to debilitating symptoms, multiorgan dysfunction or failure and shortened survival. Signs and symptoms vary by the affected organ system: skin involvement is common (maculopapular skin lesions); the gastrointestinal tract, brain, cardiovascular system, lymph nodes, bones, bone marrow, spleen and liver can also be affected. Patients are also at risk of life-threatening anaphylaxis.[4, 5] SM-AHN is the most common advanced SM subtype, comprising around 70 to 75% of cases; median overall survival is between 24 to 35 months.[2] ASM is rarer and has a median overall survival of 41 to 68 months. MCL is a rare and highly aggressive variant and is associated with the poorest prognosis of all subtypes, with a median overall survival of 2 to 23 months.[2, 4]

1.3. Treatment pathway and relevant comparators

There are a limited number of treatment options for patients with advanced SM. Treatment options include midostaurin (multitargeted protein kinase inhibitor) and off-label cytoreductive agents cladribine and interferon-alfa.[2, 6] Clinical experts consulted by SMC stated that the most relevant comparator is midostaurin. Cladribine may be used in a small group of patients who need rapid debulking due to very extensive disease, in MCL or in the second-line. Other management considerations include the avoidance of triggers, anaphylaxis management, symptom control and prevention and management of reduced bone mineral density.[6] There is no Cancer Medicines Outcomes Programme Public Health Scotland (CMOP-PHS) real-world evidence report for this submission.

1.4. Category for decision-making process

Eligibility for a PACE meeting

Avapritinib meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of avapritinib for the treatment of advanced SM comes from EXPLORER and PATHFINDER. Details are presented in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	PATHFINDER[2, 7]	EXPLORER[2, 8]
Study design	Multicentre, single-arm, open-label phase II study.	Multicentre, single-arm, open-label phase I study.

Eligible patients	• Age ≥18 years.
	• Diagnosis (confirmed centrally) based on WHO diagnostic criteria of:
	  ○ ASM
	  ○ SM-AHN
	  ○ MCL
	• Cohort 1 had advanced SM with at least one modified IWG-MRT-ECNM evaluable C-finding or MCL, regardless of C-findings. Cohort 2 had advanced SM without any modified IWG-MRT-ECNM evaluable C-findings.
	• Serum tryptase levels ≥20 nanograms/mL.
	• Patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy or intolerance.
	• Stable dose of non-antineoplastic SM therapies or corticosteroids (≤20 mg per day prednisone or equivalent) for ≥14 days before day 8 of cycle 1.
	• ECOG performance status 0 to 3.
		• Age ≥18 years.
		• Diagnosis based on WHO diagnostic criteria of:
		  ○ ASM
		  ○ SM-AHN
		  ○ MCL
		  ○ Histologically or cytologically confirmed myeloid malignancy that was relapsed or refractory to standard treatments (part 1 of the study only).
		• At least one C-finding per modified IWG-MRT-ECNM criteria at baseline attributed to SM, unless diagnosis is MCL (which does not require a C-finding) (Cohort 2 of part 2 only).
		• ECOG performance status of 0 to 3.

Treatments	Patients received avapritinib orally at a starting dose of 200 mg once daily. In the original study protocol, patients with platelet counts from 25,000 to 50,000/microlitre at baseline received avapritinib at a starting dose of 100 mg once daily; this was later updated to exclude patients with platelet counts <50,000/microlitre at baseline. In total, two patients received a starting dose of 100 mg. Dose modification to as low as 25 mg once daily was permitted and dose increases to 300 mg once daily were allowed for lack of efficacy. Treatment was to continue until progression, intolerance,	In part 1 (dose escalation), patients received avapritinib orally at increasing starting doses from 30 to 400 mg once daily; four patients received a starting dose of 200 mg once daily. In part 2 (dose expansion), patients received avapritinib orally at starting doses of 200 mg or 300 mg once daily.

	withdrawal by the investigator or patient or death.	
Randomisation	Not applicable.	Not applicable.
Primary outcome	Adjudicated ORR based on modified IWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in Cohort 1 only.	The primary objectives of EXPLORER were to determine the maximum tolerated dose, safety and the recommended phase II dose of avapritinib.
Secondary outcomes	DOR, PFS and OS.	ORR, DOR, PFS and OS.
Statistical analysis	The primary efficacy population was the response-evaluable population, defined as all patients who received at least one dose of avapritinib, were deemed evaluable per modified IWG-MRT-ECNM criteria at baseline as assessed by the study steering committee and had one of the following: ≥2 complete postbaseline bone marrow assessments and had been on study for ≥6 cycles of 28 days, or had an end of study visit.	Efficacy analyses were performed in the response-evaluable population, defined as all patients who received at least one dose of avapritinib, were deemed evaluable per modified IWG-MRT-ECNM criteria at baseline as assessed by the study steering committee and had one of the following: ≥2 complete postbaseline bone marrow assessments and had been on study for ≥6 cycles of 28 days, or had an end of study visit. An interim efficacy analysis was performed in patients who had sufficient follow-up for response evaluation.

Abbreviations: ASM = aggressive systemic mastocytosis; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukaemia; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with an associated haematological neoplasm; WHO = World Health Organisation

At the September 2023 data cut-off in PATHFINDER, the overall response rate (ORR) was 73% in response-evaluable patients who received avapritinib (n=81: starting dose 200 mg; n=2: starting dose 100 mg).[9] Similar response rates were observed in the pooled PATHFINDER and EXPLORER analysis presented by the submitting company. See Table 2.2 for details.

Table 2.2. Key efficacy results from PATHFINDER and the pooled PATHFINDER and EXPLORER analysis (response-evaluable population).[9, 10]

	PATHFINDER	**PATHFINDER and EXPLORER pooled**
	Avapritinib[a] (n=83)	**Avapritinib 200 mg starting dose (n=98)**
Data cut	September 2023	September 2023 and January 2023
Overall response rate (modified IWG-MRT-ECNM criteria)		
ORR	73%	CIC
CR	16%	CIC
CRh	13%	CIC
PR	40%	CIC
CI	4.8%	CIC
SD	16%	-

PD	2.4%	-
NE	8.4%	-
Duration of response		
Events	-	-
Median DOR	NR	CIC
12-month DOR KM estimate	-	CIC
Progression-free survival		
Events	-	CIC
Median PFS	NR	CIC
12-month PFS KM estimate	-	CIC
Overall survival		
Events	-	CIC
Median OS	NR	CIC
24-month OS KM estimate	-	CIC

[a] = starting dose of 200 mg (n=81) or 100 mg (n=2)

Abbreviations: CI = clinical improvement; CIC = commercial in confidence; CR = complete remission; CRh = complete remission with partial haematologic recovery; DOR = duration of response; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; KM = Kaplan-Meier; NE = not evaluable; NR = not reached; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

In EXPLORER and PATHFINDER, the following health-related quality of life (HRQoL) outcomes were assessed: European Organisation for Research and Treatment of Cancer Quality of Life Core 30-Item Questionnaire (EORTC-QLQ-C30), advanced systematic mastocytosis-Symptom Assessment Form (AdvSM-SAF) and Patient Global Impression of Symptom Severity (PGIS). These data were collected from baseline to cycle 17 of treatment in PATHFINDER and in part 2 of EXPLORER for 12 cycles of treatment (48 weeks). In pooled data from both studies of patients who received a starting dose of 200 mg, improvements were observed for all three HRQoL outcomes.[10]

2.3. Supportive studies

Real-world evidence is available from an open-label compassionate use programme in the United Kingdom. Avapritinib was commenced in patients with advanced SM with progressive disease-related symptoms and end-organ damage. The initial dose of avapritinib was adjusted according to tolerability and kept continuous until disease progression or unmanageable toxicity. Across 11 centres in the UK, 13 patients received avapritinib; 69% (n=9) received a starting dose of 200 mg daily. Median duration of treatment was 503.7 days (range 75 to 1,168 days). ORR (using modified IWG-MRT-ECNM criteria) was 77%; 54% had a complete response or complete response with partial haematologic recovery.[11]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing avapritinib with midostaurin or cladribine, the submitting company presented an indirect treatment comparison (ITC). This has been used to inform the economic base case. See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored ITC with inverse probability of treatment weighting (IPTW).
Population	Adults with advanced SM, including ASM, SM-AHN and MCL. Separate analyses were conducted in patients receiving avapritinib or midostaurin first-line and avapritinib or cladribine second-line and beyond.
Comparators	Best available therapy (BAT) (consisting of a variety of treatments, including midostaurin and cladribine).
Studies included	Pooled safety population from the PATHFINDER and EXPLORER studies (for avapritinib) and an external control study (for BAT).
Outcomes	OS and DOT.
Results	The results suggest that avapritinib had superior efficacy to midostaurin and cladribine for both overall survival and duration of treatment.

Abbreviations: 1L = first-line; 2L+ = second-line and beyond; ASM = aggressive systemic mastocytosis; BAT = best available therapy; DOT = duration of treatment; IPTW = inverse probability of treatment weighting; ITC = indirect treatment comparison; MCL = mast cell leukaemia; OS = overall survival; SM = systemic mastocytosis; SM-AHN = systematic mastocytosis with an associated haematological neoplasm

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Evidence from PATHFINDER and EXPLORER supports the safety of avapritinib for the treatment of patients with advanced SM. However, there are no comparative safety data available. Safety data presented below include patients from both studies who received a starting dose of 200 mg daily (n=126) at a data cut-off date of 20 April 2021. Median duration of treatment was 41 weeks (range 0.9 to 188.1 weeks).[2]

Out of the 126 patients with advanced SM who received a starting dose of 200 mg daily across both studies, 79% had a dose modification (20% had a dose increase); 100% had an adverse event (AE); 38% had a serious AE; 12% had a serious AE related to treatment; 60% had a grade 3 or higher AE related to treatment; 18% had an AE that led to discontinuation of treatment; and 6.3% had an AE that led to death (none were considered related to treatment). The most commonly reported AEs (in ≥20% of patients) were peripheral oedema (43%), anaemia (40%), periorbital oedema (40%), thrombocytopenia (40%), diarrhoea (28%) and nausea (24%). The most commonly reported grade 3 or higher AEs (in ≥5% of patients) were anaemia (21%), thrombocytopenia (18%), neutropenia (17%) and decreased neutrophil count (7.9%).[2]

Overall, the safety profile of avapritinib for the treatment of advanced SM appears consistent with the safety profile observed in patients with gastrointestinal stromal tumours and is largely in line with other TKIs, except for intracranial bleeds and cognitive disorders.[2] The SPC recommends regular monitoring of blood counts including liver function and coagulation parameters, clinical monitoring for signs and symptoms of cognitive events, and routine physical examinations for potential haemorrhagic events. Refer to SPC for details.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- At the September 2023 data cut-off in PATHFINDER, the ORR was 73% in response-evaluable patients who received avapritinib (n=81: starting dose 200 mg; n= 2: starting dose 100 mg). Similar response rates were observed in the pooled PATHFINDER and EXPLORER analysis presented by the submitting company.
- Time-to-event outcomes (duration of response [DOR], progression-free survival [PFS] and overall survival [OS]) were immature, however in the pooled PATHFINDER and EXPLORER analysis median PFS was reached.[9, 10]
- The primary ORR results, supported by the early time-to-event data, are considered promising. Regulators stated that the ORR results are likely to translate into clinically relevant benefits for patients with advanced SM.[2]

4.2. Key uncertainties

- EXPLORER and PATHFINDER are both uncontrolled, single-arm studies which have inherent limitations such as risk of selection bias and potential overestimation of treatment effect. Due to the non-randomised nature of these studies, time-to-event outcomes such as PFS and OS should be interpreted with caution.[2]
- No direct evidence is available comparing avapritinib with relevant comparators in clinical practice. The ITC was associated with some limitations. The ITC was unanchored and therefore differences between the populations, that were not adjusted for, may bias the results; key characteristics that were not adjusted for include bone marrow mast cell burden and C-findings. There were also residual imbalances across the two cohorts after weighting for important prognostic factors such as ECOG performance status. There was overlap between treatment groups, as some patients (approximately 15%) in the best available treatment group went on to receive avapritinib. The approach to censoring patients in the external control study may have led to bias in the results, and this was not explored with sensitivity analysis. OS data were immature and important clinical outcomes such as PFS, response rates, safety and HRQoL were not assessed. Additionally, key midostaurin studies were not used in the ITC; a matching adjusted indirect comparison using these studies would have been feasible and supportive of the primary analysis. Due to these limitations, there is uncertainty regarding the magnitude of benefit with avapritinib relative to currently available treatments.
- Pooled data from EXPLORER and PATHFINDER are immature. Median OS and DOR have not been reached at the time of the presented data cuts. Longer-term follow-up is awaited.
- The pooled analysis of PATHFINDER and EXPLORER had a limited sample size (n=98). The number of patients with ASM and MCL subtypes was very low.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that avapritinib fills an unmet need and is a therapeutic advancement in this setting. They highlighted that the reported response rates for

avapritinib appear better than with midostaurin (whilst acknowledging the lack of direct evidence comparing both) and anticipate that avapritinib will be better tolerated than midostaurin.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of avapritinib may have a positive impact on the service as potentially fewer clinic visits or hospital admissions may be required due to the improved efficacy and reduced toxicity of this medicine.

*Other data were also assessed but remain confidential.**

5. Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of avapritinib, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced SM is a rare haematological malignancy that significantly shortens life expectancy and causes considerable disability which impacts on quality of life. Symptoms in advanced SM can vary widely and include anaphylaxis, cramping, vomiting and diarrhoea, skin rash/hiving/itching, and low mood. Patients react to triggers in the normal environment that can frequently and unpredictably lead to reactions that range from mild to life-threatening severity. Advanced SM can also cause progressive organ damage, that can lead to fatigue, difficulty concentrating, cognitive impairment, localised and generalised pain, and susceptibility to infection. The fluctuating and sometimes sudden nature of these symptoms can create ongoing fear and uncertainty, limiting patients' ability to work, travel or plan daily activities. 'Flares' of the condition can also lead to hospital admissions which impacts both patient and their carers or family members. In addition, advanced SM comes with an emotional and psychological impact such as anxiety due to unpredictable reactions, depression related to a chronic illness with shortened life expectancy and loss of independence, and possible social isolation because many triggers are unavoidable.
- There is a considerable unmet need for advanced SM. There are a limited number of currently available treatments, and these treatments can have a slow onset of action, limited efficacy, and can cause significant side effects. Midostaurin is the only available licensed targeted therapy in NHSScotland for advanced SM. PACE participants noted that whilst some patients reported benefit from taking midostaurin it did not relieve patients of all their symptoms. Midostaurin can also cause troublesome gastrointestinal toxicity, including nausea and vomiting, which may be intolerable and can lead to lifestyle restriction or treatment discontinuation. Other agents (such as cladribine or interferon) are used only in specific circumstances and are not disease-modifying. Despite the above treatment options prognosis in advanced SM remains poor.
- Avapritinib addresses the high unmet need for patients with advanced SM by offering a highly targeted, disease-modifying treatment. The clinical data has shown that avapritinib offers fast, deep and durable disease-modifying reductions in mast cell burden for patients with advanced

SM. Early indications and indirect data suggest that avapritinib may have a survival benefit compared with midostaurin, which is valued highly by patients.

- Avapritinib is expected to provide better disease and symptom control for patients with advanced SM compared with midostaurin, allowing them to live more normal lives and contribute to society. A reduction in fatigue has been reported by patients taking avapritinib, which may allow patients to carry out daily activities such as caring for grandchildren, carrying out voluntary work, and maintaining their social lives with friends and family. For younger patients, it could enable them to remain in work or education for longer. Other benefits reported by patients who have taken avapritinib include better sleep, reduction in rashes and skin irritation, reduction in pain, diarrhoea, and in serious and unpredictable anaphylactic events. For some, avapritinib may reduce the number of days spent in hospital on an annual basis; by improving blood counts, organomegaly, and other C-findings, avapritinib may reduce the risk of potential complications such as transfusions, fractures, and infections. In addition to the benefits in physical symptom control, avapritinib likely improves the mental health and wellbeing of patients due to more predictable disease control.
- Avapritinib may also improve wellbeing by offering a treatment that is perceived by patients and clinicians as more tolerable than existing targeted therapy. This is particularly important because treatment-related nausea, vomiting and fatigue can compound symptoms already caused by the disease.
- Treating advanced SM with avapritinib has the potential to provide meaningful benefits not only for patients, but also for their families and carers, particularly by reducing the day-to-day and unpredictable burden of care. There may also be important psychosocial benefits. Living with a rare, life-threatening condition places a significant emotional burden on families, including anxiety about sudden deterioration, hospitalisation or disease progression.

Additional Patient and Carer Involvement

We received a joint patient group submission from The UK Mastocytosis Support Group and Leukaemia Care. The UK Mastocytosis Support Group is a charitable incorporated organisation and Leukaemia Care is a registered charity. The UK Mastocytosis Support Group has received 2% pharmaceutical company funding in the past two years, including from the submitting company. Leukaemia Care has received 9.48% pharmaceutical company funding in the past two years with none from the submitting company. Representatives from both patient groups participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An overview of economic analysis is presented in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis, with separate economic analyses for 1st line (1L) and 2nd line plus (2L+).
Time horizon	Lifetime. In 1L this was 22 years based on the cohort starting age of 68 years. For 2L+, the time horizon was 19 years based on a cohort starting age of 66 years.
Population	Adult patients with ASM, systemic mastocytosis with an SM-AHN, or MCL, collectively called advanced systemic mastocytosis (Advanced SM).
Comparators	Midostaurin (1L) and cladribine (2L+).
Model description	A partitioned survival model was used, with progression-free, progressive disease, and dead states. The model used a one month model cycle length.
Clinical data	Pooled PATHFINDER and EXPLORER study data were used for PFS and OS outcomes for avapritinib.[10] PATHFINDER and EXPLORER were single-arm studies, so outcome estimates for both comparators (midostaurin and cladribine) were derived from an external control study (ECS) conducted using retrospective chart data for patients with AdvSM. An unanchored ITC with IPTW was used to compare avapritinib outcomes (DOT and OS) using pooled PATHFINDER and EXPLORER data with midostaurin (1L) and cladribine (2L+) outcomes. PFS data were not available for the comparators from the ECS, hence the DOT outcome was used as a proxy for comparator PFS. The all-response-evaluable population, N=98 was used for avapritinib PFS estimation with N=35 informing the 1L analysis and N=63 the 2L+ analysis. The pooled safety analysis data (N=125, 46 in 1L and 79 in 2L+) were used for OS comparisons in the ITC used in the economic analysis. Individual patient data on DOT and OS were available from the ECS for 58 patients treated with midostaurin, and 25 (for DOT) and 29 (for OS) patients treated with cladribine. Adverse events of grade 3 or more occurring in ≥2% of patients were included in the economic analysis derived from the pooled clinical studies, the midostaurin SPC and published clinical study for cladribine.[10, 12, 13]
Extrapolation	PFS and OS were extrapolated in the economic analysis for avapritinib and the comparators (with DOT as a proxy for PFS), in the 1L and 2L+ economic analyses. The best statistically fitting functions were chosen to extrapolate PFS/DOT and OS, with alternative functions explored in scenario analysis. Each curve was fitted separately. Scenario analysis was performed using DOT outcomes to proxy PFS for avapritinib and comparators, and a scenario using the OS hazard ratios from the ITC to estimate relative PFS. The company also included treatment waning for avapritinib assuming a duration of treatment benefit fixed in the base case at 7.5 years, based on treatment response data in the pooled clinical studies.
Quality of life	For both 1L and 2L+, PF health state utility values were sourced from the pooled PATHFINDER and EXPOLRER data where EORTC-QLQ-C30 data were mapped to EQ-5D-3L using a published algorithm.[14] PD utility values were based on studies from a targeted literature review due to a lack of QLQ-C30 data for PD in the avapritinib clinical studies. Adverse event disutilities were included and a disutility was also estimated for cladribine subcutaneous infusion, based on published sources.[13, 15]
Costs and	Drug acquisition costs were included for all medicines included in the economic

resource use	analysis. Avapritinib and midostaurin are administrated orally, so no administration costs were applied. A one-off administration cost was included for subcutaneous administration of cladribine. In the base case all patients were assumed to be treated to progression before discontinuation. Health state disease management resource use costs were estimated, including health care professional visits, hospital and ICU stays and outpatient visits, tests and investigations for PF (divided into 0-6 months, 6-12 months, 12+ months) and PD. Relative dose intensity (RDI) and interruption was incorporated into the model for patients receiving midostaurin and cladribine, based on clinical expert opinion. No RDI adjustments were applied for patients receiving avapritinib, due to availability of different dosing packages. No drug wastage was assumed for avapritinib or midostaurin. Adverse event costs were included, and additional costs associated with concomitant treatments were included for patients receiving midostaurin, specifically anti-sickness therapies.
PAS/contract price	A patient access scheme (PAS) was proposed by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on list price of avapritinib. A national contract price discount is in place in Scotland for midostaurin and this was included in the results used for decision-making. There is no PAS in place for cladribine.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS and NHSScotland National Framework Contract prices. SMC is unable to present these results due to competition law issues.

The base case results are presented in Tables 6.2a and 6.2b below. For both 1L and 2L+, the disaggregated incremental QALY results showed that the QALY gains over the comparators (midostaurin and cladribine) are driven primarily by additional time spent in the PFS state. Incremental costs of avapritinib are driven by additional medicine acquisition costs, and additional health state disease management costs.

Table 6.2a Base case results for first-line with avapritinib PAS and midostaurin national contract price.

Technologies (1L)	Total			Incremental			ICER (costs per QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
avapritinib *versus*:	CIC	7.47	4.93	-	-	-	CIC
midostaurin	CIC	3.16	2.06	CIC	4.30	2.87	

Abbreviations: CIC = commercial in confidence; ICER = incremental cost-effectiveness ratio; LYs, life years; QALY = quality adjusted life years

Table 6.2b Base case results for second-line with avapritinib PAS

Technologies (2L+)	Total			Incremental			ICER (costs per QALY gained)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
avapritinib *versus*:	CIC	6.68	3.89	-	-	-	CIC

cladribine	CIC	4.13	2.03	CIC	2.55	1.86	

Abbreviations: CIC = commercial in confidence; ICER = incremental cost-effectiveness ratio; LYs, life years; QALY = quality adjusted life years.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses for both 1L and 2L+ were considered and descriptions of these key scenarios are provided in Table 6.3.

Table 6.3 Sensitivity and scenario analysis results (PAS/contract price)

	Parameter	**Base case**	**Scenarios**
1	Time horizon	Lifetime (22 years midostaurin, 19 years cladribine)	a) 10 years
			b) 15 years
2	PFS estimation for avapritinib	PFS sourced from pooled PATHFINDER & EXPLORER	DOT as proxy for PFS of avapritinib using pooled PATHFINDER & EXPLORER safety cohort
3	OS extrapolations	OS extrapolation for avapritinib: Generalised Gamma (1L) ; Exponential (2L+)	a) Avapritinib 2nd best fit OS: (1L) exponential ; (2L) log-normal
			b) Avapritinib 3rd best fit OS: (1L) Gompertz; (2L) log-logistic
		OS extrapolation for midostaurin (exponential); cladribine (log-normal)	c) Comparators 2nd best fit OS: midostaurin, log-normal; cladribine, log-logistic
			d) Comparators 3rd best fit OS: midostaurin, Gamma; cladribine, Gompertz
4	Duration of treatment benefit for avapritinib	7.5 years	a) 5 years
			b) 10 years
			c) Lifetime
5	PF utility value	PF utility (mean)	a) Lower bound of PF utility (-95% CI)
			b) Upper bound of PF utility (+95% CI)
6	Disease management costs	PF and PD costs per cycle based on expert opinion	Reduced costs by 50%: PF and PD

Abbreviations: 1L, first line of therapy; DOT, duration of treatment; OS, overall survival; PF, progression-free; PFS, progression-free survival.

6.4. Key strengths

- The model structure is appropriate.
- The comparators are relevant, with midostaurin as a primary 1L comparator (it is likely that avapritinib will be used predominantly 1L in practice). Despite some uncertainty over cladribine as the only 2L+ comparator (SMC clinical experts also mentioned imatinib and interferon) this choice seems reasonable.

6.5. Key uncertainties

- High uncertainty in the PFS and OS benefit related to clinical evidence and ITC limitations, use of duration of treatment (DOT) as proxy for PFS, and small patient numbers for 1L and 2L comparisons. There is ICER uncertainty associated with the clinical evidence used in the economic analysis.

- The extrapolation of OS outcomes is based on limited data and so is highly uncertain. The choice of parametric function used in the base case and in scenario analysis was based on top 3 in terms of best statistical fit but none of the 7 functions explored demonstrated a good visual fit to the data. For instance, the 3rd best statistical fitting function for avapritinib in the 1L context was the Gompertz (Scenario 3b, Table 6.3) but lacks plausibility as this produces a flat extrapolation beyond the data suggesting avapritinib is a potential cure.
- The company explored various of duration of treatment benefit scenarios assumed for avapritinib, with some ICER sensitivity to the duration shown (Scenario 4a-c, Table 6.3). However, there remains uncertainty in the derivation of the QALY and ICER results associated with these scenarios and some scenarios relating to OS extrapolations (Scenario 3c-d, Table 6.3), hence uncertainty in their plausibility.
- The health state disease management costs are based on resource use estimates from two clinicians and are uncertain. Although the health state costs associated with disease management were assumed to be the same between avapritinib and comparators, these appear potentially high and are a driver of the cost-effectiveness results for scenarios that improve/ reduce the survival benefit of avapritinib (scenarios 1, 3 and 4 in Table 6.3). However, exploratory scenario analysis (Scenario 6, Table 6.3) reducing the costs of PF and PD state disease management improves the cost-effectiveness results for avapritinib.

7. Conclusion

The Committee considered the benefits of avapritinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as avapritinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept avapritinib for use in NHSScotland.

8. Guidelines and Protocols

In 2022, the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM) published "Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice."[16]

9. Additional Information

9.1. Product availability date

06 November 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
avapritinib	**Recommended starting dose of avapritinib is 200 mg orally once daily.**	**£323,560**

Costs from BNF online on 06 March 2026. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 27 April 2026.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.