Avapritinib (Ayvakyt®) for the treatment of advanced systemic mastocytosis (AdvSM)

General information

Drug description [1]	Indication [2]
Avapritinib (Ayvakyt®) is a Type 1 kinase inhibitor.	**Advanced systemic mastocytosis (AdvSM):** Ayvakyt® is indicated 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), after at least one systemic therapy.

Current treatment [3]

Midostaurin is approved by the EMA as a monotherapy for the treatment of adult patients with ASM, SM-AHN or MCL.

Regulatory status

EMA [2]	FDA [4, 5]
Approval status for this indication: On 27 January 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Ayvakyt®. The CHMP adopted **two new strengths**, 25 mg and 50 mg film-coated tablets, and a **new indication:** ❖ Advanced systemic mastocytosis (AdvSM): Ayvakyt® is indicated as monotherapy for the treatment of adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy. **Other indications**: ❖ Ayvakyt® is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation. ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 16 June 2021, the FDA approved avapritinib (Ayvakit™) for adult patients with AdvSM, including patients with ASM, SM-AHN, and MCL. Limitations of use: Ayvakit™ is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L. ✓ **Priority review** ✓ **Breakthrough designation** ✓ **Orphan drug designation** **Other indications**: Ayvakit™ is indicated for ❖ the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations.

Costs

30 Ayvakyt™ tablets 200 mg = € 18,339.04 (ex-factory price) [6].

Posology for AdvSM [1]

❖ For AdvSM, the recommended starting dose of avapritinib is 200 mg orally once daily, on an empty stomach.
❖ This once daily 200 mg dose is also the maximum recommended dose that must not be exceeded by patients with AdvSM.
❖ Treatment should be continued until disease progression or unacceptable toxicity occurs.
❖ Treatment with avapritinib is not recommended in patients with platelet count < 50 x 109/L.
❖ Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 200 mg to 50 mg orally once daily.

Warnings and precautions for use [1]

❖ **Haemorrhages:** Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage in patients with unresectable or metastatic GIST and AdvSM. Gastrointestinal haemorrhagic adverse reactions were the most commonly reported haemorrhagic adverse reactions during avapritinib treatment of unresectable or metastatic GIST patients, while hepatic and tumour haemorrhage also occurred. Routine surveillance of haemorrhagic adverse reactions must

include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.

- **Intracranial haemorrhages:** Adverse reactions of intracranial haemorrhage occurred in patients who received avapritinib. Before initiating avapritinib the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with thrombocytopenia, vascular aneurysm or a history of intracranial haemorrhage or cerebrovascular accident within the prior year. Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with avapritinib must interrupt dosing of avapritinib and inform their healthcare professional immediately. Brain imaging by MRI or CT may be performed at the discretion of the physician based on severity and the clinical presentation. For patients with observed intracranial haemorrhage during treatment with avapritinib, regardless of severity grade, avapritinib must be permanently discontinued.
  - Unresectable or metastatic GIST: Serious adverse reactions of intracranial haemorrhage were reported in patients with unresectable or metastatic GIST receiving avapritinib. The exact mechanism is unknown. There is no clinical study experience using avapritinib in patients with brain metastases.
  - Advanced systemic mastocytosis: Serious adverse reactions of intracranial haemorrhage were reported in patients with AdvSM receiving avapritinib. The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts <50 x 10^9/L and in patients with a starting dose of ≥300 mg. Considering the above, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts <50 x 10^9/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 10^9/L, every 4 weeks if values are between 75 and 100 x 10^9/L, and as clinically indicated if values are greater than 100 x 10/L. Manage platelet counts of <50 x 10^9/L by temporarily interrupting avapritinib. Platelet support may be necessary, and the recommended dose modification (see product information) must be followed. Thrombocytopenia was generally reversible by reducing or interrupting avapritinib in clinical studies. The maximum dose for patients with AdvSM must not exceed 200 mg once daily.
- **Cognitive effects:** Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritini. The mechanism of the cognitive effects is not known. It is recommended that patients are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. For patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification (see product information) must be followed. In clinical studies, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.
- **Fluid retention:** Occurrences of fluid retention, including severe cases of localised oedema (facial, periorbital, peripheral oedema and/or pleural effusion) or generalised oedemas, have been reported with a frequency category of at least common in patients with unresectable or metastatic GIST taking avapritinib. Other localised oedemas (laryngeal oedema and/or pericardial effusion) have been reported uncommonly. In patients with AdvSM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common. Other localised oedemas (laryngeal oedema) have been reported uncommonly. Therefore, it is recommended that patients be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.
- **QT interval prolongation:** Prolongation of QT interval has been observed in patients with unresectable or metastatic GIST and AdvSM treated with avapritinib in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes. Avapritinib should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias. If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, see product information for dose modification instructions. Interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval.
- **Gastrointestinal disorders**

  Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with unresectable or metastatic GIST and AdvSM. Patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid properties. The hydration status of patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice.
- **Laboratory tests:** Treatment with avapritinib in patients with unresectable or metastatic GIST and AdvSM is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with avapritinib. See also intracranial haemorrhages in the product information.

  Treatment with avapritinib is associated in patients with unresectable or metastatic GIST and AdvSM with elevations in bilirubin and liver transaminases. Liver function (transaminases and bilirubin) should be monitored regularly in patients receiving avapritinib.
- **CYP3A4 inhibitors and inducers:** Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of avapritinib. Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of avapritinib.
- **Photosensitivity reaction:** Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor.
- **Sodium:** This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Study characteristics: PATHFINDER trial [7-9]								
Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
PATHFINDER NCT03580655	62[1]	200 mg avapritinib once daily[2]	none	ORR	**ongoing[3],** international, multicentre, open-label, single-arm, phase 2 registrational trial	-	Blueprint Medicines Corporation	[8]

Interim analysis of efficacy (n=32)	Interim analysis of safety (n=62)
Confirmed ORR (CR/CRh/PR/clinical improvement), median follow-up of 10.4 months: 75.0% (95% CI 57.0–89.0, p=1.6 × 10^{-9}) **CRh**: 19.0% **PR**: 31.0% **CI**: 25.0% **Median time to response**: 2 months (range 0.3–12.2) **Median time to CRh**: 5.6 months (range 1.8–6.1) **Median PFS:** NR **Median OS:** NR **Estimated 6-, 9- and 12-month PFS rates:** 91, 87 and 79%, respectively**; corresponding OS rates:** 94, 86 and 86% **In the safety population (n=62):** A **reduction of ≥50% in bone marrow mast cells** was observed in 88.0% (44/50) of patients and 60.0% (30/50) had **elimination of bone marrow mast cell aggregates**. The **serum tryptase** level decreased by ≥50.0% in 93.0% (54/58) of patients and 43.0% (25/58) of patients achieved serum tryptase levels <20 ng ml^{-1}. **Decrease of ≥50.0% in absolute monocyte counts:** 80.0% of patients with SM and chronic myelomonocytic leukemia **Decrease of ≥50.0% in absolute eosinophil counts:** 88.0% of patients with eosinophilia, including all three patients with SM and chronic eosinophilic leukaemia **Substantial (≥50.0%) reduction in KIT D816V VAF in the peripheral blood:** 60.0% **VAF of <1%: 35%** **Spleen volume reduced from baseline by ≥35%:** 66.0% <u>Patient-reported outcomes and QoL</u> ❖ Pretreatment mean EORTC–QLQ–C30–QoL score was 37.8 (range, 0–100, where 0 represents the lowest QoL and 100 the highest) and 31.0% of patients had a poor ECOG performance status of 2 or 3. ❖ Mean and median PGIS scores were 2.6 and 3.0, respectively (where 0 represents no symptoms and 4 very severe symptoms). ❖ The AdvSM–SAF (an AdvSM-specific patient-reported outcomes tool) showed that fatigue, abdominal pain, and spots were the most severe symptoms, with a mean TSS of 18.3, which was the sum of eight possible common symptoms (each scored 0–10, where 0 represents no symptoms and 10 is the worst imaginable).	**Grade ≥3 any-cause AEs**: n=42/62 (68.0%) **Grade ≥3 treatment-related AEs**: n=32/62 (52.0%) **Discontinuation due to AEs**: n=6/62 (10.0%, with n=3 considered treatment-related according to the local site investigator) **Deaths due to AEs:** n=3/62 (5%)[4] Consistent and profound reductions in measures of **mast cell burden** were observed in all enrolled patients with baseline and post-baseline assessments.

[1] ASM (n = 9), SM-AHN (n = 43) and MCL (n = 10)

[2] Two patients started at a dose of 100 mg avapritinib once daily.

[3] Estimated study completion date of the PATHFINDER trial is 05/2022.

[4] Disease progression, necrotising fasciitis and haemorrhagic shock, none of which were considered related to treatment.

- ❖ Patient-reported symptoms, as measured by TSS score, improved rapidly following treatment initiation, dropping by 7.1 points from baseline at cycle 3 (n = 51) and by 9.8 points from baseline at treatment cycle 11 (n = 22; p<0.001).
- ❖ Mean symptom scores were lower than baseline at cycles 3 and 11 for all SM symptoms, including fatigue, abdominal pain, spots, itching, flushing, nausea, diarrhoea, and vomiting.
- ❖ Mean and median PGIS scores improved to 1.6 and 2.0 (moderate symptoms that are difficult to ignore), respectively, by cycle 3 and to 1.2 and 1.0 (minimal symptoms that are easy to ignore), respectively, by cycle 11.
- ❖ QoL, as assessed by EORTC–QLQ–C30, improved on trial with noteworthy improvements in physical (strenuous activity), role (work or household jobs), emotional (irritability, feeling tense and depression), cognitive (memory and concentration), and social (family life and social activities) functioning domains.

UPDATE: Efficacy results in patients with AdvSM enrolled in the study, who received at least one prior systemic therapy and a starting dose of 200 mg avapritinib once daily, with a median duration of follow-up of 12 months (overall population, n=47) [1]:
ORR per modified IWG-MRT-ECNM: 60% (95% CI, 44.3-73.6)
Response per modified IWG-MRT-ECNM category:
CR: 2%
CRh: 9%
PR: 40%
Clinical improvement: 9%
Median DOR rate at 12 months: 100%
Median DOR rate at 24 months: 85.6%
Median time to response: 1.9 months
Median time to CR/CRh: 3.7 months

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	unclear	yes

Overall risk of bias: low

Study characteristics: EXPLORER trial [11-13]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

EXPLORER NCT02561988	86[5]	avapritinib at doses of 30–400 mg once daily	-	maximum tolerated dose, recommended phase 2 dose, safety	phase 1 international, multicentre, open-label study	-	Blueprint Medicines	[8]

Efficacy	Safety (n=69)
Maximum tolerated dose and recommended phase 2 dose ❖ Part 1 studied doses of 30, 60, 100, 130, 200, 300 and 400 mg once daily, with doses of 200 mg and higher achieving exposures consistently above, and doses of 100 mg and 130 mg partly above, the xenograft 90.0% inhibitory concentration for KIT D816V inhibition at steady state. ❖ No maximum tolerated dose was determined. ❖ During part 1, n=1 experienced dose-limiting toxicity of grade 4 vomiting at 400 mg daily. ❖ A recommended phase 2 dose of 300 mg once daily was initially selected for use in part 2; however, dose reduction to 200 mg once daily was typical, most commonly for cytopenias. ❖ 200 mg once daily had similar exposure and time to response, so a second expansion cohort with a 200 mg once daily starting dose was added by protocol amendment. ❖ In total, n=15 initiated treatment at <200 mg once daily, n=21 initiated at 200 mg once daily, n=43 initiated at 300 mg once daily and n=7 initiated at 400 mg once daily. **Efficacy in patients with AdvSM (n=53)** **ORR**: 75.0% (95% CI 62–86%) **CR or CRh**: 36.0% **PR**: 34.0% **Median time to achieve PR or better (CR/CRh/PR):** 2 months (range 2–27 months) **Median time to achieve CR/CRh**: 9 months **Median DOR**: 38 months (95% CI 22 months–NE) **Estimated 12-month and 24-month DOR rates**: 84.0% (95% CI 72–96%) and 67.0% (95% CI 49–84%), respectively. **BM mast cells decreased by ≥50.0%**: 92.0% of patients and mast cell aggregates were eliminated in 77.0% of patients. **Serum tryptase was reduced by ≥50.0%**: 99.0% of patients and reduced to <20 ng ml^{-1} in 74.0% of patients. **Spleen volume was reduced by ≥35.0%:** 82.0% (of 66 patients with a baseline spleen volume assessment). **The KIT D816V variant allele fraction in BM** was reduced from baseline by ≥50.0% in 80.0% of patients and became undetectable in 30.0% of patients. **Estimated PFS rates**: 84.0% (95% CI 73–94%) at 12 months and 63.0% (95% CI 48–79%) at 24 months. **Progression to acute myeloid leukaemia** during the study: 9.0% **Median OS** in the overall AdvSM safety population (n = 69): not reached (95% CI 47–NE) **Estimated 24-month OS rates**: 76.0% (95% CI 64–87%) overall, and 100.0%, 67.0% and 92.0% for patients with ASM, SM-AHN and MCL, respectively.	**Discontinuation due to related AEs:** n=7/69 (10%) **Discontinuation due to unrelated AEs:** n=6/69 (9%) **Deaths due to AEs:** n=6/69 (9%)[6]

[5] n=69 with centrally confirmed AdvSM; n=14 with indolent SM, n=2 with smoldering SM; n=1 with chronic myelomoncytic leukaemia.

[6] Acute myeloid leukaemia, gastric haemorrhage, ICB (considered treatment related; occurring in the setting of antecedent severe thrombocytopenia and a recent fall with head trauma), cardiac arrest, staphylococcal sepsis and septic shock.

Pharmacokinetics

- Steady state was reached by day 15.
- Steady-state plasma concentrations at doses of ≥200 mg once daily exceeded the biochemical IC90 of 189 ng ml^{-1} for inhibition of KIT D816V, as measured by immunoblot in a xenograft model, at most time points.
- Following single oral doses of 30 to 400 mg, the time to maximum plasma concentration (T_{max}) ranged from 2 to 4 h.
- After single and repeat dosing of avapritinib, systemic exposure increased in a dose-dependent manner.
- The long mean plasma elimination half-life of avapritinib (range, 19.8-38.3 h) suggests that prolonged in vivo inhibition of KIT D816V, likely contributes to observed clinical activity, and supports once daily dosing.
- The steady-state (cycle 1, day 15) geometric mean (percentage coefficient of variation; n), maximum plasma concentration and area under the plasma concentration–time curve in patients at 200 mg once daily was 433 ng ml^{-1} (62.2%; n =18) and 7,340 h ng ml^{-1} (54.2%; n =16), respectively.

Patient-reported outcomes and symptom improvement

- The AdvSM-symptom assessment form (AdvSM-SAF) patient diary evaluated symptoms across two domains—gastrointestinal and skin.
- Patients provided information about the severity of abdominal pain, nausea, vomiting, diarrhoea, spots, itching, flushing and fatigue, and the frequency of vomiting and diarrhoea.
- Reductions from baseline were seen in both the gastrointestinal and skin domains.
- Treatment with avapritinib also yielded consistent reductions in the patient-reported AdvSM-SAF TSS, which encompassed gastrointestinal and skin symptoms and fatigue.
- The mean TSS at baseline was 19.1 points (n = 40).
- Statistically significant improvements in symptoms occurred rapidly and were sustained through C11 (mean change from baseline of –10.9 points, p= 0.002, n = 20).
- At baseline, approximately one-third of patients overall (29 patients; 34.0%) were using corticosteroids.
- After baseline, as a result of improvement in SM-associated symptoms, 19 patients (66.0%) reduced their corticosteroid usage, of whom 12 (41.0%) patients discontinued corticosteroid use entirely, while 7 (24.0%) were able to reduce the dose.

Risk of bias - study level (case series) [10]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	yes	yes
Overall risk of bias: low								

Abbreviations: AdvSM=Advanced systemic mastocytosis, AdvSM-SAF=AdvSM-symptom assessment form, AE=adverse event, AJ=adjustment, ASM=aggressive systemic mastocytosis, BM=bone marrow, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CRh=complete remission with partial recovery of peripheral blood counts; DOR=duration of response, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EORTC-QLQ-C30= European Organization for Research and Treatment of Cancer Core QoL Questionnaire C30, FDA=Food and Drug Administration, GIST=gastrointestinal stromal tumour, HR=hazard ratio, I=intervention, Int.=intention, MCL=mast cell leukaemia, MG=median gain, MTD=maximum tolerated dose, n=number of patients, NE=not estimable, NR=not reached, ORR=overall response rate, OS=overall survival, PDGFRA=platelet-derived growth factor receptor alpha, PE=primary endpoint, PFS=progression-free survival, PGIS=Patient Global impression of Symptom Severity, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SAF=Symptom Assessment Form, SM=systemic mastocytosis, SM-AHN=SM with an associated hematologic neoplasm, ST=standard treatment, TSS=total symptom score

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