Avapritinib (Ayvakyt®) for the treatment of indolent systemic mastocytosis (ISM)

General information

Drug description [1]

Avapritinib (Ayvakyt®) is a tyrosine kinase inhibitor that targets KIT D816V, PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations less than 25 nM in biochemical assays. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumour and mast cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1.

Indication [2]

Avapritinib (Ayvakyt®) is indicated for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.

Incidence [3]

Systemic mastocytosis is a rare disease; the assumed incidence is 1/100,000 persons/year.

Current treatment

- Management of ISM and smoldering systemic mastocytosis is focused on the prevention and treatment of anaphylactic reactions and symptom control.
- In case of severe symptoms refractory to anti-mediator therapy or bone disease unresponsive to bisphosphonates, disease-modifying treatments with cytoreductive agents may be attempted.
- The first approach is to identify symptom triggers and suggest avoidance strategies of triggers, such as physical stimuli (heat, change of temperature, pressure, cold, rubbing), exercise, sleep deprivation, emotions, drugs (opiates, contrast media, succinylcholine, nonsteroidal anti-inflammatory drugs, agents with tetrahydroisoquinoline such as quinolones, atracurium, and rocuronium), alcohol, food, and Hymenoptera stings [4].
- **Onkopedia recommends the following** [3]:
  - Basic therapy:
    - HR1- and HR2-inhibitors
    - In case of distinct osteopenia or osteoporosis: bisphosphonates
    - In case of vitamin D deficiency: Vitamin D (+ Vitamin K2, as needed)
  - Extension of basic therapy (symptomatic/individualised):
    - Additional to HR1- inhibitor: mast cell stabilizers/ leukotriene antagonists/steroids/immunotherapy/omalizumab
    - Additional to HR2 – inhibitor: proton pump inhibitors
    - Bisphosphonate-resistant osteopathy: RANKL-inhibitor
    - In case of bone pain/ osteoporosis/ gastrointestinal symptoms resistant to treatment: IFN-alpha1
  - Targeted and cytoreductive therapy
    - Midostaurin (independent of KIT Status)
    - Imatinib (only KIT D816 negative patients)
    - In case of moderate or low progress: cladribine monotherapy
    - In patients who progress rapidly: polychemotherapy, cladribine-containing regimen
    - In eligible patients, allogeneic stem cell transplantation.

Regulatory status

EMA [2]	FDA

Approval status for this indication: On 9 November 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for **Ayvakyt®**. The CHMP adopted an extension of indication as follows: ❖ Ayvakyt® is indicated for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment. **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. ❖ 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. ✓ **Orphan status** ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[1]	**Approval status for this indication**: According to the manufacturer, the FDA approved **Ayvakit®** (avapritinib) for the treatment of ISM in May 2023 [5]. **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. ❖ the treatment of adult patients with advanced systemic mastocytosis. Advanced systemic mastocytosis includes 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 [1].

Manufacturer

Ayvakyt® is manufactured by Blueprint Medicines.

Costs

30 Ayvakyt® film tablets 25 mg = € 18,339.04 (ex-factory price) [6]

Warnings and precautions [1]

- **Intracranial haemorrhage**
  - Permanently discontinue for any occurrence of any grade.
- **Cognitive Effects**
  - A broad spectrum of cognitive adverse reactions can occur in patients receiving Ayvakit®.
  - In patients with GIST, AdvSM, or ISM depending on the severity, continue Ayvakit® at same dose, withhold and then resume at same or reduced dose upon improvement, or permanently discontinue.
- **Photosensitivity**
  - May cause photosensitivity reactions.
  - Advise patients to limit direct ultraviolet exposure.
- **Embryo-foetal toxicity**
  - Can cause foetal harm.
  - Advise females and males of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [1, 7-9]

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

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

PIONEER NCT03731260	212 2:1	once-daily 25 mg avapritinib + BSC	Placebo + BSC	mean change in ISM-SAF[2] TSS[3]	NA	**ongoing**[4], international, multicentre, randomized, double-blind, placebo-controlled phase 2 study	-	Blueprint Medicines Corporation	PIONEER trial (abstract only) [8]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (I[5])
❖ Patients <18 years with systemic mastocytosis (SM), confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria. ❖ Patient must have moderate-to-severe symptoms based on minimum mean TSS of the ISM-SAF over the 14-day eligibility screening period. ❖ Patient must have failed to achieve adequate symptom control for 1 or more baseline symptoms. ❖ For patients receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent, and the dose must be stable for ≥14 days. ❖ ECOG PS of 0-2.	❖ Diagnosis of cutaneous mastocytosis only, smoldering SM, SM with associated hematologic neoplasm, aggressive SM, mast cell leukaemia, or mast cell sarcoma. ❖ Patients must not have received prior treatment with avapritinib. ❖ Patients must not have had any cytoreductive therapy including but not limited to masitinib and midostaurin, or investigational agent for < 14 days or 5 half-lives of the drug (whichever is longer), and for cladribine, interferon alpha, pegylated interferon, or antibody therapy < 28 days or 5 half-lives of the drug (whichever is longer), before beginning the 14-day ISM-SAF eligibility TSS assessment. ❖ No previous radiotherapy or psoralen and ultraviolet A therapy < 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. ❖ Patient must not have received any hematopoietic growth factor the preceding 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. ❖ Patient must not have a QT interval corrected using Fridericia's formula of > 480 msec.	❖ Median age: 50 years (range, 18-77 years) ❖ Female sex: 71% ❖ White: 77% ❖ Asian: <1% ❖ Other race: 3% ❖ Missing race: 19% ❖ KIT D816V mutations: 93% ❖ Mean TSS at baseline: 50.17 (standard deviation: 19.15) ❖ Median serum tryptase level: 38.40 ng/mL ❖ Median KIT D816V mutant allele fraction: 0.39% by ddPCR ❖ Median bone marrow mast cell infiltrate: 7%

Patient-reported outcomes/ efficacy (I vs. C), abstract data	**Safety,** abstract data
❖ Primary and key secondary endpoints were met. ❖ Study completion rates were 96% vs. 93%. ❖ Significantly greater improvement in TSS at 24 weeks in I vs. C (15.6 vs. -9.2; p=0.003) ❖ Patients in I were more likely to achieve 30% (p=0.009) and 50% (p=0.005) reductions in symptoms measured by TSS. ❖ Significantly more avapritinib patients achieved >50% reductions in serum tryptase (54% vs. 0%; p<0.0001), BM MC aggregates (53% vs. 23%, p<0.0001), and KIT D816V VAF (68% vs. 6%; p<0.0001). ❖ Overall AEs and SAEs were lower in avapritinib vs. placebo. ❖ Absolute mean change in the ISM-SAF TSS • Change from baseline (95% CI): -15.33 (-18.36, -12.31) vs. -9.64 (-13.61, -5.68); 2-sided p-value: 0.012 • Difference from placebo (95% CI): -5.69 (-10.16, -1.23) ❖ % of patients achieving ≥50% reduction in the ISM-SAF TSS (95% CI): 25 (17.9, 32.8) vs. 10 (4.1, 19.3); 2-sided p-value: 0.009 ❖ Efficacy results related to mast cell burden for patients with ISM in PIONEER at week 24:	❖ Serious adverse reactions occurred in 1 patient (0.7%) who received avapritinib due to pelvic hematoma. ❖ Permanent discontinuation of avapritinib due to an adverse reaction occurred in 1 patient (0.7%) due to dyspnoea and dizziness. ❖ Dosage interruptions of avapritinib due to an adverse reaction occurred in 5% of patients. ❖ Adverse reactions which required dosage interruption included dizziness, blood alkaline phosphatase increased, dyspnoea, face oedema, pelvic hematoma, liver transaminase increased and respiratory tract infection (1 patient each). ❖ The most common adverse reactions (≥ 10%) in the AYVAKIT group were eye oedema, dizziness, peripheral oedema and flushing. ❖ Of all adverse reactions, 55% were Grade 1, 38% were Grade 2 and 7% were Grade 3.

[2] ISM-SAF is a patient-reported outcome measure assessing ISM signs and symptoms: abdominal pain, nausea, diarrhoea, spots, itching, flushing, bone pain, fatigue, dizziness, headache, brain fog.
[3] Based on 14-day average of patient-reported severity of 11 ISM symptoms (0=none; 10=worst imaginable).
[4] PIONEER trial is currently ongoing; the estimated study completion date is 01/2028.
[5] Study population characteristics were similar in the placebo group.

• % of patients with a ≥50% reduction in serum tryptase (95% CI): 53.9 vs. 0; 2-sided p-value <0.0001 • % of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction or undetectable (95% CI): 67.8 vs. 6.3; 2-sided p-value <0.0001 • % of patients with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI): 52.8 vs. 22.8; 2-sided p-value <0.0001	❖ Among patients with oedema adverse reactions, 95% were Grade 1 and 5% were Grade 2. ❖ Among patients with haemorrhage adverse reactions, 86% were Grade 1 and 14% were Grade 2.

ESMO-MCBS for Haematological Malignancies version 1.0 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Since there is currently only abstract data available, the ESMO-MCBS for Haematological Malignancies is not applicable.											

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting is unlikely	Other aspects which increase the risk of bias	**Risk of bias**
Since there is currently only abstract data available, the risk of bias is not evaluable.					

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT03731260/ PIONEER	Please see above.	01/2028

Available assessments

❖ No assessments were identified via NICE, CADTH, ICER and G-BA.

Other aspects and conclusions

❖ In November 2023, the **CHMP adopted an extension of indication** for Ayvakyt®, indicated for the treatment of adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment. The FDA approved Ayvakit® for the treatment of adult patients with ISM.

❖ **PIONEER** (NCT03731260) is an **ongoing,** international, multicenter, randomized, double-blind, placebo-controlled phase 2 study. Patients <18 years with SM, with moderate-to-severe symptoms based on minimum mean TSS of the ISM-SAF over the 14-day eligibility screening period who have failed to achieve adequate symptom control for 1 or more baseline symptoms and an ECOG PS of 0-2 were included. Patients with cutaneous mastocytosis only, smouldering SM, SM with associated hematologic neoplasm, aggressive SM, mast cell leukaemia, or mast cell sarcoma were excluded.

❖ **The primary endpoint** of the PIONEER trial was **mean change in TSS**, based on a 14-day average of patient-reported severity of 11 ISM symptoms. Avapritinib patients had **significantly greater improvement in TSS** at 24 weeks vs. control group patients (-15.6 vs -9.2; p=0.003) and were more likely to achieve 30% (p=0.009) and 50% (p=0.005) reductions in symptoms measured by TSS.

❖ Since there is currently **only abstract data** available, the ESMO-MCBS is **not applicable**, and the risk of bias is **not evaluable.**

❖ Besides the PIONEER trial, there were **no further ongoing clinical trials** (neither phase 3 nor 2) identified.

❖ For the assessed indication, **evidence is currently rare**. The PIONEER trial is ongoing; there is **no full text** available yet.

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Abbreviations: AE=adverse event, AJ=adjustment, ASM=aggressive systemic mastocytosis, BM MC=bone marrow mast cell, BSC=best supportive care, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GIST=gastrointestinal stromal tumours, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, INF=interferon, Int.=intention, ISM=Indolent Systemic Mastocytosis, ISM-SAF=ISM-Symptom Assessment Form , MCL=mast cell leukemia, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, OS=overall survival, PDGFRA=platelet-derived growth factor receptor alpha, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SM=systemic mastocytosis, SM-AHN=systemic mastocytosis with an associated hematological neoplasm, ST=standard treatment

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