Avapritinib (Ayvakyt®) for the treatment of gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

General information [1]

Drug description	Indication
Avapritinib (BLU-285) is a protein kinase inhibitor, designed to potently and selectively inhibit oncogenic KIT and PDGFRA mutants by targeting the active conformation of the kinase.	Avapritinib is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation.

Current treatment [2]

The following pharmacological treatment options for unresectable or metastatic GIST are recommended by NICE:

- Imatinib as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST
- Sunitinib as a treatment option for people with unresectable and/or metastatic GISTs that are imatinib resistant or intolerant
- Regorafenib as a treatment option (third-line) for people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if their ECOG performance status is 0 to 1.

Regulatory status

EMA [1, 3]	FDA
Approval status for this indication: On 23 July 2020, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Ayvakyt®. On 17 July 2017, orphan designation was granted by the European Commission to avapritinib for the treatment of gastrointestinal stromal tumours. Date of issue of marketing authorisation valid throughout the European Union: **24/09/2020** The full indication is: ❖ Ayvakyt® is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation. **Other indications**: ❖ 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. ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 9 January 2020, the FDA approved avapritinib (AYVAKIT™) for adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including D842V mutations. **Other indications**: AYVAKIT™ is indicated for: ❖ the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes o patients with ASM, SM-AHN, and MCL. o Limitations of use: AYVAKIT™ is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 109/L.

Costs

30 Ayvakyt® tablets 300 mg = € 18,339.04 (ex-factory price) [6].

Posology for GIST [7]

- For GIST, the recommended starting dose of avapritinib is 300 mg orally once daily, on an empty stomach.
- Treatment should be continued until disease progression or unacceptable toxicity occurs.
- Patient selection for treatment of unresectable or metastatic GIST harbouring the PDGFRA D842V mutation should be based on a validated test method.
- 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 300 mg to 100 mg orally once daily.

Special warnings and precautions for use [7]

- **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 109/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 109/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 109/L, every 4 weeks if values are between 75 and 100 x 109/L, and as clinically indicated if values are greater than 100 x 10/L. Manage platelet counts of <50 x 109/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 [8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
NAVIGATOR BLU-285-1101, NCT02508532	**56** (PDGFRA D842V population) **82** (safety population)	Oral avapritinib once daily in the dose-escalation part (starting dose of 30 mg, with increasing dose levels once daily in 28-day cycles until the max. tolerated dose/recommended phase 2 dose was determined; in the dose-expansion part, the starting dose was the max. tolerated dose	-	**Dose-escalation part:** max. tolerated dose + recommended phase 2 dose + evaluation of safety **Dose-expansion part:** overall response rate + overall safety profile	a two-part, open-label, dose-escalation and dose-expansion, international, phase 1 study	-	Blueprint Medicines	[8]

Efficacy (I vs. C)

Maximum tolerated dose: Avapritinib 400 mg
This dose was chosen as the starting dose for dose expansion but was subsequently **reduced to 300 mg** after joint investigator and sponsor review of available safety, pharmacokinetic, pharmacodynamic, and clinical activity data.

Overall response (in the D842V population): n=49/56 (88%; 95% CI, 76–95); 9% of patients had a CR, 79% had a PR, and 13% had stable disease.

Clinical benefit: in 55 (98%; 95% CI, 90–100) patients.

12-month duration of response: 70% (95% CI, 54–87)

PFS at 3 months: 100% (95% CI, 100–100)

PFS at 6 months: 94% (88–100)

PFS at 12 months: 81% (69–93)

OS was estimated to be 100% (95% CI, 100–100) at 6 months, 91% (83–100) at 12 months, and 81% (67–94) at 24 months.

Among patients who received a 300 mg starting dose, 26 (overall response rate 93%; 95% CI, 77–99) had an objective response (post-hoc analysis).

Safety (I vs. C)

Treatment-related grade ≥3 AEs (across doses): n=47/82 (57%)
Drug-related SAEs (any grade): n=21/82 (26%)
Deaths[1] (safety population): n=11 (13%)
Discontinuation (in the safety population)[2]: n=44/83 (54%)

[1] Causes for death were related to patients' general physical health (4%), disease progression (4%), cardiac failure (1%), hepatic failure (1%), hyperbilirubinaemia (1%), metastatic neoplasm (1%), and sepsis (1%). There were no treatment-related deaths.
[2] The most common reasons for treatment discontinuation were disease progression (32%) and AEs (18%), ten (12%) of which were considered to be related to avapritinib.

Efficacy results for PDGFRA D842V-Mutantion in GIST patients (n=38): **mRECIST 1.1 ORR (=CR + PR):** 95% (95% CI, 82.3-99.4) **CR:** 13% **PR:** 82% **Median duration of response:** 22.1 months (14.1-NE)	

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	-	-	ORR (PR+CR)≥60%	3	57% grade ≥3 AEs	-	-1	2
Adapted	-	-	-	-	-	-	-	-	-		-

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
no	no	no (open-label)	unclear[3]	yes[4]	high

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Abbreviations: AdvSM=advanced systemic mastocytosis, AE=adverse event, AJ=adjustment, ASM=aggressive systemic mastocytosis, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, ECOG=Eastern Cooperative Oncology Group, 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, GIST=gastrointestinal stromal tumours, HR=hazard ratio, I=intervention, Int.=intention, MCL=mast cell leukaemia, MG=median gain, mRECIST 1.1=Response Evaluation Criteria In Solid Tumours v1.1 modified for patients with unresectable or metastatic GIST, n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, ORR=overall response rate, OS=overall survival, PDGFRA=platelet-derived growth factor receptor alpha, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SM-AHN= systemic mastocytosis with an associated haematological neoplasm, ST=standard treatment

References:

1. European Medicines Agency (EMA). Medicines. Ayvakyt [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ayvakyt#key-facts-section].
2. National Institute for Health Research (NIHR). Avapritinib for unresectable or metastatic gastrointestinal stromal tumours (GIST) who have been treated with at least 3 prior lines of therapy and GIST harbouring the PDGFRA D842V mutation regardless of prior therapy. [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2019/06/26826-Avapritinib-for-Gastrointestinal-Stromal-Tumour-V3.0-APR2019-NONCONF-UPDATED.pdf].
3. European Medicines Agency (EMA). Medicines. Orphan Designations. EU/3/17/1889 [Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171889].
4. U.S. Food and Drug Administration (FDA). Drugs /Development & Approval Process | Drugs /Drug Approvals and Databases: Resources for Information / Approved Drugs / FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation].

[3] The trial is currently ongoing (until 01/2021)

[4] The study was designed by the funder together with the study investigators. The funder collected, analysed, and interpreted the data in conjunction with the authors. The authors wrote the first draft of the manuscript with editorial support from a medical writer paid for by the funder. Bioanalysis of plasma samples and calculation of pharmacokinetic parameters under the paid supervision of the funder.

5. U.S. Food and Drug Administration (FDA). AYVAKIT. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212608s007lbl.pdf].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. European Medicines Agency (EMA). Ayvakyt: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf].
8. Heinrich MC, Jones RL, von Mehren M, Schöffski P, Serrano C, Kang Y, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol 2020; 21: 935–46. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204520302692].