swissmedic

Date: 4 October 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ayvakyt

International non-proprietary name: avapritinib
Pharmaceutical form: film-coated tablets
Dosage strength(s): 300 mg, 200 mg, 100 mg, 50 mg, and 25 mg
Route(s) of administration: oral
Marketing authorisation holder: Blueprint Medicines (Switzerland)
Marketing authorisation no.: 68294
Decision and decision date: approved on 6 July 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AdvSM	Advanced systemic mastocytosis
AE	Adverse event
ALT	Alanine aminotransferase
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CR(h) + PR	Complete response (with partial haematological recovery) + partial response
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GLP	Good Laboratory Practice
HDPE	High-density polyethylene
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM)
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCL	Mast cell leukaemia
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Overall response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PDGFRA	Platelet-derived growth factor receptor alpha

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PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily
RE	Response-evaluable
RMP	Risk management plan
RP2D	Recommended dosage for Phase 2
SAE	Serious adverse event
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated haematological neoplasm
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TKIs	Tyrosine kinase inhibitors
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for avapritinib in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 4 January 2021 for advanced systemic mastocytosis and on 7 January 2021 for gastrointestinal stromal tumour.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Gastrointestinal Stromal Tumour (GIST)

- Ayvakyt is indicated for the treatment of adults with unresectable or metastatic GIST harbouring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

Advanced Systemic Mastocytosis (AdvSM)

- Ayvakyt is indicated for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL).

2.2.2 Approved indication

Gastrointestinal Stromal Tumour (GIST)

• AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring a platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Advanced Systemic Mastocytosis (AdvSM)

• AYVAKYT is indicated as monotherapy for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) after at least one previous systemic therapy (see "Clinical Efficacy"). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL).
AYVAKYT is not recommended for the treatment of patients with AdvSM with platelet counts below 50 x 10^9/L (see "Dosage/Administration", Table 2 and "Warnings and Precautions")

2.2.3 Requested dosage

Summary of the requested standard dosage:
Recommended dosage for GIST with PDGFRA exon 18 mutations.
The recommended dosage of Ayvakyt is 300 mg orally once daily in patients with a GIST. Treatment should be continued until disease progression or unacceptable toxicity.

Recommended dosage in advanced systemic mastocytosis.

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The recommended dosage of Ayvakyt is 200 mg orally once daily in patients with AdvSM. Treatment should be continued until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 November 2021
Formal objection	6 December 2021
Response to formal objection	10 January 2022
Formal control completed	13 January 2022
List of Questions (LoQ)	12 May 2022
Response to LoQ	2 August 2022
Preliminary decision	15 November 2022
Response to preliminary decision	15 February 2023
Labelling corrections	3 May 2023
Response to labelling corrections	26 May 2023
Final decision	6 July 2023
Decision	approval

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the FDA. This SwissPAR relates to the publicly available assessment report Ayvakyt, application number 212608 (approval date 9 January 2020) issued by the FDA.

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3 Medical context

Gastrointestinal stromal tumours (GISTs)

PDGFRA mutations are present in up to approximately 10% of GISTs, with exon 18 being the most frequently mutated region, affecting approximately 80% of *PDGFRA*-mutated GISTs. *PDGFRA* exon 18 D842V mutations are the most common mutations in exon 18, affecting approximately 90% of *PDGFRA* exon 18-mutated GISTs. While most *PDGFRA* mutations are associated with a response to treatment with tyrosine kinase inhibitors (TKIs), GISTs harbouring the D842V mutation are unlikely to benefit from available therapies, resulting in an important medical need. Avapritinib is an oral TKI that was designed to have activity against *PDGFRA* A-loop mutants including *PDGFRA* D842V.

Advanced systemic mastocytosis (AdvSM)

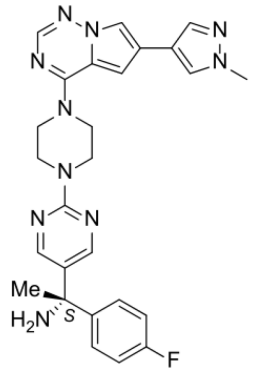
Systemic mastocytosis (SM) is a rare clonal mast cell neoplasm, primarily driven by mast cells carrying the *KIT* D816V mutation. AdvSM includes patients with ASM, SM-AHN, and MCL. The outcome of patients with AdvSM varies with the type and stage of AdvSM, with overall median overall survival (OS) ranging from as low as 2 months to more than 5 years. Available and approved treatment options for AdvSM are limited, and their efficacy and safety unsatisfactory. Therefore, there is a medical need for more efficacious and/or safer therapeutic options for patients with AdvSM. Avapritinib is an oral TKI that was designed to have activity against *KIT* mutants, including the driver *KIT* D816V mutation which is associated with resistance to approved TKIs.

4 Quality aspects

4.1 Drug substance

INN:	Avapritinib
Chemical name:	(S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethan-1-amine
Molecular formula:	$C_{26}H_{27}FN_{10}$
Molecular mass:	498.57 g/mol

Molecular structure:



Physico-chemical properties: Avapritinib drug substance is a white to off-white to yellow solid. Avapritinib contains a single asymmetrically substituted tetrahedral carbon of the 'S' absolute configuration. Avapritinib in the preferred crystalline Form A is non-hygroscopic.

Synthesis: The drug substance is manufactured by a multiple step chemical synthesis with final isolation by crystallisation.

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Specification: The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, determination of crystal form, assay, impurities, and particle size.

Stability: Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug product

Description and composition: Avapritinib drug product is an immediate release tablet for oral administration. The tablets are available in 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg strengths. All tablet strengths are coated with a white film, and the 25 mg and 50 mg strengths have debossed text reading “BLU” on one side and the tablet strength on the other side, while the 100 mg, 200 mg, and 300 mg strengths are printed in blue ink reading “BLU” on one side and the tablet strength on the other side.

Pharmaceutical development: The composition of the drug product is adequately described, qualitatively and quantitatively. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA), and the Critical Process Parameters (CPP).

Manufacture: The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

Specification: The drug product specification covers relevant physicochemical characteristics and identification, and also includes assay and purity tests. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

Container Closure System: Avapritinib bulk tablets are packaged in a 60 ml wide-mouth, square, white, high-density polyethylene (HDPE) bottle with a 33 mm diameter child-resistant, pictorial cap with foil induction seal liner and 0.5 g silica gel desiccant canister.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority FDA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Ayvakyt, application number 212608 (approval date 9 January 2020) issued by the FDA.

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6 Clinical aspects

A marketing authorisation application was submitted according to Article 13 of the Swiss Therapeutic Products Act (“Heilmittelgesetz”), selecting the US Food and Drug Administration (FDA) as the reference authority, which had previously granted regular approval for unresectable or metastatic GIST harbouring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, and AdvSM.

The Swiss marketing authorisation application proposed the same indications as approved by the FDA, but excluded the limitations of use requested by the FDA for the treatment of patients with AdvSM.

While Swissmedic’s clinical assessment has primarily relied on the results of the assessment of the FDA as the reference authority (and EMA where considered appropriate), selected aspects of dose finding / dose recommendation, efficacy, and safety have been evaluated in depth (see below). For further details regarding the primary data relating to clinical aspects of this application, the reader is referred to the publicly available assessment reports of the FDA and EMA.

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data in this application has been based on previous regulatory decisions by FDA and EMA. The available assessment reports and respective product information from FDA and EMA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose finding and dose recommendation

GIST

For GIST, the dose intended for marketing was selected based on the dose-escalation Part 1 of the Phase 1 registrational GIST Study BLU-285-1101 (NAVIGATOR), using a maximum tolerated dose (MTD) approach. This led to the selection of 400 mg once daily (QD), and Part 2 of the study was initiated at this dosage. However, based on the emerging data, which suggested a trend toward a higher incidence of Grade 3 neurological AEs and more dose reductions at 400 mg QD, a lower dosage of 300 mg QD was eventually chosen as the recommended dosage for Phase 2 (RP2D).

The dose finding for the proposed GIST indication has important limitations. It was based on a small number of patients and used an MTD approach without considering efficacy aspects. Clinical data and the exposure-response relationship analysis show no meaningful differences, suggesting that the investigated dose/exposure range is in the flat (maximum) part of the exposure-response curve. This means that dosages lower than 300 mg QD could still demonstrate efficacy similar to that of the proposed therapeutic dosage. Conversely, clinical data and the exposure-safety relationship do suggest a dose-/exposure-dependent increase in incidences of safety events, including Grade 3/4 adverse events (AEs), AEs leading to dose reduction and adverse cognitive effects. This is of particular relevance as avapritinib has demonstrated substantial toxicity, as shown by high incidences of Grade ≥3 and serious AEs, including life-threatening and fatal events. Avapritinib-related toxicities include cognitive effects in almost half of treated patients, while clinical data suggest a trend toward a higher incidence of Grade 3 neurological AEs with higher dose/exposure.

Nevertheless, a recommended starting dosage of 300 mg QD was finally accepted for the treatment of patients with unresectable / metastatic PDGFRA-D842V mutated GIST based on the available evidence of efficacy, the lack of satisfactory therapeutic alternatives, and the overall manageable safety profile, particularly if individual dose modifications are made per the information for healthcare professionals. In addition, as a prerequisite for approval, Swissmedic clinical assessment requested the inclusion in the information for healthcare professionals of descriptive information on the proportion of treated GIST patients whose starting dosage was reduced, the actual exposure

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achieved, and the fact that efficacy did not appear to be diminished in patients whose dose had been reduced due to adverse events (see Information for Healthcare Professionals for details).

AdvSM

For AdvSM, the dose intended for marketing was selected based on the dose-escalation Part 1 of the Phase 1 Study BLU-285-2101 (EXPLORER). The MTD was not reached during Part 1 and, based on safety, PK, pharmacodynamic, and antitumour activity, 300 mg QD was considered the RP2D and was used as the starting dose for initiation of the expansion Part 2. However, patients with an avapritinib starting dose of 300 mg QD were noted to require more frequent dose reductions for cytopenias (at least 50% of patients in the 300 mg dose cohort experienced cytopenias), fluid retention, gastrointestinal (GI) AEs, and cognitive effects. In addition, an elevated risk of intracranial bleeding in patients treated with doses of 300 mg and higher was recognised, particularly in association with thrombocytopenia (platelet count <50,000/µL). Because efficacy appeared to be maintained on reduced avapritinib dosages, 200 mg QD was eventually considered the RP2D and was used for the remainder of Part 2 of Study BLU-285-2101 (EXPLORER) as well as in the following Study BLU-285-2202 (PATHFINDER).

The dose finding for the proposed AdvSM indication has important limitations. The comparison of clinical safety across the different starting dosages is hampered by the small sample sizes and, even more so, by the substantial differences in duration of exposure to avapritinib. While all patients dosed at lower than 200 mg QD were enrolled in Part 1 and thus had the longest median duration of treatment of all dose groups (42 months), most patients in the 200 mg QD cohort were enrolled toward the end of Part 2 and thus had the shortest median duration of treatment (8 months). Despite these exposure differences, patients in the <200 mg QD cohort (vs. 200mg QD and 300 mg QD cohorts) had the lowest proportion of intracranial bleeding (0 vs. 10% and 14%) and AEs leading to dose reduction (0 vs. 67% and 91%).

In terms of efficacy, neither the clinical data nor the exposure-response relationship analyses demonstrate superiority of the proposed starting dosage of 200 mg QD when compared with lower starting dosages. The comparative overall response rate (ORR) and progression-free survival (PFS) were even numerically higher in the <200 mg QD cohort. Conversely, in terms of safety, clinical data and the exposure-response relationship in patients with SM and advanced malignancies do suggest a dose-/exposure-dependent increase in incidences of safety events, including Grade ≥3 treatment-emergent AEs, AEs leading to dose reduction and adverse central nervous system (CNS) effects, including cognitive effects, and intracranial bleeding. Although comparisons between the different dosages should be interpreted with caution because of the small sample sizes, non-randomised dose assignments, immature time-to-event endpoints, and differences in exposure, the provided evidence is still insufficient to establish 200 mg QD as the optimum dosage in terms of the benefit-risk ratio for the therapy of AdvSM.

Nevertheless, a recommended starting dosage of 200 mg QD was finally accepted for the treatment of patients with AdvSM based on the available evidence of efficacy, limited therapeutic alternatives, and the overall manageable safety profile, particularly if individual dose modifications are made per the information for healthcare professionals. In addition, as a prerequisite for approval, Swissmedic Clinical Assessment requested the inclusion in the information for healthcare professionals of descriptive information on the proportion of treated AdvSM patients whose starting dosage was reduced, the actual exposure achieved, and the fact that efficacy did not appear to be diminished in patients whose dose had been reduced due to adverse events (see Information for Healthcare Professionals for details).

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6.3 Efficacy

GIST

Based on the available data, avapritinib showed compelling ORR results in patients with unresectable / metastatic *PDGFRA*-D842V mutated GISTs. In the registrational Study BLU-285-1101 (NAVIGATOR), an ORR >90% has been reported. Although the ORR in supportive studies BLU-285-1303 (VOYAGER) and BLU-285-1105 was lower, 43% and 63% *(updated 79%)* respectively, these rates are still substantially higher than in the historical data for advanced *PDGFRA*-D842V mutated GISTs (ORR of 0 to 12%), as are the PFS (median: approximately 24 months) and OS (approximately 70% at 3 years) results in Study BLU-285-1101. In addition, PFS, ORR, and OS results for *PDGFRA*-D842V mutated ≥3L GISTs were better on avapritinib (N=7) than on regorafenib (N=6) in Study BLU-285-1303. It is also of note that, in registrational Study BLU-285-1101, the ORR data for patients naïve to TKIs appeared consistent with that of the overall D842V-mutant group, although the data were limited (N=5).

Nevertheless, efficacy data presented the following uncertainties:

- Evidence was based on small patient numbers, less than 40 patients in the registrational study (N=38, 10 of these patients had a starting dosage of 400 mg QD, which is higher than the proposed 300 mg QD), and slightly more than 50 if the supportive studies are also considered, and mainly on single-arm study data. The small sample size combined with the lack of a control treatment complicates the interpretation of the study results, especially regarding important efficacy endpoints other than ORR, such as OS and PFS.
- The surrogacy of ORR for GIST has not been validated.
- Besides the small patient numbers and the lack of a control arm (see above), the evidence for survival endpoints PFS and OS is reduced further by the immaturity of the data.

In addition, insufficient evidence was provided for the following aspects of the initially proposed GIST indication.

- There is insufficient evidence for the efficacy of avapritinib in patients with GIST harbouring non-D842V *PDGFRA* exon 18 mutations. The eligibility and primary endpoint of registrational Study BLU-285-1101 (NAVIGATOR) were limited to patients with *PDGFRA*-D842V mutated GIST and did not include other *PDGFRA* mutations. Moreover, only a very limited number of patients with GIST harbouring non-D842V *PDGFRA* exon 18 mutations were included (N=5), and mutations did not represent the full spectrum of PDGFRA exon 18 mutations. In addition, the efficacy in terms of ORR (40%) was substantially lower than for the patients with *PDGFRA*-D842V mutated GISTs. Because a control arm was missing, it cannot be excluded that avapritinib has reduced comparative efficacy in GISTs with non-D842V *PDGFRA* exon 18 mutations, given that other TKIs have shown effectiveness in GISTs with non-D842V *PDGFRA* exon 18 mutations. Imatinib, for example, may have profound activity in patients with *PDGFRA* exon 18 mutant GISTs that are non-D842V, and is being recommended as the preferred first-line regimen for unresectable, progressive, or metastatic GISTs harbouring *PDGFRA* exon 18 mutations that are not D842V mutations. It is of note that resistance to imatinib in these patients may also cause cross-resistance to avapritinib.
- Evidence has only been provided for avapritinib used as monotherapy for GIST; no evidence is available for combinations with other agents used for the treatment of GIST.

Overall, the evidence of efficacy was accepted, despite the limitations above. The main reasons for this conclusion included the rarity of PDGFRA-D842V mutated GIST, comprising only a minority of the total GIST population, and the lack of satisfactory therapeutic options, while the comparative efficacy of avapritinib appeared notably higher than for other TKIs that were used in this setting, especially for ORR, but also for PFS and OS.

Based on the available evidence, Swissmedic Clinical Assessment requested the GIST indication to be limited to monotherapy with avapritinib and to PDGFRA-D842V mutated GIST.

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AdvSM

Swissmedic Clinical Assessment evaluated efficacy and safety data including updated results for AdvSM from the registrational Phase 2 Study BLU-285-2202 and the supportive Phase 1 Study BLU-285-2101 (EXPLORER).

Despite the data update, the follow-up (median: 14.3 months) and duration of treatment (median: 11.2 months) in the registrational AdvSM Study BLU-285-2202 were still short, and the time-to-event endpoints were immature (maturity: duration of response (DOR) 4.5%, progression-free survival (PFS) 18%, and overall survival (OS) 17%). Nevertheless, the updated data provided by the applicant increased the level of evidence. For instance, for the registrational AdvSM Study BLU-285-2202 there was an additional period of 10 months between the respective data cut-offs, and the number of patients who formed the primary population increased from 31 to 47 patients (see below for the definition of the primary population), increasing the availability of the limited clinical data for MCL and ASM from 4 to 10 patients and from 2 to 8 patients, respectively.

In the registrational Phase 2 Study BLU-285-2202 (PATHFINDER), based on the primary population (N=47), avapritinib achieved an ORR (CR(h) + PR) of 51% in patients with response-evaluable (RE) AdvSM comprising SM-AHN, MCL, and ASM. This efficacy compared favourably with the historical registrational study data for AdvSM therapy that had been previously approved for the same indication: ORR (based on modified IWG-MRT-ECNM criteria) 51% (95%CI 36, 66) vs. 17% (95%CI 10, 25) [US Prescribing Information RYDAPT®] and OS Kaplan-Meier estimates at 12 months of 83% vs. 70% [Swiss information for healthcare professionals RYDAPT®]. However, the available evidence has important limitations, including low patient numbers, lack of a control arm with the use of cross-study comparisons, lacking surrogacy of ORR for OS in AdvSM, immature time-to-event endpoints, and short duration of follow-up. However, ORR results were supported by the results of the Phase 1 Study BLU-285-2101: 73 % (95%CI 39, 94) in 11 patients with AdvSM, who had received at least one prior systemic therapy for AdvSM and were treated with the recommended avapritinib starting dosage of 200 mg QD. In addition, positive OS effects of avapritinib were also supported by the results of Study BLU-285-2405, which used propensity score-adjusted (inverse probability of treatment weighted) real-world data of patients receiving the best available therapy.

Overall, the evidence of efficacy was accepted. The main reasons for this conclusion included the rarity of AdvSM and the limited therapeutic alternatives, while the comparative efficacy of avapritinib compared favourably with available AdvSM therapy.

However, the evidence level of efficacy for AdvSM patients without prior antineoplastic therapy, i.e., for the first-line (1L) treatment setting, was considered insufficient, as data were uncontrolled and the surrogacy of ORR for AdvSM unproven while, at the same time, duration of follow-up was short and the survival time-to-event endpoints, especially OS, were immature. Therefore, Swissmedic Clinical Assessment mandated the AdvSM indication to be restricted to patients who have received at least one prior systemic therapy for AdvSM and, for labelling efficacy, in AdvSM the primary population was to be limited to the 47 patients in registrational Study BLU-285-2202 who had received at least one prior systemic therapy for AdvSM and were treated with the recommended avapritinib starting dosage of 200 mg QD.

Based on the updated OS data, no meaningful OS differences were observed between RE and non-RE patients and, in particular, there was no indication of a worse OS among non-RE patients. Thus, it was accepted to not restrict the indication to patients with RE AdvSM, which is in line with approved FDA and EMA indications.

Finally, based on the available evidence, Swissmedic Clinical Assessment requested the indication to be limited to avapritinib monotherapy, the inclusion of a “Limitations of Use” advising against the treatment of patients with platelet counts lower than 50 x 10^9/L, and the submission of final data from both AdvSM studies, BLU-285-2101 and BLU-285-2202, as a post-approval requirement.

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6.4 Safety

The safety profile for avapritinib is characterised by oedema (peripheral, periorbital, and increased lacrimation, pleural effusion, ascites), adverse gastrointestinal reactions (nausea, vomiting, diarrhoea, decreased appetite, abdominal pain, constipation, increased bilirubin), fatigue/asthenia, infections (sepsis, pneumonia), rash, kidney injury, cytopenias, haemorrhages and CNS/cognitive effects. While toxicities such as gastrointestinal and haematological adverse events are also known from other TKIs, when compared with the TKI regorafenib in Study BLU-285-1303 (VOYAGER), which provides the only available comparative safety data, the following AEs were reported more frequently in the avapritinib arm: Anaemia, leukopenia, nausea, vomiting, increased bilirubin, and oedema (facial, peripheral). Diarrhoea, hypertension, dysphonia, stomatitis, and PPE (palmar-plantar erythrodysaesthesia) were reported less often. Of particular concern are the very common CNS effects, particularly cognitive effects, and the increased incidence of intracranial haemorrhage in patients treated with avapritinib.

However, despite the substantial toxicity associated with avapritinib, the safety profile is not considered prohibitive for approval, given the promising efficacy results, poor prognosis of the underlying diseases, and limited effective alternative therapies. As requested by Swissmedic, relevant safety aspects have been appropriately reflected in the information for healthcare professionals, such as cognitive effects and intracranial haemorrhages, including potentially increased bleeding risks in case of comedication with drugs that are known to increase the bleeding risk in the section warnings and precautions.

6.5 Final clinical benefit risk assessment

Based on the available evidence of efficacy, the lack of satisfactory therapeutic alternatives, and the overall manageable safety profile, particularly if individual dose modifications are made per the information for healthcare professionals, an overall positive benefit-risk ratio for the use of avapritinib in treating GIST and AdvSM was concluded.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Ayvakyt was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

AYVAKYT®

Composition

Active substances

Avapritinib

Excipients

Tablet core: Microcrystalline cellulose, copovidone, croscarmellose sodium, magnesium stearate

Tablet coat: Talc, Macrogol 3350, poly(vinyl alcohol), titanium dioxide (E171)

Printing ink (for 100 mg, 200 mg and 300 mg film-coated tablets only): Shellac, Brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172), propylene glycol, ammonium hydroxide

Each 25 mg film-coated tablet contains 0.271 mg sodium
Each 50 mg film-coated tablet contains 0.543 mg sodium
Each 100 mg film-coated tablet contains 1.086 mg sodium
Each 200 mg film-coated tablet contains 2.172 mg sodium
Each 300 mg film-coated tablet contains 3.257 mg sodium

Pharmaceutical form and active substance quantity per unit

Film-coated tablet for oral use.
1 film-coated tablet contains 25 mg avapritinib (round, white film-coated tablet of 5 mm diameter with debossed text, one side reads “BLU” and the other side reads “25”)
1 film-coated tablet contains 50 mg avapritinib (round, white film-coated tablet of 6 mm diameter with debossed text, one side reads “BLU” and the other side reads “50”)
1 film-coated tablet contains 100 mg avapritinib (round, white film-coated tablet of 9 mm diameter, printed with blue ink “BLU” on one side and “100” on the other side)
1 film-coated tablet contains 200 mg avapritinib (oval, white film-coated tablet of 16 mm in length and 8 mm in width, printed with blue ink “BLU” on one side and “200” on the other side)
1 film-coated tablet contains 300 mg avapritinib (oval, white film-coated tablet of 18 mm in length and 9 mm in width, printed with blue ink “BLU” on one side and “300” on the other side)

Indications/Uses

Gastrointestinal Stromal Tumour (GIST)

- AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring a platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Advanced Systemic Mastocytosis (AdvSM)

- AYVAKYT is indicated as monotherapy for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) after at least one previous systemic therapy (see “Clinical Efficacy”). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL).

  AYVAKYT is not recommended for the treatment of patients with AdvSM with platelet counts below 50 x 10^9/L (see “Dosage/Administration”, Table 2 and “Warnings and Precautions”).

Dosage/Administration

Therapy should be initiated by a physician experienced in the diagnosis and treatment of conditions for which avapritinib is indicated.

Select patients for treatment with AYVAKYT based on the presence of a PDGFRA D842V mutation.

Patient selection for treatment of unresectable or metastatic GIST harbouring the PDGFRA D842V mutation should be based on a validated test method.

Recommended Dosage for GIST Harbouring a PDGFRA D842V Mutation

The recommended starting dosage of AYVAKYT is 300 mg orally once daily in patients with GIST. This once-daily 300 mg dose is also the maximum recommended dose that must not be exceeded by patients with GIST. The daily dose is to be adjusted as required according to tolerability (see “Dose adjustment due to undesirable effects/interactions”).

Continue treatment until disease progression or unacceptable toxicity.

Recommended Dosage for Advanced Systemic Mastocytosis

The recommended starting dosage of AYVAKYT is 200 mg orally once daily in patients with AdvSM. This once-daily 200 mg dose is also the maximum recommended dose that must not be exceeded by patients with AdvSM. The daily dose is to be adjusted as required according to tolerability (see “Dose adjustment due to undesirable effects/interactions”). Continue treatment until disease progression or unacceptable toxicity.

Recommended Administration

Administer AYVAKYT orally on an empty stomach, at least 1 hour before or 2 hours after a meal.

A missed dose should not be made up unless the time to the next scheduled dose is at least 8 hours.

Do not repeat dose if vomiting occurs after AYVAKYT but continue with the next scheduled dose.

Dose adjustment following undesirable effects/interactions

The recommended dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2.

In the pivotal clinical trials, the dose of AYVAKYT had to be reduced at least once in the majority of treated patients – in up to 82% with GIST and 68% with AdvSM – due to adverse reactions (see "Undesirable Effects"). The median daily dose in these trials was 184 mg for the treatment of GIST and 104 mg for the treatment of AdvSM. No negative impact on the efficacy of the treatment was observed in those patients whose dose of AYVAKYT was reduced due to adverse reactions.

Table 1. Recommended Dose Reductions for AYVAKYT for Adverse Reactions

Dose Reduction	**GIST (starting dose 300 mg)***	**AdvSM (starting dose 200 mg)****
First	200 mg once daily	100 mg once daily
Second	100 mg once daily	50 mg once daily
Third	-	25 mg once daily

* Permanently discontinue AYVAKYT in patients with GIST who are unable to tolerate a dose of 100 mg once daily.

** Permanently discontinue AYVAKYT in patients with AdvSM who are unable to tolerate a dose of 25 mg once daily.

Table 2. Recommended Dosage Modifications for AYVAKYT for Adverse Reactions

Adverse Reaction	**Severity***	**Dosage Modification**
Patients with GIST or AdvSM		
Intracranial Haemorrhage (*see Warnings and Precautions)*	Any grade	Permanently discontinue AYVAKYT.
Cognitive Effects (*see Warnings and Precautions)*	Grade 1	Continue AYVAKYT at same dose or reduced dose or withhold until improvement to baseline or resolution. Resume at same dose or reduced dose.
	Grade 2 or Grade 3	Withhold AYVAKYT until improvement to baseline, Grade 1, or resolution. Resume at same dose or reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.

Other (*see Adverse Reactions)*	Grade 3 or Grade 4	Withhold AYVAKYT until improvement to less than or equal to Grade 2. Resume at same dose or reduced dose, as clinically appropriate.
Patients with AdvSM		
Thrombocytopenia (*see Warnings and Precautions)*	<50 x 10^9/L	Interrupt AYVAKYT until platelet count is ≥50 x 10^9/L, then resume at reduced dose (as per Table 1). If platelet counts do not recover to above 50 x 10^9/L, consider platelet support.

*Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Avoid concomitant use of AYVAKYT with strong or moderate CYP3A4 inhibitors. If concomitant use with a moderate CYP3A4 inhibitor cannot be avoided, the starting dosage of AYVAKYT is as follows *(see "CYP3A4 inhibitors and inducers")*:

- GIST: 100 mg orally once daily
- AdvSM: 50 mg orally once daily

Patients with hepatic disorders

No dose adjustment is recommended for patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 times ULN and any AST] or moderate [total bilirubin >1.5 to 3 times ULN and any AST] hepatic impairment. AYVAKYT has not been studied in patients with severe (Child-Pugh class C) hepatic impairment and therefore its use in these patients is not recommended (see "Clinical Pharmacology").

Patients with renal disorders

No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min estimated by Cockcroft-Gault]. Since AYVAKYT has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (CLcr <15 mL/min), its use is not recommended in these patients (see Clinical Pharmacology).

Elderly patients

No dose adjustment is recommended for patients aged 65 years and above.

Children and adolescents

AYVAKYT is not approved for use in children and adolescents.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

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 (see section “Undesirable effects”).

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), antiplatelet agents or other concomitant medicinal products that increase the risk of bleeding, for example glucocorticoids or acetylsalicylic acid.

Intracranial haemorrhages
Intracranial haemorrhage occurred as adverse reactions in patients who received AYVAKYT. The exact mechanism is unknown (see section "Undesirable effects"). There is no clinical study experience using AYVAKYT in patients with brain metastases.

Before initiating treatment with AYVAKYT the risk of intracranial haemorrhage should be carefully considered in patients with a potentially 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 AYVAKYT must interrupt dosing of AYVAKYT and inform their healthcare professional immediately. Brain imaging by magnetic resonance imaging (MRI) or computed tomography (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 the severity grade, avapritinib must be permanently discontinued (see section "Dosage/Administration").

In patients with AdvSM the risk of intracranial haemorrhage was increased in patients with the concomitant presence of thrombocytopenia with platelet counts <50 x 10^9/L and with treatment at a starting dose of ≥300 mg.

Therefore, a platelet count must be performed prior to initiating therapy. AYVAKYT should not be used for the treatment of AdvSM in patients with platelet counts <50 x 10^9/L (see "Indications/Uses"). 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 if 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 10^9/L.

If platelet counts fall below 50 x 10^9/L, treatment with AYVAKYT should be interrupted. Platelet support may be required, and the recommended dose modification in Table 2 must be followed (see section "Dosage/Administration"). Thrombocytopenia was generally reversible after reducing or interrupting AYVAKYT in clinical studies.

Cognitive effects

Cognitive effects, such as memory impairment, cognitive disorders, confusional states, and encephalopathy, can occur in patients receiving AYVAKYT (see section "Undesirable effects"). 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 AYVAKYT, the recommended dose modification in Table 2 must be followed (see section "Dosage/Administration"). 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, pulmonary oedema and pleural effusion) or generalised oedemas and ascites, have been reported with a frequency category of at least common in patients taking avapritinib. Other types of localised oedema (laryngeal oedema and pericardial effusion) have been reported uncommonly (see section “Undesirable effects”).

Therefore, it is recommended that patients be assessed for these adverse reactions including regular assessment of weight and respiratory symptoms. 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 given. For patients presenting with ascites, it is recommended to evaluate the aetiology of the ascites.

QT interval prolongation
Prolongation of the QT interval has been observed in patients with unresectable or metastatic GIST and AdvSM treated with avapritinib in clinical studies. QT interval prolongation may result in an increased risk of ventricular arrhythmias, including torsade de pointes.

Therefore, AYVAKYT 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 CYP3A4 inhibitors must be avoided and concomitant administration with moderate CYP3A4 inhibitors should likewise be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias (see section *“Interactions”*). If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, see section Dosage/Administration for dose modification instructions.

Assessments of the QT interval using electrocardiogram (ECG) should be considered, especially if AYVAKYT is taken concurrently with medicinal products that can prolong the QT interval.

Gastrointestinal disorders
Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions (see section “Undesirable effects”). Patients with diarrhoea, nausea and vomiting should be assessed to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrhoeal, 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 treatment with AYVAKYT. See also intracranial haemorrhages above in this section and the section Undesirable effects.

Treatment with avapritinib is associated with elevations of bilirubin and liver transaminases (see section “Undesirable effects”). Liver function (transaminases and bilirubin) should be monitored regularly in patients receiving AYVAKYT.

CYP3A4 inhibitors and inducers

Co-administration with strong CYP3A4 inhibitors must be avoided and co-administration with moderate CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of avapritinib (see sections “Dosage/Administration” and “Interactions”).

Co-administration with strong or moderate CYP3A4 inducers should be avoided because it may decrease the plasma concentrations of avapritinib (see section “Interactions”).

Photosensitivity reaction

Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with AYVAKYT. Patients must be instructed to use measures such as protective clothing and sunscreen with a high sun protection factor (SPF).

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, AYVAKYT can cause fetal harm when administered to pregnant women *(see preclinical data)*.

Additional excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Interactions

Effect of other medicinal products on avapritinib

Strong and Moderate CYP3A Inhibitors

Co-administration of avapritinib with a strong CYP3A inhibitor (itraconazole) increased avapritinib plasma concentrations and may result in increased adverse reactions. Co-administration of itraconazole (200 mg twice daily on Day 1 followed by 200 mg once daily for 13 days) with a single 200 mg dose of avapritinib on Day 4 in healthy subjects increased the avapritinib C_{max} 1.4-fold and the $AUC_{0\text{-}inf}$ 4.2-fold compared with a 200 mg dose of avapritinib administered alone.

Co-administration of avapritinib with strong or moderate CYP3A inhibitors (such as antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin; active substances to treat human immunodeficiency virus infections/acquired immunodeficiency syndrome (HIV/AIDS) such as cobicistat, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir; as well as conivaptan for hyponatraemia and boceprevir to treat hepatitis), including grapefruit or grapefruit juice, should be avoided. If co-administration with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib should be reduced from 300 mg to 100 mg orally once daily for patients with GIST and from 200 mg to 50 mg orally once daily for patients with AdvSM (see section “Dosage and Administration” and “Warnings and Precautions”).

Strong and Moderate CYP3A Inducers

Co-administration of avapritinib with a strong CYP3A inducer (rifampicin) decreased avapritinib plasma concentrations and may result in reduced efficacy of avapritinib. Co-administration of rifampicin (600 mg once daily for 18 days) with a single 400 mg dose of avapritinib on Day 9 in healthy subjects reduced the avapritinib C_{max} by 74% and the $AUC_{0\text{-}inf}$ by 92% compared with a 400 mg dose of avapritinib administered alone.

Co-administration of avapritinib with strong and moderate CYP3A inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, fosphenytoin, primidone, bosentan, efavirenz, etravirine, modafinil, dabrafenib, nafcillin or *Hypericum perforatum*, also known as St. John’s wort) should be avoided.

Effect of acid-reducing agents on avapritinib

No clinical drug-drug interaction studies have been conducted. Based on population pharmacokinetic analyses for patients with GIST and AdvSM taking gastric acid–reducing agents, the effect of gastric acid–reducing agents on the bioavailability of avapritinib is not clinically significant.

Other interactions

In vitro, avapritinib is not a substrate of P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K or BSEP at clinically relevant concentrations.

Based on *in-vitro* data, clinical drug-drug interactions are unlikely to occur as a result of avapritinib-mediated inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6 at clinically relevant concentrations.

In vitro, avapritinib did not induce CYP1A2 or CYP2B6 at clinically relevant concentrations.

Effect of avapritinib on other active substances

CYP3A substrates

In-vitro studies have demonstrated that avapritinib is a time-dependent inhibitor of CYP3A. Therefore, avapritinib may have the potential to increase plasma concentrations of co-administered medicinal products that are substrates of CYP3A.

In-vitro studies have indicated that avapritinib is an inducer of CYP3A. Therefore, avapritinib may have the potential to reduce plasma concentrations of co-administered medicinal products that are substrates of CYP3A.

Caution must be exercised in the co-administration of avapritinib with CYP3A substrates with a narrow therapeutic index, as their plasma concentrations may be altered.

Transporter substrates

Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP *in vitro*. Therefore, avapritinib has the potential to alter concentrations of co-administered substrates of these transporters.

In vitro avapritinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 at clinically relevant concentrations.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be informed that avapritinib may cause fetal harm (see section “Preclinical data”).

The pregnancy status of women of childbearing potential must be verified prior to initiating AYVAKYT treatment.

Women of childbearing potential must use an effective method of contraception during treatment and for 6 weeks after the last dose of AYVAKYT.

Patients must be advised to contact their doctor immediately if they become pregnant, or if pregnancy is suspected, while taking AYVAKYT.

Men with female partners of childbearing potential should be instructed to use an effective method of contraception during treatment with AYVAKYT and for 6 weeks after the last dose.

Pregnancy

There are currently no data from the use of avapritinib in pregnant women. Studies in animals have shown reproductive toxicity (see section *"Preclinical data"*).

AYVAKYT is not recommended during pregnancy and in women of childbearing potential not using contraception.

If AYVAKYT is used during pregnancy or if the patient becomes pregnant while taking AYVAKYT, the patient must be advised of the potential risk to the fetus.

Lactation

It is not known whether avapritinib/metabolites are excreted in human milk.

A risk to the newborn infant/child cannot be ruled out.

Breast-feeding must be interrupted during treatment with AYVAKYT and for 2 weeks following the final dose.

Fertility

Females

Based on findings from animal studies, AYVAKYT may adversely affect early embryogenesis in humans (see preclinical data).

Males

Based on findings from animal studies, AYVAKYT may impair spermatogenesis.

Effects on ability to drive and use machines

No studies have been conducted on the effects on the ability to drive and operate machines. However, AYVAKYT may cause adverse reactions such as cognitive effects that may influence the ability to drive and use machines. Patients should be made aware of the potential for adverse reactions that affect their ability to concentrate and react. Patients are advised not to drive a car or operate machinery if they experience such adverse reactions.

Undesirable effects

Summary of the safety profile

The safety database includes a total of 610 patients with GIST (all doses), of whom 525 patients received avapritinib at a starting dose of 300 mg, as well as 193 patients enrolled in studies for AdvSM (all doses), of whom 126 patients received avapritinib at a starting dose of 200 mg (see section “Properties/Effects”).

Unresectable or metastatic GIST

The most common adverse reactions of any grade during treatment with AYVAKYT at a starting dose of 300 mg were anaemia (54%), nausea (48%), fatigue (45%), diarrhoea (33%), periorbital oedema (32%), vomiting (28%), facial oedema (28%), elevated serum bilirubin (28%), decreased appetite (27%), peripheral oedema (26%), increased lacrimation (22%) and abdominal pain (22%).

Serious adverse reactions occurred in 53% of GIST patients receiving avapritinib at a starting dose of 300 mg. The most common serious adverse reactions during treatment with avapritinib were anaemia (11%), abdominal pain (4%), vomiting (2%), gastrointestinal haemorrhage (2%) and sepsis (2%).

The most common adverse reactions in GIST patients receiving avapritinib at a starting dose of 300 mg leading to permanent treatment discontinuation were anaemia and fatigue (≥1% each). Adverse reactions leading to a dose reduction included anaemia, fatigue, reduced neutrophil count, elevated serum bilirubin, memory impairment, cognitive disorders, periorbital oedema, nausea and facial oedema.

In GIST patients treated at a starting dose of 300 mg, 17.7% had adverse reactions leading to permanent treatment discontinuation. The most common adverse reactions, occurring in ≥1% of the patients, leading to treatment discontinuation included: anaemia (2.1%) and fatigue (1.1%). Adverse reactions leading to a dose reduction occurred in 53.7% and the most common (≥1%) included anaemia, reduced neutrophil count/neutropenia, fatigue, elevated serum bilirubin/hyperbilirubinaemia, memory impairment, cognitive disorders, facial oedema, periorbital oedema, nausea, reduced white blood cell count, pleural effusion, peripheral oedema, hypophosphataemia and hypokalaemia.

Advanced systemic mastocytosis

The most common adverse reactions of any grade during treatment with AYVAKYT at a starting dose of 200 mg were peripheral oedema (43%), anaemia (40%), periorbital oedema (40%), thrombocytopenia (40%), diarrhoea (28%) and nausea (24%).

Serious adverse reactions occurred in 38% of patients receiving avapritinib at a starting dose of 200 mg once daily. The most common serious adverse reactions during treatment with avapritinib were subdural haematoma (3%), anaemia (3%) and ascites (2%).

In AdvSM patients treated at 200 mg, 18.3% had adverse reactions leading to permanent treatment discontinuation. The most common adverse reactions, occurring in ≥1% and leading to treatment discontinuation, included: thrombocytopenia and subdural haematoma (2.4% each). Adverse reactions leading to a dose reduction occurred in 72.2% of cases and the most common (≥2%) included thrombocytopenia/reduced platelet count, neutropenia/reduced neutrophil count, periorbital oedema, peripheral oedema, cognitive disorder, anaemia, fatigue and elevated serum alkaline phosphatase.

Tabulated list of adverse reactions

Adverse reactions that were reported in clinical studies in patients with GIST are listed below. For patients with AdvSM, adverse reactions that were reported in clinical studies are listed below.

Frequencies are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Unresectable or metastatic GIST

Infections and infestations
Common: Urinary tract infection, conjunctivitis, pneumonia (including lower respiratory tract infection, lung infection, *Escherichia coli* pneumonia), sepsis, nasopharyngitis, influenza, oral candidiasis, bronchitis, *Herpes zoster*, dental abscess, viral infection.
Uncommon: Candida infection, gastroenteritis, sinusitis, bacteraemia, infection, peritonitis, catheter site infection, *Clostridium difficile* colitis, device-related infection, eye infection, viral gastroenteritis, gingivitis, oral fungal infection, vaginal infection, wound infection.

Neoplasms benign, malignant, and unspecified (including cysts and polyps)
Common: Tumour haemorrhage.

Blood and lymphatic system disorders
Very common: Anaemia (including iron deficiency anaemia, reduced haematocrit, reduced haemoglobin, reduced red blood cell count) (54.3%), neutropenia (including reduced neutrophil count) (18.1%), leucopenia (including reduced neutrophil count) (15.2%), thrombocytopenia (including reduced platelet count) (10.1%).
Common: Lymphopenia (including reduced lymphocyte count).
Uncommon: Leukocytosis (including reduced neutrophil count), macrocytic anaemia, febrile neutropenia, granulocytopenia.

Endocrine disorders
Uncommon: Hypothyroidism.

Metabolism and nutrition disorders
Very common: Decreased appetite (26.9%), hypokalaemia (including reduced serum potassium) (16.8%), hypophosphataemia (including reduced serum phosphate) (12.0%).
Common: Hypomagnesaemia (including reduced serum magnesium), hypoalbuminaemia (including reduced serum albumin, hypoproteinaemia), hypocalcaemia, hyponatraemia (including reduced serum sodium), dehydration, hyperglycaemia, hyperuricaemia (including elevated serum uric acid), hypoglycaemia.
Uncommon: Hypernatraemia, hypochloraemia (including reduced serum chloride), folate deficiency, hypercalcaemia (including elevated serum calcium), hyperkalaemia, hyperphosphataemia (including elevated serum phosphate), increased appetite, fluid overload, gout, malnutrition, metabolic acidosis, vitamin B12 deficiency, vitamin D deficiency.

Psychiatric disorders
Very common: Insomnia (10.5%).
Common: Depression (including depressed mood, major depression), anxiety disorders, confusional state, sleep disorder, delirium, hallucination (including auditory hallucination, visual hallucination), altered mood.
Uncommon: Agitation, bradyphrenia, restlessness, apathy, mental disorder, personality change, affective disorder, disorientation, psychosis.

Nervous system disorders
Very common: Memory impairment (including amnesia, retrograde amnesia) (22.5%), dizziness (14.1%), headache (13.9%), effects on taste (including ageusia, dysgeusia) (13.9%), cognitive disorder (13.5%).
Common: Peripheral neuropathy (including dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy), mental impairment (including dementia, disturbance in attention, mental state changes), speech disorder (including dysarthria, slow speech, dysphonia), tremor, aphasia, intracranial haemorrhage (including subdural haematoma, cerebral haemorrhage), somnolence, balance disorder, transient ischaemic attack.
Uncommon: Encephalopathy, hypokinesia, sciatica, anosmia, lacunar infarction, myoclonus, post-herpetic neuralgia, restless legs syndrome, syncope.

Eye disorders
Very common: Increased lacrimation (21.5%).
Common: Dryness, blurred vision, conjunctival haemorrhage, photophobia, ocular icterus, eye pain, eye pruritus, ocular haemorrhage (including retinal haemorrhage, vitreous haemorrhage, eye haemorrhage).
Uncommon: Papilloedema, scleral disorder, visual impairment, blepharitis, cataract, eye irritation, ocular hyperaemia, retinal vein occlusion, scleral discoloration, scleral haemorrhage.

Ear and labyrinth disorders
Common: Vertigo, tinnitus.
Uncommon: Hearing impairment, ear congestion, earache.

Cardiac disorders
Common: Atrial fibrillation, palpitations, pericardial effusion, tachycardia.
Uncommon: Sinus bradycardia, heart failure, congestive heart failure, sinus tachycardia, supraventricular extrasystoles, ventricular arrhythmia, bradycardia, sinus arrhythmia, ventricular extrasystoles.

Vascular disorders
Common: Hypertension (including elevated blood pressure), hypotension, hot flush.
Uncommon: Deep vein thrombosis, flushing, peripheral coldness.

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea (including exertional dyspnoea) (14.1%).
Common: Cough (including productive cough, upper-airway cough syndrome), pleural effusion, upper respiratory tract infection, nasal congestion, epistaxis, rhinorrhoea (including rhinitis), oropharyngeal pain, hiccups.
Uncommon: Hypoxia, pneumonitis, pulmonary embolism, respiratory failure, chronic obstructive pulmonary disease, pulmonary oedema, sleep apnoea syndrome, snoring.

Gastrointestinal disorders
Very common: Nausea (48.2%), diarrhoea (32.6%), abdominal pain (including abdominal discomfort, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort) (31.6%), vomiting (including retching) (28.2%), gastro-oesophageal reflux disease (including dyspepsia) (17.9%), ascites (including abdominal bloating) (16.2%), constipation (15.0%).
Common: Gastrointestinal haemorrhage (including duodenal ulcer haemorrhage, gastric haemorrhage, gastritis haemorrhage, gastroduodenal haemorrhage, large bowel haemorrhage, lower gastrointestinal haemorrhage, melaena, rectal haemorrhage, small bowel haemorrhage, upper gastrointestinal haemorrhage), dryness (including dry lips, dry mouth), dysphagia, stomatitis, flatulence, gastritis, salivary hypersecretion, haemorrhoids, oesophagitis, colitis, enteritis, intra-abdominal haemorrhage.
Uncommon: Enterocolitis, faecal discoloration, gingival bleeding, peritoneal haemorrhage, proctalgia, tongue oedema (pool), toothache, chapped lips, bloody diarrhoea, eructation, gingival pain, haematochezia, intra-abdominal haematoma.

Hepatobiliary disorders
Very common: Hyperbilirubinaemia (including elevated conjugated bilirubin, elevated serum bilirubin) (33.0%).
Common: Jaundice, abnormal liver function.
Uncommon: Hepatic haemorrhage, cholangitis, hepatic haematoma, hepatocellular injury (pool), portal hypertension.

Skin and subcutaneous tissue disorders
Very common: Rash (dermatitis, erythematous rash, follicular rash, generalised rash, macular rash, maculopapular rash, morbilliform rash, papular rash, pruritic rash) (15.2%), hair colour changes (15.0%), alopecia (10.7%).
Common: Dryness, pruritus, erythema, night sweats, palmar-plantar erythrodysaesthesia syndrome, hyperhidrosis, photosensitivity reaction, eczema, skin discoloration, skin hypopigmentation.
Uncommon: Petechiae, purpura, blisters, angio-oedema, allergic dermatitis, hair texture abnormal, hyperkeratosis, nail discoloration, onychoclasis, skin disorder, urticaria.

Musculoskeletal and connective tissue disorders
Common: Back pain, myalgia, arthralgia, pain in the extremities, muscle cramps, flank pain, musculoskeletal chest pain, musculoskeletal pain, neck pain.
Uncommon: Arthritis, groin pain, musculoskeletal stiffness, osteopenia, spinal pain.

Renal and urinary disorders
Common: Elevated serum creatinine, acute kidney injury (including renal failure), haematuria (including blood in the urine, red blood cells in the urine, urine positive for red blood cells), pollakiuria, proteinuria (including protein in the urine), dysuria, urinary retention.
Uncommon: Micturition urgency, nephrolithiasis, hydronephrosis, leukocyturia.

Reproductive system and breast disorders
Common: Pelvic pain.
Uncommon: Sexual dysfunction, testicular oedema, testicular pain, vaginal haemorrhage.

General disorders and administration site conditions
Very common: Oedema (including conjunctival oedema, eye oedema, eye swelling, eyelid oedema, orbital oedema, periorbital oedema, lip swelling, swollen tongue, tongue oedema, facial oedema,

generalised oedema, peripheral oedema, swelling, fluid retention, laryngeal oedema, swollen face) (74.3%), fatigue (including asthenia, lethargy, muscle weakness) (54.1%), pyrexia (10.7%).
Common: Malaise, chills, asthenia (pool), feeling cold, general physical health deterioration, influenza-like illness, chest pain, mucosal inflammation, early satiety, pain.
Uncommon: Feeling abnormal, ribcage discomfort, joint swelling, non-cardiac chest pain, gait disturbance, hernia, hyperthermia (pool), hypothermia, local swelling.

Investigations
Very common: Elevated transaminases (including elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated gamma-glutamyltransferase) (16.6%), weight loss (12.8%).
Common: Weight gain, elevated serum creatine phosphokinase, prolonged QT in electrocardiogram, elevated serum alkaline phosphatase, elevated serum lactate dehydrogenase, elevated serum unconjugated bilirubin, elevated blood urea, prolonged activated partial thromboplastin time, increased fibrin D-dimer.
Uncommon: Increased amylase, ST-T change in the electrocardiogram, abnormal T wave in the electrocardiogram, increased International Normalised Ratio, elevated serum creatine, elevated C-reactive protein, reduced total protein, reduced urine output, reduced serum fibrinogen, increased serum fibrinogen, elevated lipase, occult blood in urine positive, prolonged prothrombin time, waist circumference increased.

Injury, poisoning and procedural complications
Common: Contusion, fall, post-procedural pain.
Uncommon: Haematoma, spinal fracture.

Advanced systemic mastocytosis

Infections and infestations
Common: Urinary tract infection, conjunctivitis, *Herpes zoster*, sinusitis, cellulitis, gastroenteritis, oral candidiasis, oral herpes, pneumonia (including lower respiratory tract infection, lung infection, *Escherichia coli* pneumonia), cystitis, diverticulitis, nasopharyngitis, respiratory tract infection.

Blood and lymphatic system disorders
Very common: Thrombocytopenia (including reduced platelet count) (50.0%), anaemia (including iron-deficiency anaemia, reduced haematocrit, reduced haemoglobin, reduced red blood cell count) (41.3%), neutropenia (including reduced neutrophil count) (25.4%), leucopenia (including reduced neutrophil count) (10.3%).
Common: Increased tendency to bruise, haemorrhagic diathesis, leucocytosis (including reduced neutrophil count), lymphopenia (including reduced lymphocyte count).

Metabolism and nutrition disorders
Common: Hypokalaemia (including reduced serum potassium), decreased appetite, hyperuricaemia (including elevated serum uric acid), hypophosphataemia (including reduced serum phosphate), hypomagnesaemia (including reduced serum magnesium), dehydration, hyperphosphataemia (including elevated serum phosphate),hypocalcaemia, fluid overload, gout, hyperglycaemia, hyperkalaemia, hypertriglyceridaemia (including elevated serum triglycerides), hypoalbuminaemia (including reduced serum albumin, hypoproteinaemia).

Psychiatric disorders
Common: Insomnia, depression (including depressed mood, major depression), confusional state, irritability, reduced libido, sleep disorder.
Uncommon: Delirium, disorientation.

Nervous system disorders
Very common: Effects on taste (including ageusia, dysgeusia) (18.3%), headache (15.1%), cognitive disorder (11.9%), dizziness (11.9%).

Common: Peripheral neuropathy (including dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy), memory impairment ((including amnesia, retrograde amnesia), intracranial haemorrhage (including subdural haematoma, cerebral haemorrhage), mental impairment (including dementia, disturbance in attention, mental state changes), speech disorder (including dysarthria, slow speech, dysphonia), restless legs syndrome, syncope, aphasia, balance disorder, orthostatic dizziness, Parkinson's disease, tremor.
Uncommon: Somnolence.

Eye disorders
Common: Increased lacrimation, ocular haemorrhage (pool), conjunctival haemorrhage, blurred vision, dryness (pool), erythema of eyelid, ocular hyperaemia, vitreous floaters.

Ear and labyrinth disorders
C*ommon:* Vertigo, deafness.

Cardiac disorders
Common: Heart failure.

Vascular disorders
Common: Flushing, hypertension (pool), hypotension, hot flush, haemorrhage.

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis (12.7%), dyspnoea (including exertional dyspnoea) (11.9%).
Common: Pleural effusion, upper respiratory tract infection, cough (including productive cough, upper-airway cough syndrome), haemoptysis, nasal congestion, oropharyngeal pain, pneumothorax, pulmonary hypertension, pulmonary oedema, rhinorrhoea (including rhinitis), throat irritation.

Gastrointestinal disorders
Very common: Diarrhoea (27.8%), nausea (23.8%), vomiting (including retching) (19.0%), abdominal pain (including abdominal discomfort, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort) (15.1%), constipation (13.5%), gastro-oesophageal reflux disease (including dyspepsia) (13.5%), ascites (including abdominal bloating) (11.9%).
Common: Dryness (including dry lips, dry mouth), gastrointestinal haemorrhage (including duodenal ulcer haemorrhage, gastric haemorrhage, gastritis haemorrhage, gastroduodenal haemorrhage, large bowel haemorrhage, lower gastrointestinal haemorrhage, melaena, rectal haemorrhage, small bowel haemorrhage, upper gastrointestinal haemorrhage), inguinal hernia, dental caries, intra-abdominal haemorrhage, salivary hypersecretion.

Hepatobiliary disorders
Very common: Hyperbilirubinaemia (including elevated conjugated bilirubin, elevated serum bilirubin) (15.1%).
Common: Cholelithiasis.

Skin and subcutaneous tissue disorders
Very common: Hair colour changes (15.1%), rash (including dermatitis, erythematous rash, follicular rash, generalised rash, macular rash, maculopapular rash, morbilliform rash, papular rash, pruritic rash) (15.1%), pruritus (12.7%)
Common: Alopecia, night sweats, petechiae, hyperhidrosis, generalised pruritus, blood blister, contact dermatitis, dryness, erythema, skin haemorrhage, skin lesion.

Musculoskeletal and connective tissue disorders
Very common: Arthralgia (12.7%).
Common: Pain in the extremities, bone pain, back pain, muscle cramps, myalgia, musculoskeletal pain, musculoskeletal stiffness, joint stiffness, neck pain.

Renal and urinary disorders
Very common: Elevated serum creatinine (11.9%).
Common: Acute kidney injury (including renal failure), chronic kidney disease, haematuria (including blood in the urine, red blood cells in the urine, urine positive for red blood cells), dysuria, nephrolithiasis, pollakiuria, urinary incontinence.

Reproductive system and breast disorders
Common: Scrotal oedema.

General disorders and administration site conditions
Very common: Oedema (including conjunctival oedema, eye oedema, eye swelling, eyelid oedema, orbital oedema, periorbital oedema, lip swelling, swollen tongue, tongue oedema, facial oedema, generalised oedema, peripheral oedema, swelling, fluid retention, laryngeal oedema, swollen face) (77.8%), fatigue (including asthenia, lethargy, muscle weakness) (24.6%).
Common: Pyrexia, pain, non-cardiac chest pain, gait disturbance, feeling abnormal, cyst, joint swelling, malaise.

Investigations
Very common: Elevated serum alkaline phosphatase (12.7%), elevated transaminases (including elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated gamma-glutamyltransferase) (11.1%), weight gain (10.3%).
Common: Elevated serum lactate dehydrogenase, heart murmur, abnormal breath sounds, prolonged QT in the electrocardiogram, increased reticulocyte count.

Injury, poisoning and procedural complications
Common: Fall, contusion, haematoma, laceration, post procedural haemorrhage, procedural pain, skin abrasion, traumatic haematoma.

Description of selected adverse reactions

Intracranial haemorrhage

Unresectable or metastatic GIST

Intracranial haemorrhage occurred in 13 (2.1%) of the 610 patients with GIST (all doses) and in 12 (2.3%) of the 525 patients with GIST who received AYVAKYT at a starting dose of 300 mg once daily (see section "*Warnings and precautions"*).

Events of intracranial haemorrhage (all grades) occurred in a range from 8 weeks to 84 weeks after initiating AYVAKYT at a starting dose of 300 mg once daily, with a median time to onset of 19 weeks. The median time to improvement and resolution was 2 weeks for intracranial haemorrhage of Grade ≥2.

Advanced systemic mastocytosis

Intracranial haemorrhage occurred in a total (regardless of causality) of 4 (3.2%) of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg once daily, regardless of platelet count prior to initiation of therapy. In 3 of these 4 patients, the event was assessed as related to avapritinib (2.4%). The risk of intracranial haemorrhage is higher in patients with platelet counts <50 x 10^9/L. Intracranial haemorrhage occurred in a total (regardless of causality) of 3 (2.5%) of the

121 patients with AdvSM who received a starting dose of 200 mg once daily and had a platelet count ≥50 x 10^9/L prior to initiation of therapy (see section *"Warnings and precautions"*). In 2 of the 3 patients, the event was assessed as related to avapritinib (1.7%). Of 126 patients treated with the recommended starting dose of 200 mg once daily, 5 had platelet counts <50 x 10^9/L prior to initiation of therapy, of whom one patient experienced an intracranial haemorrhage.

Events of intracranial haemorrhage (all grades) occurred in a range from 12.0 weeks to 15.0 weeks after initiating avapritinib, with a median time to onset of 12.4 weeks.

In clinical studies with avapritinib, the incidence of intracranial haemorrhage was higher in AdvSM patients who received a starting dose of ≥300 mg once daily, as compared with patients who received the recommended starting dose of 200 mg once daily. Of the 50 patients who received a starting dose of ≥300 mg once daily, 8 (16.0%) experienced an event of intracranial bleeding (regardless of causality), irrespective of platelet count prior to initiation of therapy. In 6 of the 8 patients, the event was assessed as related to avapritinib (12.0%). Of these 50 patients, 7 had platelet counts <50 x 10^9/L prior to initiation of therapy, of whom 4 patients experienced intracranial haemorrhages, which were assessed as related to avapritinib in 3 of the 4 cases. Four of 43 patients with platelet counts ≥50 x 10^9/L prior to initiation of therapy experienced intracranial haemorrhages, which were assessed as related to avapritinib in 3 of the 4 cases.

Fatal events of intracranial haemorrhage occurred in less than 1% of patients with AdvSM (all doses).

The maximum dose for patients with AdvSM must not exceed 200 mg once daily.

Cognitive effects

A broad spectrum of cognitive effects that are generally reversible can occur in patients receiving AYVAKYT. The most common cognitive effects in clinical studies were memory impairment, cognitive disorders, confusional states, amnesia, somnolence, speech disorders, delirium and encephalopathy.

Cognitive effects were managed with dose interruption and/or reduction, and 2.6% led to permanent discontinuation of AYVAKYT treatment.

Unresectable or metastatic GIST

Cognitive effects occurred in 262 (43%) of the 610 patients with GIST (all doses) and in 216 (41%) of the 525 patients with GIST who received AYVAKYT at a starting dose of 300 mg once daily (see section "*Warnings and precautions"*). In the patients who had an event (any grade), the median time to onset was 8 weeks (0.1-81.6).

Most cognitive effects were Grade 1, with Grade ≥2 occurring in 16% of 525 patients. Among patients who experienced a cognitive effect of Grade ≥2 (impacting activities of daily living) the median time to improvement was 8 weeks.

Memory impairment occurred in 19% of patients, <1% of these events were Grade 3. Cognitive disorder occurred in 14% of patients; <1% of these events were Grade 3. Confusional state occurred in 5% of patients; <1% of these events were Grade 3. Amnesia occurred in 3% of patients; <1% of these events were Grade 3. Somnolence occurred in 2% of patients, with no Grade 3 events. Mental impairment occurred in 1% of patients, <1% of these events were Grade 3. Speech disorders occurred in 1% of patients, with no Grade 3 events. Delirium occurred in 1% of patients, <1% of these events were Grade 3. The other events occurred in less than 1% of patients. Serious adverse reactions of a cognitive nature were reported for 24 of 610 (3.9%) of the GIST patients (all doses); 15 of these were observed in patients from among the 525 (2.9%) patients in the GIST group receiving a starting dose of 300 mg once daily.

Overall, 1.9% of patients required permanent discontinuation of AYVAKYT at a starting dose of 300 mg daily because of a cognitive effect.

Cognitive effects occurred in 45% of the patients aged ≥65 years receiving a starting dose of 300 mg once daily.

Advanced systemic mastocytosis

Cognitive effects occurred in 59 (31%) of the 193 patients with AdvSM (all doses) and in 24 (19%) of the 126 patients with AdvSM who received AYVAKYT at a starting dose of 200 mg (see section "*Warnings and precautions"*). In the patients with AdvSM treated with 200 mg who had an event (any grade), the median time to onset was 12 weeks (range: 0.1 weeks to 108.1 weeks).

Most cognitive effects were Grade 1, with Grade ≥2 occurring in 5% of 126 patients treated with a starting dose of 200 mg once daily. Among patients who experienced a cognitive effect of Grade ≥2 (impacting activities of daily living) the median time to improvement was 6 weeks.

For patients with AdvSM treated with a starting dose of 200 mg once daily, cognitive disorders occurred in 12% of patients, memory impairment occurred in 6% of patients and confusional state occurred in 2% of patients. None of these events was Grade 4.

Serious cognitive adverse reactions were reported for 5 of 193 (2.6%) AdvSM patients (all doses), and for 1 of 126 patients (<1%) in the AdvSM group receiving a starting dose of 200 mg once daily.

Overall, 2.6% of AdvSM patients (all doses) and 1.6% of AdvSM patients receiving a starting dose of 200 mg once daily required permanent discontinuation of AYVAKYT because of a cognitive adverse reaction. 6.3% and 7.1% of patients receiving a starting dose of 200 mg once daily required a dose interruption and dose reduction, respectively.

Cognitive effects occurred in 21% of the patients aged ≥65 years receiving a starting dose of 200 mg once daily.

Elderly

Unresectable or metastatic GIST"

In patients treated with a starting dose of 300 mg once daily in the NAVIGATOR and VOYAGER studies (N=525) (see section “Properties/Effects”), 38% of patients were 65 years of age and older, and 9% were 75 years of age and older. Compared with younger patients (<65), more patients aged ≥65 years reported adverse reactions that led to dose reductions (57% versus 48%) and dose discontinuation (2.5% versus 0.34%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared with younger patients (66% versus 53%).

Advanced systemic mastocytosis"

In patients treated at a starting dose of 200 mg once daily in the EXPLORER and PATHFINDER studies (N=126), 63% of patients were 65 years of age or older, and 21% were 75 years of age and older. Compared with younger patients (<65), more patients aged ≥65 years reported adverse reactions that led to dose reductions (62% versus 73%). A similar proportion of patients reported adverse reactions that led to dose discontinuation (9% versus 6%). The types of adverse reactions were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions (63.3%) compared with younger patients (53.2%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS (Electronic Vigilance System) portal. You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported in clinical trials with avapritinib. The maximum dose of AYVAKYT studied clinically is 600 mg orally once daily. Adverse reactions observed at this dose were consistent with the safety profile at 300 mg once daily (see undesirable effects).'

Properties/Effects

ATC code

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitors, ATC code L01EX18

Mechanism of action

Avapritinib is a Type 1 kinase inhibitor that has demonstrated *in-vitro* biochemical activity on the PDGFRA D842V and KIT D816V mutants associated with resistance to imatinib, sunitinib and regorafenib with half maximum inhibitory concentrations (IC_{50}) of 0.24 nM and 0.27 nM, respectively, and greater potency against clinically relevant KIT exon 11, KIT exon 11/17 and KIT exon 17 mutants than against the KIT wild-type enzyme.

In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V with an IC_{50} of 4 nM and 30 nM, respectively. In cellular assays, avapritinib inhibited proliferation in KIT mutant cell lines, including a murine mastocytoma cell line and a human mast cell leukaemia cell line. Avapritinib also showed growth inhibitory activity in a xenograft model of murine mastocytoma with KIT exon 17 mutation.

Pharmacodynamics

Exposure-Response Relationships

Based on the data from four clinicals trials conducted in patients with advanced malignancies and systemic mastocytosis, including NAVIGATOR, EXPLORER, and PATHFINDER, higher exposure was associated with increased risk of Grade ≥3 adverse effects, any Grade pooled cognitive adverse effects, Grade ≥2 pooled cognitive adverse effects, and Grade ≥2 pooled oedema adverse effects over the dose range of 30 mg to 400 mg (0.1 to 1.33 times the recommended dose for GIST and 0.15 to 2 times the recommended dose for AdvSM) once daily.'

Based on exposure and efficacy data from EXPLORER and PATHFINDER (n=84), higher avapritinib exposure was associated with faster time to response over the dose range of 30 mg to 400 mg (0.15 to 2 times the recommended dose for AdvSM) once daily.

Cardiac Electrophysiology

The effect of AYVAKYT on the QTc interval was evaluated in the context of the open-label, single-arm NAVIGATOR study in 27 patients with GIST who were administered a dose of 300 mg or 400 mg (1.33 times the recommended GIST dose of 300 mg) once daily (see “Clinical efficacy”). No large mean increase in QTc (i.e. >20 ms) was detected at the mean steady state maximum concentration (Cmax) of 899 ng/mL (see “Warnings and Precautions”).

Clinical efficacy

Gastrointestinal Stromal Tumours (GIST) with a PDGFRA-D842V-mutation

The efficacy of AYVAKYT was investigated in NAVIGATOR, a multicentre, single-arm, open-label clinical trial. Eligible patients were required to have a confirmed diagnosis of GIST and an ECOG performance status (PS) of 0 to 2. The study initially enrolled patients at a starting dose of 400 mg once daily, which was later reduced to the recommended dose of 300 mg once daily due to toxicity. Patients received AYVAKYT until disease progression or unacceptable toxicity. A total of 28 patients with PDGFRA-D842V-mutated unresectable or metastatic GIST were treated with the recommended starting dose of 300 mg once daily in the NAVIGATOR trial. PDGFRA- D842V mutations were identified by local or central assessment with a PCR- or NGS-based assay. In 71% of patients who had the PDGFRA-D842V mutation, the dose was reduced to 200 mg or 100 mg once daily in the course of treatment.

Baseline demographic data and disease characteristics were: median age of 64 years (range: 29 to 90 years), 66% male, 66% white, ECOG PS of 0-2 (61% and 5% of patients had ECOG status 1 and 2, respectively), 97% had metastatic disease, the largest target lesion was >5 cm in 58%, 90% had previous surgical resection, and the median number of prior lines of tyrosine kinase inhibitors was 1 (range: 0 to 5).

The primary efficacy endpoint was the overall response rate (ORR) based on disease assessment by independent radiological review using modified RECIST v1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressive growth of new tumour nodules within a pre-existing tumour mass was regarded as progression. An additional efficacy outcome measure was duration of response (DOR) and progression-free survival (PFS).

The data represent a median duration of follow-up of 33 months across all patients with PDGFRA D842V mutations who were alive. The median OS had not been reached with 68% of patients still alive. The median progression-free survival was 24 months.

Efficacy results in patients with GIST harbouring PDGFRA D842V mutations treated in NAVIGATOR with the recommended starting dose of 300 mg once daily are summarised in Table 3.

Table 3. Efficacy Results for Patients with GIST Harbouring PDGFRA D842V Mutation in NAVIGATOR treated with the recommended starting dose of 300 mg once daily (primary analysis, data cut-off date 16 November 2018)

Efficacy Parameter	**N = 28**
mRECIST 1.1 ORR[1], (%) (95% CI) **CR** **PR**	92.9 (76.5; 99.1) 3.6 89.3

Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; 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; ORR = overall response rate; PR = partial response
[1] ORR is defined as patients who achieved a CR or PR (CR + PR).

The median duration of response (DOR) was 22.1 months (14.1; NE).

There was no apparent difference in ORR between patients receiving 300 mg daily (N=28) compared with those receiving 400 mg daily (N=10).

Based on results from the phase 3 study VOYAGER in a subset of 13 patients with PDGFRA-D842V mutations, a partial response was reported in 3 out of 7 patients in the avapritinib group (43% ORR) and none of the 6 patients in the regorafenib group (0% ORR). The median PFS was not estimable in patients with PDGFRA D842V mutations randomised to avapritinib (95% CI: 9.7; NE) compared with 4.5 months in patients receiving regorafenib (95% CI: 1.7; NE).

Advanced Systemic Mastocytosis (AdvSM)

The efficacy of AYVAKYT was investigated in PATHFINDER, a multicentre, single-arm, open-label Phase 2 clinical study. Eligible patients had to have a confirmed diagnosis of AdvSM according to the World Health Organization (WHO) and an ECOG performance status (PS) of 0 to 3. Patients with high- and very-high-risk AHN, such as AML or high-risk MDS, and Philadelphia chromosome-positive malignancies were excluded. Of the 107 patients enrolled in the study, 105 patients were treated at a starting dose of 200 mg orally once daily and the treatment was given until disease progression or unacceptable toxicity. Palliative drugs and supportive measures were allowed. The primary efficacy analysis was limited to patients deemed evaluable according to the modified criteria of the international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (mIWG-MRT-ECNM), who received at least 1 dose of AYVAKYT, had at least 2 post-baseline bone marrow assessments, and had taken part in the study for at least 24 weeks or had an end of study visit. The primary efficacy endpoint for AYVAKYT in the treatment of AdvSM was overall response rate (ORR) according to the mIWG-MRT-ECNM criteria, as adjudicated by the central committee. Additional efficacy outcome measures were duration of response (DOR), time to response, PFS and overall survival (OS). In the PATHFINDER study, a total, of 47 patients found to have a response and who received at least one prior systemic therapy were

treated with the recommended starting dose of 200 mg once daily and had a median duration of treatment of 11 months with 48.6% of patients treated for longer than one year.

The median duration of follow-up for these patients was 14.6 months (95% confidence interval: 11.2; 17.8).

The study population characteristics were: median age 69 years (range: 31 to 86 years), 70% were male, 92% were white, 66% had an ECOG PS of 0-1, 34% had an ECOG PS of 2-3, 36% had ongoing corticosteroid therapy for AdvSM at baseline, 65% had prior antineoplastic therapy, 84% of patients that had prior antineoplastic therapy had received midostaurin, and 89% had a D816V mutation. The median bone marrow mast cell infiltrate was 70%, the median serum tryptase level was 325 ng/mL, and the median KIT D816V mutant allele fraction was 26.2%.

Efficacy results for response-evaluable patients with AdvSM enrolled in PATHFINDER who received at least one prior systemic therapy and were treated with avapritinib at a starting dose of 200 mg once daily are summarised in Table 4.

Table 4. Efficacy Results for response-evaluable Patients with AdvSM in PATHFINDER who received at least one prior systemic therapy treated with avapritinib at a starting dose of 200 mg once daily (primary analysis, data cut-off date 20 April 2021)

	All evaluable patients	ASM	SM-AHN	MCL
Overall Response Rate[1], % per modified IWG-MRT-ECNM (95% CI[2])	**N=47** 51.1 (36.1, 65.9)	**N=8** 62.5 (24.5, 91.5)	**N=29** 55.2 (35.7, 73.6)	**N=10** 30 (6.7, 65.2)
CR, %	2	0	3	0
CRh, %	9	25	7	0
PR, %	40	38	45	30
CI, %	9	0	10	10

Abbreviations: CI = Clinical Improvement, CI[2] = confidence interval; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; PR = partial remission, SD = stable disease

[1] Overall Response Rate (ORR) as per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh or PR; PR (CR + CRh + PR)

For all response-evaluable patients treated with avapritinib at a starting dose of 200 mg once daily, the median duration of response was not estimable (NE) (95% confidence interval: NE; NE) and the median time to response was 1.9 months.

For all response-evaluable patients who had received at least one prior systemic therapy and were treated with avapritinib at a starting dose of 200 mg once daily (N = 47), the median progression-free survival (PFS) was NE (95% confidence interval: 17.5; NE). The median overall survival (OS) for evaluable patients treated with avapritinib at a starting dose of 200 mg once daily (N = 105) was also NE (95% confidence interval: 17.5; NE).

In a supportive, multicentre, single-arm, open-label, phase 1 study (EXPLORER), the ORR according to mIWG-MRI-ECNM criteria for 11 patients with AdvSM who had received at least one prior systemic therapy and received a starting dose of 200 mg avapritinib once daily was 73% (95% confidence interval: 39; 94).

Elderly patients

Of the 204 patients with unresectable or metastatic GIST who received AYVAKYT in NAVIGATOR, 40% were 65 years or older, while 6% were 75 years and older. Of the 131 patients with AdvSM who received AYVAKYT in EXPLORER and in PATHFINDER, 62% were 65 years or older, while 21% were 75 years and older. No overall differences in efficacy were observed between these patients and younger adult patients.

Pharmacokinetics

Avapritinib C_{max} and AUC increased dose-proportionally in the dose range of 30 mg to 400 mg once daily in patients with GIST (0.1 to 1.33 times the recommended 300 mg dose). Avapritinib C_{max} and AUC increased dose-proportionally in the dose range of 200 mg to 400 mg once daily in patients with AdvSM (1 to 2 times the recommended 200 mg dose). Steady state concentration of avapritinib was reached within 15 days following daily dosing. Steady state pharmacokinetic parameters as per the recommended dosing regimen are described in Table 5.

Table 5. Steady State Pharmacokinetic Parameters of AYVAKYT Following a Different Dosing Regimen

Dosing Regimen	**200 mg once daily (AdvSM)**	**300 mg once daily (GIST)**
Geometric Mean (CV%) steady state C_{max} (ng/mL)	377 (62%, n=18)	813 (52%, n=110)
Geometric Mean (CV%) steady state $AUC_{0\text{-}24h}$ (h•ng/mL)	6600 (54%, n=16)	15,400 (48%, n=110)
Mean accumulation ratio	6.41 (n=9)	3.82 (n=34)

Absorption

The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of avapritinib 30 mg to 400 mg in patients with GIST and single doses of avapritinib 30 mg to 300 mg in patients with AdvSM.[,]

Effect of Food

The C_{max} of avapritinib was increased by 59% and the AUC_{0-INF} was increased by 29% when AYVAKYT was taken with a high-calorie, high-fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to those in the fasted state.

Distribution

The mean (CV%) apparent volume of distribution of avapritinib is 1310 L (43%) at 300 mg for patients with GIST, and 1900 L (43%) at 200 mg in patients with AdvSM. *In-vitro* protein binding of avapritinib is 98.8% and is independent of concentration. The blood-to-plasma ratio is 0.95.

Metabolism

In vitro, avapritinib is primarily metabolised by CYP3A4, CYP3A5 and to a lesser extent by CYP2C9. Following a single oral dose of approximately 310 mg of radiolabelled avapritinib in healthy subjects, unchanged avapritinib (49%) and its metabolites M690 (hydroxy glucuronide; 35%) and M499 (oxidative deamination; 14%) were the major circulating compounds. The formation of the glucuronide M690 is catalysed mainly by UGT1A3. Following oral administration of AYVAKYT 300 mg once daily in patients, the steady state AUC of M499 is approximately 80% of the AUC of avapritinib. M499 is not likely to contribute to efficacy at the recommended dose of avapritinib.

Elimination

The mean plasma elimination half-life of avapritinib was 32 hours to 57 hours following single doses of 30 mg to 400 mg avapritinib (0.1 to 1.33 times the recommended 300 mg dose) in patients with GIST, and 20 hours to 39 hours following single doses of 30 mg to 400 mg avrapritinib (0.15 to 2 times the recommended 200 mg dose) in patients with AdvSM. The steady state mean (CV%) apparent oral clearance of avapritinib is 21.8 L/h (12%) at 300 mg for patients with GIST, and 40.3 L/h (86%) at 200 mg in patients with AdvSM.[,]

Excretion

Following a single oral dose of approximately 310 mg of radiolabelled avapritinib in healthy subjects, 70% of the radioactive dose was recovered in faeces (11% unchanged) and 18% in urine (0.23% unchanged).

Kinetics in specific patient groups

No clinically meaningful differences in the pharmacokinetics of avapritinib were observed based on age (18 to 90 years), sex, race (White, Black, or Asian) or body weight (39.5 to 156.3 kg).

Patients with impaired renal function

No clinically relevant differences were observed in the pharmacokinetics of avapritinib in patients with mild or moderate (CLcr 30 to 89 mL/min estimated by Cockcroft-Gault) renal impairment. The effect of severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (CLcr <15 mL/min) on the pharmacokinetics of avapritinib is unknown.

Patients with impaired hepatic function

No clinically relevant differences were observed in the pharmacokinetics of avapritinib in patients with mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of avapritinib is unknown.

Preclinical data

Repeated dose toxicity

In repeat dose toxicology studies, administration of avapritinib to rats and dogs for up to 3 months resulted in tremors at doses greater than or equal to 30 mg/kg/day (approximately 1.5 times the human exposure based on AUC at the 300 mg dose). Haemorrhage in the brain and spinal cord and choroid plexus oedema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 0.4 times the human exposure based on AUC at the 300 mg dose), but were not observed in a 9-month study at 5 mg/kg/day.

Genotoxicity

Avapritinib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test). Avapritinib was positive in the in vitro chromosome aberration test in human peripheral blood lymphocytes but negative in the in vivo rat bone marrow micronucleus tests, overall non-genotoxic.

Carcinogenicity

Carcinogenicity studies with avapritinib have not been conducted.

Reproductive toxicity

Avapritinib may impair spermatogenesis and adversely affect early embryogenesis. Reduction in sperm production and testicular weight was observed in male rats and hypospermatogenesis in dogs

administered avapritinib at exposure of 1 to 5 times and 1 time the 200 mg human dose, respectively. There were no direct effects on fertility in rats of either sex. Avapritinib partitioned into seminal fluids at up to 0.5 times the concentration found in human plasma at 200 mg. In female rats there was an increase in pre-implantation loss at the dose of 20 mg/kg/day (12.6 times the human exposure at 200 mg) and in early resorptions at doses ≥10 mg/kg (6.3 times the human exposure at 200 mg) with an overall decrease in viable embryos at doses ≥10 mg/kg. Cystic degeneration of corpora lutea and vaginal mucification were also observed in female rats administered avapritinib for up to 6 months at doses greater than or equal to 3 mg/kg per day (approximately 3.0 times the human exposure based on AUC at the 200 mg dose).

Infertility

Females

In repeat dose toxicology studies of 6 months in rats, cystic degeneration of corpora lutea was not reversible within a two-month recovery period. Vaginal mucification was observed but was not present at the end of recovery period. In a fertility study, females presented an increase in pre-implantation loss and in early resorptions with an overall decrease in viable embryos.

Males

There were no direct effects on fertility in rats. In repeat dose toxicology studies of 9 months in dogs, hypospermatogenesis was observed and it was not reversible within a two-month recovery period. In a fertility study in rats, a reduction in sperm production and testicular weight was observed. The reversibility of the effects on sperm production and testicular weight is unknown.

Other data

An in vitro phototoxicity study in 3T3 mouse fibroblasts and an in vivo phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the pack.

Special precautions for storage

Do not store above 25°C.

Keep out of the reach of children.

Authorisation number

68294 (Swissmedic)

Packs

Film-coated tablets 25 mg: 30 [A]

Film-coated tablets 50 mg: 30 [A]

Film-coated tablets 100 mg: 30 [A]

Film-coated tablets 200 mg: 30 [A]

Film-coated tablets 300 mg: 30 [A]

Marketing authorisation holder

Blueprint Medicines (Switzerland) GmbH, Zug

Date of revision of the text

July 2023