swissmedic

Date: 2 December 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

AYVAKYT

International non-proprietary name:	avapritinib
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	25 mg, 50 mg, 100 mg, 200 mg, and 300 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Blueprint Medicines (Switzerland)
Marketing authorisation no.:	68294
Decision and decision date:	extension of therapeutic indication approved on 07.08.2025

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
AE	Adverse event
ALT	Alanine aminotransferase
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
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)
GLP	Good Laboratory Practice
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
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
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	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA. Orphan drug status was granted on 4 February 2021.

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

Indolent systemic mastocytosis (ISM)
AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

2.2.2 Approved indication

Indolent systemic mastocytosis (ISM)

- AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (see "Clinical Efficacy").
  AYVAKYT should not be used for the treatment of patients with ISM with platelet counts below 50 × 10^9/L (see "Dosage/Administration" and "Warnings and Precautions").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Indolent systemic mastocytosis (ISM)
For ISM, the recommended dose of avapritinib is 25 mg orally once daily, on an empty stomach (see "Method of administration"). Treatment of ISM should be continued until disease progression or unacceptable toxicity occurs.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 January 2025
Formal control completed	19 February 2025
Preliminary decision	1 May 2025
Response to preliminary decision	29 June 2025
Final decision	7 August 2025
Decision	approval

Based on Art. 13 TPA 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 EMA. This SwissPAR relates to the assessment report for AYVAKYT (EMA/548651/2023) dated 9 November 2023 issued by the EMA.

3 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, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report for AYVAKYT (EMA/548651/2023) dated 9 November 2023 issued by the EMA (see section 2.3 “Regulatory history (milestones)”).

4 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report for AYVAKYT (EMA/548651/2023) dated 9 November 2023 issued by the EMA (see section 2.3 “Regulatory history (milestones)”).

5 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.

6 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.

▼ 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)[1]

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.[2]

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).[3,4]

  AYVAKYT should not be used 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”).

Indolent systemic mastocytosis (ISM)

- AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (see “Clinical Efficacy”).[5]

  AYVAKYT should not be used for the treatment of patients with ISM with platelet counts below 50 x 10^9/L (see “Dosage/Administration” and “Warnings and Precautions”).

Dosage/Administration

Therapy should be initiated by a healthcare professional 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.

[1] *2.3.P Drug Product - Avapritinib Tablets, Juniper and Patheon, Section 1.1. Description and Dosage Form, p.6 (reference dossier eCTD Sequence 0058)]*

[2] *[2.5 Clinical Overview (GIST NDA), 1.2. Proposed Indication, p.9, (reference dossier eCTD Sequence 0001)]*

[3] *[2.5 Clinical Overview (AdvSM sNDA), 1.4. Proposed Indication, p.14 (reference dossier eCTD Sequence 0058)]*

[4] *[1.3.4 US Product Information, Section 1]*

[5] *[EU SmPC, Section 4.1]*

Recommended Dosage for GIST Harbouring a PDGFRA D842V Mutation[6,7]

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[8,9]

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 Dosage for Indolent Systemic Mastocytosis[10,11]

For ISM, the recommended dose of avapritinib is 25 mg orally once daily, on an empty stomach (see Method of administration). This once daily 25 mg dose is also the maximum recommended dose that must not be exceeded in patients with ISM. Treatment of ISM should be continued until disease progression or unacceptable toxicity occurs.

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors must be avoided (see “Dose adjustment for use with strong or moderate CYP3A4 inhibitors” and section “Interactions”).

Recommended Administration[12,13,14,15]

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

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[6] *6 [2.5 Clinical Overview (GIST NDA), 1.2. Dosing Recommendations, p.9, (reference dossier eCTD Sequence 0001)]*

[7] *[2.7.3 Summary of Clinical Efficacy (GIST NDA, Section 4.4. Conclusion, Page 71, (reference dossier eCTD Sequence 0001)]*

[8] *[2.5 Clinical Overview (AdvSM sNDA), 1.4. Dosing Recommendations, p.14, (reference dossier eCTD Sequence 0058)]*

[9] *[2.7.3 Summary of Clinical Efficacy (AdvSM sNDA), Section 4.5. Conclusion, Page 102], (reference dossier eCTD Sequence 0058)*

[10] *[2.5 Clinical Overview (ISM), 1.4. Dosing Recommendations, p.16]*

[11] *[2.7.3 Summary of Clinical Efficacy (ISM), Section 4.4. Conclusion on Dosing Recommendations, Page 46]*

[12] *[2.5 Clinical Overview (GIST NDA), 1.2. Dosing Recommendations, p.9, (reference dossier eCTD Sequence 0001)]*

[13] *[2.5 Clinical Overview (AdvSM sNDA), 1.4. Dosing Recommendations, p.14, (reference dossier eCTD Sequence 0058)]*

[14] *[2.7.2 Summary of Clinical Pharmacology, Section 3.6 Justification of Dose and Dosing Regimen, p. 99, reference dossier eCTD Sequence 0001]*

[15] *[2.7.2 Summary of Clinical Pharmacology, Section 3.6 Justification of Dose and Dosing Regimen, p. 69 (AdvSM sNDA, reference dossier eCTD Sequence 0058]*

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[16,17,18]
Irrespective of indication, interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation.
The dose should be adjusted as recommended, based on safety and tolerability.

Dose reductions and dose modifications for adverse reactions are recommended in patients with GIST, AdvSM or ISM and are provided in Tables 1 and 2.

In the pivotal clinical trials, the dose of AYVAKYT had to be reduced at least once due to adverse reactions in the majority of treated patients with GIST and AdvSM, in up to 82% with GIST and 68% with AdvSM (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.

In patients with ISM in Part 2 of the BLU-285-2203 (PIONEER) study, 0.7% of patients needed to reduce their dose 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)****	**ISM (starting dose 25 mg)*****
First	200 mg once daily	100 mg once daily	25 mg once every other day
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.
*** Permanently discontinue AYVAKYT in patients with ISM who do not tolerate a dose of 25 mg once every other day.

[16] *[2.5 Clinical Overview (GIST NDA, reference dossier eCTD Sequence 0001), Section 6.3. Risks, p.74]*
[17] *[2.5 Clinical Overview (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 6.4. Benefit-Risk Assessment, p.74]*
[18] *[2.5 Clinical Overview (ISM), Section 6.3. Risks, p.76]*

Table 2. Recommended Dosage Modifications for AYVAKYT for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Patients with GIST, AdvSM or ISM		
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 adverse reactions (*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

Dose adjustment for administration with strong or moderate CYP3A4 inhibitors

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")*:[19, 20, 21]

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

For ISM, avoid concomitant use of AYVAKYT with strong or moderate CYP3A inhibitors.

[19] *[2.7.2 Summary of Clinical Pharmacology, Section 3.6. Justification of Dose and Dosing Regimen, p.99 (GIST NDA, reference dossier eCTD Sequence 0001)]*

[20] *[2.7.2 Summary of Clinical Pharmacology, Section 3.6.2. Modification of Selected Dose, p. 71 (AdvSM sNDA, reference dossier eCTD Sequence 0058)]*

[21] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.3.2. Drug-Drug Interactions, p.48*

Patients with hepatic disorders[22, 23, 24]

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. A modified starting dose of avapritinib is recommended for patients with severe hepatic impairment (Child-Pugh Class C). The starting dose of avapritinib should be reduced from 300 mg to 200 mg orally once daily for patients with GIST, from 200 mg to 100 mg orally once daily for patients with AdvSM, and from 25 mg orally once daily to 25 mg orally every other day for patients with ISM (see section "Pharmacokinetics").

Patients with renal disorders[25, 26 ,27]

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[28, 29]

No dose adjustment is recommended for patients aged 65 years and above. Clinical data in ISM patients aged 75 years and above is limited (see "Pharmacodynamics").

Children and adolescents[30]

AYVAKYT is not approved for use in children and adolescents.

Contraindications

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

[22] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA, reference dossier eCTD Sequence 0001), Section 3.2.2. Hepatic Impairment, p.95]*

[23] *[2.7.2 Summary of Clinical Pharmacology Studies (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 3.2.2. Hepatic Impairment, p.67]*

[24] *[2.7.2 Summary of Clinical Pharmacology Studies (BLU-285-0107 CSR Hepatic Impairment, Section 3.2.2. Hepatic Impairment, p.17, CH eCTD Sequence 0007]*

[25] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA, reference dossier eCTD Sequence 0001), Section 3.2.3. Renal Impairment, p.96]*

[26] *[2.7.2 Summary of Clinical Pharmacology Studies (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 3.2.3. Renal Impairment, p.67]*

[27] *[2.7.2 Summary of Clinical Pharmacology Studies (ISM), Section 3.2.3. Renal Impairment, p.47]*

[28] *[2.7.3 Summary of Clinical Efficacy (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 3.3.1. Efficacy of Avapritinib by Demographic Subgroup, p.89]*

[29] *[2.7.3 Summary of Clinical Efficacy (ISM), Section 2.1.2. Demographic and Baseline Characteristics, p.22]*

[30] *[Module1.10 Information Relating to Paediatrics]*

Warnings and precautions

Haemorrhages[31, 32, 33, 34]

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 in GIST patients (see section “Undesirable effects”).

Routine surveillance of haemorrhagic adverse reactions in patients with GIST or AdvSM must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored in patients with GIST or AdvSM, 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[35, 36, 37, 38]

Intracranial haemorrhage occurred as adverse reactions in GIST and AdvSM patients who received AYVAKYT (see section "Undesirable effects").

Before initiating treatment with AYVAKYT at any dose the risk of intracranial haemorrhage should be carefully considered in patients with a potentially increased risk including those with a history of vascular aneurysm, intracranial haemorrhage or cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia.

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

[31] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), Section 3.2.3. Renal Impairment, p.96]*

[32] *[2.7.4 Summary of Clinical Safety (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 8.1.3 Adverse Events of Special Interest, p.170]*

[33] *[EU SmPC, 4.4 Special warnings and precautions for use, p.4]*

[34] *[2.7.4 Summary of Clinical Safety (ISM), Section 2.1.6. Other Serious Adverse Events, p.44]*

[35] *RMP Version 1.0 (), SVII.3Details of Important Identified Risks, Important Potential Risks, and Missing Information, p.47]*

[36] *[Module 2.7.4 Summary of Clinical Safety, 120-Day Safety Update, reference dossier eCTD sequence 0074)]*

[37] *EU SmPC, 4.4 Special warnings and precautions for use, p.4*

[38] *[2.7.4 Summary of Clinical Safety (ISM), Section 2.1.8. Adverse Events of Special Interest, p.50]*

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 in any indication, regardless of the severity grade, avapritinib must be permanently discontinued (see section “Dosage/Administration”).

Unresectable or metastatic GIST
Serious adverse reactions of intracranial haemorrhage were reported in patients with unresectable or metastatic GIST receiving avapritinib. The exact mechanism is unknown (see section "Undesirable effects").
There is no clinical study experience using AYVAKYT in patients with brain metastases.

Advanced systemic mastocytosis
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 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[39, 40]

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 with GIST or AdvSM are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients with GIST or AdvSM must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms.

For GIST or AdvSM 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 conducted in patients with GIST and AdvSM, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.
In patients with ISM, cognitive effects can be one of the disease symptoms. Patients with ISM must notify their healthcare professional if they experience new or worsening cognitive symptoms.

Fluid retention[41, 42]

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 with GIST or AdvSM 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 GIST or AdvSM patients presenting with ascites, it is recommended to evaluate the aetiology of the ascites.

[39] *[2.5 Clinical Overview (AdvSM sNDA, reference dossier eCTD sequence 0058), 5.4.6.2. Cognitive Effects, p.54]*

[40] *[2.7.4 Summary of Clinical Safety (ISM), Section 2.1.8. Adverse Events of Special Interest, p.50]*

[41] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), Section 5.2. Exposure-Response Analysis, p.155]*

[42] *[2.7.4 Summary of Clinical Safety (ISM), Section 2.1.2. Common Adverse Events, p.36]*

In patients with ISM, localised (peripheral, facial) oedemas have been reported with a frequency category of at least “common” (see section “Undesirable effects”).

QT interval prolongation[43, 44]

Prolongation of the QT interval has been observed in patients with unresectable or metastatic GIST and AdvSM treated with avapritinib in clinical studies (see section “Undesirable effects” and “Pharmacodynamics”). QT interval prolongation may result in an increased risk of ventricular arrhythmias, including *torsade de pointes*.

Therefore, AYVAKYT should be used with caution in GIST or AdvSM 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.

In patients with GIST or AdvSM, assessment of the QT interval by electrocardiogram (ECG) should be considered, especially if AYVAKYT is taken concurrently with medicinal products that can prolong the QT interval.

In patients with ISM, QT interval assessments by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g. age, pre-existing heart rhythm disorders, etc.).

Gastrointestinal disorders[45, 46, 47]

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions (see section “Undesirable effects”). GIST or AdvSM 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, antidiarrheal, or antacid properties.

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[43] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 4.2.1. Summary of Cardiac Safety Report, p.137]*

[44] *[2.7.4 Summary of Clinical Safety (ISM), Section 4.2. Cardiovascular Effects p.66]*

[45] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 2.1.8.1. Gastrointestinal Disorders, p.112]*

[46] *[2.7.4 Summary of Clinical Safety (AdvSM sNDA, reference dossier eCTD Sequence 0058), Section 2.1.9.3. Gastrointestinal Disorders, p.101]*

[47] *[2.7.4 Summary of Clinical Safety (ISM), 2.1.9. Analysis of Adverse Events by Organ System or Syndrome, p.52]*

The hydration status of GIST or AdvSM patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice.

Laboratory tests[48, 49]

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 in patients with GIST or AdvSM. 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 with GIST or AdvSM receiving AYVAKYT.

CYP3A4 inhibitors and inducers[50]

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[51]

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[52, 53, 54]

[48] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 2.1.8.8. Investigations, p.120]*

[49] *[2.7.4 Summary of Clinical Safety (ISM), 3. Clinical Laboratory Evaluations/ 3.1.1. Part 2, p. 56*

[50] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 5.3. Drug Interactions, p.160]*

[51] *[2.4 Nonclinical Overview, (GIST NDA, reference dossier eCTD Sequence 0001), 4.5.1. Phototoxicity Potential of Avapritinib, p.29]*

[52] *[2.5 Clinical Overview (GIST NDA), Section 5.2. Summary of Safety Results. P.52, reference dossier eCTD Sequence 0001]*

[53] *[2.5 Clinical Overview (AdvSM sNDA), Section 5.4. Adverse Events, p.46, reference dossier eCTD Sequence 0058]*

[54] *[Section “Warnings and precautions” is aligned with the approved EU SmPC.*

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 [55]
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[56]

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. For patients with ISM, concomitant use of avapritinib with strong or moderate CYP3A inhibitors must be avoided (see section "Dosage and Administration" and "Warnings and Precautions").

[55] *[2.3.P Drug Product - Avapritinib Tablets, Juniper and Patheon, Section 1.2. Composition, p.7, reference dossier eCTD Sequence 0058]*
[56] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 5.3. Drug Interactions, p.160]*

Strong and Moderate CYP3A Inducers[57, 58, 59, 60]

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[61]

No clinical drug-drug interaction studies have been conducted. Based on population pharmacokinetic analyses, 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.

[57] *[2.7.2 Summary of Clinical pharmacology (GIST NDA), section 1.2.5 Potential for Drug-Drug Interactions p.15, reference dossier eCTD sequence 0001]*

[58] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 5.3. Drug Interactions, p.160]*

[59] *[2.7.2 Summary of Clinical pharmacology (ISM), section 3.3.2. Drug-Drug Interactions p.48]*

[60] *2.5 Clinical Overview (ISM), section 3.3.1. Effect of Other Drugs on Avapritinib Exposure, p. 31*

[61] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 3.3.2.1.3. Gastric Acid Reducing Agents, p.97, reference dossier eCTD sequence 0001]*

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.

Hormonal contraceptives
Co-administration of AYVAKYT 25 mg once daily with an oral contraceptive did not have a clinically significant effect on the pharmacokinetics of levonorgestrel (LNG) or ethinyl estradiol (EE).

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 2 weeks after the last dose.

Pregnancy [62]

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[63]

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[64, 65, 66]

There are no data on the effect of AYVAKYT on human fertility. However, based on nonclinical findings in animals, male and female fertility may be compromised by treatment with avapritinib (see section *"Preclinical data"*).

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.[67]

[62] *[2.5 Clinical Overview (ISM), section 5.4. 1.5.1. Overview, p.16]*

[63] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 5.4. Use in Pregnancy and Lactation, p.161]*

[64] *[2.5 Clinical Overview (GIST NDA), Section 6.3. Risks, p.74, reference dossier eCTD sequence 0001)]*

[65] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 5.4. Use in Pregnancy and Lactation, p.161, reference dossier eCTD sequence 0001)]*

[66] *[EU SmPC, 4.6 Fertility, pregnancy and lactation, p.9]*

[67] *[Module 2.7.4 Summary of Clinical Safety, 90-Day Update, reference dossier, eCTD sequence 0007]*

Undesirable effects

Summary of the safety profile [68, 69, 70, 71]

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;193 patients enrolled in studies for AdvSM (all doses), of whom 126 patients received avapritinib at a starting dose of 200 mg, and 246 patients with ISM (all doses), of which 141 patients received avapritinib at the recommended dose of 25 mg in Part 2, pivotal part of the PIONEER study (see section “Properties/Effects”).

Unresectable or metastatic GIST[72, 73]

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.[74, 75]

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

[68] *[Module 2.5. Clinical Overview (AdvSM sNDA) Section 5. Overview of Safety, Page 44f, reference dossier eCTD sequence 0058]*

[69] *[Module 5.3.5.3 90-Day Update, Section 2.1 Analysis of Adverse Events, reference dossier eCTD sequence 0007]*

[70] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[71] *[Module 2.5. Clinical Overview (ISM), section 1.5.2. Study BLU-285-2203, Page 18]*

[72] *[Module 2.5. Clinical Overview (GIST NDA), Section 5.2.2 Common Adverse Events, Page 53, reference dossier eCTD sequence 0001]*

[73] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[74] *[Module 2.5. Clinical Overview (GIST NDA), Section 5.2.6. Adverse Events Leading to Study Drug Discontinuation, Page 58, reference dossier eCTD sequence 0001]*

[75] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

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 [76, 77]

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%).[78, 79]

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.[80]

Indolent systemic mastocytosis [81]

In Part 2 of PIONEER, the most common adverse reaction during treatment with avapritinib at the recommended dose of 25 mg was peripheral oedema (12%). Overall, the majority of oedema adverse reactions reported were Grade 1 (94% for peripheral oedema, 90% for face oedema); none were Grade ≥3 or led to treatment discontinuation.

No serious adverse reactions or fatal adverse reactions occurred in 141 patients receiving avapritinib at the recommended dose of 25 mg in Part 2 of PIONEER. Treatment discontinuation due to adverse reactions occurred in <1% of patients receiving avapritinib.

[76] *[Module 2.5. Clinical Overview (AdvSM sNDA), Section 5.4.1. Overview of Adverse Events, Page 46, reference dossier eCTD sequence 0058]*

[77] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[78] *[Module 2.5. Clinical Overview (AdvSM sNDA), Section 5.4.3. Serious Adverse Events, Page 49, reference dossier eCTD sequence 0058]*

[79] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[80] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[81] *[Module 2.5. Clinical Overview (ISM), Section 5.4.9. Adverse Drug Reactions, p. 68]*

Tabulated list of adverse reactions

Adverse reactions that were reported in clinical studies in patients with GIST, AdvSM and ISM are listed below.[82]

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 [83, 84, 85]

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

[82] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*
[83] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*
[84] *[GIST ADR section is aligned with the approved EU SmPC. See explanation in annex to cover letter]*
[85] *[Module 2.5. Clinical Overview (GIST NDA), Section 5.2. Summary of Safety Results, Page 52f, reference dossier eCTD sequence 0001]*

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[86, 87]
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.

[86] *[AdvSM ADR section in line with table T.99.3.5.5 "Summary of related adverse events (SMPC pooling) by System Organ Class and Preferred Term Safety Population 2101 & 2202 Studies". See explanation in annex to cover letter]*
[87] *[Module 2.5. Clinical Overview (AdvSM sNDA), Section 5.4. Adverse Events, Page 46, reference dossier eCTD sequence 0058]*

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-glutamyl transferase) (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.

Indolent systemic mastocytosis[88]

[88] *[Module 2.5. Clinical Overview (ISM), Section 5.4.9. Adverse Drug Reactions, p. 68]*

For patients with ISM, adverse reactions reported in Part 2 of the PIONEER study are listed.

Blood and lymphatic system disorders
Common: Lymphadenopathy, neutropenia (including neutrophil count decreased)

Ear and labyrinth disorders
Common: Tinnitus, vertigo

Eye disorders
Common: Dry eye, lacrimation increased

Gastrointestinal disorders
Common: Abdominal distension, dry mouth, dyspepsia, gastroesophageal reflux disease, haemorrhoids, mouth ulceration, oesophageal spasm

General disorders and administration site conditions
Very Common: Peripheral oedema (including oedema peripheral, peripheral swelling) (12.1%)
Common: Facial oedema, asthenia, feeling abnormal, general oedema (including fluid retention, generalised oedema, oedema), influenza like illness

Infections and infestations
Common: Sinusitis, upper respiratory tract infection, respiratory tract infection, tooth infection, bronchitis, hordeolum, tonsillitis (including tonsillitis bacterial)

Injury, poisoning and procedural complications
Common: Contusion, limb injury

Investigations:
Common: Blood alkaline phosphatase increased, aspartate aminotransferase increased, blood lactate dehydrogenase increased, blood bilirubin increased

Metabolism and nutrition disorders
Common: Hypokalaemia, decreased appetite, iron deficiency, hypophosphatemia

Musculoskeletal and connective tissue disorders
Common: Back pain, bone pain, muscle spasms, joint swelling, tendonitis

Nervous system disorders

Common: Taste effects (dysgeusia and taste disorder), hypoaesthesia, syncope, tremor

Psychiatric disorders

Common: Insomnia, anxiety, depression

Renal and urinary disorders

Common: Bladder pain

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea (including dyspnoea exertional), epistaxis, hyperventilation, oropharyngeal pain, sleep apnoea syndrome

Skin and subcutaneous tissue disorders

Common: Photosensitivity reaction, skin lesion and rosacea

Vascular disorders

Common: Flushing

Description of selected adverse reactions

Intracranial haemorrhage [89]

Unresectable or metastatic GIST [90, 91]

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.

[89] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[90] *[Module 2.5. Clinical Overview (GIST NDA), Section 5.2.9.2. Intracranial Bleeding, Page 63, reference dossier eCTD sequence 0001]*

[91] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

Advanced systemic mastocytosis [92, 93]

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.

Indolent systemic mastocytosis [94]

No intracranial haemorrhages were reported in 141 patients with ISM receiving 25 mg of avapritinib during the 24-week duration of Part 2 of the PIONEER study.

Cognitive effects [95]

[92] *[Module 2.5. Clinical Overview (AdvSM sNDA), Section 5.4.6.1. Intracranial Bleeding, Page 52, reference dossier eCTD sequence 0058]*

[93] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[94] *[Module 2.5. Clinical Overview (ISM), section* 5.4.8.2. *Intracranial Bleeding, p. 67]*

[95] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

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 in patients with GIST and AdvSM.

Unresectable or metastatic GIST [96, 97]

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.

[96] *[Module 2.5. Clinical Overview (GIST NDA), Section 5.2.9.1. Cognitive Effects, Page 51, reference dossier eCTD sequence 0001]*

[97] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

Advanced systemic mastocytosis [98, 99]

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.

Indolent systemic mastocytosis [100]

In Part 2 of the PIONEER study, cognitive effects occurred in 2.8% of patients with ISM who received 25 mg of avapritinib (see section "Warnings and precautions"); all cognitive effects were Grade 1 or 2. Overall, none of the patients who received avapritinib in Part 2 of PIONEER required permanent treatment discontinuation for cognitive effects.

Anaphylactic adverse reactions

Indolent systemic mastocytosis

Anaphylaxis is a common clinical manifestation of ISM. In Part 2 of the PIONEER study, patients who received 25 mg of avapritinib had fewer episodes of anaphylaxis over time (5% during the ~8-week screening period versus 1% during Part 2).

[98] *[Module 2.5. Clinical Overview (AdvSM sNDA), Section 5.4.6.2. Cognitive Effects, Page 54, reference dossier eCTD sequence 0058]*

[99] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[100] *[Module 2.5. Clinical Overview (ISM), section 5.4.8.1. Cognitive Effects, p. 66]*

Elderly

Unresectable or metastatic GIST [101, 102, 103]

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 [104, 105, 106]

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%).

Indolent systemic mastocytosis [107]

In Part 2 of PIONEER (N = 141) (see section “Properties/Effects”), 9 (6%) patients were 65 years of age or older, and 1 (<1%) patient was 75 years of age or older. No patients over the age of 84 were included. Overall, no meaningful differences in safety were observed between patients ≥65 years and those <65 years.

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

[101] *[Module 5.3.5.3 ISS, reference dossier eCTD sequence 0074]*

[102] *[Module 2.7.3 Summary of Clinical Efficacy, (GIST NDA), Section 2.1.2.2. Demographics and Baseline Characteristics, Page 23, reference dossier eCTD sequence 0001]*

[103] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[104] *[Module 5.3.5.3 ISS, reference dossier eCTD sequence 0074]*

[105] *[Module 2.7.3 Summary of Clinical Efficacy, (AdvSM sNDA), Section 3.1.2. Demographics and [Baseline Characteristics, Page 50, reference dossier eCTD sequence 0058]*

[106] *[Appendix 2 to the cover letter Methodology for Determination of Adverse Drug Reactions]*

[107] *[Module 2.7.3 Summary of Clinical Efficacy, (ISM), Section 2.1.2. Demographics and Baseline Characteristics, p. 22]*

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

There is limited experience with cases of overdose reported in clinical studies 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).[108, 109, 110]

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

Gastrointestinal Stromal Tumors or Advanced Systemic Mastocytosis

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

[108] *[2.7.4 Summary of Clinical Safety (GIST NDA), Section 5.5. Overdose, p162, reference dossier eCTD sequence 0001]*

[109] *[2.7.4 Summary of Clinical Safety (AdvSM sNDA), Section 5.5. Overdose, p134, reference dossier eCTD sequence 0001]*

[110] *[2.7.4 Summary of Clinical Safety (ISM), Section 5.5. Overdose, p73]*

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.[111, 112]

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.[113]

Cardiac Electrophysiology [114, 115, 116]

The ability of avapritinib to prolong the QT interval was assessed in 27 patients administered avapritinib at doses of 300/400 mg (1.33 times the 300 mg dose recommended for GIST patients, 12 to 16 times the 25 mg dose recommended for ISM patients) once daily in an open-label, single-arm study in patients with GIST. The estimated mean change from baseline in QTcF was 6.55 ms (90% confidence interval [CI]: 1.80 to 11.29) at the observed steady state geometric mean C_{max} of 899 ng/mL (12.8-fold higher than the steady state geometric mean C_{max} of avapritinib at 25 mg dose once daily in patients with ISM). No effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed (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

[111] *[Module 2.4. Nonclinical Overview, Section 2.1. Pharmacodynamics and Mechanism of Action, Page 10, reference dossier eCTD sequence 0001]*

[112] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 5.1. Highlights of Clinical Pharmacology, p.104, reference dossier eCTD sequence 0001]*

[113] *[2.5 Clinical Overview (AdvSM sNDA), Section 3.4. Exposure-Response Analyses, p.19, reference dossier eCTD sequence 0001]*

[114] *[2.5 Clinical Overview (GIST NDA), Section 3.2.7. Evaluation of the Effect of Avapritinib on Cardiac Repolarization. p.23, reference dossier eCTD sequence 0001]*

[115] *[2.7.4 Summary of Clinical Safety (GIST NDA, reference dossier eCTD Sequence 0001), 4.2.1. Summary of Cardiac Safety Report, p.137]*

[116] *[2.5 Clinical Overview (ISM), 3.4. Potential for Effect of Avapritinib on Cardiac Repolarization, p. 32]*

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).[117,118]

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)	92.9 (76.5; 99.1)
CR	3.6
PR	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)

[117] *[2.5 Clinical Overview (GIST NDA), Section 4. Overview of Efficacy. p.25, reference dossier eCTD Sequence 0001]*
[118] *[Module 2.7.3 Summary of Clinical Efficacy, Section 2.1. Study BLU-285 -1101 (NAVIGATOR, page 21, reference dossier eCTD Sequence 0001*

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) [119]

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.

[119] *[2.5 Clinical Overview (AdvSM sNDA),), Section 4. Overview of Efficacy. p. 21, reference dossier eCTD sequence 0058]*

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).

Clinical studies in indolent systemic mastocytosis[120]

The efficacy and safety of avapritinib was assessed in study BLU-285-2203 (PIONEER), a randomised, double-blind, placebo-controlled, 3-part clinical study conducted in adult patients with ISM with moderate-to-severe symptoms not adequately controlled by best supportive care. In Part 2

[120] *[2.5 Clinical Overview (ISM),), Section 4. Overview of Efficacy. p. 36]*

(pivotal part), patients were randomised to receive avapritinib at the recommended dose of 25 mg orally once daily with best supportive care (141 patients) or versus placebo with best supportive care (71 patients). The randomized portion of the study consisted of a 24-week period. Part 3 of study BLU-285-2203 is ongoing.

The primary end point in Part 2 was mean change from baseline to Week 24 in total symptom score (TSS) as measured by the ISM Symptom Assessment Form (ISM-SAF). The ISM-SAF is a patient-reported outcome tool made up of a 12-item questionnaire developed specifically to assess symptoms in patients with ISM. Patient-reported severity scores for 11 ISM symptoms (bone pain, abdominal pain, nausea, spots, itching, flushing, fatigue, dizziness, brain fog, headache, diarrhoea; 0 = none; 10 = worst imaginable) are summed to calculate the TSS (range 0-110), with higher scores representing greater symptom burden. The 12th item of the questionnaire assesses the number of diarrhoea episodes.

For the purpose of the study, enrolled patients needed a total symptom score (TSS) of 28 or greater at screening (defining moderate to severe symptoms). Patients were required to have failed to achieve adequate symptom control for 1 or more baseline symptoms with at least 2 symptomatic therapies, including but not limited to: H1 antihistamines, H2 antihistamines, proton pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab.

Additional patient-reported key secondary efficacy end points were the proportion of avapritinib-treated patients achieving ≥50% and ≥30% reduction from baseline through Week 24 in TSS compared to placebo. Objective of mast cell burden were also reported as key secondary efficacy end points and included the proportion of patients with a ≥50% reduction from baseline through Week 24 in serum tryptase, peripheral blood KIT D816V allele fraction and in bone marrow mast cells.

The study population characteristics were: median age of 51 years (range: 18 to 79 years), 73% were female, 80% were white, and 94% had a KIT D816V mutation. At baseline, the mean TSS was 50.93 (range: 12.1 to 104.4), the median serum tryptase level was 39.20 ng/mL (range: 3.6 to 501.6 ng/mL), the median KIT D816V mutant allele fraction was 0.32% by digital-droplet polymerase chain reaction (ddPCR) and the median bone marrow mast cell infiltrate was 7%.

The majority of patients (99.5%) received concomitant best supportive care at baseline (median of 3 therapies). The most common therapies were H1 antihistamines (98.1%), H2 antihistamines (66%), leukotriene inhibitors (34.9%) and cromolyn sodium (32.1%).

Avapritinib treatment demonstrated statistically significant improvements for all primary and key secondary efficacy end points compared to placebo, as summarized in Table 5.

Table 5. Reduction in ISM-SAF TSS and measures of mast cell burden in patients with indolent systemic mastocytosis in PIONEER at Week 24

Efficacy Parameter	AYVAKYT (25 mg once daily) + BSC N = 141	Placebo + BSC N = 71	One-sided p-value
ISM-SAF TSS			
Mean change in TSS			
Change from baseline (95% CI)	-15.58 (-18.61, -12.55)	-9.15 (-13.12, -5.18)	0.003
Difference from placebo (95% CI)	-6.43* (-10.90, -1.96)		
% of patients achieving ≥50% reduction in TSS (95% CI)	25 (17.9, 32.8)	10 (4.1, 19.3)	0.005
% of patients achieving ≥30% reduction in TSS (95% CI)	45 (37.0, 54.0)	30 (19.3, 41.6)	0.009
Parameters of mast cell burden			
% of patients with a ≥50% reduction in serum tryptase (95% CI)	N = 141 **54** (45.3, 62.3)	N = 71 **0** (0.0, 5.1)	<0.0001
% of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction, or undetectable (95% CI)	N = 118 **68** (58.6, 76.1)	N = 63 **6** (1.8, 15.5)	<0.0001
% of patients with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI)	N = 106 **53** (42.9, 62.6)	N = 57 **23** (12.7, 35.8)	<0.0001

Abbreviations: BSC=best supportive care, CI=confidence interval, ISM-SAF=indolent systemic mastocytosis symptom assessment form, TSS=total symptom score
* Reduction in TSS is a result of a mean decrease in all individual symptoms that make up the ISM-SAF.

The long-term efficacy of avapritinib is assessed in an open-label extension of PIONEER in patients receiving 25 mg of avapritinib (Part 3). Overall, 201 patients rolled over from Part 2 into Part 3 of PIONEER. Avapritinib-treated patients from Part 2 continued to report improvements in TSS over time out to approximately 48 weeks (Part 3 C7D1) of treatment with a mean change from baseline in TSS of -18.05 points (95% CI -21.55, -14.56). Placebo-treated patients from Part 2 who received avapritinib in Part 3 reported substantial additional reductions in their TSS scores within the first 24 weeks of treatment (Part 3 C7D1) with a total mean change from baseline in TSS of -19.71 points (95% CI -24.32, -15.11), which included a further 10.78-point reduction from Part 3 baseline just prior to rolling over to avapritinib.

Elderly patients [121,122]

Unresectable or metastatic GIST

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.

Advanced systemic mastocytosis

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.

Indolent systemic mastocytosis

Of the 141 patients with ISM who received AYVAKYT in Part 2 (pivotal part) of PIONEER, 9 (6%) patients were 65 years or older, while 1 (<1%) patient was 75 years and older. No patients over the age of 84 were included. Overall, no meaningful differences in efficacy were observed between patients ≥65 years and those <65 years.

Pharmacokinetics

Avapritinib C_{max} and AUC increased dose-proportionally in the dose range of 25 mg to 400 mg once daily. Steady state concentrations of avapritinib were reached within 15 days following daily dosing. Steady state pharmacokinetic parameters as per the recommended dosing regimen are described in Table 6. [123, 124]

[121] *[Module 2.7.3 Summary of Clinical Efficacy (AdvSM sNDA), Section 3. Comparison and analyses of results across studies and subpopulations, page 47 , reference dossier eCTD sequence 0058]*

[122] *[Module 2.7.3 Summary of Clinical Efficacy (ISM), 2.1.2. Demographic and Baseline Characteristics, p.22]*

[123] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 2.1. Study BLU-285-1101; Pharmacokinetics, Pharmacodynamics, and Exposure-Response in Patients with GIST. p.33, reference dossier eCTD Sequence 0001]*

[124] *[2.7.2 Summary of Clinical Pharmacology Studies (AdvSM sNDA), Section AdvSM sNDA. p.24, reference dossier eCTD Sequence 0058]*

Table 6. Steady State Pharmacokinetic Parameters of AYVAKYT Following a Different Dosing Regimen

Pharmacokinetic Parameters	25 mg once daily (ISM)	200 mg once daily (AdvSM)	300 mg once daily (GIST)
C_{max} (ng/mL) Geometric mean (CV%)	70.2 (47.8 %, n = 9)	377 (62%, n = 18)	813 (52%, n = 110)
AUC_{0-24h} (h•ng/mL) Geometric mean (CV%)	1330 (49.5 %, n = 9)	6600 (54%, n = 16)	15400 (48%, n = 110)
Mean accumulation ratio of AUC_{0-24h}	4.06 (n = 9)	6.41 (n = 9)	3.82 (n = 34)
Abbreviations: CV%: coefficient of variation			

Absorption

Following administration of single oral doses of avapritinib of 25 to 400 mg, the median time to peak concentration (T_{max}) 2 to 4 hours postdose. The absolute bioavailability has not been determined. The population estimated mean oral bioavailability of avapritinib in patients with GIST and AdvSM is 16% and 47% lower, respectively, compared to that in patients with ISM.[125, 126, 127]

Effect of Food [128,129]

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

Avapritinib is 98.8% bound to human plasma proteins *in vitro,* and the binding is not concentration-dependent. The blood-to-plasma ratio is 0.95. Population estimated apparent central volume of distribution of avapritinib (Vc/F) is 971 L at median lean body weight of 54 kg. The inter-individual variability of Vc/F is 50.1%.[130, 131]

[125] *[2.5 Clinical Overview (AdvSM sNDS) Section 3.1. Pharmacokinetics of Avapritinib, p.17]*

[126] *[2.7.3 Summary of Clinical Efficacy (AdvSM sNDA), Section 4.2. Pharmacokinetic Considerations, p.100]*

[127] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.1.4.1. Absorption p.45]*

[128] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 3.1.4.1.2. Effect of Food. p.94]*

[129] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.3.1. Effect of Food. p.47]*

[130] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 3.1.4.2. Distribution. p.94]*

[131] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.1.4.2. Distribution. p.46]*

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 the constitutive enantiomers of M499, BLU111207 and BLU111208 are approximately 35% and 42% of the AUC of avapritinib. At a dose of 25 mg once daily, the metabolite to parent ratio for BLU111207 and BLU111208 was 10.3% and 17.5 %, respectively. Compared to avapritinib (IC_{50} = 4 nM), the enantiomers BLU111207 (IC_{50} = 41.8 nM) and BLU111208 (IC_{50} = 12.4 nM) are 10.5- and 3.1-fold less potent, respectively, against KIT D816V *in vitro*.

In vitro studies demonstrated that avapritinib is a direct inhibitor of CYP3A4 and a time-dependent inhibitor of CYP3A4, at clinically relevant concentrations (see section “Interactions”). *In vitro*, avapritinib did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 at clinically relevant concentrations.

In vitro, at clinically relevant concentrations, avapritinib induced CYP3A (see section *“Interactions”*). *In vitro*, avapritinib did not induce CYP1A2 or CYP2B6 at clinically relevant concentrations.[132,133,134]

Elimination

The mean plasma elimination half-life of avapritinib was 32 to 57 hours in patients with GIST, 20 to 39 hours in patients with AdvSM, and 38 to 45 hours in patients with ISM. Population estimated mean apparent clearance (CL/F) of avapritinib is 16.9 L/h. In AdvSM patients, time-dependent CL/F on Day 9 was reduced to 39.4% compared to GIST and ISM patients. The inter-individual variability in CL/F is 44.4%.[135,136,137,138]

[132] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 3.1.4.3. Metabolism. p.94]*

[133] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.1.4.3. Metabolism. p.46]*

[134] *[EU SmPC, Section 5.2 Pharmacokinetic properties/ Biotransformation p.25]*

[135] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), Section 3.1.4.4. Elimination. p.95]*

[136] *[2.7.2 Summary of Clinical Pharmacology Studies (AdvSM sNDA), Section 3.1.4.4. Elimination. p.94]*

[137] *[2.7.2 Summary of Clinical Pharmacology (ISM), Section 3.1.4.4. Elimination. p.46]*

[138] *[EU SmPC, Section 5.2 Pharmacokinetic properties/ Elimination p.25]*

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).

Effects of avapritinib on transport proteins

Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP *in vitro* (see section *Interactions*). *In vitro,* avapritinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 at clinically relevant concentrations.

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.[139]

Patients with impaired hepatic function[140]

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. In a clinical study investigating the effect of severe hepatic impairment on the pharmacokinetics of avapritinib following administration of a single oral dose of 100 mg avapritinib, the mean unbound AUC was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function. A lower starting dose is recommended in patients with severe hepatic impairment (see section Dosage/Administration).

Hormonal Contraceptives:

The PK results demonstrate that co-administration of multiple doses of avapritinib (25 mg QD) with a single dose of LNG/EE (0.15 mg LNG/0.03 mg EE) does not have a clinically meaningful effect on the pharmacokinetics of LNG or EE. The 90% CI of LNG and EE AUC_{0-inf} fall within the clinical significance bounds [0.8, 1.40] and the 90% CI for GMR of LNG Cmax falls within no-effect

[139] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), 3.1.4.4. Elimination. p.95, reference dossier eCTD sequence 0001]*

[140] *[2.7.2 Summary of Clinical Pharmacology Studies (BLU-285-0107 CSR Hepatic Impairment, Section 3.2.2. Hepatic Impairment, p.17, CH eCTD Sequence 0007]*

boundaries of 0.8 - 1.40. Although a moderate increase in EE Cmax of 45.8% (90% CI: 117.16 - 181.46) was seen with co-administration of multiple doses of avapritinib, this <2-fold excursion in Cmax given the small increase in exposure (upper bound for AUC0-inf of 127.93) is not considered clinically relevant at 25 mg of avapritinib.

Preclinical data

Repeated dose toxicity[141, 142, 143, 144]

Haemorrhage in the brain and spinal cord occurred in dogs at doses greater than or equal to 15 mg/kg/day (approximately 9.0, 1.8 and 0.8 times the human exposure based on AUC at 25 mg, 200 mg and 300 mg once daily, respectively) and choroid plexus oedema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 4.7, 1.0 and 0.4 times the human exposure based on AUC at the clinical doses of 25 mg, 200 mg and 300 mg once daily, respectively). Rats manifested convulsions, which was potentially secondary to inhibition of Nav 1.2 at systemic exposures ≥96, 12 and ≥8-fold higher than the exposure in patients at the clinical dose of 25 mg, 200 mg and 300 mg once daily, respectively.

In a 6 month repeat dose toxicology study in rats, females manifested haemorrhagic and cystic degeneration of the ovarian corpus lutea and vaginal mucification at dose levels greater or equal to 3 mg/kg/day with exposure margins of 15, 3 and 1.3 times the human exposure based on AUC at 25 mg, 200 mg and 300 mg, respectively. In a 9 month repeat dose toxicology study in dogs, hypospermatogenesis (3/4 males) was observed at the highest dose tested, 5 mg/kg/day (5.7, 1.2 and <1 times the human exposure (AUC) at 25 mg, 200 mg and 300 mg dose, respectively).

[141] *[2.7.2 Summary of Clinical Pharmacology Studies (GIST NDA), 3.1.4.4. Elimination. p.95, reference dossier eCTD sequence 0001]*

[142] *2.6.6 Toxicology Written Summary, (GIST NDA) Section 3 Repeated-dose toxicity (including supportive toxicokinetic evaluation), p.13, reference dossier, eCTD sequence 0001]*

[143] *[2.4 Nonclinical Overview (ISM), Section 4.2. Repeat-Dose Toxicity in Dog, p11]*

[144] *[2.6.6 Toxicology Written Summary (ISM), Section 3 Repeated-dose toxicity (including supportive toxicokinetic evaluation), p.7]*

Genotoxicity [145, 146]

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 both in the in vivo rat bone marrow micronucleus tests and in the rat liver Comet assay for chromosome damage, and therefore, overall non-genotoxic.

Carcinogenicity[147, 148, 149]

The carcinogenic potential of avapritinib was evaluated in a 6-month transgenic mouse study where higher incidences of lower thymic cortical cellularity were noted at 10 and 20 mg/kg/day doses. A long-term carcinogenicity study with avapritinib is ongoing.

Reproductive toxicity[150, 151, 152, 153]

A dedicated combined male and female fertility and early embryonic development study was conducted in rats at oral avapritinib doses of 3, 10, and 30 mg/kg/day for males, and 3, 10, and 20 mg/kg/day for females. No direct effects on male or female fertility were noted at the highest dose levels tested in this study (100.8 and 62.6 times the human exposure (AUC) at 25 mg, 20.3 and 9.5 times the human exposure (AUC) at 200 mg, and 8.7 and 4.1 times the human exposure (AUC) at 300 mg).

Avapritinib partitioned into seminal fluids up to 0.1 times the concentration found in human plasma at 25 mg. There was an increase in pre-implantation loss and in early resorptions with exposure margins of 15, 3 and 1.3 times the human exposure (AUC) at the clinical doses of 25 mg, 200 mg and 300 mg, respectively. Reduction in sperm production and relative testicular weight were observed in male rats

[145] *[2.6.6 Toxicology Written Summary (GIST NDA), Section 4 Genotoxicity, page 34, reference dossier, eCTD sequence 0001]*

[146] *[2.6.6 Toxicology Written Summary (ISM), Section 4 Genotoxicity, p.9]*

[147] *[2.6.6 Toxicology Written Summary (GIST NDA), Section 5 Carcinogenicity (including supportive toxicokinetic evaluations), page 36, reference dossier, eCTD sequence 0001]*

[148] *[2.6.6 Toxicology Written Summary (GIST NDA), Section 5 Carcinogenicity (including supportive toxicokinetic evaluations), page 10*

[149] *[EU SmPC, section 5.3, Preclinical safety data/ Genotoxicity/carcinogenicity, p.27]*

[150] *[2.4 Nonclinical Overview (GIST NDA), 4.1. Overview of the Nonclinical Safety Studies, p.22, reference dossier eCTD sequence 0001]*

[151] *[2.4 Nonclinical Overview (GIST NDA), 4.2. General Toxicology Profile of Avapritinib in Rat and Dog Studies, p.22, reference dossier eCTD sequence 0001]*

[152] *[2.4 Nonclinical Overview (GIST NDA), Integrated Overview and Conclusions. 5.1. Overview, p.31, reference dossier eCTD sequence 0001]*

[153] *[EU SmPC, section 5.3, Preclinical safety data/ Toxicity to reproduction and development, p.27]*

administered avapritinib at exposures of 7 and 30 times, 1 and 5 times, and 0.6 and 3 times the 25 mg, 200 mg, and 300 mg human doses, respectively.

In an embryo-foetal development toxicity study in rats, avapritinib showed embryotoxic and teratogenic effects (decreases in foetal weights and viability and increases in visceral and skeletal malformations). Oral administration of avapritinib during the period of organogenesis was teratogenic and embryotoxic in rats at exposures approximately 31.4, 6.3 and 2.7 times the human exposure (AUC) at 25 mg, 200 mg, and 300 mg dose, respectively.

Phototoxicity
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.[154]

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.[155, 156]
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

[154] *[2.4 Nonclinical Overview (GIST NDA), 4.5.1. Phototoxicity Potential of Avapritinib, p.29, reference dossier eCTD sequence 0001]*
[155] *[Module 3.2.P.8.1, Section 7.1 Expiration dating period, p. 25 reference dossier, eCTD sequence 0001]*
[156] *[Module 3.2.P.8.1, Section 7.1, Expiration dating period, p 19 reference dossier, eCTD sequence 0058]*

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