

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 25 mg film-coated tablets
AYVAKYT 50 mg film-coated tablets
AYVAKYT 100 mg film-coated tablets
AYVAKYT 200 mg film-coated tablets
AYVAKYT 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AYVAKYT 25 mg film-coated tablets

Each film-coated tablet contains 25 mg of avapritinib.

AYVAKYT 50 mg film-coated tablets

Each film-coated tablet contains 50 mg of avapritinib.

AYVAKYT 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of avapritinib.

AYVAKYT 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of avapritinib.

AYVAKYT 300 mg film-coated tablets

Each film-coated tablet contains 300 mg of avapritinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

AYVAKYT 25 mg film-coated tablets

Round, white film-coated tablet of 5 mm diameter with debossed text. One side reads “BLU” and the other side reads “25”.

AYVAKYT 50 mg film-coated tablets

Round, white film-coated tablet of 6 mm diameter with debossed text. One side reads “BLU” and the other side reads “50”.

AYVAKYT 100 mg film-coated tablets

Round, white film-coated tablet of 9 mm diameter, printed with blue ink “BLU” on one side and “100” on the other.

AYVAKYT 200 mg film-coated tablets

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.

AYVAKYT 300 mg film-coated tablets

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Unresectable or metastatic gastrointestinal stromal tumour (GIST)

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

Advanced systemic mastocytosis (AdvSM)

AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy.

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 section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a healthcare professional experienced in the diagnosis and treatment of conditions for which avapritinib is indicated (see section 4.1).

Posology

Unresectable or metastatic GIST

For GIST, the recommended starting dose of avapritinib is 300 mg orally once daily, on an empty stomach (see Method of administration). Treatment should be continued until disease progression or unacceptable toxicity occurs.

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

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 300 mg to 100 mg orally once daily (see section 4.5).

Advanced systemic mastocytosis

For AdvSM, the recommended starting dose of avapritinib is 200 mg orally once daily, on an empty stomach (see Method of administration). This once daily 200 mg dose is also the maximum recommended dose that must not be exceeded by patients with AdvSM. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Treatment with avapritinib is not recommended in patients with platelet count < 50 x 10⁹/L (see Table 2 and section 4.4).

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 200 mg to 50 mg orally once daily (see section 4.5).

Indolent systemic mastocytosis

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 section 4.5).

Dose modifications for adverse reactions

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

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	-

* ISM patients requiring dose reduction below 25 mg once every other day must discontinue treatment.

Table 2. Recommended dose modifications for AYVAKYT for adverse reactions

Adverse reaction	Severity*	Dose modification
Patients with GIST, AdvSM or ISM		
Intracranial haemorrhage (see section 4.4)	All Grades	Permanently discontinue AYVAKYT.
Cognitive effects** (see section 4.4)	Grade 1	Continue at the same dose, reduce dose or interrupt until improvement to baseline or resolution. Resume at the same dose or at a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.
Other adverse reactions (also see section 4.4 and section 4.8)	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.
Patients with AdvSM		
Thrombocytopenia	Less than 50 x 10 ⁹ /L	Interrupt dosing until platelet

(see section 4.4)		count is $\geq 50 \times 10^9/L$, then resume at reduced dose (see Table 1). If platelet count does not recover above $50 \times 10^9/L$, consider platelet support.
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* The severity of adverse reactions graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0

** Adverse reactions with impact on Activities of Daily Living (ADLs) for Grade 2 or higher adverse reactions

Missed doses

If a dose of avapritinib is missed, the patient should make up for the missed dose unless the next scheduled dose is within 8 hours (see Method of administration). If the dose has not been taken at least 8 hours prior to the next dose, then that dose must be omitted and the patient should resume treatment with the next scheduled dose.

If vomiting occurs after taking a dose of avapritinib, the patient must not take an additional dose but continue with the next scheduled dose.

Special populations

Elderly

No dose adjustment is recommended for patients aged 65 years and above (see section 5.2). Clinical data in ISM patients aged 75 years and above is limited (see section 5.1).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST) and moderate hepatic impairment (total bilirubin >1.5 to 3.0 times ULN and any AST). 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 5.2).

Renal impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min estimated by Cockcroft-Gault). Avapritinib has not been studied in patients with severe renal impairment (CLcr 15-29 mL/min) or end-stage renal disease (CLcr <15 mL/min), therefore its use in patients with severe renal impairment or end-stage renal disease cannot be recommended (see section 5.2).

Paediatric population

The safety and efficacy of AYVAKYT in children aged 0 to 18 years have not yet been established. No data are available.

Method of administration

AYVAKYT is for oral use.

The tablets must be taken on an empty stomach at least 1 hour before or at least 2 hours after a meal (see section 5.2).

Patients must swallow the tablets whole with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haemorrhages

Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage, in patients with unresectable or metastatic GIST and AdvSM. Gastrointestinal haemorrhagic adverse reactions were the most commonly reported haemorrhagic adverse reactions during avapritinib treatment of unresectable or metastatic GIST patients, while hepatic and tumour haemorrhage also occurred in GIST patients (see section 4.8).

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) or other concomitant medicinal products that increase the risk of bleeding.

Intracranial haemorrhages

Adverse reactions of intracranial haemorrhage occurred in GIST and AdvSM patients who received avapritinib.

Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with a history of vascular aneurysm, intracranial haemorrhage, 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 avapritinib must interrupt dosing of avapritinib 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 severity grade, avapritinib must be permanently discontinued (see section 4.2).

Unresectable or metastatic GIST

Serious adverse reactions of intracranial haemorrhage were reported in patients with unresectable or metastatic GIST receiving avapritinib (see section 4.8). The exact mechanism is unknown.

There is no clinical study experience using avapritinib in patients with brain metastases.

Advanced systemic mastocytosis

Serious adverse reactions of intracranial haemorrhage were reported in patients with AdvSM receiving avapritinib (see section 4.8). The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts $<50 \times 10^9/L$ and in patients with a starting dose of ≥ 300 mg.

Considering the above, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts $<50 \times 10^9/L$. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically

indicated) if values are less than $75 \times 10^9/L$, every 4 weeks if values are between 75 and $100 \times 10^9/L$, and as clinically indicated if values are greater than $100 \times 10^9/L$.

Manage platelet counts of $<50 \times 10^9/L$ by temporarily interrupting avapritinib. Platelet support may be necessary, and the recommended dose modification in Table 2 must be followed (see section 4.2). Thrombocytopenia was generally reversible by reducing or interrupting avapritinib in clinical studies. The maximum dose for patients with AdvSM must not exceed 200 mg once daily.

Cognitive effects

Cognitive effects, such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritinib (see section 4.8). 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 avapritinib, the recommended dose modification in Table 2 must be followed (see section 4.2). 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

Occurrences of fluid retention, including severe cases of localised oedema (facial, periorbital, peripheral oedema and/or pleural effusion) or generalised oedemas, have been reported with a frequency category of at least common in patients with unresectable or metastatic GIST taking avapritinib. Other localised oedemas (laryngeal oedema and/or pericardial effusion) have been reported uncommonly (see section 4.8).

In patients with AdvSM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common (see section 4.8). Other localised oedemas (laryngeal oedema) have been reported uncommonly.

Therefore, it is recommended that patients with GIST or AdvSM be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For GIST or AdvSM patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

In patients with ISM, localised (peripheral, facial) oedemas have been reported with a frequency category of at least common (see section 4.8).

QT interval prolongation

Prolongation of QT interval has been observed in patients with unresectable or metastatic GIST and AdvSM treated with avapritinib in clinical studies (see section 4.8 and 5.1). QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes.

Avapritinib 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 or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias (see section 4.5). If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, see section 4.2 for dose modification instructions.

In patients with GIST or AdvSM, interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong 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

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with unresectable or metastatic GIST and AdvSM (see section 4.8). GIST or AdvSM patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease-related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid properties.

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

Laboratory tests

Treatment with avapritinib in patients with unresectable or metastatic GIST and AdvSM is associated with anaemia, neutropenia and/or thrombocytopenia. Complete blood counts must be performed on a regular basis during the treatment with avapritinib in patients with GIST or AdvSM. See also intracranial haemorrhages above in this section and in section 4.8.

Treatment with avapritinib is associated in patients with unresectable or metastatic GIST and AdvSM with elevations in bilirubin and liver transaminases (see section 4.8). Liver function (transaminases and bilirubin) should be monitored regularly in patients with GIST or AdvSM receiving avapritinib.

CYP3A4 inhibitors and inducers

Co-administration with strong or moderate CYP3A inhibitors should be avoided because it may increase the plasma concentration of avapritinib (see sections 4.2 and 4.5).

Co-administration with strong or moderate CYP3A inducers should be avoided because it may decrease the plasma concentrations of avapritinib (see section 4.5).

Photosensitivity reaction

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may have an effect on avapritinib

Strong and moderate CYP3A inhibitors

Co-administration of avapritinib with a strong CYP3A inhibitor 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 avapritinib C_{max} by 1.4-fold and AUC_{0-inf} by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone.

Concomitant use 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 hyponatremia and boceprevir to treat hepatitis) including grapefruit or grapefruit juice should be avoided. If concomitant use 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 sections 4.2 and 4.4).

Strong and moderate CYP3A inducers

Co-administration of avapritinib with a strong CYP3A inducer decreased avapritinib plasma concentrations and may result in decreased 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 decreased avapritinib C_{max} by 74% and AUC_{0-inf} by 92%, relative to 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 avapritinib on other active substances

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

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

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

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be informed that avapritinib may cause foetal harm (see section 5.3).

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

Women of childbearing potential must use effective contraception during treatment and for 6 weeks after the last dose of AYVAKYT. Males with female partners of childbearing potential must use effective contraception during treatment and for 2 weeks after the last dose of AYVAKYT.

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

Pregnancy

There are no data from the use of avapritinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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 foetus.

Breast-feeding

It is unknown whether avapritinib/metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

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

Fertility

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 5.3).

4.7 Effects on ability to drive and use machines

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 who experience these adverse effects must take special care when driving a car or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The safety database includes a total of 585 patients with GIST (all doses), of which 550 patients received avapritinib at a starting dose of 300 mg or 400 mg; 193 patients enrolled in studies for AdvSM (all doses), of which 126 patients received avapritinib at a starting dose of 200 mg, and 246 patients with ISM (doses 25 mg – 100 mg), of which 141 patients received avapritinib at the recommended dose of 25 mg in Part 2, pivotal part of the PIONEER study (see section 5.1).

Unresectable or metastatic GIST

The most common adverse reactions of any grade during treatment with avapritinib at a starting dose of 300 mg or 400 mg were nausea (45%), fatigue (40%), anaemia (39%), periorbital oedema (33%), face oedema (27%), hyperbilirubinaemia (28%), diarrhoea (26%), vomiting (24%), oedema peripheral (23%), lacrimation increased (22%), decreased appetite (21%) and memory impairment (20%).

Serious adverse reactions occurred in 23% of patients receiving avapritinib. The most common serious adverse reactions during treatment with avapritinib were anaemia (6%), and pleural effusion (1%).

The most common adverse reactions leading to permanent treatment discontinuation were fatigue, encephalopathy and intracranial haemorrhage (< 1% each). Adverse reactions leading to a dose reduction included anaemia, fatigue, neutrophil count decreased, blood bilirubin increased, memory impairment, cognitive disorder, periorbital oedema, nausea and face oedema.

Advanced systemic mastocytosis

The most common adverse reactions of any grade during treatment with avapritinib at a starting dose of 200 mg were periorbital oedema (38%), thrombocytopenia (37%), oedema peripheral (33%), and anaemia (22%).

Serious adverse reactions occurred in 12% of patients receiving avapritinib. The most common serious adverse reactions during treatment with avapritinib were subdural haematoma (2%), anaemia (2%), and haemorrhage (2%).

In AdvSM patients treated at 200 mg, 7.1% had adverse reactions leading to permanent treatment discontinuation. In two patients (1.6%), subdural haematoma occurred. Cognitive disorder, depressed mood, diarrhoea, disturbance in attention, haemoglobin decreased, hair colour changes, libido decreased, nausea, neutropenia, premature menopause and thrombocytopenia occurred in one patient (0.8% each). Adverse reactions leading to a dose reduction included thrombocytopenia, neutropenia, periorbital oedema, cognitive disorder, oedema peripheral, platelet count decreased, neutrophil count decreased, anaemia, asthenia, fatigue, arthralgia, blood alkaline phosphatase increased, blood bilirubin increased, and white blood cell count decreased.

Indolent systemic mastocytosis

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.

Tabulated list of adverse reactions

Adverse reactions that were reported in clinical studies in $\geq 1\%$ of patients with GIST are listed below (Table 3) except for adverse reactions mentioned in the section 4.4 which are included regardless of frequency, according to the MedDRA System Organ Class and frequency. For patients with AdvSM, adverse reactions that were reported in clinical studies in $\geq 3\%$ of patients are listed below (Table 4). For patients with ISM, adverse reactions reported in Part 2 of the PIONEER study in $\geq 5\%$ of patients are listed in Table 5.

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

Table 3. Adverse reactions reported in clinical studies in patients with unresectable or metastatic GIST treated with avapritinib

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥ 3 %
Infections and infestations			
Common	Conjunctivitis	2.0	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon	Tumour haemorrhage	0.2	0.2
Blood and lymphatic system disorders			
Very common	Anaemia	39.6	20.4
	White blood cell count decreased	14.0	3.1
	Neutrophil count decreased	15.8	8.9
Common	Thrombocytopenia	8.4	0.9
	Lymphocyte count decreased	4.7	2.2
Metabolism and nutrition disorders			
Very common	Decreased appetite	21.1	0.5
Common	Hypophosphataemia	8.9	2.5
	Hypokalaemia	6.0	0.9
	Hypomagnesaemia	3.8	0.4
	Hyponatraemia	1.3	0.7
	Dehydration	1.8	0.5
	Hypoalbuminaemia	2.4	-
	Hypocalcaemia	2.2	0.4
Psychiatric disorders			
Common	Confusional state	4.7	0.5
	Depression	4.2	0.4
	Anxiety	1.8	-
	Insomnia	3.8	-
Nervous system disorders			
Very common	Memory impairment	22.7	0.9
	Cognitive disorder	11.8	0.9
	Dizziness	10.5	0.2
	Taste effect	12.7	-
Common	Intracranial haemorrhage ¹	1.6	1.1
	Mental impairment ²	5.6	0.7
	Neuropathy peripheral	8.5	0.4
	Somnolence	1.8	-
	Aphasia	1.8	-
	Hypokinesia	1.3	0.2
	Headache	8.0	0.2
	Balance disorder	1.6	-
	Speech disorder	4.5	-
	Tremor	2.2	0.2
Uncommon	Encephalopathy	0.9	0.5
Eye disorders			
Very common	Lacrimation increased	22.2	-
Common	Ocular haemorrhage ³	1.1	-
	Vision blurred	2.9	-
	Conjunctival haemorrhage	2.4	-
	Photophobia	1.6	-
Ear and labyrinth disorders			
Common	Vertigo	2.4	-

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥ 3 %
Cardiac disorders			
Uncommon	Pericardial effusion	0.9	0.2
Vascular disorders			
Common	Hypertension	3.3	1.1
Respiratory, thoracic and mediastinal disorders			
Common	Pleural effusion	6.0	0.9
	Dyspnoea	6.0	0.7
	Nasal congestion	1.5	-
	Cough	2.2	-
Gastrointestinal disorders			
Very common	Abdominal pain	10.9	1.1
	Vomiting	24.2	0.7
	Diarrhoea	26.4	2.7
	Nausea	45.1	1.5
	Dryness	10.9	0.2
	Gastroesophageal reflux disease	12.9	0.5
Common	Gastrointestinal haemorrhage ⁴	2.2	1.6
	Ascites	7.5	1.3
	Constipation	5.8	-
	Dysphagia	2.4	0.4
	Stomatitis	2.4	-
	Flatulence	1.6	-
	Salivary hypersecretion	1.5	-
Hepatobiliary disorders			
Very common	Hyperbilirubinaemia	27.5	5.8
Uncommon	Hepatic haemorrhage	0.2	0.2
Skin and subcutaneous tissue disorders			
Very common	Hair colour changes	15.3	0.2
	Rash	12.7	1.6
Common	Palmar-plantar erythrodysesthesia syndrome	1.3	-
	Photosensitivity reaction	1.1	-
	Skin hypopigmentation	1.1	-
	Pruritus	2.9	-
	Alopecia	9.6	-
Musculoskeletal and connective tissue disorders			
Common	Myalgia	2.0	-
	Arthralgia	1.8	-
	Back pain	1.1	-
	Muscle spasms	1.6	-
Renal and urinary disorders			
Common	Acute kidney injury	2.0	0.9
	Blood creatinine increased	4.4	-
	Haematuria	1.1	-
General disorders and administration site conditions			
Very common	Oedema ⁵	70.2	4.7
	Fatigue	39.6	5.3
Common	Asthenia	7.8	1.6
	Pyrexia	1.8	0.2
	Malaise	2.5	0.2
	Feeling cold	2.9	-
Investigations			
Very common	Transaminases increased	12.4	0.9

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥ 3 %
Common	Electrocardiogram QT prolonged	2.0	0.2
	Blood creatine phosphokinase increased	3.3	0.4
	Weight decreased	7.5	0.2
	Weight increased	4.7	-
	Blood lactate dehydrogenase increased	1.3	-

¹Intracranial haemorrhage (including Cerebral haemorrhage, Haemorrhage intracranial, Subdural haematoma, Cerebral haematoma)

²Mental impairment (including Disturbance in attention, Mental impairment, Mental status changes, Dementia)

³Ocular haemorrhage (including Eye haemorrhage, Retinal haemorrhage, Vitreous haemorrhage)

⁴Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Rectal haemorrhage, Melaena)

⁵Oedema (including Periorbital oedema, Oedema peripheral, Face oedema, Eyelid oedema, Fluid retention, Generalised oedema, Orbital oedema, Eye oedema, Oedema, Peripheral swelling, Swelling face, Eye swelling, Conjunctival oedema, Laryngeal oedema, Localised oedema, Lip swelling)

-: no adverse reactions reported with Grades ≥ 3

Advanced systemic mastocytosis

Table 4. Adverse reactions reported in clinical studies in patients with advanced systemic mastocytosis treated with avapritinib starting at 200 mg

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥ 3 %
Blood and lymphatic system disorders			
Very common	Thrombocytopenia*	46.8	23.0
	Anaemia*	23.0	11.9
	Neutropenia*	21.4	19.0
Common	Leukopenia*	8.7	2.4
Psychiatric disorders			
Common	Confusional state	1.6	-
Nervous system disorders			
Very common	Taste effect*	15.9	0.8
	Cognitive disorder	11.9	1.6
Common	Headache	7.9	-
	Memory impairment*	5.6	-
	Dizziness	5.6	-
	Neuropathy peripheral ¹	4.8	-
	Intracranial haemorrhage ²	2.4	0.8
Eye disorders			
Common	Lacrimation increased	6.3	-
Cardiac disorders			
Uncommon	Pericardial effusion	0.8	-
Respiratory, thoracic and mediastinal disorders			
Common	Epistaxis	5.6	-
	Pleural effusion	2.4	-
Gastrointestinal disorders			
Very common	Diarrhoea	14.3	1.6
	Nausea	12.7	-
Common	Vomiting*	8.7	0.8

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥ 3 %
	Gastroesophageal reflux disease*	4.8	-
	Ascites*	4.0	0.8
	Dryness*	4.0	-
	Constipation	3.2	-
	Abdominal pain*	3.2	-
	Gastrointestinal haemorrhage ³	2.4	1.6
Hepatobiliary disorders			
Common	Hyperbilirubinaemia*	7.9	0.8
Skin and subcutaneous tissue disorders			
Very common	Hair colour changes	15.1	-
Common	Rash*	7.9	0.8
	Alopecia	7.1	-
Uncommon	Photosensitivity reaction	0.8	-
Renal and urinary disorders			
Uncommon	Acute kidney injury*	0.8	-
Musculoskeletal and connective tissue disorders			
Common	Arthralgia	4.8	0.8
General disorders and administration site conditions			
Very common	Oedema ⁴	69.8	4.8
	Fatigue*	18.3	2.4
Common	Pain	3.2	-
Investigations			
Common	Weight increased	6.3	-
	Blood alkaline phosphatase increased	4.8	1.6
	Transaminases increased*	4.8	-
	Electrocardiogram QT prolonged	1.6	0.8
Injury, poisoning and procedural complications			
Common	Contusion	3.2	-

¹Neuropathy peripheral (including Paraesthesia, Neuropathy peripheral, Hypoaesthesia)

²Intracranial haemorrhage (including Haemorrhage intracranial, Subdural haematoma)

³Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Melaena)

⁴Oedema (including Periorbital oedema, Oedema peripheral, Face oedema, Eyelid oedema, Fluid retention, Generalised oedema, Oedema, Peripheral swelling, Swelling face, Eye swelling, Conjunctival oedema, Laryngeal oedema, Localised oedema)

*Comprises pooled terms representing similar medical concepts.

-: no adverse reactions reported

Indolent systemic mastocytosis

Table 5. Adverse reactions reported in clinical studies in patients with indolent systemic mastocytosis

System Organ Class / frequency category	Adverse reactions	Avapritinib (25 mg once daily) + Best Supportive Care All grades%	Grades ≥ 3 %
Psychiatric disorders			
Common	Insomnia	5.7	-
Vascular disorders			
Common	Flushing	9.2	1.4

System Organ Class / frequency category	Adverse reactions	Avapritinib (25 mg once daily) + Best Supportive Care All grades%	Grades ≥ 3 %
Skin and subcutaneous tissue disorders			
Common	Photosensitivity reaction	2.8	-
General disorders and administration site conditions			
Very common	Peripheral oedema ¹	12.1	-
Common	Face oedema	7.1	-
Investigations			
Common	Blood alkaline phosphatase increased	6.4	0.7

¹Peripheral oedema (including oedema peripheral and peripheral swelling)

-: no adverse reactions reported

Description of selected adverse reactions

Intracranial haemorrhage

Unresectable or metastatic GIST

Intracranial haemorrhage occurred in 10 (1.7%) of the 585 patients with GIST (all doses) and in 9 (1.6%) of the 550 patients with GIST who received avapritinib at a starting dose of 300 mg or 400 mg once daily (see section 4.4).

Events of intracranial haemorrhage (all grades) occurred in a range from 8 weeks to 84 weeks after initiating avapritinib, with a median time to onset of 22 weeks. The median time to improvement and resolution was 25 weeks for intracranial haemorrhage of Grade ≥ 2 .

Advanced systemic mastocytosis

Intracranial haemorrhage occurred in a total (regardless of causality) of 4 (3.2%) of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg once daily regardless of platelet count prior to initiation of therapy. In 3 of these 4 patients, the event was assessed as related to avapritinib (2.4%). The risk of intracranial haemorrhagic events is higher in patients with platelet counts $< 50 \times 10^9/L$. 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 $\geq 50 \times 10^9/L$ prior to initiation of therapy (see section 4.4). 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 $< 50 \times 10^9/L$ prior to initiation of therapy, of which 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 12.1 weeks.

In clinical studies with avapritinib, the incidence of intracranial haemorrhage was higher in patients who received a starting dose of ≥ 300 mg once daily, as compared to 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 (regardless of causality) of intracranial bleeding regardless 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 $< 50 \times 10^9/L$ prior to initiation of therapy, of which 4 patients experienced an intracranial haemorrhage, that were assessed as related to avapritinib in 3 of 4 cases. Four of 43 patients with platelet counts $\geq 50 \times 10^9/L$ prior to initiation of therapy experienced an intracranial haemorrhage, which were assessed as related to avapritinib in 3 of 4 cases.

Fatal events of intracranial haemorrhage have 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

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

A broad spectrum of cognitive effects that are generally reversible (with intervention) can occur in patients receiving avapritinib. Cognitive effects were managed with dose interruption and/or reduction, and 2.7% led to permanent discontinuation of avapritinib treatment in patients with GIST and AdvSM.

Unresectable or metastatic GIST

Cognitive effects occurred in 194 (33%) of the 585 patients with GIST (all doses) and in 182 (33%) of the 550 patients with GIST who received avapritinib at starting doses of either 300 or 400 mg once daily (see section 4.4). In the patients who had an event (any grade), the median time to onset was 8 weeks.

Most cognitive effects were Grade 1, with Grade ≥ 2 occurring in 11% of 550 patients. Among patients who experienced a cognitive effect of Grade ≥ 2 (impacting activities of daily living) the median time to improvement was 15 weeks.

Memory impairment occurred in 20% of patients, <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; <1% of these events were Grade 3. Confusional state occurred in 5% of patients; <1% of these events were Grade 3. Encephalopathy occurred in <1% of patients; <1% of these events were Grade 3. Serious adverse reactions of cognitive effects were reported for 9 of 585 (1.5%) of the GIST patients (all doses), of which 7 of the 550 (1.3%) patients were observed in the GIST group receiving a starting dose of either 300 or 400 mg once daily.

Overall, 1.3% of patients required permanent discontinuation of avapritinib for a cognitive effect.

Cognitive effects occurred in 37% of the patients aged ≥ 65 years receiving a starting dose of either 300 or 400 mg once daily.

Advanced systemic mastocytosis

Cognitive effects occurred in 51 (26%) of the 193 patients with AdvSM (all doses) and in 23 (18%) of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg (see section 4.4). In the patients with AdvSM treated at a starting dose of 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 7% of 126 patients treated at a starting dose of 200 mg. 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 at a starting dose of 200 mg, cognitive disorder occurred in 12% of patients, memory impairment occurred in 6% of patients and confusional state occurred in 2% of patients. None of these events were Grade 4.

Serious adverse reactions of cognitive effects were reported for 1 of 193 (<1%) AdvSM patients (all doses), none were observed in the AdvSM group receiving a starting dose of 200 mg once daily.

Overall, 1.6% of AdvSM patients (all doses) required permanent discontinuation of avapritinib for a cognitive adverse reaction, 8% required a dose interruption, and 9% required dose reduction.

Cognitive effects occurred in 20% of the patients aged ≥ 65 years receiving a starting dose of 200 mg once daily.

Indolent systemic mastocytosis

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 4.4); 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).

Elderly

Unresectable or metastatic GIST

In NAVIGATOR and VOYAGER (N=550) (see section 5.1), 39% 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 ≥65 years old had reported adverse reactions that led to dose reductions (55% versus 45%) and dose discontinuation (18% versus 4%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (63% versus 50%).

Advanced systemic mastocytosis

In patients treated at 200 mg in EXPLORER and PATHFINDER (N=126) (see section 5.1), 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 ≥65 years old reported adverse reactions that led to dose reductions (62% versus 73%). A similar fraction of patients reported adverse reactions that led to dose discontinuation (9% versus 6%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions (63.3%) compared to younger patients (53.2%).

Indolent systemic mastocytosis

In Part 2 of PIONEER (N=141) (see section 5.1), 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 important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is limited experience with cases of overdose reported in clinical studies with avapritinib. The maximum dose of avapritinib studied clinically is 600 mg orally once daily. Adverse reactions observed at this dose were consistent with the safety profile at 300 mg or 400 mg once daily (see section 4.8).

Management

There is no known antidote for avapritinib overdose. In the event of suspected overdose, avapritinib should be interrupted and supportive care instituted. Based on the large volume of distribution of

avapritinib and extensive protein binding, dialysis is unlikely to result in significant removal of avapritinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitor, ATC code: L01EX18.

Mechanism of action

Avapritinib is a Type 1 kinase inhibitor that has demonstrated biochemical *in vitro* activity on the PDGFRA D842V and KIT D816V mutants associated with resistance to imatinib, sunitinib and regorafenib with half maximal inhibitory concentrations (IC₅₀) 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 IC₅₀ of 4 nM and 30 nM, respectively. In cellular assays, avapritinib inhibited the 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.

Pharmacodynamic effects

Potential to prolong the QT interval

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.

Clinical efficacy and safety

Clinical studies in unresectable or metastatic GIST

The efficacy and safety of avapritinib was assessed in a multi-centre, single-arm, open-label clinical study (BLU-285-1101; NAVIGATOR). Patients with a confirmed diagnosis of GIST and an Eastern Clinical Oncology Group (ECOG) performance status (PS) of 0 to 2 (58% and 3% of patients had ECOG status 1 and 2, respectively) were included in the study. A total of 217 patients received a starting dose of either 300 mg or 400 mg once daily.

Efficacy was assessed on the basis of overall response rate (ORR) according to Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 modified for patients with unresectable or metastatic GIST (mRECIST v1.1) and duration of response (DOR), as evaluated by a Blinded Independent Central Review (BICR).

In addition, a total of 239 patients have received treatment with avapritinib at the relevant starting dose in an ongoing open-label, randomised phase 3 study (BLU-285-1303; VOYAGER) in which PFS is the primary endpoint. Ninety six additional patients received avapritinib in this study after disease progression on the regorafenib control treatment (crossover). As of the last data cut-off date, 9th March 2020, the median treatment duration was 8.9 months in patients with GIST harbouring the PDGFRA D842V mutation included in this study, which provides some preliminary comparative safety data.

PDGFRA D842V mutation

A total of 38 patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation were enrolled and treated with avapritinib at a starting dose of either 300 mg or 400 mg once daily. In the NAVIGATOR study 71% of patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation had dose reductions to 200 mg or 100 mg once daily during the course of therapy. Median time to dose reduction was 12 weeks. The GIST patients were required to have unresectable or metastatic disease and have a documented PDGFRA D842V mutation determined by a locally available diagnostic test. At 12 months, 27 patients were still on avapritinib with 22% receiving 300 mg once daily, 37% receiving 200 mg once daily and 41% receiving 100 mg once daily.

Baseline demographics 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, largest target lesion was >5 cm for 58%, 90% had prior surgical resection, and median number of prior lines of tyrosine kinase inhibitors of 1 (range: 0 to 5).

Efficacy results from study BLU-285-1101 (NAVIGATOR) for GIST patients harbouring the PDGFRA D842V mutation are summarised in Table 6. The data represent a median duration of follow-up of 26 months across all patients with PDGFRA D842V mutations who were alive, the median OS had not been reached with 74% of patients alive. The median progression free survival was 24 months. Radiographic tumour reductions were observed in 98% of patients.

Table 6. Efficacy results for PDGFRA D842V-Mutation in GIST patients (NAVIGATOR study)

Efficacy Parameter	N = 38
mRECIST 1.1 ORR¹, (%) (95% CI)	95 (82.3, 99.4)
CR	13
PR	82
DOR (months), median (CI)	22.1 (14.1, NE)

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)

In patients with PDGFRA D842V-mutant GIST treated at starting doses of 300 or 400 mg once daily the ORR based on central radiology review by mRECIST v1.1 criteria was 95%.

Based on preliminary results from the ongoing phase 3 study BLU-285-1303 (VOYAGER) in a subset of 13 patients with PDGFRA D842V mutations, partial response was reported in 3 out of 7 patients in the avapritinib group (43% ORR) and none of the 6 patients in the regorafenib group (0% ORR). The median PFS there was not estimable in patients with PDGFRA D842V mutations randomized to avapritinib (95% CI: 9.7, NE) compared to 4.5 months in patients receiving regorafenib (95% CI: 1.7, NE).

Clinical studies in advanced systemic mastocytosis

The efficacy and safety of avapritinib was assessed in a multi-center, single-arm, open-label Phase 2 study BLU-285-2202 (PATHFINDER). Eligible patients were required to have an ECOG PS of 0 to 3. Patients with high and very high risk AHNs such as AML or high risk MDS, and Philadelphia chromosome-positive malignancies were excluded. Palliative and supportive care medications were allowed. The response-evaluable population according to modified IWG-MRT-ECNM criteria as adjudicated by a central committee includes patients with a diagnosis of AdvSM, who had received at least 1 dose of avapritinib, had at least 2 post-baseline bone marrow assessments and had been on

study for at least 24 weeks, or had an end of study visit. The primary efficacy outcome measure was ORR per modified IWG-MRT-ECNM criteria as adjudicated by the central committee. Of 107 patients enrolled in the study, 67 patients had at least one prior systemic therapy and were treated at a starting dose of 200 mg orally once daily.

The assessment of the primary efficacy endpoint was based on a total of 47 AdvSM patients, evaluable according to the modified IWG-MRT-ECNM response criteria, enrolled in the study, who received at least one prior systemic therapy and a starting dose of 200 mg avapritinib once daily with 78.7% of patients having received prior midostaurin, 17.0% prior cladribine, 14.9 % prior interferon alpha, 10.6% prior hydroxycarbamide and 6.4% prior azacytidine. Thirty seven (79%) out of the 47 patients with AdvSM who received at least one prior systemic therapy and a starting dose of 200 mg avapritinib had one or more dose reductions during the course of therapy with a median time to dose reduction of 6 weeks. The study population characteristics were: median age of 69 years (range: 31 to 86 years), 70% male, 92% white, ECOG PS of 0-3 (66% and 34% of patients had an ECOG PS of 0-1 and 2-3, respectively), and 89% had a detectable KIT D816V mutation. Before initiation of avapritinib treatment, 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 (MAF) was 26.2%.

Efficacy results in patients with AdvSM enrolled in the study, who received at least one prior systemic therapy and a starting dose of 200 mg avapritinib once daily, with a median duration of follow-up of 12 months are summarized in Table 7.

Table 7. Efficacy results for patients with advanced systemic mastocytosis who received at least one prior systemic therapy in PATHFINDER

Efficacy parameter	Overall	ASM	SM-AHN	MCL
ORR¹ per modified IWG-MRT-ECNM, n (%) (95% confidence interval)	N = 47 28 (60) (44.3, 73.6)	N = 8 5 (63) (24.5, 91.5)	N = 29 19 (66) (45.7, 82.1)	N = 10 4 (40) (12.2, 73.8)
Response per modified IWG-MRT-ECNM category, n (%)				
CR	1 (2)	0	1 (3)	0
CRh	4 (9)	2 (25)	2 (7)	0
PR	19 (40)	3 (38)	13 (45)	3 (30)
CI	4 (9)	0	3 (10)	1 (10)
DOR² (months), median (95% confidence interval)	N = 28 NR (NE, NE)	N = 5 NR (NE, NE)	N = 19 NR (NE, NE)	N = 4 NR (NE, NE)
DOR rate at 12 months, %	100.0	100.0	100.0	100.0
DOR rate at 24 months, %	85.6	NE	83.3	NE
Time to response (months), median (min, max)	N = 28 1.9 (0.5, 12.2)	N = 5 2.3 (1.8, 5.5)	N = 19 1.9 (0.5, 5.5)	N = 4 3.6 (1.7, 12.2)
Time to CR/CRh (months), median (min, max)	N = 5 3.7 (1.8, 14.8)	N = 2 2.8 (1.8, 3.7)	N = 3 5.6 (1.8, 14.8)	N = 0 NE

Abbreviations: CI=clinical improvement; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; DOR=duration of response; NE=not estimable; NR=not reached; ORR=overall response rate; PR=partial remission

¹ ORR per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh, PR or CI (CR + CRh + PR+CI)

² Estimated from Kaplan-Meier analysis

Among patients treated with avapritinib at a starting dose of 200 mg once daily following at least one prior systemic therapy, 83.1% of patients had $\geq 50\%$ decrease of bone marrow mast cells with 58.5% patients having complete elimination of bone marrow mast cell aggregates; 88.1% of patients had $\geq 50\%$ reduction in serum tryptase with 49.3% reducing serum tryptase < 20 ng/mL; 68.7% of patients had a $\geq 50\%$ decrease in KIT D816V MAF in blood and 60.0% of patients had $\geq 35\%$ spleen volume reduction from baseline.

In a supportive multi-center, single-arm, open-label Phase 1 study BLU-285-2101 (EXPLORER), the ORR according to the mIWG-MRT-ECNM criteria was 73% (95% confidence interval: 39.0, 94.0) for 11 AdvSM patients who received at least one prior systemic therapy and a starting dose of 200 mg avapritinib once daily.

Clinical studies in indolent systemic mastocytosis

The efficacy and safety of avapritinib was assessed in study BLU-285-2203 (PIONEER), a randomised, double-blind, placebo-controlled, 3-part study conducted in adult patients with ISM with moderate-to-severe symptoms not adequately controlled by best supportive care. In Part 2 (pivotal part), patients were randomised to receive avapritinib at the recommended dose of 25 mg orally once daily with best supportive care (141 patients) 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 endpoint 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. 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 endpoints were the proportion of avapritinib-treated patients achieving $\geq 50\%$ and $\geq 30\%$ reduction from baseline through Week 24 in TSS compared to placebo. Objective measures of mast cell burden were also reported as key secondary efficacy endpoints and included the proportion of patients with a $\geq 50\%$ 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 endpoints compared to placebo, as summarized in Table 8.

Table 8. 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
Measures 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 population

Unresectable or metastatic GIST

Forty-two percent of the patients who received AYVAKYT at a starting dose of 300 mg and 400 mg once daily in NAVIGATOR were 65 years or older. No overall differences in efficacy were observed in comparison with younger patients. Only limited data are available from the use of avapritinib in patients aged 75 years or older (8% (3 out of 38)).

Advanced systemic mastocytosis

Of the 47 patients who received AYVAKYT at a starting dose of 200 mg and who received at least one prior systemic therapy in PATHFINDER, 64% were 65 years or older, while 21% were 75 years and older. No overall differences in efficacy were observed between patients ≥ 65 years and those < 65 years.

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with AYVAKYT in one or more subsets of the paediatric population with a relapsed/refractory solid tumour harbouring mutations in either KIT or PDGFRA (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with AYVAKYT in all subsets of the paediatric population with mastocytosis (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following administration of avapritinib once daily, steady state was reached by 15 days.

Unresectable or metastatic GIST (300 mg once daily dose)

After a single dose and repeat dosing of avapritinib, systemic exposure of avapritinib was dose-proportional over the dose range of 30 to 400 mg once daily in patients with unresectable or metastatic GIST. The steady state geometric mean (CV%) maximum concentration (C_{max}) and area under the concentration-time curve (AUC_{0-tau}) of avapritinib at 300 mg once daily was 813 ng/mL (52%) and 15400 h•ng/mL (48%), respectively. The geometric mean accumulation ratio after repeat dosing was 3.1 to 4.6.

Advanced systemic mastocytosis (200 mg once daily dose)

Steady-state C_{max} and AUC of avapritinib increased proportionally over the dose range of 30 mg to 400 mg once daily in patients with AdvSM. The steady state geometric mean (CV%) C_{max} and AUC_{0-24} of avapritinib at 200 mg once daily was 377 ng/mL (62%) and 6600 h•ng/mL (54%), respectively. The geometric mean accumulation ratio after repeat dosing (30-400 mg) was 2.6 to 5.8.

Indolent systemic mastocytosis (25 mg once daily dose)

The C_{\max} and AUC of avapritinib increased proportionally over the dose range of 25 mg to 100 mg once daily in patients with ISM. The steady state geometric mean (CV%) C_{\max} and AUC₀₋₂₄ of avapritinib at 25 mg once daily was 70.2 ng/mL (47.8%) and 1330 h•ng/mL (49.5%), respectively. The geometric mean accumulation ratio after repeat dosing was 3.59.

Absorption

Following administration of single oral doses of avapritinib of 25 to 400 mg, the median time to peak concentration (T_{\max}) ranged from 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.

Effect of food

Avapritinib C_{\max} and AUC_{inf} were increased by 59% and 29%, respectively, in healthy subjects administered avapritinib after a high fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to the C_{\max} and AUC_{inf} after overnight fasting.

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 (V_c/F) is 971 L at median lean body weight of 54 kg. The inter-individual variability of V_c/F is 50.1%.

Biotransformation

In vitro studies demonstrated that oxidative metabolism of avapritinib is predominantly mediated by CYP3A4, CYP3A5 and to a minor extent by CYP2C9. The relative contributions of CYP2C9 and CYP3A to the *in vitro* metabolism of avapritinib were 15.1% and 84.9%, respectively. The formation of the glucuronide M690 is catalysed mainly by UGT1A3.

Following a single dose of approximately 310 mg (~100 μ Ci) [¹⁴C]avapritinib to healthy subjects, oxidation, glucuronidation, oxidative deamination and *N*-dealkylation were the primary metabolic pathways. Unchanged avapritinib (49%) and metabolites, M690 (hydroxy glucuronide; 35%) and M499 (oxidative deamination; 14%) were the major circulating radioactive components. Following oral administration of avapritinib 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 4.5). *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 4.5). *In vitro*, avapritinib did not induce CYP1A2 or CYP2B6 at clinically relevant concentrations.

Elimination

Following single doses of AYVAKYT in patients with GIST, AdvSM and ISM, the mean plasma elimination half-life of avapritinib was 32 to 57 hours, 20 to 39 hours and 38 to 45 hours, respectively.

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%.

Following a single oral dose of approximately 310 mg (~100 µCi) [¹⁴C]avapritinib to healthy subjects, 70% of the radioactive dose was recovered in faeces and 18% excreted in urine. Unchanged avapritinib accounted for 11% and 0.23% of the administered radioactive dose excreted in faeces and urine, respectively.

Effects of avapritinib on transport proteins

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

Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP *in vitro* (see section 4.5). *In vitro*, avapritinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2 at clinically relevant concentrations.

Gastric acid reducing active substances

No clinical drug-drug interaction studies have been conducted. Based on both population and noncompartmental pharmacokinetic analyses, the effect of gastric acid reducing agents on the bioavailability of avapritinib is not clinically relevant.

Special populations

Population pharmacokinetic analyses indicate that age (18-90 years), body weight (40-156 kg), sex and albumin concentration have no effect on the exposure of avapritinib. Concomitant use of proton pump inhibitors (PPI) on bioavailability (F) and lean body weight on the apparent central volume of distribution (V_c/F) were identified as statistically significant covariates with impact on avapritinib exposure. Lean body weight (30 kg to 80 kg) showed modest impact on C_{max} at steady state (+/- 5%), while concomitant use of PPIs led to ~19% reduction in AUC and C_{max}. These minor effects on exposure are not clinically significant given the PK variability (>40% CV) and are not expected to impact efficacy or safety. No significant effect of race on the pharmacokinetics of avapritinib was found, although the low number of Black (N=27) and Asian (N=26) subjects limits the conclusions that can be derived based on race.

Hepatic impairment

As hepatic elimination is a major route of excretion for avapritinib, hepatic impairment may result in increased plasma avapritinib concentrations. Based on a population pharmacokinetic analysis, avapritinib exposures were similar between 72 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST), 13 subjects with moderate hepatic impairment (total bilirubin >1.5 to 3.0 times ULN and any AST), and 402 subjects with normal hepatic function (total bilirubin and AST within ULN). 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 4.2).

Renal impairment

Based on a population pharmacokinetic analysis, avapritinib exposures were similar among 136 subjects with mild renal impairment (CL_{cr} 60-89 mL/min), 52 subjects with moderate renal impairment (CL_{cr} 30-59 mL/min) and 298 subjects with normal renal function (CL_{cr} ≥90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics of avapritinib in patients with severe renal impairment (CL_{cr} 15-29 mL/min) or end-stage renal disease (CL_{cr} <15 mL/min) has not been studied.

5.3 Preclinical safety data

Repeat dose toxicology studies

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 dose 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 dose 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.

In a 6 month repeat dose toxicology study in rats, rats 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).

Genotoxicity/carcinogenicity

Avapritinib was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test). It was positive in the *in vitro* chromosome aberration test in cultured human peripheral blood lymphocytes but negative in the rats for both the bone marrow micronucleus test and for the chromosomal damage liver comet assays, and thus, overall non-genotoxic. 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.

Toxicity to reproduction and development

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 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 the 25 mg, 200 mg, and 300 mg dose, respectively.

Phototoxicity studies

An *in vitro* phototoxicity study in 3T3 mouse fibroblasts as well as a phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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 glaze 45% (20% esterified) in ethanol
Brilliant blue FCF (E133)
Titanium dioxide (E171)
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with child-resistant cap (polypropylene) with foiled induction seal liner (pulp backed heat induction foil) and a desiccant in canister.

Each carton contains one bottle with 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

AYVAKYT 25 mg film-coated tablets
EU/1/20/1473/004

AYVAKYT 50 mg film-coated tablets
EU/1/20/1473/005

AYVAKYT 100 mg film-coated tablets
EU/1/20/1473/001

AYVAKYT 200 mg film-coated tablets
EU/1/20/1473/002

AYVAKYT 300 mg film-coated tablets
EU/1/20/1473/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 2020

Date of latest renewal: 24 July 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V-mutant GIST.	Q1 2027

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 25 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 25 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AYVAKYT 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 25 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 25 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 50 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AYVAKYT 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 50 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 50 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 100 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AYVAKYT 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 100 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 100 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 200 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AYVAKYT 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 200 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 200 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 300 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 300 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AYVAKYT 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 300 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

AYVAKYT 300 mg film-coated tablets
avapritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 300 mg avapritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Do not swallow the desiccant canister found in the bottle.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1473/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

AYVAKYT 25 mg film-coated tablets avapritinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AYVAKYT is and what it is used for
2. What you need to know before you take AYVAKYT
3. How to take AYVAKYT
4. Possible side effects
5. How to store AYVAKYT
6. Contents of the pack and other information

1. What AYVAKYT is and what it is used for

What AYVAKYT is

AYVAKYT is a medicine containing the active substance avapritinib.

What AYVAKYT is used for

AYVAKYT is used in adults to treat aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy. These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter various organs of your body, such as the liver, bone marrow or spleen. These mast cells also release substances such as histamine which cause various general symptoms that you may be experiencing as well as damage to involved organs. ASM, SM-AHN and MCL are collectively referred to as advanced systemic mastocytosis (AdvSM).

AYVAKYT is also used for the treatment of adults with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment. This is a disorder in which your body has many abnormal mast cells. Mast cells are the white blood cells responsible for allergic reactions. These cells may be in any tissue in your body but are often found in your skin, your intestines and your bone marrow. These abnormal mast cells can cause symptoms such as severe allergic reactions, diarrhoea, rash and difficulty thinking.

How AYVAKYT works

AYVAKYT stops the activity of a group of proteins in the body called kinases. Mast cells in patients with AdvSM and ISM usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells.

If you have any questions about how AYWAKYT works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take AYWAKYT

Do not take AYWAKYT:

- if you are allergic to avapritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking AYWAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.
- **if you have low platelet counts.**
- **If you are taking a medicine that thins the blood to prevent blood clots such as warfarin or phenprocoumon.**

Take special care with this medicine:

- You may develop symptoms such as **severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain)**. If these occur, contact your doctor immediately and temporarily stop treatment. For patients with AdvSM, your doctor will evaluate your platelet counts before you start treatment and monitor them as needed during your treatment with avapritinib.
- Treatment with this medicine may lead to a **higher risk of bleeding** in patients with AdvSM. Avapritinib can cause bleeding in the digestive system such as stomach, rectum, or intestine. Tell your doctor if you had or have any bleeding problems. Before you start taking avapritinib your doctor may decide to do blood tests. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood.
- You may also develop **memory loss, changes in memory, or be confused (signs of a cognitive effect)**. Avapritinib can sometimes change how you think and how you remember information. Contact your doctor in case you experience these symptoms or in case a family member, caregiver or someone who knows you notices that you are getting forgetful or confused.
- During treatment with this medicine, tell your doctor straight away **if you put on weight very quickly, develop swelling of your face or limbs, have difficulty breathing or become short of breath**. This medicine may cause your body to retain water (severe fluid retention can occur in patients with AdvSM).
- Avapritinib may cause **abnormality of your heart rhythm**. Your doctor may conduct tests to evaluate these problems during your treatment with avapritinib. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking this medicine.
- You may get **severe stomach and bowel problems (diarrhoea, nausea and vomiting)** if you have AdvSM. Get medical help immediately if you experience these symptoms.
- You may become **more sensitive to the sun** while taking this medicine. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

While you are taking avapritinib, your doctor will ask you to have regular blood tests and weigh you regularly if you have AdvSM.

For more information see section 4.

Children and adolescents

AYWAKYT has not been studied in children and adolescents under age 18. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and AYVAKYT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. AYVAKYT may affect the way other medicines work, and certain other medicines may affect how this medicine works.

Tell your doctor or pharmacist before taking AYVAKYT if you are taking any of the following medicines:

The following medicines can increase the effects of avapritinib and may increase its side effects:

- Boceprevir – used to treat hepatitis C
- Cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)

The following medicines can reduce the effects of avapritinib:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy
- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

This medicine may affect how well the following medicines work or increase their side effects:

- Alfentanil – used to control pain during operations and medical procedures
- Atazanavir – used to treat HIV infection/AIDS
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

Ask your doctor or pharmacist for advice before taking any medicine.

AYVAKYT with food and drink

You should not drink grapefruit juice or eat grapefruit while on treatment with AYVAKYT.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking AYVAKYT during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Women who are able to become pregnant should use effective contraception during treatment and for at least 6 weeks after completion of treatment. Males with female partners who are able to become pregnant should use effective contraception during treatment and for at least 2 weeks after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if AYVAKYT passes into breast milk. You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility

AYVAKYT may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

Driving and using machines

AYVAKYT may cause symptoms that affect your ability to concentrate and react (see section 4). Therefore, AYVAKYT may influence the ability to drive and use machines. Take special care when driving a car or operating machines if you experience these side effects.

AYVAKYT contains sodium

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

3. How to take AYVAKYT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength of AYVAKYT to use

The recommended dose of AYVAKYT will depend on your illness – see below.

AYVAKYT is available in different strength tablets. The strengths are 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. Your doctor will advise you about the strength and number of tablets you should take:

Treatment of AdvSM

The recommended dose is 200 mg by mouth once daily.

Treatment of ISM

The recommended dose is 25 mg by mouth once daily.

If you have liver problems, your doctor may start you on a lower dose of AYVAKYT.

If you get side effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking AYVAKYT unless your doctor tells you to.

Swallow the AYVAKYT tablet(s) whole with a glass of water, on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking AYVAKYT.

If you vomit after taking a dose of AYVAKYT, do not take an extra dose. Take your next dose at your scheduled time.

If you take more AYVAKYT than you should

If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention.

If you forget to take AYVAKYT

If you miss a dose of AYVAKYT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.

Do not take two doses within 8 hours to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects in patients with AdvSM

Some side effects may be serious. Tell your doctor straight away if you get any of the following (see also section 2.):

- severe headache, vision problems, severe sleepiness, severe weakness on one side of your body (signs of bleeding in your brain)
- memory loss, changes in memory, or confusion (signs of a cognitive effect)

Other side effects in patients with AdvSM may include

Very common (may affect more than 1 in 10 people):

- altered taste
- memory loss, changes in memory, or confusion (cognitive effects)
- diarrhoea
- nausea, retching and vomiting
- change in hair colour
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing decrease in red blood cells (anaemia) and white blood cells

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- bleeding in your brain
- increased tear production
- nose bleed
- shortness of breath
- heartburn
- increased fluid in the abdomen
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- gastrointestinal bleed
- rash
- hair loss
- pain
- weight gain
- changes in the electric activity of the heart
- bruising
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Uncommon (may affect up to 1 in 100 people):

- fluid around the heart
- red or itchy skin
- blood tests showing decreased kidney function

Side effects in patients with ISM may include

Very common (may affect more than 1 in 10 people):

- swelling of arms and legs

Common (may affect up to 1 in 10 people):

- trouble falling asleep (insomnia)

- flushing
- red or itchy skin
- face swelling
- blood test showing effect on the bone (blood alkaline phosphatase increased)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AYVAKYT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AYVAKYT contains

- The active substance is avapritinib. Each film-coated tablet contains 25 mg avapritinib.
- The other ingredients are:
 - The tablet core contains: microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate (see section 2 "AYVAKYT contains sodium").
 - The tablet coating contains: talc, macrogol 3350, poly(vinyl alcohol), and titanium dioxide (E171).

What AYVAKYT looks like and contents of the pack

AYVAKYT 25 mg film-coated tablets are round, white tablets of 5 mm diameter, debossed with "BLU" on one side and "25" on the other.

AYVAKYT is supplied in a bottle containing 30 film-coated tablets. Each carton contains one bottle.

Keep the desiccant canister in the bottle.

Marketing Authorisation Holder and Manufacturer

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Deutschland, Eesti, España, France, Hrvatska, Ireland, Ísland,

Ελλάδα, Κύπρος
Swixx Biopharma S.M.S.A.
Τηλ: +30 214 444 9670

**Italia, Latvija, Lietuva,
Luxembourg/Luxemburg, Magyarország,
Malta, Nederland, Norge, Österreich, Polska,
Portugal, România, Slovenija, Slovenská
republika, Suomi/Finland, Sverige, United
Kingdom (Northern Ireland)**

Blueprint Medicines (Netherlands) B.V., NL
Tel/ Tél/ Тел/ Tlf/ Sími/ Puh: +31 85 064 4001
e-mail: MedinfoEurope@blueprintmedicines.com

This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and
this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/en>.

Package leaflet: Information for the patient

AYVAKYT 50 mg film-coated tablets avapritinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AYVAKYT is and what it is used for
2. What you need to know before you take AYVAKYT
3. How to take AYVAKYT
4. Possible side effects
5. How to store AYVAKYT
6. Contents of the pack and other information

1. What AYVAKYT is and what it is used for

What AYVAKYT is

AYVAKYT is a medicine containing the active substance avapritinib.

What AYVAKYT is used for

AYVAKYT is used in adults to treat aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy. These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter various organs of your body, such as the liver, bone marrow or spleen. These mast cells also release substances such as histamine which cause various general symptoms that you may be experiencing as well as damage to involved organs. ASM, SM-AHN and MCL are collectively referred to as advanced systemic mastocytosis (AdvSM).

How AYVAKYT works

AYVAKYT stops the activity of a group of proteins in the body called kinases. Mast cells in patients with AdvSM usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells.

If you have any questions about how AYVAKYT works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take AYWAKYT

Do not take AYWAKYT:

- if you are allergic to avapritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking AYWAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.
- **if you have low platelet counts.**
- **If you are taking a medicine that thins the blood to prevent blood clots such as warfarin or phenprocoumon.**

Take special care with this medicine:

- You may develop symptoms such as **severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain)**. If these occur, contact your doctor immediately and temporarily stop treatment. For patients with AdvSM, your doctor will evaluate your platelet counts before you start treatment and monitor them as needed during your treatment with avapritinib.
- Treatment with this medicine may lead to a **higher risk of bleeding**. Avapritinib can cause bleeding in the digestive system such as stomach, rectum, or intestine. Tell your doctor if you had or have any bleeding problems. Before you start taking avapritinib your doctor may decide to do blood tests. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood.
- You may also develop **memory loss, changes in memory, or be confused (signs of a cognitive effect)**. Avapritinib can sometimes change how you think and how you remember information. Contact your doctor in case you experience these symptoms or in case a family member, caregiver or someone who knows you notices that you are getting forgetful or confused.
- During treatment with this medicine, tell your doctor straight away **if you put on weight very quickly, develop swelling of your face or limbs, have difficulty breathing or become short of breath**. This medicine may cause your body to retain water (severe fluid retention).
- Avapritinib may cause **abnormality of your heart rhythm**. Your doctor may conduct tests to evaluate these problems during your treatment with avapritinib. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking this medicine.
- You may get **severe stomach and bowel problems (diarrhoea, nausea and vomiting)**. Get medical help immediately if you experience these symptoms.
- You may become **more sensitive to the sun** while taking this medicine. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

While you are taking avapritinib, your doctor will ask you to have regular blood tests. You will also be weighed regularly.

For more information see section 4.

Children and adolescents

AYVAKYT has not been studied in children and adolescents under age 18. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and AYWAKYT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. AYWAKYT may affect the way other medicines work, and certain other medicines may affect how this medicine works.

Tell your doctor or pharmacist before taking AYVAKYT if you are taking any of the following medicines:

The following medicines can increase the effects of avapritinib and may increase its side effects:

- Boceprevir – used to treat hepatitis C
- Cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)

The following medicines can reduce the effects of avapritinib:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy
- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

This medicine may affect how well the following medicines work or increase their side effects:

- Alfentanil – used to control pain during operations and medical procedures
- Atazanavir – used to treat HIV infection/AIDS
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

Ask your doctor or pharmacist for advice before taking any medicine.

AYVAKYT with food and drink

You should not drink grapefruit juice or eat grapefruit while on treatment with AYVAKYT.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking AYVAKYT during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Women who are able to become pregnant should use effective contraception during treatment and for at least 6 weeks after completion of treatment. Males with female partners who are able to become pregnant should use effective contraception during treatment and for at least 2 weeks after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if AYVAKYT passes into breast milk. You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility

AYVAKYT may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

Driving and using machines

AYVAKYT may cause symptoms that affect your ability to concentrate and react (see section 4). Therefore, AYVAKYT may influence the ability to drive and use machines. Take special care when driving a car or operating machines if you experience these side effects.

AYVAKYT contains sodium

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

3. How to take AYVAKYT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength of AYVAKYT to use

The recommended dose of AYVAKYT will depend on your illness – see below.

AYVAKYT is available in different strength tablets. The strengths are 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. Your doctor will advise you about the strength and number of tablets you should take:

Treatment of AdvSM

The recommended dose is 200 mg by mouth once daily.

If you have liver problems, your doctor may start you on a lower dose of AYVAKYT.

If you get side effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking AYVAKYT unless your doctor tells you to.

Swallow the AYVAKYT tablet(s) whole with a glass of water, on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking AYVAKYT.

If you vomit after taking a dose of AYVAKYT, do not take an extra dose. Take your next dose at your scheduled time.

If you take more AYVAKYT than you should

If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention.

If you forget to take AYVAKYT

If you miss a dose of AYVAKYT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.

Do not take two doses within 8 hours to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects

Some side effects may be serious. Tell your doctor straight away if you get any of the following (see also section 2.):

- severe headache, vision problems, severe sleepiness, severe weakness on one side of your body (signs of bleeding in your brain)

- memory loss, changes in memory, or confusion (signs of a cognitive effect)

Other side effects may include

Very common (may affect more than 1 in 10 people):

- altered taste
- memory loss, changes in memory, or confusion (cognitive effects)
- diarrhoea
- nausea, retching and vomiting
- change in hair colour
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing decrease in red blood cells (anaemia) and white blood cells

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- bleeding in your brain
- increased tear production
- nose bleed
- shortness of breath
- heartburn
- increased fluid in the abdomen
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- gastrointestinal bleed
- rash
- hair loss
- pain
- weight gain
- changes in the electric activity of the heart
- bruising
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Uncommon (may affect up to 1 in 100 people):

- fluid around the heart
- red or itchy skin
- blood tests showing decreased kidney function

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AYVAKYT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AYVAKYT contains

- The active substance is avapritinib. Each film-coated tablet contains 50 mg avapritinib.
- The other ingredients are:
 - The tablet core contains: microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate (see section 2 “AYVAKYT contains sodium”).
 - The tablet coating contains: talc, macrogol 3350, poly(vinyl alcohol), and titanium dioxide (E171).

What AYVAKYT looks like and contents of the pack

AYVAKYT 50 mg film-coated tablets are round, white tablets of 6 mm diameter, debossed with “BLU” on one side and “50” on the other.

AYVAKYT is supplied in a bottle containing 30 film-coated tablets. Each carton contains one bottle.

Keep the desiccant canister in the bottle.

Marketing Authorisation Holder and Manufacturer

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Deutschland, Eesti, España, France, Hrvatska, Ireland, Ísland, Italia, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska, Portugal, România, Slovenija, Slovenská republika, Suomi/Finland, Sverige, United Kingdom (Northern Ireland)

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Ελλάδα, Κύπρος
Swixx Biopharma S.M.S.A.
Τηλ: +30 214 444 9670

This leaflet was last revised in

This medicine has been given ‘conditional approval’.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/en>.

Package leaflet: Information for the patient

AYVAKYT 100 mg film-coated tablets avapritinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AYVAKYT is and what it is used for
2. What you need to know before you take AYVAKYT
3. How to take AYVAKYT
4. Possible side effects
5. How to store AYVAKYT
6. Contents of the pack and other information

1. What AYVAKYT is and what it is used for

What AYVAKYT is

AYVAKYT is a medicine containing the active substance avapritinib.

What AYVAKYT is used for

AYVAKYT is used in adults to treat:

- a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic) and that has a specific mutation (D842V) in the gene for platelet-derived growth factor receptor alpha (PDGFRA) protein kinase.
- aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy. These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter-various organs of your body, such as the liver, bone marrow or spleen. These mast cells also release substances such as histamine which cause various general symptoms that you may be experiencing as well as damage to involved organs.
ASM, SM-AHN and MCL are collectively referred to as advanced systemic mastocytosis (AdvSM).

How AYVAKYT works

AYVAKYT stops the activity of a group of proteins in the body called kinases. Mast cells in patients with AdvSM or cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells.

If you have any questions about how AYVAKYT works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take AYVAKYT

Do not take AYVAKYT:

- if you are allergic to avapritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking AYVAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.
- **if you have low platelet counts.**
- **If you are taking a medicine that thins the blood to prevent blood clots such as warfarin or phenprocoumon.**

Take special care with this medicine:

- You may develop symptoms such as **severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain)**. If these occur, contact your doctor immediately and temporarily stop treatment. For patients with AdvSM, your doctor will evaluate your platelet counts before you start treatment and monitor them as needed during your treatment with avapritinib.
- Treatment with this medicine may lead to a **higher risk of bleeding**. Avapritinib can cause bleeding in the digestive system such as stomach, rectum, or intestine. In patients with GIST, avapritinib can also cause bleeding in the liver, as well as bleeding of the tumour. Tell your doctor if you had or have any bleeding problems. Before you start taking avapritinib your doctor may decide to do blood tests. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood.
- You may also develop **memory loss, changes in memory, or be confused (signs of a cognitive effect)**. Avapritinib can sometimes change how you think and how you remember information. Contact your doctor in case you experience these symptoms or in case a family member, caregiver or someone who knows you notices that you are getting forgetful or confused.
- During treatment with this medicine, tell your doctor straight away **if you put on weight very quickly, develop swelling of your face or limbs, have difficulty breathing or become short of breath**. This medicine may cause your body to retain water (severe fluid retention).
- Avapritinib may cause **abnormality of your heart rhythm**. Your doctor may conduct tests to evaluate these problems during your treatment with avapritinib. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking this medicine.
- You may get **severe stomach and bowel problems (diarrhoea, nausea and vomiting)**. Get medical help immediately if you experience these symptoms.
- You may become **more sensitive to the sun** while taking this medicine. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

While you are taking avapritinib, your doctor will ask you to have regular blood tests. You will also be weighed regularly.

For more information see section 4.

Children and adolescents

AYVAKYT has not been studied in children and adolescents under age 18. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and AYVAKYT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. AYVAKYT may affect the way other medicines work, and certain other medicines may affect how this medicine works.

Tell your doctor or pharmacist before taking AYVAKYT if you are taking any of the following medicines:

The following medicines can increase the effects of avapritinib and may increase its side effects:

- Boceprevir – used to treat hepatitis C
- Cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)

The following medicines can reduce the effects of avapritinib:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy
- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

This medicine may affect how well the following medicines work or increase their side effects:

- Alfentanil – used to control pain during operations and medical procedures
- Atazanavir – used to treat HIV infection/AIDS
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

Ask your doctor or pharmacist for advice before taking any medicine.

AYVAKYT with food and drink

You should not drink grapefruit juice or eat grapefruit while on treatment with AYVAKYT.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking AYVAKYT during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Women who are able to become pregnant should use effective contraception during treatment and for at least 6 weeks after completion of treatment. Males with female partners who are able to become pregnant should use effective contraception during treatment and for at least 2 weeks after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if AYVAKYT passes into breast milk. You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility

AYVAKYT may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

Driving and using machines

AYVAKYT may cause symptoms that affect your ability to concentrate and react (see section 4). Therefore, AYVAKYT may influence the ability to drive and use machines. Take special care when driving a car or operating machines if you experience these side effects.

AYVAKYT contains sodium

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

3. How to take AYVAKYT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength of AYVAKYT to use

The recommended dose of AYVAKYT will depend on your illness – see below.

AYVAKYT is available in different strength tablets. The strengths are 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. Your doctor will advise you about the strength and number of tablets you should take:

Treatment of GIST

The recommended dose is 300 mg by mouth once daily.

Treatment of AdvSM

The recommended dose is 200 mg by mouth once daily.

If you have liver problems, your doctor may start you on a lower dose of AYVAKYT.

If you get side effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking AYVAKYT unless your doctor tells you to.

Swallow the AYVAKYT tablet(s) whole with a glass of water, on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking AYVAKYT.

If you vomit after taking a dose of AYVAKYT, do not take an extra dose. Take your next dose at your scheduled time.

If you take more AYVAKYT than you should

If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention.

If you forget to take AYVAKYT

If you miss a dose of AYVAKYT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.

Do not take two doses within 8 hours to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects

Some side effects may be serious. Tell your doctor straight away if you get any of the following (see also section 2.):

- severe headache, vision problems, severe sleepiness, severe weakness on one side of your body (signs of bleeding in your brain)
- memory loss, changes in memory, or confusion (signs of a cognitive effect)

Other side effects in patients with GIST may include

Very common (may affect more than 1 in 10 people):

- decreased appetite
- memory loss, changes in memory, or confusion (cognitive effects)
- dizziness
- altered taste
- increased tear production
- abdominal (belly) pain
- nausea, retching and vomiting
- diarrhoea
- dryness affecting eyes, lips, mouth and skin
- heartburn
- change in hair colour
- rash
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing decrease in red blood cells (anaemia) and white blood cells
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Common (may affect up to 1 in 10 people):

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- feeling weak or unusually sleepy
- speech disorder or hoarse voice
- movement disorder
- headache
- tremor
- bleeding in the eye
- increased sensitivity to light
- increased blood pressure
- shortness of breath
- stuffy nose
- cough including cough that produces mucus
- gastrointestinal bleed
- increased fluid in the abdomen
- constipation, flatulence (gas)
- difficulty swallowing
- painful mouth, lips or tongue, thrush

- increase in saliva production
- red or itchy skin
- skin discolouration
- hair loss
- pain
- muscle spasms
- blood in urine
- fever or feeling of general discomfort
- changes in the electric activity of the heart
- weight gain or loss
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing altered amounts of blood minerals
- blood tests showing decreased kidney function
- blood tests showing increased break down of muscle

Uncommon (may affect up to 1 in 100 people):

- bleeding in the tumour
- fluid around the heart
- bleeding in the liver

Other side effects in patients with AdvSM may include

Very common (may affect more than 1 in 10 people):

- altered taste
- memory loss, changes in memory, or confusion (cognitive effects)
- diarrhoea
- nausea, retching and vomiting
- change in hair colour
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing decrease in red blood cells (anaemia) and white blood cells

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- bleeding in your brain
- increased tear production
- nose bleed
- shortness of breath
- heartburn
- increased fluid in the abdomen
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- gastrointestinal bleed
- rash
- hair loss
- pain
- weight gain
- changes in the electric activity of the heart
- bruising
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Uncommon (may affect up to 1 in 100 people):

- fluid around the heart

- red or itchy skin
- blood tests showing decreased kidney function

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AYVAKYT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AYVAKYT contains

- The active substance is avapritinib. Each film-coated tablet contains 100 mg avapritinib.
- The other ingredients are:
 - The tablet core contains: microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate (see section 2 "AYVAKYT contains sodium").
 - The tablet coating contains: talc, macrogol 3350, poly(vinyl alcohol), and titanium dioxide (E171).
 - The printing ink contains: Shellac glaze 45% (20% esterified) in ethanol, Brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172) and propylene glycol.

What AYVAKYT looks like and contents of the pack

AYVAKYT 100 mg film-coated tablets are round, white tablets of 9 mm diameter, printed with blue ink "BLU" on one side and "100" on the other.

AYVAKYT is supplied in a bottle containing 30 film-coated tablets. Each carton contains one bottle.

Keep the desiccant canister in the bottle.

Marketing Authorisation Holder and Manufacturer

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Deutschland, Eesti, España, France, Hrvatska, Ireland, Ísland,

Ελλάδα, Κύπρος
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This leaflet was last revised in

This medicine has been given ‘conditional approval’.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and
this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/en>.

Package leaflet: Information for the patient

AYVAKYT 200 mg film-coated tablets avapritinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AYVAKYT is and what it is used for
2. What you need to know before you take AYVAKYT
3. How to take AYVAKYT
4. Possible side effects
5. How to store AYVAKYT
6. Contents of the pack and other information

1. What AYVAKYT is and what it is used for

What AYVAKYT is

AYVAKYT is a medicine containing the active substance avapritinib.

What AYVAKYT is used for

AYVAKYT is used in adults to treat:

- a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic) and that has a specific mutation (D842V) in the gene for platelet-derived growth factor receptor alpha (PDGFRA) protein kinase.
- aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy. These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter various organs of your body, such as the liver, bone marrow or spleen. These mast cells also release substances such as histamine which cause various general symptoms that you may be experiencing as well as damage to involved organs.
ASM, SM-AHN and MCL are collectively referred to as advanced systemic mastocytosis (AdvSM).

How AYVAKYT works

AYVAKYT stops the activity of a group of proteins in the body called kinases. Mast cells in patients with AdvSM or cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells.

If you have any questions about how AYWAKYT works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take AYWAKYT

Do not take AYWAKYT:

- if you are allergic to avapritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking AYWAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.
- **if you have low platelet counts.**
- **If you are taking a medicine that thins the blood to prevent blood clots such as warfarin or phenprocoumon.**

Take special care with this medicine:

- You may develop symptoms such as **severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain)**. If these occur, contact your doctor immediately and temporarily stop treatment. For patients with AdvSM, your doctor will evaluate your platelet counts before you start treatment and monitor them as needed during your treatment with avapritinib.
- Treatment with this medicine may lead to a **higher risk of bleeding**. Avapritinib can cause bleeding in the digestive system such as stomach, rectum, or intestine. In patients with GIST, avapritinib can also cause bleeding in the liver, as well as bleeding of the tumour. Tell your doctor if you had or have any bleeding problems. Before you start taking avapritinib your doctor may decide to do blood tests. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood.
- You may also develop **memory loss, changes in memory, or be confused (signs of a cognitive effect)**. Avapritinib can sometimes change how you think and how you remember information. Contact your doctor in case you experience these symptoms or in case a family member, caregiver or someone who knows you notices that you are getting forgetful or confused.
- During treatment with this medicine, tell your doctor straight away **if you put on weight very quickly, develop swelling of your face or limbs, have difficulty breathing or become short of breath**. This medicine may cause your body to retain water (severe fluid retention).
- Avapritinib may cause **abnormality of your heart rhythm**. Your doctor may conduct tests to evaluate these problems during your treatment with avapritinib. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking this medicine.
- You may get **severe stomach and bowel problems (diarrhoea, nausea and vomiting)**. Get medical help immediately if you experience these symptoms.
- You may become **more sensitive to the sun** while taking this medicine. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

While you are taking avapritinib, your doctor will ask you to have regular blood tests. You will also be weighed regularly.

For more information see section 4.

Children and adolescents

AYWAKYT has not been studied in children and adolescents under age 18. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and AYVAKYT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. AYVAKYT may affect the way other medicines work, and certain other medicines may affect how this medicine works.

Tell your doctor or pharmacist before taking AYVAKYT if you are taking any of the following medicines:

The following medicines can increase the effects of avapritinib and may increase its side effects:

- Boceprevir – used to treat hepatitis C
- Cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)

The following medicines can reduce the effects of avapritinib:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy
- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

This medicine may affect how well the following medicines work or increase their side effects:

- Alfentanil – used to control pain during operations and medical procedures
- Atazanavir – used to treat HIV infection/AIDS
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

Ask your doctor or pharmacist for advice before taking any medicine.

AYVAKYT with food and drink

You should not drink grapefruit juice or eat grapefruit while on treatment with AYVAKYT.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking AYVAKYT during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Women who are able to become pregnant should use effective contraception during treatment and for at least 6 weeks after completion of treatment. Males with female partners who are able to become pregnant should use effective contraception during treatment and for at least 2 weeks after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if AYVAKYT passes into breast milk. You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility

AYVAKYT may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

Driving and using machines

AYVAKYT may cause symptoms that affect your ability to concentrate and react (see section 4). Therefore, AYVAKYT may influence the ability to drive and use machines. Take special care when driving a car or operating machines if you experience these side effects.

AYVAKYT contains sodium

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

3. How to take AYVAKYT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength of AYVAKYT to use

The recommended dose of AYVAKYT will depend on your illness – see below.

AYVAKYT is available in different strength tablets. The strengths are 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. Your doctor will advise you about the strength and number of tablets you should take:

Treatment of GIST

The recommended dose is 300 mg by mouth once daily.

Treatment of AdvSM

The recommended dose is 200 mg by mouth once daily.

If you have liver problems, your doctor may start you on a lower dose of AYVAKYT.

If you get side effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking AYVAKYT unless your doctor tells you to.

Swallow the AYVAKYT tablet(s) whole with a glass of water, on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking AYVAKYT.

If you vomit after taking a dose of AYVAKYT, do not take an extra dose. Take your next dose at your scheduled time.

If you take more AYVAKYT than you should

If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention.

If you forget to take AYVAKYT

If you miss a dose of AYVAKYT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.

Do not take two doses within 8 hours to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects

Some side effects may be serious. Tell your doctor straight away if you get any of the following (see also section 2.):

- severe headache, vision problems, severe sleepiness, severe weakness on one side of your body (signs of bleeding in your brain)
- memory loss, changes in memory, or confusion (signs of a cognitive effect)

Other side effects in patients with GIST may include:

Very common (may affect more than 1 in 10 people):

- decreased appetite
- memory loss, changes in memory, or confusion (cognitive effects)
- dizziness
- altered taste
- increased tear production
- abdominal (belly) pain
- nausea, retching and vomiting
- diarrhoea
- dryness affecting eyes, lips, mouth and skin
- heartburn
- change in hair colour
- rash
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing decrease in red blood cells (anaemia) and white blood cells
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Common (may affect up to 1 in 10 people):

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- feeling weak or unusually sleepy
- speech disorder or hoarse voice
- movement disorder
- headache
- tremor
- bleeding in the eye
- increased sensitivity to light
- increased blood pressure
- shortness of breath
- stuffy nose
- cough including cough that produces mucus
- gastrointestinal bleed
- increased fluid in the abdomen
- constipation, flatulence (gas)
- difficulty swallowing
- painful mouth, lips or tongue, thrush

- increase in saliva production
- red or itchy skin
- skin discolouration
- hair loss
- pain
- muscle spasms
- blood in urine
- fever or feeling of general discomfort
- changes in the electric activity of the heart
- weight gain or loss
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing altered amounts of blood minerals
- blood tests showing decreased kidney function
- blood tests showing increased break down of muscle

Uncommon (may affect up to 1 in 100 people):

- bleeding in the tumour
- fluid around the heart
- bleeding in the liver

Other side effects in patients with AdvSM may include

Very common (may affect more than 1 in 10 people):

- altered taste
- memory loss, changes in memory, or confusion (cognitive effects)
- diarrhoea
- nausea, retching and vomiting
- change in hair colour
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing decrease in red blood cells (anaemia) and white blood cells

Common (may affect up to 1 in 10 people):

- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- bleeding in your brain
- increased tear production
- nose bleed
- shortness of breath
- heartburn
- increased fluid in the abdomen
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- gastrointestinal bleed
- rash
- hair loss
- pain
- weight gain
- changes in the electric activity of the heart
- bruising
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Uncommon (may affect up to 1 in 100 people):

- fluid around the heart
- red or itchy skin
- blood tests showing decreased kidney function

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AYVAKYT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AYVAKYT contains

- The active substance is avapritinib. Each film-coated tablet contains 200 mg avapritinib.
- The other ingredients are:
 - The tablet core contains: microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate (see section 2 "AYVAKYT contains sodium").
 - The tablet coating contains: talc, macrogol 3350, poly(vinyl alcohol), and titanium dioxide (E171).
 - The printing ink contains: Shellac glaze 45% (20% esterified) in ethanol, Brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172) and propylene glycol.

What AYVAKYT looks like and contents of the pack

AYVAKYT 200 mg film-coated tablets are oval, white tablets of 16 mm in length and 8 mm in width, printed with blue ink "BLU" on one side and "200" on the other.

AYVAKYT is supplied in a bottle containing 30 film-coated tablets. Each carton contains one bottle.

Keep the desiccant canister in the bottle.

Marketing Authorisation Holder and Manufacturer

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká **Ελλάδα, Κύπρος**

republika, Danmark, Deutschland, Eesti, España, France, Hrvatska, Ireland, Ísland, Italia, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska, Portugal, România, Slovenija, Slovenská republika, Suomi/Finland, Sverige, United Kingdom (Northern Ireland)

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Swixx Biopharma S.M.S.A.
Τηλ: +30 214 444 9670

This leaflet was last revised in

This medicine has been given ‘conditional approval’.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<https://www.ema.europa.eu/en>.

Package leaflet: Information for the patient

AYVAKYT 300 mg film-coated tablets avapritinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What AYVAKYT is and what it is used for
2. What you need to know before you take AYVAKYT
3. How to take AYVAKYT
4. Possible side effects
5. How to store AYVAKYT
6. Contents of the pack and other information

1. What AYVAKYT is and what it is used for

What AYVAKYT is

AYVAKYT is a medicine containing the active substance avapritinib.

What AYVAKYT is used for

AYVAKYT is used in adults to treat a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic) and that has a specific mutation (D842V) in the gene for platelet-derived growth factor receptor alpha (PDGFRA) protein kinase.

How AYVAKYT works

AYVAKYT stops the activity of a group of proteins in the body called kinases. Cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of these cells.

If you have any questions about how AYVAKYT works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take AYVAKYT

Do not take AYVAKYT:

- if you are allergic to avapritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking AYVAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.
- **If you are taking a medicine that thins the blood to prevent blood clots such as warfarin or phenprocoumon.**

Take special care with this medicine:

- You may develop symptoms such as **severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain)**. If these occur, contact your doctor immediately and temporarily stop treatment.
- Treatment with this medicine may lead to a **higher risk of bleeding**. Avapritinib can cause bleeding in the digestive system such as stomach, rectum, or intestine. In patients with GIST, avapritinib can also cause bleeding in the liver, as well as bleeding of the tumour. Tell your doctor if you had or have any bleeding problems. Before you start taking avapritinib your doctor may decide to do blood tests. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood.
- You may also develop **memory loss, changes in memory, or be confused (signs of a cognitive effect)**. Avapritinib can sometimes change how you think and how you remember information. Contact your doctor in case you experience these symptoms or in case a family member, caregiver or someone who knows you notices that you are getting forgetful or confused.
- During treatment with this medicine, tell your doctor straight away **if you put on weight very quickly, develop swelling of your face or limbs, have difficulty breathing or become short of breath**. This medicine may cause your body to retain water (severe fluid retention).
- Avapritinib may cause **abnormality of your heart rhythm**. Your doctor may conduct tests to evaluate these problems during your treatment with avapritinib. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking this medicine.
- You may get **severe stomach and bowel problems (diarrhoea, nausea and vomiting)**. Get medical help immediately if you experience these symptoms.
- You may become **more sensitive to the sun** while taking this medicine. It is important to cover sun-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

While you are taking avapritinib, your doctor will ask you to have regular blood tests. You will also be weighed regularly.

For more information see section 4.

Children and adolescents

AYVAKYT has not been studied in children and adolescents under age 18. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and AYVAKYT

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. AYVAKYT may affect the way other medicines work, and certain other medicines may affect how this medicine works.

Tell your doctor or pharmacist before taking AYVAKYT if you are taking any of the following medicines:

The following medicines can increase the effects of avapritinib and may increase its side effects:

- Boceprevir – used to treat hepatitis C
- Cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)

The following medicines can reduce the effects of avapritinib:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy
- St. John’s wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

This medicine may affect how well the following medicines work or increase their side effects:

- Alfentanil – used to control pain during operations and medical procedures
- Atazanavir – used to treat HIV infection/AIDS
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

Ask your doctor or pharmacist for advice before taking any medicine.

AYVAKYT with food and drink

You should not drink grapefruit juice or eat grapefruit while on treatment with AYVAKYT.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

This medicine is not recommended for use during pregnancy unless clearly necessary. Avoid becoming pregnant while being treated with this medicine as it may harm your unborn baby. Your doctor will discuss with you the potential risks of taking AYVAKYT during pregnancy.

Your doctor may check if you are pregnant before you start treatment with this medicine.

Women who are able to become pregnant should use effective contraception during treatment and for at least 6 weeks after completion of treatment. Males with female partners who are able to become pregnant should use effective contraception during treatment and for at least 2 weeks after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. It is not known if AYVAKYT passes into breast milk. You should not breast-feed during treatment with this medicine and for at least 2 weeks following the last dose. Talk to your doctor about the best way to feed your baby during this time.

Fertility

AYVAKYT may cause fertility problems in males and females. Talk to your doctor if this is a concern for you.

Driving and using machines

AYVAKYT may cause symptoms that affect your ability to concentrate and react (see section 4). Therefore, AYVAKYT may influence the ability to drive and use machines. Take special care when driving a car or operating machines if you experience these side effects.

AYVAKYT contains sodium

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

3. How to take AYVAKYT

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Which strength of AYVAKYT to use

The recommended dose of AYVAKYT will depend on your illness – see below.

AYVAKYT is available in different strength tablets. The strengths are 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. Your doctor will advise you about the strength and number of tablets you should take:

Treatment of GIST

The recommended dose is 300 mg by mouth once daily.

If you have liver problems, your doctor may start you on a lower dose of AYVAKYT.

If you get side effects, your doctor may change your dose, temporarily stop, or permanently stop treatment. Do not change your dose or stop taking AYVAKYT unless your doctor tells you to.

Swallow the AYVAKYT tablet(s) whole with a glass of water, on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking AYVAKYT.

If you vomit after taking a dose of AYVAKYT, do not take an extra dose. Take your next dose at your scheduled time.

If you take more AYVAKYT than you should

If you have accidentally taken too many tablets, talk to your doctor straight away. You may require medical attention.

If you forget to take AYVAKYT

If you miss a dose of AYVAKYT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.

Do not take two doses within 8 hours to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects

Some side effects may be serious. Tell your doctor straight away if you get any of the following (see also section 2.):

- severe headache, vision problems, severe sleepiness, severe weakness on one side of your body (signs of bleeding in your brain)
- memory loss, changes in memory, or confusion (signs of a cognitive effect)

Other side effects may include

Very common (may affect more than 1 in 10 people):

- decreased appetite
- memory loss, changes in memory, or confusion (cognitive effects)
- dizziness
- altered taste
- increased tear production
- abdominal (belly) pain
- nausea, retching and vomiting
- diarrhoea

- dryness affecting eyes, lips, mouth and skin
- heartburn
- change in hair colour
- rash
- swelling (e.g. feet, ankle, face, eye, joint)
- tiredness
- blood tests showing decrease in red blood cells (anaemia) and white blood cells
- blood tests showing increased stress on the liver and high levels of bilirubin, a substance produced by the liver

Common (may affect up to 1 in 10 people):

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- feeling weak or unusually sleepy
- speech disorder or hoarse voice
- movement disorder
- headache
- tremor
- bleeding in the eye
- increased sensitivity to light
- increased blood pressure
- shortness of breath
- stuffy nose
- cough including cough that produces mucus
- gastrointestinal bleed
- increased fluid in the abdomen
- constipation, flatulence (gas)
- difficulty swallowing
- painful mouth, lips or tongue, thrush
- increase in saliva production
- red or itchy skin
- skin discolouration
- hair loss
- pain
- muscle spasms
- blood in urine
- fever or feeling of general discomfort
- changes in the electric activity of the heart
- weight gain or loss
- blood tests showing low blood platelets, often associated with easy bruising or bleeding
- blood tests showing altered amounts of blood minerals
- blood tests showing decreased kidney function
- blood tests showing increased break down of muscle

Uncommon (may affect up to 1 in 100 people):

- bleeding in the tumour
- fluid around the heart
- bleeding in the liver

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AYVAKYT

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and outer carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the bottle is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AYVAKYT contains

- The active substance is avapritinib. Each film-coated tablet contains 300 mg avapritinib.
- The other ingredients are:
 - The tablet core contains: microcrystalline cellulose, copovidone, croscarmellose sodium and magnesium stearate (see section 2 "AYVAKYT contains sodium").
 - The tablet coating contains: talc, macrogol 3350, poly(vinyl alcohol), and titanium dioxide (E171).
 - The printing ink contains: Shellac glaze 45% (20% esterified) in ethanol, Brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172) and propylene glycol.

What AYVAKYT looks like and contents of the pack

AYVAKYT 300 mg film-coated tablets are oval, white tablets of 18 mm in length and 9 mm in width, printed with blue ink "BLU" on one side and "300" on the other.

AYVAKYT is supplied in a bottle containing 30 film-coated tablets. Each carton contains one bottle.

Keep the desiccant canister in the bottle.

Marketing Authorisation Holder and Manufacturer

Blueprint Medicines (Netherlands) B.V.
Gustav Mahlerplein 2
1082 MA Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien, България, Česká republika, Danmark, Deutschland, Eesti, España, France, Hrvatska, Ireland, Ísland, Italia, Latvija, Lietuva, Luxembourg/Luxemburg, Magyarország, Malta, Nederland, Norge, Österreich, Polska,

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This leaflet was last revised in

This medicine has been given ‘conditional approval’.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<https://www.ema.europa.eu/en>.