

**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  $< 50 \times 10^9/L$  (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**

| <b>Dose reduction</b> | <b>GIST (starting dose 300 mg)</b> | <b>AdvSM (starting dose 200 mg)</b> | <b>ISM (starting dose 25 mg)*</b> |
|-----------------------|------------------------------------|-------------------------------------|-----------------------------------|
| 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**

| <b>Adverse reaction</b>                                                  | <b>Severity*</b>             | <b>Dose modification</b>                                                                                                                       |
|--------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Patients with GIST, AdvSM or ISM</b>                                  |                              |                                                                                                                                                |
| <b>Intracranial haemorrhage</b><br>(see section 4.4)                     | All Grades                   | Permanently discontinue AYVAKYT.                                                                                                               |
| <b>Cognitive effects**</b><br>(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.                                                                                                               |
| <b>Other adverse reactions</b><br>(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.                             |
| <b>Patients with AdvSM</b>                                               |                              |                                                                                                                                                |
| <b>Thrombocytopenia</b>                                                  | Less than $50 \times 10^9/L$ | 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. |
|-------------------|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

\* 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  $\geq 300$  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  $\geq 2$  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  $AUC_{0-\infty}$  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  $AUC_{0-\infty}$  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

Co-administration of avapritinib 300 mg once daily with oral midazolam increased the midazolam AUC and  $C_{\max}$  by 51% and 20%, respectively. These results indicate that avapritinib 300 mg once daily is a weak inhibitor of CYP3A. Physiologically based pharmacokinetic simulations predict that avapritinib is not an inhibitor of CYP3A at doses of 200 mg once daily and below. Therefore, caution must be exercised with co-administration of avapritinib 300 mg once daily with narrow therapeutic index CYP3A substrates as their plasma concentrations may be increased.

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  $\geq 3$  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.

**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 $\geq 3$ % |
|---------------------------------------------------------------------------------|---------------------------------------|--------------|-------------------|
| <b>Infections and infestations</b>                                              |                                       |              |                   |
| Common                                                                          | Conjunctivitis                        | 2.0          | -                 |
| <b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b> |                                       |              |                   |
| Uncommon                                                                        | Tumour haemorrhage                    | 0.2          | 0.2               |
| <b>Blood and lymphatic system disorders</b>                                     |                                       |              |                   |
| 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               |
| <b>Metabolism and nutrition disorders</b>                                       |                                       |              |                   |
| 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               |
| <b>Psychiatric disorders</b>                                                    |                                       |              |                   |
| Common                                                                          | Confusional state                     | 4.7          | 0.5               |
|                                                                                 | Depression                            | 4.2          | 0.4               |
|                                                                                 | Anxiety                               | 1.8          | -                 |
|                                                                                 | Insomnia                              | 3.8          | -                 |
| <b>Nervous system disorders</b>                                                 |                                       |              |                   |
| 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 <sup>1</sup> | 1.6          | 1.1               |
|                                                                                 | Mental impairment <sup>2</sup>        | 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               |
| <b>Eye disorders</b>                                                            |                                       |              |                   |
| Very common                                                                     | Lacrimation increased                 | 22.2         | -                 |
| Common                                                                          | Ocular haemorrhage <sup>3</sup>       | 1.1          | -                 |
|                                                                                 | Vision blurred                        | 2.9          | -                 |
|                                                                                 | Conjunctival haemorrhage              | 2.4          | -                 |
|                                                                                 | Photophobia                           | 1.6          | -                 |
| <b>Ear and labyrinth disorders</b>                                              |                                       |              |                   |
| Common                                                                          | Vertigo                               | 2.4          | -                 |

| System Organ Class / frequency category                     | Adverse reactions                          | All grades % | Grades $\geq 3$ % |
|-------------------------------------------------------------|--------------------------------------------|--------------|-------------------|
| <b>Cardiac disorders</b>                                    |                                            |              |                   |
| Uncommon                                                    | Pericardial effusion                       | 0.9          | 0.2               |
| <b>Vascular disorders</b>                                   |                                            |              |                   |
| Common                                                      | Hypertension                               | 3.3          | 1.1               |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                                            |              |                   |
| Common                                                      | Pleural effusion                           | 6.0          | 0.9               |
|                                                             | Dyspnoea                                   | 6.0          | 0.7               |
|                                                             | Nasal congestion                           | 1.5          | -                 |
|                                                             | Cough                                      | 2.2          | -                 |
| <b>Gastrointestinal disorders</b>                           |                                            |              |                   |
| 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 <sup>4</sup>  | 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          | -                 |
| <b>Hepatobiliary disorders</b>                              |                                            |              |                   |
| Very common                                                 | Hyperbilirubinaemia                        | 27.5         | 5.8               |
| Uncommon                                                    | Hepatic haemorrhage                        | 0.2          | 0.2               |
| <b>Skin and subcutaneous tissue disorders</b>               |                                            |              |                   |
| 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          | -                 |
| <b>Musculoskeletal and connective tissue disorders</b>      |                                            |              |                   |
| Common                                                      | Myalgia                                    | 2.0          | -                 |
|                                                             | Arthralgia                                 | 1.8          | -                 |
|                                                             | Back pain                                  | 1.1          | -                 |
|                                                             | Muscle spasms                              | 1.6          | -                 |
| <b>Renal and urinary disorders</b>                          |                                            |              |                   |
| Common                                                      | Acute kidney injury                        | 2.0          | 0.9               |
|                                                             | Blood creatinine increased                 | 4.4          | -                 |
|                                                             | Haematuria                                 | 1.1          | -                 |
| <b>General disorders and administration site conditions</b> |                                            |              |                   |
| Very common                                                 | Oedema <sup>5</sup>                        | 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          | -                 |
| <b>Investigations</b>                                       |                                            |              |                   |
| Very common                                                 | Transaminases increased                    | 12.4         | 0.9               |

| System Organ Class / frequency category | Adverse reactions                      | All grades % | Grades $\geq 3$ % |
|-----------------------------------------|----------------------------------------|--------------|-------------------|
| 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          | -                 |

<sup>1</sup>Intracranial haemorrhage (including Cerebral haemorrhage, Haemorrhage intracranial, Subdural haematoma, Cerebral haematoma)

<sup>2</sup>Mental impairment (including Disturbance in attention, Mental impairment, Mental status changes, Dementia)

<sup>3</sup>Ocular haemorrhage (including Eye haemorrhage, Retinal haemorrhage, Vitreous haemorrhage)

<sup>4</sup>Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Rectal haemorrhage, Melaena)

<sup>5</sup>Oedema (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  $\geq 3$

#### 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 $\geq 3$ % |
|--------------------------------------------------------|---------------------------------------|--------------|-------------------|
| <b>Blood and lymphatic system disorders</b>            |                                       |              |                   |
| Very common                                            | Thrombocytopenia*                     | 46.8         | 23.0              |
|                                                        | Anaemia*                              | 23.0         | 11.9              |
|                                                        | Neutropenia*                          | 21.4         | 19.0              |
| Common                                                 | Leukopenia*                           | 8.7          | 2.4               |
| <b>Psychiatric disorders</b>                           |                                       |              |                   |
| Common                                                 | Confusional state                     | 1.6          | -                 |
| <b>Nervous system disorders</b>                        |                                       |              |                   |
| 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 <sup>1</sup>    | 4.8          | -                 |
|                                                        | Intracranial haemorrhage <sup>2</sup> | 2.4          | 0.8               |
| <b>Eye disorders</b>                                   |                                       |              |                   |
| Common                                                 | Lacrimation increased                 | 6.3          | -                 |
| <b>Cardiac disorders</b>                               |                                       |              |                   |
| Uncommon                                               | Pericardial effusion                  | 0.8          | -                 |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                       |              |                   |
| Common                                                 | Epistaxis                             | 5.6          | -                 |
|                                                        | Pleural effusion                      | 2.4          | -                 |
| <b>Gastrointestinal disorders</b>                      |                                       |              |                   |
| 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 $\geq 3$ % |
|-------------------------------------------------------------|-------------------------------------------|--------------|-------------------|
|                                                             | Gastroesophageal reflux disease*          | 4.8          | -                 |
|                                                             | Ascites*                                  | 4.0          | 0.8               |
|                                                             | Dryness*                                  | 4.0          | -                 |
|                                                             | Constipation                              | 3.2          | -                 |
|                                                             | Abdominal pain*                           | 3.2          | -                 |
|                                                             | Gastrointestinal haemorrhage <sup>3</sup> | 2.4          | 1.6               |
| <b>Hepatobiliary disorders</b>                              |                                           |              |                   |
| Common                                                      | Hyperbilirubinaemia*                      | 7.9          | 0.8               |
| <b>Skin and subcutaneous tissue disorders</b>               |                                           |              |                   |
| Very common                                                 | Hair colour changes                       | 15.1         | -                 |
| Common                                                      | Rash*                                     | 7.9          | 0.8               |
|                                                             | Alopecia                                  | 7.1          | -                 |
| Uncommon                                                    | Photosensitivity reaction                 | 0.8          | -                 |
| <b>Renal and urinary disorders</b>                          |                                           |              |                   |
| Uncommon                                                    | Acute kidney injury*                      | 0.8          | -                 |
| <b>Musculoskeletal and connective tissue disorders</b>      |                                           |              |                   |
| Common                                                      | Arthralgia                                | 4.8          | 0.8               |
| <b>General disorders and administration site conditions</b> |                                           |              |                   |
| Very common                                                 | Oedema <sup>4</sup>                       | 69.8         | 4.8               |
|                                                             | Fatigue*                                  | 18.3         | 2.4               |
| Common                                                      | Pain                                      | 3.2          | -                 |
| <b>Investigations</b>                                       |                                           |              |                   |
| Common                                                      | Weight increased                          | 6.3          | -                 |
|                                                             | Blood alkaline phosphatase increased      | 4.8          | 1.6               |
|                                                             | Transaminases increased*                  | 4.8          | -                 |
|                                                             | Electrocardiogram QT prolonged            | 1.6          | 0.8               |
| <b>Injury, poisoning and procedural complications</b>       |                                           |              |                   |
| Common                                                      | Contusion                                 | 3.2          | -                 |

<sup>1</sup>Neuropathy peripheral (including Paraesthesia, Neuropathy peripheral, Hypoaesthesia)

<sup>2</sup>Intracranial haemorrhage (including Haemorrhage intracranial, Subdural haematoma)

<sup>3</sup>Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Melaena)

<sup>4</sup>Oedema (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 $\geq 3$ % |
|-----------------------------------------|-------------------|-------------------------------------------------------------------|-------------------|
| <b>Psychiatric disorders</b>            |                   |                                                                   |                   |
| Common                                  | Insomnia          | 5.7                                                               | -                 |
| <b>Vascular disorders</b>               |                   |                                                                   |                   |
| Common                                  | Flushing          | 9.2                                                               | 1.4               |

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

<sup>1</sup>Peripheral 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  $\geq 2$ .

##### *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  $\geq 300$  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  $\geq 300$  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  $\geq 2$  occurring in 11% of 550 patients. Among patients who experienced a cognitive effect of Grade  $\geq 2$  (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  $\geq 65$  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  $\geq 2$  occurring in 7% of 126 patients treated at a starting dose of 200 mg. Among patients who experienced a cognitive effect of Grade  $\geq 2$  (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  $\geq 65$  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 Agenzia Italiana del Farmaco website <https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse>.

## **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 ( $IC_{50}$ ) of 0.24 nM and 0.27 nM, respectively, and greater potency against clinically relevant KIT exon 11, KIT exon 11/17 and KIT exon 17 mutants than against the KIT wild-type enzyme.

In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V with  $IC_{50}$  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          |
|--------------------------------------------------|-----------------|
| <b>mRECIST 1.1 ORR<sup>1</sup>, (%) (95% CI)</b> | 95 (82.3, 99.4) |
| <b>CR</b>                                        | 13              |
| <b>PR</b>                                        | 82              |
| <b>DOR (months), median (CI)</b>                 | 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

<sup>1</sup> 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**

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

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

<sup>2</sup> 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 12<sup>th</sup> 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<br>N = 141 | Placebo + BSC<br>N = 71      | One-sided p-value |
|------------------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------|-------------------|
| ISM-SAF TSS                                                                                                |                                             |                              |                   |
| Mean change in TSS                                                                                         |                                             |                              |                   |
| Change from baseline (95% CI)                                                                              | -15.58<br>(-18.61, -12.55)                  | -9.15<br>(-13.12, -5.18)     | 0.003             |
| Difference from placebo (95% CI)                                                                           | -6.43*<br>(-10.90, -1.96)                   |                              |                   |
| % of patients achieving ≥50% reduction in TSS (95% CI)                                                     | 25<br>(17.9, 32.8)                          | 10<br>(4.1, 19.3)            | 0.005             |
| % of patients achieving ≥30% reduction in TSS (95% CI)                                                     | 45<br>(37.0, 54.0)                          | 30<br>(19.3, 41.6)           | 0.009             |
| Measures of mast cell burden                                                                               |                                             |                              |                   |
| % of patients with a ≥50% reduction in serum tryptase (95% CI)                                             | N = 141<br>54<br>(45.3, 62.3)               | N = 71<br>0<br>(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<br>68<br>(58.6, 76.1)               | N = 63<br>6<br>(1.8, 15.5)   | <0.0001           |
| % of patients with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI)                    | N = 106<br>53<br>(42.9, 62.6)               | N = 57<br>23<br>(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  $\geq 65$  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  $\geq 65$  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 AUC<sub>0-24</sub> 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<sub>inf</sub> 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<sub>inf</sub> 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  $\mu$ Ci) [<sup>14</sup>C]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*, 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) [<sup>14</sup>C]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<sub>c</sub>/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<sub>max</sub> at steady state (+/- 5%), while concomitant use of PPIs led to ~19% reduction in AUC and C<sub>max</sub>. 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<sub>cr</sub> 60-89 mL/min), 52 subjects with moderate renal impairment (CL<sub>cr</sub> 30-59 mL/min) and 298 subjects with normal renal function (CL<sub>cr</sub> ≥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<sub>cr</sub> 15-29 mL/min) or end-stage renal disease (CL<sub>cr</sub> <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  $\geq 96$ , 12 and  $\geq 8$ -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: 28 July 2025

## 10. DATE OF REVISION OF THE TEXT

11/2025

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

## PRICE AND CLASSIFICATION APPROVED IN ITALY:

| Pack                                                                | National identification number | Public price (VAT included)* | Ex-factory price (VAT excluded)* |
|---------------------------------------------------------------------|--------------------------------|------------------------------|----------------------------------|
| AYVAKYT (avapritinib)<br>“25 mg film-coated tablets”<br>30 tablets  | 049033044                      | €35,280.60                   | €21,377.00                       |
| AYVAKYT (avapritinib)<br>“50 mg film-coated tablets”<br>30 tablets  | 049033057                      | €35,280.60                   | €21,377.00                       |
| AYVAKYT (avapritinib)<br>“100 mg film-coated tablets”<br>30 tablets | 049033018                      | €35,280.60                   | €21,377.00                       |

| Pack                                                                   | National identification number | Public price (VAT included)* | Ex-factory price (VAT excluded)* |
|------------------------------------------------------------------------|--------------------------------|------------------------------|----------------------------------|
| AYVAKYT<br>(avapritinib)<br>“200 mg film-coated tablets”<br>30 tablets | 049033020                      | €35,280.60                   | €21,377.00                       |

\*price gross of legal reductions

Class H. Medicinal product subject to non-renewable limitative prescription to be sold to the public on prescription of hospital centers or specialists - haematologist and oncologist (RNRL).

**THE INDICATION IN INDOLENT SYSTEMIC MASTOCYTOSIS IS NOT REIMBURSED BY THE NATIONAL HEALTH SYSTEM IN ITALY.**