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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of avapritinib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, white film-coated tablet of 6 mm diameter with debossed text. One side reads “BLU” and the other side reads “25”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

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 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. Continue treatment until SM disease progression or unacceptable toxicity.

Treatment with avapritinib is not recommended in patients with a platelet count of less than 50 x 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).

Posology for ISM

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 AdvSM or ISM and are provided in Tables 1 and 2.

Table 1. Recommended dose reductions for AYVAKYT for adverse reactions

Dose reduction	**AdvSM (starting dose 200 mg)**	**ISM (starting dose 25 mg)***
First	100 mg once daily	25 mg once every other day
Second	50 mg once daily	-
Third	25 mg once daily	-

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

Table 2. Recommended dose modifications for AYVAKYT for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
Patients with AdvSM or ISM		
Intracranial haemorrhage (see section 4.4)	All Grades	Permanently discontinue AYVAKYT.
Cognitive effects** (see section 4.4)	Grade 1	Continue at the same dose, reduce dose or interrupt until improvement to baseline or resolution. Resume at the same dose or at a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.
Other adverse reactions (also see section 4.4 and section 4.8)	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.
Patients with AdvSM		
Thrombocytopenia (see section 4.4)	Less than 50 x 10^9/L	Interrupt dosing until platelet count is ≥ 50 x 10^9/L, then resume at reduced dose (see Table 1). If platelet count does not recover above 50 x 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 should be omitted and the patient should resume treatment with the next scheduled dose.

If vomiting occurs after taking a dose of avapritinib, the patient should 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 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 should be taken on an empty stomach at least 1 hour before or at least 2 hours after a meal (see section 5.2).

Patients should swallow the tablet(s) 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 AdvSM (see section 4.8).

Routine surveillance of haemorrhagic events in patients with AdvSM should include physical examination, and blood counts and coagulation parameters should be monitored, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin, phenprocoumon, rivaroxaban, dabigatran, apixaban and edoxaban) or other concomitant medicinal products that increase the risk of bleeding (including antiplatelet therapy).

Intracranial haemorrhages

Serious adverse reactions of intracranial haemorrhage were reported in patients with AdvSM receiving avapritinib (see section 4.8). Fatal events have occurred in <1% of patients across all doses. The exact mechanism is unknown.

Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with risk factors such as concomitant use of anticoagulants, severe thrombocytopenia, a history of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident or transient ischaemic attack within the prior year.

Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) during treatment with avapritinib should interrupt treatment 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 should be permanently discontinued (see section 4.2).

Advanced systemic mastocytosis
The incidence of intracranial haemorrhage was higher in patients with platelet counts $<50 \times 10^9$/L and in patients with a starting dose of ≥300 mg.

Considering the above, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts $<50 \times 10^9$/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75×10^9/L, every 4 weeks if values are between 75 and 100×10^9/L, and as clinically indicated if values are greater than 100×10^9/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 can occur in patients with AdvSM receiving avapritinib (see section 4.8). These include, but are not limited to, memory impairment, cognitive disorder, confusional state, and encephalopathy. The mechanism of the cognitive effects is not known.

It is recommended that patients with AdvSM are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, or difficulty with cognitive functioning. Patients with AdvSM should notify their healthcare professional immediately if they experience new or worsening cognitive symptoms.

For AdvSM patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification in Table 2 should be followed (see section 4.2). In clinical studies conducted in patients with AdvSM, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.

In patients with ISM, cognitive effects can be one of the disease symptoms. Patients with ISM must notify their healthcare professional if they experience new or worsening cognitive symptoms.

Fluid retention

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

Therefore, it is recommended that patients with 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 should be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For 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 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 AdvSM patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products that can prolong QT interval such as amiodarone, citalopram, escitalopram, ondansetron; pre-existing cardiac disease; and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A 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 CYP3A inhibitors cannot be avoided, see section 4.2 for dose modification instructions.

In patients with 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 AdvSM (see section 4.8). 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 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 AdvSM is associated with anaemia, neutropenia and/or thrombocytopenia (see section 4.8). Complete blood counts should be performed on a regular basis during the treatment with avapritinib in patients with AdvSM (see also the guidance under intracranial haemorrhages above in this section).

Treatment with avapritinib is associated in patients with AdvSM with elevations in bilirubin and liver transaminases (see section 4.8). Liver function (transaminases bilirubin) should be monitored regularly in patients with 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 should be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients should 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 $AUC_{0\text{-}inf}$ by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone.

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors (such as antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin; active substances to treat human immunodeficiency virus infections/acquired immunodeficiency syndrome (HIV/AIDS) such as cobicistat, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir; as well as conivaptan for hyponatremia and boceprevir to treat hepatitis) including grapefruit or grapefruit juice should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib should be reduced from 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 $AUC_{0\text{-}inf}$ by 92%, relative to a 400 mg dose of avapritinib administered alone.

Co-administration of avapritinib with strong and moderate CYP3A inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital,

fosphenytoin, primidone, bosentan, efavirenz, etravirine, modafinil, dabrafenib, nafcillin or *Hypericum perforatum*, also known as St. John's wort) should be avoided.

Effect of avapritinib on other active substances

Co-administration of avapritinib 300 mg once daily with oral midazolam, a sensitive substrate for CYP3A4, increased the midazolam AUC and C_{max} by 51% and 20%, respectively, in a clinical study. These results indicate that avapritinib 300 mg once daily is a weak inhibitor of CYP3A. Physiologically based pharmacokinetic simulations predict that avapritinib 200 mg once daily administered to patients with GIST is a weak inhibitor of CYP3A4. No inhibition is predicted in patients with AdvSM or ISM administered with the recommended dose of avapritinib.

Caution should be exercised with co-administration of avapritinib with medicinal products that can increase the risk of QT prolongation (e.g. amiodarone, citalopram, escitalopram, ondansetron).

In a drug-drug interaction study of 15 subjects, co-administration of avapritinib 25 mg once daily with a combined oral contraceptive (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) resulted in a mean ethinyl estradiol AUC ratio of 1.15 (90% confidence interval [CI]: 1.04, 1.28) and a mean ethinyl estradiol C_{max} ratio of 1.46 (90% CI: 1.17, 1.81) relative to participants administered the combined oral contraceptive alone. This increase in ethinyl estradiol C_{max} may lead to an increased risk of ethinyl estradiol-related adverse reactions in patients receiving avapritinib at doses greater than 25 mg once daily, such as headache, nausea and breast tenderness.
If the patient is unable to use or tolerate an effective nonhormonal contraceptive or an effective hormonal contraceptive without estrogen, use a formulation of ethinyl estradiol containing 20 mcg or less unless a higher dose is necessary.

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 should be informed that avapritinib may cause foetal harm (see section 5.3).

The pregnancy status of women of reproductive potential should be verified prior to initiating avapritinib treatment.

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

childbearing potential must use effective contraception during treatment and for 2 weeks after the last dose of avapritinib.

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

Pregnancy

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

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

If avapritinib is used during pregnancy or if the patient becomes pregnant while taking avapritinib, the patient should 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 should be discontinued during treatment with avapritinib and for 2 weeks following the final dose.

Fertility

There are no data on the effect of avapritinib 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

Avapritinib 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 should 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 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).

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

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

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

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

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

Tabulated list of adverse reactions

For patients with AdvSM, adverse reactions that were reported in clinical studies in ≥3% of patients 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 ISM, adverse reactions reported in Part 2 of the PIONEER study in ≥5% of patients are listed in Table 4.

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

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

Advanced systemic mastocytosis

Table 3. Adverse reactions reported in clinical studies in patients with advanced systemic mastocytosis treated with avapritinib starting at 200 mg

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
Blood and lymphatic system disorders			
Very common	Thrombocytopenia*	46.8	23.0
	Anaemia*	23.0	11.9
	Neutropenia*	21.4	19.0
Common	Leukopenia*	8.7	2.4
Nervous system disorders			
Very common	Cognitive effects[1]	18.3	1.6
	Taste effect*	15.9	0.8
Common	Headache	7.9	-
	Dizziness	5.6	-
	Neuropathy peripheral[2]	4.8	-
	Intracranial haemorrhage[3]	2.4	0.8
Eye disorders			
Common	Lacrimation increased	6.3	-
Cardiac disorders			
Uncommon	Pericardial effusion	0.8	-
Respiratory, thoracic and mediastinal disorders			
Common	Epistaxis	5.6	-
	Pleural effusion	2.4	-
Gastrointestinal disorders			
Very common	Diarrhoea	14.3	1.6
	Nausea	12.7	-
Common	Vomiting*	8.7	0.8
	Gastroesophageal reflux disease*	4.8	-
	Ascites*	4.0	0.8
	Dryness*	4.0	-
	Constipation	3.2	-
	Abdominal pain*	3.2	-
	Gastrointestinal haemorrhage[4]	2.4	1.6
Hepatobiliary disorders			
Common	Hyperbilirubinaemia*	7.9	0.8
Skin and subcutaneous tissue disorders			

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
Very common	Hair colour changes	15.1	-
Common	Rash*	7.9	0.8
	Alopecia	7.1	-
Uncommon	Photosensitivity reaction	0.8	-
Musculoskeletal and connective tissue disorders			
Common	Arthralgia	4.8	0.8
General disorders and administration site conditions			
Very common	Oedema[5]	69.8	4.8
	Fatigue*	18.3	2.4
Common	Pain	3.2	-
Investigations			
Common	Weight increased	6.3	-
	Blood alkaline phosphatase increased	4.8	1.6
	Transaminases increased*	4.8	-
	Electrocardiogram QT prolonged	1.6	0.8
Injury, poisoning and procedural complications			
Common	Contusion	3.2	-

[1]Cognitive effects (including cognitive disorder, memory impairment and confusional state)
[2]Neuropathy peripheral (including Paraesthesia, Neuropathy peripheral, Hypoaesthesia)
[3]Intracranial haemorrhage (including Haemorrhage intracranial, Subdural haematoma)
[4]Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Melaena)
[5]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 4. Adverse reactions reported in clinical studies in patients with indolent systemic mastocytosis

System Organ Class / frequency category	Adverse reactions	Avapritinib (25 mg once daily) + Best Supportive Care All grades%	Grades ≥3 %
Psychiatric disorders			
Common	Insomnia	5.7	-
Vascular disorders			
Common	Flushing	9.2	1.4
Skin and subcutaneous tissue disorders			
Common	Photosensitivity reaction	2.8	-
General disorders and administration site conditions			
Very common	Peripheral oedema[1]	12.1	-
Common	Face oedema	7.1	-
Investigations			
Common	Blood alkaline phosphatase increased	6.4	0.7

[1]Peripheral oedema (including oedema peripheral and peripheral swelling)
-: no adverse reactions reported

Description of selected adverse reactions

Intracranial haemorrhage

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

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 2.5% of the 121 patients with AdvSM with platelet counts of $\geq 50 \times 10^9$/L prior to initiation of therapy who received avapritinib at the recommended starting dose of 200 mg.

Events of intracranial haemorrhage (all grades) occurred in a range from 12.0 weeks to 15.0 weeks after initiating avapritinib, with a median time to onset of 12.1 weeks.

In clinical studies with avapritinib, the incidence of intracranial haemorrhage was higher in patients who received a starting dose of ≥300 mg once daily, as compared to patients who received the recommended starting dose of 200 mg once daily. 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.

Advanced systemic mastocytosis
Cognitive effects occurred in 51 (26%) of the 193 patients with AdvSM (all doses) and in 23 (18%) of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg (see section 4.4). In the patients with AdvSM treated at a starting dose of 200 mg who had an event (any grade), the median time to onset was 12 weeks (range: 0.1 weeks to 108.1 weeks).

Most cognitive effects were Grade 1, with Grade ≥2 occurring in 7% of 126 patients treated at a starting dose of 200 mg. Among patients who experienced a cognitive effect of Grade ≥2 (impacting activities of daily living) the median time to improvement was 6 weeks.

For patients with AdvSM treated at a starting dose of 200 mg cognitive disorder occurred in 12% of patients; 1.6% of these events were Grade 3. Memory impairment occurred in 6% of patients; none of these events were Grade 3. Confusional state occurred in 2% of patients; none of these events were Grade 3. No Grade 4 and no fatal events were reported.

Of the 126 AdvSM patients treated at a starting dose of 200 mg one patient (<1%) required permanent discontinuation of avapritinib for a cognitive adverse reaction, 7% required a dose interruption, and 6% required dose reduction.

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

Indolent systemic mastocytosis
In Part 2 of the PIONEER study, cognitive effects occurred in 2.8% of patients with ISM who received 25 mg of avapritinib (see section 4.4); all cognitive effects were Grade 1 or 2. Overall, none of the patients who received avapritinib in Part 2 of PIONEER required permanent treatment discontinuation for cognitive effects.

Anaphylactic adverse reactions

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

Elderly

Advanced systemic mastocytosis
Of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg once daily in EXPLORER and in PATHFINDER, 63% were 65 years or older and 21% were 75 years of age or older. Compared with younger patients (<65), more patients ≥65 years old reported adverse reactions that led to dose reductions (62% versus 73%). A similar fraction of patients reported adverse reactions that led to dose discontinuation (9% versus 6%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions (63.3%) compared to younger patients (53.2%).

Indolent systemic mastocytosis
In Part 2 of PIONEER (N=141) (see section 5.1), 9 (6%) patients were 65 years of age or older, and 1 (<1%) patient was 75 years of age or older. No patients over the age of 84 were included. Overall, no meaningful differences in safety were observed between patients ≥65 years and those <65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 the recommended dose (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 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 mutations.

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 advanced systemic mastocytosis
The efficacy and safety of avapritinib was assessed in BLU-285-2202 (PATHFINDER), a multi-centre, single-arm, open-label Phase 2 clinical study. 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. Response-evaluable patients included those with a confirmed diagnosis of AdvSM per the World Health Organisation (WHO) and deemed evaluable by modified IWG-MRT-ECNM criteria at baseline as adjudicated by an independent central committee, who 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.

In PATHFINDER, patients were enrolled at the starting dose of 200 mg orally once daily. The primary efficacy outcome measure was ORR according to modified IWG-MRT-ECNM criteria as evaluated by the central committee in 72 patients treated with avapritinib starting dose of 200 mg daily. Additional efficacy outcome measures were duration of response (DOR), time to response, overall survival (OS) and changes in individual measures of mast cell burden.

The assessment of the primary efficacy endpoint, the ORR, was based on a total of 72 patients with AdvSM, enrolled in PATHFINDER, who were evaluable for response. The median duration of follow up for these patients was 14.3 months (95% confidence interval 11.2 to 16.9 months).

The study population characteristics were: median age of 68 years (range: 31 to 88 years), 58% male, 85% white, 75% had an ECOG PS of 0-1, 25% had an ECOG PS of 2-3, 33% had ongoing corticosteroid therapy use for systemic mastocytosis at baseline, 90% of patients had a detectable KIT D816V mutation, 64% had prior antineoplastic therapy and 53% had received prior midostaurin. Before initiation of avapritinib treatment, the median bone marrow mast cell infiltrate was 50%, the median serum tryptase level was 259.20 ng/mL, and the median KIT D816V mutant allele fraction (MAF) was 15%.

Efficacy results in patients with AdvSM enrolled in the PATHFINDER study, who were treated with a starting dose of 200 mg once daily is summarized in Table 5.

Table 5. Efficacy results for patients with advanced systemic mastocytosis in PATHFINDER per modified IWG-MRT-ECNM criteria

Efficacy Parameter	**Overall**	**ASM**	**SM-AHN**	**MCL**
ORR, (%) (95% CI)[a]	N = 72 68 (56, 78.6)	N = 12 67 (34.9, 90.1)	N = 48 77 (62.7, 88)	N = 12 33 (9.9, 65.1)
CR	4	0	6	0
CRh	14	25	15	0
CR+CRh	18	25	21	0
PR	43	42	48	25
Clinical improvement	7	0	8	8
Median DOR[b] (months), (CI)	N = 49 NE (NE, NE)	N = 8 NE (NE, NE)	N = 37 NE (NE, NE)	N = 4 NE (NE, NE)
KM Estimate at 12 months, %	100	100	100	100
KM Estimate at 24 months, %	85.6	-	83	-
Time to response CR/CRh/PR/Clinical improvement (months), median	N = 49 1.94	N = 8 2	N = 37 1.94	N =4 3.60
Time to response CR/CRh (months), median	N = 13 5.55	N = 3 2.10	N = 10 5.83	N = 0 0
Time to CR/CRh/PR	N = 44 3.19	N = 8 2.20	N = 33 3.65	N = 3 5.59

(months), median				
Median OS (months), (CI)	NE (NE, NE)	NE (NE, NE)	NE (13.5, NE)	NE (NE, NE)

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

[a] ORR is defined as patients who achieved a CR, CRh, PR or clinical improvement

[b] DOR is defined as duration of response for patients who achieve a CR, CRh, PR or clinical improvement, DOR is estimated from Kaplan-Meyer analysis

The assessment of the following secondary efficacy endpoints was based on AdvSM patients with baseline and post baseline values for mast cell burden. 83.5% of patients had a decrease in bone marrow infiltration that exceeded 50% with 60.2% patients having complete elimination of bone marrow mast cell aggregates; 90.5% had a decrease in serum tryptase levels that exceeded 50%, with 53.3% reducing serum tryptase <20 ng/mL; and 76.2% of patients had a decrease in KIT D816V variant allele fraction in blood that exceeded 50% with decrease to <1% in 45.7% of patients and 62.1% of patients had a reduction of ≥35% in spleen volume, which correlates with a 50% decrease by palpation.

Among the 35 patients receiving 200 mg orally daily with baseline corticosteroid use in the AdvSM population, 51% of patients reduced their corticosteroid use or discontinued corticosteroids completely.

SM symptoms were a secondary endpoint in the PATHFINDER study and were measured using the AdvSM-Symptom Assessment Form (AdvSM-SAF) questionnaire. The AdvSM-SAF is a 10-item questionnaire to assess 8 symptoms (abdominal pain, nausea, vomiting, diarrhoea, spots on skin, itching, flushing, fatigue) and 2 functional domains (GI and skin) specific to AdvSM. Total symptom score (TSS) is the sum of all 8 symptoms (scored 0 to 80). The assessment of the following secondary efficacy endpoints was based on AdvSM patients with a baseline value for the respected symptom/domain/TSS. In patients on treatment for > 10 cycles, mean change in AdvSM-SAF TSS from baseline to C11D1 was statistically significant (p value< 0.001). The mean reduction from baseline was −6.70 points (95% confidence interval: −9.30 to −4.11).

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 68.8% (95% confidence interval: 41.3, 89.0) for 16 AdvSM patients who received a starting dose of 200 mg avapritinib once daily.

Clinical studies in indolent systemic mastocytosis

The efficacy and safety of avapritinib was assessed in study BLU-285-2203 (PIONEER), a randomised, double-blind, placebo-controlled, 3-part study conducted in adult patients with ISM with moderate-to-severe symptoms not adequately controlled by best supportive care. In Part 2 (pivotal part), patients were randomised to receive avapritinib at the recommended dose of 25 mg orally once daily with best supportive care (141 patients) versus placebo with best supportive care (71 patients).

The randomized portion of the study consisted of a 24-week period. Part 3 of study BLU-285-2203 is ongoing.
The primary endpoint in Part 2 was mean change from baseline to Week 24 in total symptom score (TSS) as measured by the ISM Symptom Assessment Form (ISM-SAF). The ISM-SAF is a patient-reported outcome tool made up of a 12-item questionnaire developed specifically to assess symptoms in patients with ISM. Patient-reported severity scores for 11 ISM symptoms (bone pain, abdominal pain, nausea, spots, itching, flushing, fatigue, dizziness, brain fog, headache, diarrhoea; 0=none; 10=worst imaginable) are summed to calculate the TSS (range 0-110), with higher scores representing greater symptom burden. The 12th item of the questionnaire assesses the number of diarrhoea episodes.
For the purpose of the study, enrolled patients needed a total symptom score (TSS) of 28 or greater at screening. Patients were required to have failed to achieve adequate symptom control for 1 or more baseline symptoms with at least 2 symptomatic therapies, including but not limited to: H1 antihistamines, H2 antihistamines, proton pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab.
Additional patient-reported key secondary efficacy endpoints were the proportion of avapritinib-treated patients achieving ≥50% and ≥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 ≥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 6.

Table 6. Reduction in ISM-SAF TSS and measures of mast cell burden in patients with indolent systemic mastocytosis in PIONEER at Week 24

Efficacy Parameter	**AYVAKYT (25 mg once daily) + BSC** **N = 141**	**Placebo + BSC** **N = 71**	**One-sided p-value**
ISM-SAF TSS			
Mean change in TSS[1]			
Change from baseline (95% CI)	-15.33 (-18.36, -12.31)	-9.64 (-13.61, -5.68)	0.006
Difference from placebo (95% CI)	-5.69[2] (-10.16, -1.23)		

% of patients achieving ≥50% reduction in TSS (95% CI)	25 (17.9, 32.8)	10 (4.1, 19.3)	0.005
% of patients achieving ≥30% reduction in TSS (95% CI)	45 (37.0, 54.0)	30 (19.3, 41.6)	0.009
Measures of mast cell burden			
% of patients with a ≥50% reduction in serum tryptase (95% CI)	N = 141 **54** (45.3, 62.3)	N = 71 **0** (0.0, 5.1)	<0.0001
% of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction or undetectable (95% CI)	N = 118 **68** (58.6, 76.1)	N = 63 **6** (1.8, 15.5)	<0.0001
% of patients with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI)	N = 106 **53** (42.9, 62.6)	N = 57 **23** (12.7, 35.8)	<0.0001

Abbreviations: BSC=best supportive care, CI=confidence interval, ISM-SAF=indolent systemic mastocytosis symptom assessment form, TSS=total symptom score

[1] Markov chain Monte Carlo simulation was used to impute the missing values at Baseline or C7D1.

[2] 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

Advanced systemic mastocytosis

Of the 126 patients with AdvSM who received avapritinib at a starting dose of 200 mg once daily in EXPLORER and in PATHFINDER 63% were 65 years or older. No overall differences in efficacy were observed in comparison with younger patients.

Indolent systemic mastocytosis

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

meaningful differences in efficacy were observed between patients ≥65 years and those <65 years.

Paediatric population

The Medicines and Healthcare products Regulatory Agency (MHRA) 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 Medicines and Healthcare products Regulatory Agency (MHRA) 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.

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 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_{0-24} of avapritinib at 25 mg once daily was 70.2 ng/mL (47.8%) and 1330 h•ng/mL (49.5%), respectively. The geometric mean accumulation ratio after repeat dosing was 3.59.

Absorption

Following administration of single oral doses of avapritinib of 25 to 400 mg, the median time to peak concentration (T_{max}) ranged from 2 to 4 hours post dose. The absolute bioavailability has not been determined. The population estimated mean oral bioavailability of avapritinib in patients with AdvSM is 47% lower, compared to that in patients with ISM.

Effect of food
Avapritinib C_{max} and AUC_{inf} were increased by 59% and 29%, respectively, in healthy subjects administered avapritinib after a high fat meal (approximately 909 calories,

58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to the C_{max} and AUC_{inf} after overnight fasting.

Distribution

Avapritinib is 98.8% bound to human plasma proteins *in vitro* and the binding is not concentration-dependent. The blood-to-plasma ratio is 0.95. Following a single 200 mg oral dose of avapritinib, the mean (% CV) apparent volume of distribution (V_z/F) was 1900 L (43%) in patients with AdvSM, and following a single 25 mg oral dose of avapritinib, V_z/F was 1400 L (59.1%) in patients with ISM, indicating extensive distribution into tissues from plasma.

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 µCi) [^{14}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 avapritinib of 30 to 400 mg in patients with AdvSM, and single doses of 25 to 100 mg in patients with ISM, the mean plasma elimination half-life of avapritinib was 20 to 39 hours and 38 to 45 hours, respectively.

Following oral administration of avapritinib 200 mg once daily, the steady state mean apparent oral clearance (CL/F) of avapritinib was 40.3 L/h in patients with AdvSM. Following oral administration of avapritinib 25 mg once daily, CL/F of avapritinib was 21.6 L/h in patients with ISM.

Following a single oral dose of approximately 310 mg (~100 µCi) [^{14}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, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of avapritinib. In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients (see also section 4.8 and section 5.1).

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 (CLcr 60-89 mL/min), 52 subjects with moderate renal impairment (CLcr 30-59 mL/min) and 298 subjects with normal renal function (CLcr ≥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 (CLcr 15-29 mL/min) or end-stage renal disease (CLcr <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 and 1.8 times the human exposure based on AUC at the 25 mg and 200 mg clinical 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 and 1.0 times the human exposure based on AUC at the 25 mg and 200 mg clinical dose once daily, respectively). These findings were not observed in a subsequent 9-month study.

Rats manifested convulsions, which was potentially secondary to inhibition of Nav 1.2 at systemic exposures ≥96 and 12-fold higher than the exposure in patients at the clinical dose of 25 mg and 200 mg once daily, respectively.

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 and 3 times the human exposure based on AUC at the 25 mg and 200 mg clinical dose, respectively. In a 9-month repeat dose toxicology study in dogs, minimal to mild hypospermatogenesis (3/4 males) was observed at the highest dose tested, 5 mg/kg/day (5.7 and 1.2 times the human exposure (AUC) at the 25 mg and 200 mg clinical 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 rat bone marrow micronucleus test, 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 and 20.3 and 9.5 times the human exposure (AUC) at 200 mg).

There was however an increase in pre-implantation loss and in early resorptions (approximately 15 and 3 times the human exposure based on AUC at the 25 mg and 200 mg clinical dose, respectively). Reduction in sperm production and relative testicular weight were observed in male rats administered avapritinib at exposures of 7 and 30 times and 1 and 5 times the 25 mg and 200 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 and 6.3 times the human exposure (AUC) at the 25 mg and 200 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)

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

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