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 300 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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

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.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the administration of anticancer therapy.

Posology for GIST

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

The recommended starting dose of avapritinib is 300 mg orally once daily, on an empty stomach (see Method of administration). The dose should be adjusted based on safety and tolerability.

Treatment should be continued until disease progression or unacceptable toxicity.

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 should be reduced from 300 mg to 100 mg orally once daily (see section 4.5).

Dose modifications for adverse reactions
Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation.

Patients may have their dose reduced by 100 mg increments to a minimum dose of 100 mg once daily.

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 and are provided in Tables 1 and 2.

Table 1. Recommended dose reductions for AYVAKYT for adverse reactions

Dose reduction	**GIST (starting dose 300 mg)**
First	200 mg once daily
Second	100 mg once daily

Table 2. Recommended dose modifications for AYVAKYT for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
Patients with GIST		
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.

* 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).

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 (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 substances 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. Gastrointestinal haemorrhagic adverse reactions were the most commonly reported haemorrhagic adverse reactions during avapritinib treatment of unresectable or metastatic GIST patients, while hepatic and tumour haemorrhage also occurred (see section 4.8).

Routine surveillance of haemorrhagic events 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 unresectable or metastatic GIST receiving avapritinib (see section 4.8). 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, regardless of severity grade, avapritinib should be permanently discontinued (see section 4.2).

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

Cognitive effects

Cognitive effects can occur in patients with unresectable or metastatic GIST 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 are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, or difficulty with cognitive functioning. Patients should notify their healthcare professional immediately if they experience new or worsening cognitive symptoms.

For 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 GIST, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.

Fluid retention

Occurrences of fluid retention, including severe cases of localised oedema (facial, periorbital, peripheral oedema and/or pleural effusion), generalised oedemas and ascites, 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).

Therefore, it is recommended that patients 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 patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

QT interval prolongation

Prolongation of QT interval has been observed in patients with unresectable or metastatic GIST 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 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 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.

Interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval.

Gastrointestinal disorders

Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with unresectable or metastatic GIST (see section 4.8). 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 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 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 GIST (see also the guidance under intracranial haemorrhages above in this section).

Treatment with avapritinib is associated in patients with unresectable or metastatic GIST with elevations in bilirubin and liver transaminases (see section 4.8). Liver function (transaminases, bilirubin) should be monitored regularly in patients with GIST 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 300 mg to 100 mg orally once daily for patients with GIST (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.

Caution should be exercised with co-administration of avapritinib in patients with GIST taking avapritinib 200 mg once daily and higher with narrow therapeutic index CYP3A substrates (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, sirolimus, tacrolimus) and with medicinal products that can increase the risk of QT prolongation (e.g. amiodarone, citalopram, escitalopram, ondansetron) as their plasma concentrations may be increased.

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 AYVAKYT. 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 585 patients with GIST (all doses), of which 550 patients received avapritinib at a starting dose of 300 mg or 400 mg, see section 5.1.

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.

Tabulated list of adverse reactions

Adverse reactions that were reported in clinical studies in ≥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.

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.

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

System Organ Class / frequency category	**Adverse reactions**	**All grades %**	**Grades ≥3 %**
Infections and infestations			
Common	Conjunctivitis	2.0	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon	Tumour haemorrhage	0.2	0.2
Blood and lymphatic system disorders			
Very common	Anaemia	39.6	20.4

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
	White blood cell count decreased	14.0	3.1
	Neutrophil count decreased	15.8	8.9
Common	Thrombocytopenia	8.4	0.9
	Lymphocyte count decreased	4.7	2.2
Metabolism and nutrition disorders			
Very common	Decreased appetite	21.1	0.5
Common	Hypophosphataemia	8.9	2.5
	Hypokalaemia	6.0	0.9
	Hypomagnesaemia	3.8	0.4
	Hyponatraemia	1.3	0.7
	Dehydration	1.8	0.5
	Hypoalbuminaemia	2.4	-
	Hypocalcaemia	2.2	0.4
Psychiatric disorders			
Common	Confusional state	4.7	0.5
	Depression	4.2	0.4
	Anxiety	1.8	-
	Insomnia	3.8	-
Nervous system disorders			
Very common	Memory impairment	22.7	0.9
	Cognitive disorder	11.8	0.9
	Dizziness	10.5	0.2
	Taste effect	12.7	-
Common	Intracranial haemorrhage[1]	1.6	1.1
	Mental impairment[2]	5.6	0.7
	Neuropathy peripheral	8.5	0.4
	Somnolence	1.8	-
	Aphasia	1.8	-
	Hypokinesia	1.3	0.2
	Headache	8.0	0.2
	Balance disorder	1.6	-
	Speech disorder	4.5	-
	Tremor	2.2	0.2

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
Uncommon	Encephalopathy	0.9	0.5
Eye disorders			
Very common	Lacrimation increased	22.2	-
Common	Ocular haemorrhage[3]	1.1	-
	Vision blurred	2.9	-
	Conjunctival haemorrhage	2.4	-
	Photophobia	1.6	-
Ear and labyrinth disorders			
Common	Vertigo	2.4	-
Cardiac disorders			
Uncommon	Pericardial effusion	0.9	0.2
Vascular disorders			
Common	Hypertension	3.3	1.1
Respiratory, thoracic and mediastinal disorders			
Common	Pleural effusion	6.0	0.9
	Dyspnoea	6.0	0.7
	Nasal congestion	1.5	-
	Cough	2.2	-
Gastrointestinal disorders			
Very common	Abdominal pain	10.9	1.1
	Vomiting	24.2	0.7
	Diarrhoea	26.4	2.7
	Nausea	45.1	1.5
	Dryness	10.9	0.2
	Gastrooesophageal reflux disease	12.9	0.5
Common	Gastrointestinal haemorrhage[4]	2.2	1.6
	Ascites	7.5	1.3
	Constipation	5.8	-
	Dysphagia	2.4	0.4
	Stomatitis	2.4	-
	Flatulence	1.6	-
	Salivary hypersecretion	1.5	-
Hepatobiliary disorders			

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
Very common	Hyperbilirubinaemia	27.5	5.8
Uncommon	Hepatic haemorrhage	0.2	0.2
Skin and subcutaneous tissue disorders			
Very common	Hair colour changes	15.3	0.2
	Rash	12.7	1.6
Common	Palmar-plantar erythrodysaesthesia syndrome	1.3	-
	Photosensitivity reaction	1.1	-
	Skin hypopigmentation	1.1	-
	Pruritus	2.9	-
	Alopecia	9.6	-
Musculoskeletal and connective tissue disorders			
Common	Myalgia	2.0	-
	Arthralgia	1.8	-
	Back pain	1.1	-
	Muscle spasms	1.6	-
Renal and urinary disorders			
Common	Acute kidney injury	2.0	0.9
	Blood creatinine increased	4.4	-
	Haematuria	1.1	-
General disorders and administration site conditions			
Very common	Oedema[5]	70.2	4.7
	Fatigue	39.6	5.3
Common	Asthenia	7.8	1.6
	Pyrexia	1.8	0.2
	Malaise	2.5	0.2
	Feeling cold	2.9	-
Investigations			
Very common	Transaminases increased	12.4	0.9
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	-

System Organ Class / frequency category	Adverse reactions	All grades %	Grades ≥3 %
	Blood lactate dehydrogenase increased	1.3	-

Intracranial haemorrhage (including Cerebral haemorrhage, Haemorrhage intracranial, Subdural haematoma, Cerebral haematoma)
[2]Mental impairment (including Disturbance in attention, Mental impairment, Mental status changes, Dementia)
[3]Ocular haemorrhage (including Eye haemorrhage, Retinal haemorrhage, Vitreous haemorrhage)
[4]Gastrointestinal haemorrhage (including Gastric haemorrhage, Gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Rectal haemorrhage, Melaena)
[5]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 ≥3

Description of selected adverse reactions

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

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

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.

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

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

Memory impairment occurred in 20% of patients, <1% of these events were Grade 3.
Cognitive disorder occurred in 12% of patients; <1% of these events were Grade 3.
Confusional state occurred in 5% of patients; <1% of these events were Grade 3.
Encephalopathy occurred in <1% of patients; <1% of these events were Grade 3.
Serious adverse reactions of cognitive effects were reported for 9 of 585 (1.5%) of the

GIST patients (all doses), of which 7 of the 550 (1.3%) patients were observed in the GIST group receiving a starting dose of either 300 or 400 mg once daily.

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

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

Elderly
In NAVIGATOR and VOYAGER (N=550), 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%).

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 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 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. No effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed.

Clinical efficacy and safety

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 trial 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 4. 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 4. Efficacy results for PDGFRA D842V-Mutation in GIST patients (NAVIGATOR study)

Efficacy Parameter	**N = 38**
mRECIST 1.1 ORR[1], (%) (95% CI) **CR** **PR**	95 (82.3, 99.4) 13 82
DOR (months), median (CI)	22.1 (14.1, NE)

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; mRECIST 1.1=Response Evaluation Criteria In Solid Tumours v1.1 modified for patients with unresectable or metastatic GIST; N=number of patients; NE=not estimable; ORR=overall response rate; PR=partial response
[1] ORR is defined as patients who achieved a CR or PR (CR + PR)

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

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

Elderly population

Forty-two percent of the patients who received avapritinib 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)).

Paediatric population

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

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. 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 ($AUC_{0\text{-}tau}$) 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.

Absorption

Following administration of single oral doses of avapritinib of 30 to 400 mg, the median time to peak concentration (T_{max}) ranged from 2.0 to 4.0 hours postdose. The absolute bioavailability has not been determined. The population estimated mean oral bioavailability of avapritinib in patients with AdvSM is 20% lower, compared to that in the patients with GIST.

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 300 mg oral dose of avapritinib in patients with GIST, the geometric mean (% CV) apparent volume of distribution (V_z/F) of avapritinib was 1200L (43%), 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. 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 GIST, the mean plasma elimination half-life of avapritinib was 32 to 57 hours.

Following oral administration of avapritinib 300 mg once daily, the steady state mean apparent oral clearance (CL/F) of avapritinib was 21.8 L/h in patients with GIST.

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), 6 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 0.8 times the human exposure based on AUC at the 300 mg clinical dose once daily) and choroid plexus oedema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 0.4

times the human exposure based on AUC at the 300 mg clinical dose once daily).

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 ≥8-fold higher than the exposure in patients at the clinical dose of 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 1.3 times the human exposure based on AUC at the 300 mg clinical dose. 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 (<1 times the human exposure (AUC) at the 300 mg clinical dose).

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 (8.7 and 4.1 times the human exposure (AUC) at 300 mg).

There was however an increase in pre-implantation loss and in early resorptions (approximately 1.3 times the human exposure based on AUC at the 300 mg clinical dose). Reduction in sperm production and relative testicular weight were observed in male rats administered avapritinib at exposures of 0.6 and 3 times the 300 mg human dose.

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 2.7 times the human exposure (AUC) at the 300 mg dose.

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

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.
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1082 MA Amsterdam
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 52115/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/08/2025

10 DATE OF REVISION OF THE TEXT

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