

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### AYVAKYT 100 mg film-coated tablets

Each film-coated tablet contains 100 mg of avapritinib.

### AYVAKYT 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of avapritinib.

### AYVAKYT 300 mg film-coated tablets

Each film-coated tablet contains 300 mg of avapritinib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

### AYVAKYT 100 mg film-coated tablets

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

### AYVAKYT 200 mg film-coated tablets

Oval, white film-coated tablet of 16 mm in length and 8 mm in width, printed with blue ink “BLU” on one side and “200” on the other.

### AYVAKYT 300 mg film-coated tablets

Oval, white film-coated tablet of 18 mm in length and 9 mm in width, printed with blue ink “BLU” on one side and “300” on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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.

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

### Posology

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 orally once daily to 100 mg orally once daily (see section 4.5).

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

### *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.

### *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.

Recommended dose modifications are indicated in Table 1.

**Table 1. Recommended dose modifications for AYVAKYT for adverse reactions**

<b>Adverse reaction</b>	<b>Severity*</b>	<b>Dosage modification</b>
<b>Intracranial haemorrhage</b> (see section 4.4)	All Grades	Permanently discontinue AYVAKYT.
<b>Cognitive effects**</b> (see section 4.4)	Grade 1	Continue at the same dose or interrupt until improvement to baseline or resolution. Resume at the same dose or a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.
<b>Other</b> (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

### Special populations

#### *Elderly*

No dose adjustment is recommended for patients aged 65 years and above.

#### *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). Avapritinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (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

In patients with unresectable or metastatic GIST, avapritinib has been associated with an increased incidence of haemorrhagic events, including serious and severe events, like gastrointestinal haemorrhage, hepatic, tumour and intracranial haemorrhages. Gastrointestinal haemorrhagic events were the most commonly reported haemorrhagic events during avapritinib treatment (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 and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.

### 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 AYVAKYT the risk for intracranial haemorrhage should be carefully considered in patients with risk factors such as severe thrombocytopenia, and in patients with increased risk of intracranial haemorrhage such as those with a vascular aneurysm or a history of intracranial haemorrhage within the prior year, a history of a cerebrovascular accident or transient ischaemic attack. Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) during treatment with AYVAKYT should 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 Grade, avapritinib should be permanently discontinued (see section 4.2).

There is no clinical trial experience using AYVAKYT in patients with brain metastases.

### Cognitive effects

Cognitive effects can occur in patients with unresectable or metastatic GIST receiving AYVAKYT (see section 4.8). These include 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 AYVAKYT, the recommended dose modification in Table 1 should be followed (see section 4.2). In clinical trials, dose reductions or interruptions improved Grade  $\geq 2$  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) or generalised oedemas, have been reported with a frequency category of at least common in patients with unresectable or metastatic GIST taking avapritinib. Other localised oedemas (laryngeal oedema and/or pericardial effusion) have been reported uncommonly (see section 4.8).

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.

### QT interval prolongation

Prolongation of QT interval has been observed in patients with unresectable or metastatic GIST treated with avapritinib in clinical trials. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes.

AYVAKYT 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, pre-existing cardiac disease and/or electrolyte disturbances). Concomitant administration with moderate or strong 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 ECG should be considered if AYVAKYT 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). 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 thrombocytopenia (see section 4.8). Complete blood counts should be performed on a regular basis during the treatment with AYVAKYT.

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 receiving AYVAKYT.

#### 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 AYVAKYT. 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 AYVAKYT

##### *Strong and moderate CYP3A inhibitors*

Co-administration of AYVAKYT with a strong CYP3A inhibitor increased avapritinib plasma concentrations and may result in increased adverse reactions. Co-administration of itraconazole (200 mg twice daily on Day 1 followed by 200 mg once daily for 13 days) with a single 200 mg dose of avapritinib on Day 4 in healthy subjects increased avapritinib  $C_{max}$  by 1.4-fold and  $AUC_{0-inf}$  by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone.

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors (such as antifungals including ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin; active substances to treat human immunodeficiency virus infections/acquired immunodeficiency syndrome (HIV/AIDS) such as cobicistat, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir; as well as conivaptan for hyponatremia and boceprevir

to treat hepatitis) including grapefruit or grapefruit juice should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of AYVAKYT should be reduced from 300 mg orally once daily to 100 mg orally once daily (see section 4.2 and 4.4).

#### *Strong and moderate CYP3A inducers*

Co-administration of AYVAKYT with a strong CYP3A inducer decreased avapritinib plasma concentrations and may result in decreased efficacy of avapritinib. Co-administration of rifampin (600 mg once daily for 18 days) with a single 400 mg dose of avapritinib on Day 9 in healthy subjects decreased avapritinib  $C_{max}$  by 74% and  $AUC_{0-inf}$  by 92%, relative to a 400 mg dose of avapritinib administered alone.

Co-administration of AYVAKYT 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 Worth) should be avoided.

#### Effect of AYVAKYT on other active substances

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

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

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

Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP *in vitro*. Therefore, avapritinib has the potential to alter concentrations of co-administered substrates of these transporters.

## **4.6 Fertility, pregnancy and lactation**

### Women of childbearing potential/Contraception

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 AYVAKYT treatment.

Women of childbearing potential should use effective contraception during treatment and for 1 month after the last dose of AYVAKYT.

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

### Pregnancy

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

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

If AYVAKYT is used during pregnancy or if the patient becomes pregnant while taking AYVAKYT, the patient 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 AYVAKYT and for 2 weeks following the final dose.

## Fertility

There are no data on the effect of AYVAKYT on human fertility. No relevant effects on fertility were observed in a rat fertility study (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

AYVAKYT may cause adverse reactions such as cognitive effects that may influence the ability to drive and use machines.

Patients should be made aware of the potential for adverse reactions that affect their ability to concentrate and react. Patients who experience these adverse effects 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 frequently reported adverse reactions of any Grade during treatment with AYVAKYT 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 trials in  $\geq 1\%$  of patients are listed below (Table 2) 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

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



**Table 2. Adverse reactions reported in clinical trials in patients treated with AYWAKYT**

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

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

<b>System Organ Class / Frequency Category</b>	<b>Adverse reactions</b>	<b>All Grades %</b>	<b>Grades <math>\geq 3</math> %</b>
	Weight decreased	7.5	0.2
	Weight increased	4.7	-
	Blood lactate dehydrogenase increased	1.3	-

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

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

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

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

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

-: no adverse reactions reported with Grades  $\geq 3$

### Description of selected adverse reactions

#### *Intracranial haemorrhage*

Intracranial haemorrhage (e.g., subdural hematoma, intracranial haemorrhage, cerebral haemorrhage, and cerebral haematoma) 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 AYVAKYT 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 AYVAKYT, with a median time to onset of 22 weeks. The median time to improvement and resolution was 25 weeks for intracranial haemorrhage of Grade  $\geq 2$ .

#### *Cognitive effects*

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 AYVAKYT at starting doses of either 300 or 400 mg once daily (see section 4.4). In the patients who had an event (any Grade), the median time to onset was 8 weeks.

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

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

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

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

#### *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  $\geq 65$  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 national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

#### Symptoms

No cases of overdose have been reported in clinical trials with avapritinib. The maximum dose of AYWAKYT studied clinically is 600 mg orally once daily. Adverse reactions observed at this dose were consistent with the safety profile at 300 mg or 400 mg once daily (see section 4.8).

#### Management

There is no known antidote for AYWAKYT overdose. In the event of suspected overdose, AYWAKYT 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<sub>50</sub>) 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.

#### Pharmacodynamic effects

##### *Potential to prolong the QT interval*

The ability of avapritinib to prolong the QT interval was assessed in 27 patients administered AYWAKYT 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<sub>max</sub> 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 AYWAKYT was assessed in a multi-centre, single-arm, open-label clinical trial (**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 trial (**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 AYVAKYT at a starting dose of either 300 mg or 400 mg once daily. In the NAVIGATOR trial 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 AYVAKYT 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 3. 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 3. Efficacy results for PDGFRA D842V-Mutation in GIST patients (NAVIGATOR study)**

<b>Efficacy Parameter</b>	<b>N = 38</b>
<b>mRECIST 1.1 ORR<sup>1</sup>, (%) (95% CI)</b>	95 (82.3, 99.4)
<b>CR</b>	13
<b>PR</b>	82
<b>DOR (months), median (CI)</b>	22.1 (14.1, NE)

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; mRECIST 1.1=Response Evaluation Criteria In Solid Tumours v1.1 modified for patients with unresectable or metastatic GIST; N=number of patients; NE=not estimable; ORR=overall response rate; PR=partial response

<sup>1</sup> ORR is defined as patients who achieved a CR or PR (CR + PR)

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

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

### Elderly population

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

### Paediatric population

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

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

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

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

## **5.2 Pharmacokinetic properties**

Following administration of avapritinib once daily, steady state was reached by 15 days. 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. The geometric mean accumulation ratio after repeat dosing was 3.1 to 4.6.

The steady state geometric mean (CV%) maximum concentration ( $C_{max}$ ) and area under the concentration-time curve ( $AUC_{0-tau}$ ) of avapritinib at 300 mg once daily was 813 ng/mL (52%) and 15400 h•ng/mL (48%), respectively.

### 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 4.1 hours postdose. The absolute bioavailability has not been determined.

### *Effect of food*

Avapritinib  $C_{max}$  and  $AUC_{inf}$  were increased by 59% and 27%, 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, the geometric mean apparent volume of distribution ( $V_z/F$ ) of avapritinib was 17 L/kg, 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  $\mu$ Ci) [ $^{14}$ 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 ( $IC_{50} = 4 \text{ nM}$ ), the enantiomers BLU111207 ( $IC_{50} = 41.8 \text{ nM}$ ) and BLU111208 ( $IC_{50} = 12.4 \text{ nM}$ ) are 10.5- and 3.1-fold less potent against KIT D816V *in vitro*.

*In vitro* studies demonstrated that avapritinib is a direct inhibitor of CYP3A and a time-dependent inhibitor of CYP3A4, at clinically relevant concentrations (see section 4.5). *In vitro*, avapritinib did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

*In vitro*, at clinically relevant concentrations, avapritinib induced CYP3A (see section 4.5). *In vitro*, avapritinib did not induce CYP1A2 or CYP2B6 at clinically relevant concentrations.

### Elimination

Following single doses of AYVAKYT of 30 to 400 mg, the mean plasma elimination half-life of avapritinib was 32 to 57 hours.

Following oral administration of AYVAKYT 300 mg once daily, the steady state geometric mean apparent oral clearance (CL/F) of avapritinib was 19.5 L/h.

Following a single oral dose of approximately 310 mg (~100  $\mu\text{Ci}$ ) [ $^{14}\text{C}$ ]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 for patients with GIST taking gastric acid reducing agents, 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 53 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 284 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of avapritinib in patients with severe hepatic impairment (total bilirubin >3.0 times ULN and any AST) has not been studied.

### *Renal impairment*

Based on a population pharmacokinetic analysis, avapritinib exposures were similar among 88 subjects with mild renal impairment (CLcr 60-89 mL/min), 24 subjects with moderate renal impairment (CLcr 30-59 mL/min) and 230 subjects with normal renal function (CLcr  $\geq$ 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

Repeat dose studies in dogs indicated haemorrhage and choroid plexus oedema in the brain at  $\geq$  0.4 times the human exposure at the clinical dose of 300 mg once daily. Rats manifested convulsions, which was potentially secondary to inhibition of Nav 1.2 at systemic exposures  $\geq$ 8-fold higher than the exposure in patients at the clinical dose of 300 mg once daily. This effect was not seen in dogs.

### Mutagenicity/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.

Carcinogenicity studies with avapritinib have not been conducted.

### Embryotoxicity / Teratogenicity

A 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. Male rats were dosed 4 weeks prior to mating and through mating and female rats were dosed 2 weeks prior to mating and to gestation day 7. No effect on male or female fertility was noted. The high dose of 30 mg/kg/day is approximately equivalent to the human recommended dose, based on body surface area.

Avapritinib showed embryotoxic and teratogenic effects (decreases in foetal weights and viability, and increases in visceral and skeletal malformations) in an embryo-foetal development toxicity study in rats.

### 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  
Copolydione  
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**

2 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 with foiled induction seal liner and a desiccant in canister.

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

### **6.6 Special precautions for disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

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

## **8. MARKETING AUTHORISATION NUMBER(S)**

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

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

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

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorization: 24 September 2020

## **10. DATE OF REVISION OF THE TEXT**

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

## **ANNEX II**

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

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

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

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

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

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1303	June 2021

<b>Description</b>	<b>Due date</b>
(efficacy data of the PDGFRA D842V-mutant population and safety data from the overall safety population), an ongoing open-label, randomized, Phase 3 study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST.	
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1101, an ongoing single-arm, open-label multiple-cohort Phase 1 study in patients with GIST and other relapsed and refractory solid tumours.	December 2021
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V-mutant GIST.	December 2027

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON 100 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 100 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 100 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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



**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

AYVAKYT 100 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL – 100 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 100 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 100 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Blueprint Medicines (Netherlands) B.V.  
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1082 MA Amsterdam  
Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON 200 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 200 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 200 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

AYVAKYT 200 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL – 200 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 200 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 200 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/002

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON 300 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 300 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 300 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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



**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

AYVAKYT 300 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BOTTLE LABEL – 300 MG FILM-COATED TABLETS**

**1. NAME OF THE MEDICINAL PRODUCT**

AYVAKYT 300 mg film-coated tablets  
avapritinib

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 300 mg avapritinib.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablets  
30 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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1082 MA Amsterdam  
Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/20/1473/003

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### AYVAKYT 100 mg film-coated tablets avapritinib

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

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

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

#### **What is in this leaflet**

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

#### **1. What AYVAKYT is and what it is used for**

AYVAKYT is a cancer medicine containing the active substance avapritinib.

This medicine is used to treat adults with a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic).

AYVAKYT inhibits the activity of a group of proteins in the body called kinases. Cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of cancer cells. This medicine is intended to treat GIST that has a specific mutation (D842V) in the gene responsible for making a kinase called platelet-derived growth factor receptor alpha (PDGFRA).

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

#### **2. What you need to know before you take AYVAKYT**

##### **Do not take AYVAKYT:**

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

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking AYVAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.

Take special care with this medicine:

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

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

For more information see section 4.

### **Children and adolescents**

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

### **Other medicines and AYVAKYT**

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

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

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

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

The following medicines can reduce the effects of AYVAKYT:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy

- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

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

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

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

### **AYVAKYT with food and drink**

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

### **Pregnancy and breast-feeding**

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

Pregnancy:

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

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

Women should use effective contraception during treatment and for at least 1 month after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding:

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

### **Driving and using machines**

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

### **AYVAKYT contains sodium**

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

## **3. How to take AYVAKYT**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 300 mg by mouth once daily.

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

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

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

**If you take more AYVAKYT than you should**

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

**If you forget to take AYVAKYT**

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

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

#### **4. Possible side effects**

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

**Most serious side effects**

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

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

**Other side effects may include:**

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

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

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

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain



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

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

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

### **Reporting of side effects**

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

## **5. How to store AYVAKYT**

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

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

This medicine does not require any special storage conditions.

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

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

## **6. Contents of the pack and other information**

### **What AYVAKYT contains**

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

### **What AYVAKYT looks like and contents of the pack**

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

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

Keep the desiccant canister in the bottle.

### **Marketing Authorisation Holder and Manufacturer**

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

For any information about this medicine, please contact the Marketing Authorization Holder:

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

### **This leaflet was last revised in**

This medicine has been given ‘conditional approval’.

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

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

### **Other sources of information**

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

<http://www.ema.europa.eu>.

## Package leaflet: Information for the patient

### AYVAKYT 200 mg film-coated tablets avapritinib

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

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

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

#### **What is in this leaflet**

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

#### **1. What AYVAKYT is and what it is used for**

AYVAKYT is a cancer medicine containing the active substance avapritinib.

This medicine is used to treat adults with a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic).

AYVAKYT inhibits the activity of a group of proteins in the body called kinases. Cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of cancer cells. This medicine is intended to treat GIST that has a specific mutation (D842V) in the gene responsible for making a kinase called platelet-derived growth factor receptor alpha (PDGFRA).

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

#### **2. What you need to know before you take AYVAKYT**

##### **Do not take AYVAKYT:**

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

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking AYVAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.

Take special care with this medicine:

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

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

For more information see section 4.

### **Children and adolescents**

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

### **Other medicines and AYVAKYT**

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

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

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

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

The following medicines can reduce the effects of AYVAKYT:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy

- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

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

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

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

### **AYVAKYT with food and drink**

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

### **Pregnancy and breast-feeding**

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

Pregnancy:

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

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

Women should use effective contraception during treatment and for at least 1 month after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding:

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

### **Driving and using machines**

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

### **AYVAKYT contains sodium**

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

## **3. How to take AYVAKYT**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 300 mg by mouth once daily.

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

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

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

**If you take more AYVAKYT than you should**

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

**If you forget to take AYVAKYT**

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

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

#### **4. Possible side effects**

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

**Most serious side effects**

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

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

**Other side effects may include:**

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

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

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

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain

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

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

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

### **Reporting of side effects**

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

## **5. How to store AYVAKYT**

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

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

This medicine does not require any special storage conditions.

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

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

## **6. Contents of the pack and other information**

### **What AYVAKYT contains**

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

### **What AYVAKYT looks like and contents of the pack**

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

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

Keep the desiccant canister in the bottle.

### **Marketing Authorisation Holder and Manufacturer**

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

For any information about this medicine, please contact the Marketing Authorization Holder:

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

### **This leaflet was last revised in**

This medicine has been given ‘conditional approval’.

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

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

### **Other sources of information**

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

<http://www.ema.europa.eu>.



## Package leaflet: Information for the patient

### AYVAKYT 300 mg film-coated tablets avapritinib

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

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

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

#### **What is in this leaflet**

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

#### **1. What AYVAKYT is and what it is used for**

AYVAKYT is a cancer medicine containing the active substance avapritinib.

This medicine is used to treat adults with a type of digestive tract cancer called gastrointestinal stromal tumour (GIST), when it cannot be treated with surgery (unresectable) or has spread to other parts of the body (metastatic).

AYVAKYT inhibits the activity of a group of proteins in the body called kinases. Cells that make up the cancer usually have changes (mutations) in the genes involved in making specific kinases associated with the growth and spread of cancer cells. This medicine is intended to treat GIST that has a specific mutation (D842V) in the gene responsible for making a kinase called platelet-derived growth factor receptor alpha (PDGFRA).

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

#### **2. What you need to know before you take AYVAKYT**

##### **Do not take AYVAKYT:**

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

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking AYVAKYT:

- **if you have suffered a vascular aneurysm** (bulging and weakening of a blood vessel wall) or **bleeding in your brain** in the last year.

Take special care with this medicine:

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

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

For more information see section 4.

### **Children and adolescents**

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

### **Other medicines and AYVAKYT**

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

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

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

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

The following medicines can reduce the effects of AYVAKYT:

- Rifampicin – used to treat tuberculosis (TB) and some other bacterial infections
- Carbamazepine, phenytoin, fosphenytoin, primidone, phenobarbital – used to treat epilepsy

- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Efavirenz and etravirine – used to treat HIV infections/AIDS
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation

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

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

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

### **AYVAKYT with food and drink**

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

### **Pregnancy and breast-feeding**

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

Pregnancy:

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

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

Women should use effective contraception during treatment and for at least 1 month after completion of treatment. Talk to your doctor about effective contraception methods that may be right for you.

Breast-feeding:

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

### **Driving and using machines**

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

### **AYVAKYT contains sodium**

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

## **3. How to take AYVAKYT**

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is 300 mg by mouth once daily.

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

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

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

**If you take more AYVAKYT than you should**

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

**If you forget to take AYVAKYT**

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

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

#### **4. Possible side effects**

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

**Most serious side effects**

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

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

**Other side effects may include:**

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

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

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

- red, or painful eye, blurry vision
- dehydration
- low albumin in the blood
- depression
- anxiety
- trouble falling asleep (insomnia)
- bleeding in your brain

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

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

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

### **Reporting of side effects**

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

## **5. How to store AYVAKYT**

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

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

This medicine does not require any special storage conditions.

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

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

## **6. Contents of the pack and other information**

### **What AYVAKYT contains**

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

### **What AYVAKYT looks like and contents of the pack**

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

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

Keep the desiccant canister in the bottle.

### **Marketing Authorisation Holder and Manufacturer**

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

For any information about this medicine, please contact the Marketing Authorization Holder:

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### **This leaflet was last revised in**

This medicine has been given ‘conditional approval’.

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

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

### **Other sources of information**

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

<http://www.ema.europa.eu>.