PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]AYVAKYT®

Avapritinib tablets

Tablets, 25 mg, 50 mg, 100 mg and 200 mg, Oral

Antineoplastic agent

Manufacturer:

Blueprint Medicines Corporation
45 Sidney Street
Cambridge, MA 02139

Imported and Distributed by:

Medison Pharma Canada Inc.
400-154 University Avenue
Toronto, Ontario
Canada, M5H 3Y9

Date of Initial Authorization:
SEP 18, 2024

Submission Control Number: 278913

RECENT MAJOR LABEL CHANGES

Not applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AYVAKYT (avapritinib tablets) is indicated for:

- the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

  AYVAKYT is not recommended for the treatment of patients with platelet counts of less than 50 x 10^9/L (see 7 WARNINGS AND PRECAUTIONS, Intracranial Hemorrhage).

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: No overall differences in safety or efficacy were observed for geriatric patients in comparison with younger patients (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Avapritinib is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment with AYVAKYT is not recommended in patients with a platelet count of less than 50 x 10^9/L (see 7 WARNINGS AND PRECAUTIONS, Intracranial Hemorrhage).
- Avoid concomitant use of AYVAKYT with strong or moderate CYP3A inhibitors. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dosage of AYVAKYT should be reduced to 50 mg orally once daily (see 9 DRUG INTERACTIONS).
- A reduced starting dose of AYVAKYT 100 mg orally once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C) (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

- The recommended dose of AYVAKYT is 200 mg orally once daily. Continue treatment until disease progression or unacceptable toxicity.

Dosage Adjustment

The recommended dose reductions and dosage modifications for adverse reactions are provided in Table 1 and Table 2.

Table 1: **Recommended Dose Reductions for AYVAKYT for Adverse Reactions in Patients with AdvSM**

Dose Reduction	Dose Level
First dose reduction	100 mg once daily
Second dose reduction	50 mg once daily
Third dose reduction	25 mg once daily

Permanently discontinue AYVAKYT in patients with AdvSM who are unable to tolerate a dose of 25 mg once daily.

Table 2: Recommended Dosage Modifications for AYVAKYT for Adverse Reactions in Patients with AdvSM

Adverse Reaction	Severity*	Dosage Modification
Intracranial hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Neurologic)	Any grade	Permanently discontinue AYVAKYT.
Cognitive effects (see 7 WARNINGS AND PRECAUTIONS, Neurologic)	Grade 1	Continue AYVAKYT at same dose or reduced dose or withhold until improvement to baseline or resolution. Resume at same dose or reduced dose.
	Grade 2 or Grade 3	Withhold AYVAKYT until improvement to baseline, Grade 1, or resolution. Resume at same dose or reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.
Thrombocytopenia (see 7 WARNINGS AND PRECAUTIONS, Neurologic)	< 50 X 10^9/L	Interrupt AYVAKYT until platelet count is ≥ 50 X 10^9/L, then resume at reduced dose (per Table 1). If platelet counts do not recover ≥ 50 X 10^9/L, consider platelet support.
Other adverse reactions (see 8 ADVERSE REACTIONS)	Grade 3 or Grade 4	Withhold AYVAKYT until improvement to less than or equal to Grade 2. Resume at same dose or reduced dose, as clinically appropriate.

*Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

Special Populations

Pediatrics

Health Canada has not authorized an indication for pediatric use (See 1.1 Pediatrics).

Geriatrics

No dose adjustment is recommended for patients aged 65 years and above (See 10.3 Pharmacokinetics).

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30-89 mL/min estimated by Cockcroft-Gault). The pharmacokinetics and safety of AYVAKYT in patients with severe renal impairment (CLcr 15-29 mL/min) or end-stage renal disease (CLcr <15 mL/min) have not been studied (See 10.3 Pharmacokinetics).

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and 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 value for AST).

Unbound avapritinib $AUC_{0\text{-}inf}$ was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function. A reduced starting dose of AYVAKYT 100 mg orally once daily is recommended for patients with severe hepatic impairment (Child-Pugh class C) (See 10.3 Pharmacokinetics).

4.4 Administration

AYVAKYT is for oral use.

Take AYVAKYT orally once daily on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking AYVAKYT).

Swallow tablets whole with a glass of water.

4.5 Missed Dose

If a dose of AYVAKYT is missed, the patient should make up for the missed dose unless the next scheduled dose is within 8 hours.

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

5 OVERDOSAGE

There is limited experience with cases of overdose reported in clinical studies with AYVAKYT. The highest dose of AYVAKYT studied clinically is 600 mg orally once daily.

There is no known antidote for AYVAKYT overdose. In the event of suspected overdose, AYVAKYT should be interrupted and supportive care instituted. The patient should be closely monitored for signs and symptoms of adverse reactions. Based on the large volume of distribution of avapritinib and

extensive protein binding (see 10.3 Pharmacokinetics), dialysis is unlikely to result in significant removal of avapritinib.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet, 25 mg, 50 mg, 100 mg, and 200 mg	*Tablet*: copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose *Tablet coating:* Polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide *Blue printing ink (100 mg and 200 mg tablets):* ammonium hydroxide 28%, FD&C blue #1/brilliant blue FCF, ferrosoferric oxide/ black iron oxide, isopropyl alcohol, N-butyl alcohol, propylene glycol, shellac glaze 45% (20% esterfied) in ethanol, titanium dioxide

AYVAKYT is supplied in high-density polyethylene (HDPE) bottle with child-resistant cap with foiled induction seal liner and a desiccant in canister.

Each bottle contains 30 film-coated tablets.

25 mg tablet: round, white film-coated tablet with debossed text. One side reads “BLU”, and the other side reads “25”.

50 mg tablet: round, white film-coated tablet with debossed text. One side reads “BLU”, and the other side reads “50”.

100 mg tablet: round, white film-coated tablet, printed with blue ink “BLU” on one side and “100” on the other side.

200 mg tablet: capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “200” on the other side.

7 WARNINGS AND PRECAUTIONS

General

Fluid Retention

In patients with AdvSM, localized (facial, periorbital, peripheral, pulmonary edema, pericardial and/or pleural effusion) or generalized edema, and ascites have been observed with a frequency category of at

least common. Other localized edemas (laryngeal edema) have been reported uncommonly. 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 must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be undertaken. For patients presenting with ascites, it is recommended to evaluate the etiology of ascites.

Driving and Operating Machinery

AYVAKYT may cause cognitive effects that may influence the ability to drive and use machines. Patients who experience these side effects should avoid or take special care when driving a vehicle or operating potentially dangerous machinery.

Monitoring and Laboratory Tests

- In patients with AdvSM, a platelet count must be performed prior to initiating therapy. Following treatment initiation, platelet counts must be monitored every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 10^9/L, monthly if values are between 75 and 100 x 10^9/L and as clinically indicated if values are greater than 100 x 10^9/L.
- Verify the pregnancy status of females of reproductive potential prior to initiating AYAVAKIT.

Neurologic

Cognitive Effects

Cognitive effects can occur in patients receiving AYVAKYT 8 ADVERSE REACTIONS. Cognitive events occurred in 24 (19.0%) of 126 patients who received AYVAKYT at the recommended starting dose of 200 mg once daily, including cognitive disorder in 15 (11.9%) patients, memory impairment in 7 (5.6%) patients, and confusional state in 3 (2.4%) patients. Of these 24 patients, 14 patients (11.1%) experienced Grade 1 events, 6 patients (4.8%) experienced Grade 2 events, and 4 patients (3.2%) experienced Grade 3 events. Overall, 9 (7.1%) patients with AdvSM who received AYVAKYT at the recommended starting dose of 200 mg daily required a dosage interruption, 8 (6.3%) required a dose reduction, and 2 (1.6%) required permanent discontinuation due to a cognitive adverse reaction.

Monitor patients for cognitive effects and instruct patients to notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. Depending on the severity, interrupt AYVAKYT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKYT (see 4.2 Recommended Dose and Dosage Adjustment).

Intracranial Hemorrhage

Intracranial hemorrhage (e.g. subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in patients with AdvSM who received AYVAKYT in clinical trials. Fatal events have occurred in <1% of patients across all doses. Symptoms of intracranial hemorrhage may include headache, nausea, vomiting, vision changes, or altered mental status.

Severe thrombocytopenia (platelet count < 50 x 10^9/L) was associated with an increased risk of intracranial hemorrhage in patients receiving AYVAKYT. Other risk factors may include history of vascular aneurysm, intracranial hemorrhage or cerebrovascular accident within the prior year, and concomitant use of anticoagulant drugs.

Of 126 AdvSM patients treated with the recommended starting dose of 200 mg once daily, intracranial

hemorrhage occurred in 3 (2.5%) of the 121 patients who had a platelet count ≥50 x 10^9/L prior to initiation of therapy, and 1 of the 5 patients who had platelet counts <50 x 10^9/L prior to initiation of therapy.

Monitor patients closely for risk factors of intracranial hemorrhage. See Monitoring and Laboratory Tests for platelet count monitoring recommendations.

AYVAKYT is not recommended for AdvSM patients with platelet counts of less than 50 x 10^9/L at baseline (see 1 INDICATIONS). Manage platelet counts of <50 x 10^9/L by temporarily interrupting AYVAKYT and reducing the dose (see 4.2 Recommended Dose and Dosage Adjustment). Platelet support may be necessary. Thrombocytopenia was generally reversible by reducing or interrupting AYVAKYT. Advise patients to seek immediate medical attention for signs or symptoms of intracranial hemorrhage. Permanently discontinue AYVAKYT if intracranial hemorrhage of any grade occurs (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health: Female and Male Potential

- **Contraception**

  AYVAKYT may cause fetal harm when administered to a pregnant woman.

  Females

  Advise females of reproductive potential to use effective contraception during treatment with AYVAKYT and for at least 6 weeks after the final dose.

  Males

  Advise male patients with female partners of reproductive potential to use effective contraception during and for 2 weeks following the final dose.

- **Fertility**

  There are no data on the effect of AYVAKYT on human fertility. No direct effect on male or female fertility was observed in combined male and female fertility and early embryonic development study in rats. Avapritinib may impair spermatogenesis and adversely affect early embryogenesis. Reduction in sperm production and testicular weight were observed in rats and hypospermatogenesis in dogs administered avapritinib at exposure of 7.5 times and 1.2 times the 200 mg human dose, respectively.

- **Teratogenic Risk**

  Based on findings from animal studies, AYVAKYT may cause fetal harm when administered to pregnant women. Oral administration of avapritinib during the period of organogenesis was teratogenic and embryotoxic in rats at exposures approximately 6.3 times the human exposure based on area under the curve (AUC) at the 200 mg dose. If AYVAKYT is used during pregnancy or if the patient becomes pregnant while taking AYVAKYT, advise the patient of the potential risk to the fetus.

  Advise females and males of reproductive potential to use effective contraception during treatment with AYVAKYT and for 6 weeks (females) or 2 weeks (males) after the final dose. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking AYVAKYT.

Skin

Photosensitivity Reactions

AYVAKYT may cause photosensitivity reactions (see 8.3 Less Common Clinical Trial Adverse Reactions). Patients should be instructed to avoid or minimize exposure to direct sunlight, and to use measures such as protective clothing and sunscreen with high sun protection factor (SPF) during treatment with AYVAKYT and for one week after discontinuation of treatment.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data in pregnant women exposed to AYVAKYT to assess the risks. Based on findings from animal reproduction studies, AYVAKYT may cause fetal harm when administered to a pregnant woman. Oral administration of avapritinib to pregnant rats during the period of organogenesis was teratogenic and embryotoxic at exposure levels approximately 6.3 times the human exposure based on AUC at the 200 mg dose. If AYVAKYT is used during pregnancy or if the patient becomes pregnant while taking AYVAKYT, advise the patient of the potential risk to a fetus.

Advise females of reproductive potential to avoid becoming pregnant while receiving AYVAKYT.

7.1.2 Breast-feeding

There are no data regarding the secretion of avapritinib or its metabolites in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants from avapritinib, advise women not to breastfeed during treatment with AYVAKYT and for 2 weeks following the final dose.

7.1.3 Pediatrics

The safety and efficacy of AYVAKYT in pediatric patients have not been established. Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Among the 126 patients with AdvSM treated with AYVAKYT at the 200 mg daily starting dose, 47 patients (37.3%) were < 65 years and 79 patients (62.7%) were ≥ 65 years. No overall difference in safety or efficacy was observed for patients aged 65 and over in comparison with younger patients, but greater sensitivity of older patients to adverse reactions cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of AYVAKYT was evaluated in 126 patients with AdvSM who received a starting dose of 200 mg daily in Studies EXPLORER and in PATHFINDER. The median duration of treatment was 41 weeks.

The most common adverse reactions of all Grades (reported in ≥ 20% of patients) were edema peripheral (42.9%), anemia (40.5%), periorbital edema (39.7%), thrombocytopenia (39.7%), diarrhea (27.8%), and nausea (23.8%). The most common Grade ≥ 3 adverse reactions (in ≥ 5% of patients) were

anemia (21.4%), thrombocytopenia (18.3%), neutropenia (16.7%), neutrophil count decreased (7.9%), and platelet count decreased (6.3%).

Serious adverse events occurred in 48 (38.1%) of patients. The most common serious adverse reactions (in ≥ 1% of patients) were subdural hematoma (3.2%), anemia (3.2%), ascites (2.4%), pleural effusion (1.6%), acute kidney injury (1.6%), gastrointestinal hemorrhage (1.6%), intra-abdominal hemorrhage (1.6%), and hemorrhage (1.6%). Fatal adverse reactions occurred in 2.4% of patients. No specific adverse event leading to death was reported in more than one patient.

Dose interruption due to an adverse event occurred in 66.7% of patients. The most common adverse reactions (in > 3% of patients) leading to dose interruption were thrombocytopenia (17.5%), neutropenia (11.1%), anemia (6.3%), cognitive disorder (6.3%), neutrophil count decreased (5.6%), platelet count decreased (4.8%), periorbital edema (3.2%), and white blood cell count decreased (3.2%).

Dose reduction due to an adverse event occurred in 72.2% of patients. The most common adverse reactions (in > 3% of patients) requiring dosage reduction were thrombocytopenia (19.0%), neutropenia (9.5%), periorbital edema (7.9%), edema peripheral (7.1%), platelet count decreased (6.3%), cognitive disorder (6.3%), neutrophil count decreased (5.6%), and anemia (4.8%).

Adverse events leading to permanent discontinuation of AYVAKYT occurred in 23 (18.3%) patients. The most common adverse reactions (in > 1% of patients) leading to AYVAKYT discontinuation were thrombocytopenia and subdural hematoma (2.4% each).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 4 displays adverse reactions observed in patients with AdvSM who received a starting dose of 200 mg daily in studies EXPLORER and PATHFINDER.

Table 4: Adverse Reactions Reported in ≥ 10% of Patients with AdvSM in EXPLORER and PATHFINDER

Adverse Reactions	AYVAKYT (200 mg Once Daily) N=126	
	All Grades* %	Grade ≥ 3 %
Blood and lymphatic system		
Thrombocytopenia[a]	50.0	23.8
Anemia[b]	41.3	21.4
Neutropenia[c]	25.4	23.0
Leukopenia[d]	10.3	3.2
Gastrointestinal		
Diarrhea	27.8	4.0
Nausea	23.8	0.8
Vomiting	19.0	2.4
Abdominal pain[e]	15.1	0.8
Constipation	13.5	0
General		
Edema[f]	77.8	5.6
Fatigue[g]	24.6	3.2
Investigations		
Weight increased	10.3	2.4
Musculoskeletal and connective tissue		
Arthralgia	12.7	0.8
Nervous system		
Cognitive effects[h]	19.0	3.2
Taste effects[i]	18.3	0.8
Headache	15.1	0
Dizziness	11.9	0
Respiratory, thoracic and mediastinal		
Epistaxis	12.7	0
Dyspnea[j]	11.9	1.6
Skin and subcutaneous tissue		
Hair color changes	15.1	0
Rash[k]	15.1	1.6
Pruritus	12.7	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0; MedDRA version 18.1

[a] Thrombocytopenia includes thrombocytopenia and platelet count decreased.

[b] Anemia includes anemia, hematocrit decreased, hemoglobin decreased and red blood cell count decreased.

[c] Neutropenia includes neutropenia and neutrophil count decreased.

[d] Leukopenia includes leukopenia and white blood cell count decreased.

[e] Abdominal pain includes abdominal pain, abdominal discomfort, and abdominal pain upper.

[f] Edema includes edema peripheral, face edema, edema, periorbital edema, conjunctival edema, eyelid edema, orbital edema, generalized edema, localized edema, peripheral swelling, eye swelling, lip swelling and swelling face.

[g] Fatigue includes fatigue, asthenia, muscular weakness and lethargy.

[h] Cognitive effects includes memory impairment, cognitive disorder, confusional state, somnolence, Delirium, Dementia, Disorientation and mental status change

[i] Taste effects include dysgeusia and ageusia.
[j] Dyspnea includes dyspnea and exertional dyspnea.
[k] Rash includes rash, erythematous rash, generalized rash, maculopapular rash, and pruritic rash.

8.3 Less Common Clinical Trial Adverse Reactions

Adverse reactions occurring in <10% of patients with AdvSM who received the starting dose of 200 mg daily in Studies EXPLORER and PATHFINDER:

Blood and lymphatic system: increased tendency to bruise (3.2%), hemorrhagic diathesis (2.4%), leukocytosis* (2.4%), lymphopenia* (1.6%)

Cardiac: cardiac failure (1.6%)

Ear and labyrinth: vertigo (3.2%), deafness (1.6%)

Eye: lacrimation increased (6.3%), ocular hemorrhage* (4.0%), vision blurred (2.4%), conjunctival hemorrhage (2.4%), dryness* (1.6%), ocular hyperemia (1.6%), erythema of eyelid (1.6%), vitreous floaters (1.6%)

Gastrointestinal: dryness* (5.6%), gastrointestinal hemorrhage* (5.6%), inguinal hernia (3.2%), dental caries (1.6%), intra-abdominal hemorrhage (1.6%), salivary hypersecretion (1.6%)

General disorders and administration site conditions: pyrexia (5.6%), pain (4.8%), non-cardiac chest pain (4.0%), gait disturbance (3.2%), feeling abnormal (2.4%), joint swelling (1.6%), malaise (1.6%), cyst (1.6%)

Hepatobiliary: cholelithiasis (1.6%)

Infections and infestations: urinary tract infection (6.3%), conjunctivitis (3.2%), herpes zoster (3.2%), sinusitis (3.2%), cellulitis (2.4%), oral candidiasis (2.4%), gastroenteritis (2.4%), oral herpes (2.4%), pneumonia* (2.4%), cystitis (1.6), diverticulitis (1.6), nasopharyngitis (1.6%), respiratory tract infection (1.6%)

Injury, poisoning and procedural complications: fall (5.6%), contusion (4.8%%), hematoma (3.2%), procedural pain (2.4%), laceration (2.4%), post-procedural hemorrhage (2.4%), skin abrasion (1.6%), traumatic hematoma (1.6%)

Metabolism and nutrition: decreased appetite (6.3%), dehydration (2.4%), fluid overload (1.6%), gout (1.6%)

Musculoskeletal and connective tissue: pain in extremity (9.5%), bone pain (4.8%), back pain (4.0%), muscle spasms (3.2%) myalgia (3.2%), musculoskeletal pain (2.4%), musculoskeletal stiffness (2.4%), neck pain (1.6%), joint stiffness (1.6%)

Nervous system: neuropathy peripheral* (9.5%), intracranial hemorrhage*(3.2%), mental impairment* (3.2%), speech disorder* (3.2%), restless legs syndrome (2.4%), syncope (2.4%), aphasia (1.6%), balance disorder (1.6%), dizziness postural (1.6%), tremor (1.6%)

Psychiatric: insomnia (8.7%), depression* (4.0%), irritability (1.6%), libido decreased (1.6%), sleep disorder (1.6%)

Renal and urinary: acute renal injury* (4.8%), chronic kidney disease (3.2%), hematuria* (2.4%), dysuria (1.6%), pollakiuria (1.6%), nephrolithiasis (1.6%), urinary incontinence (1.6%)

Reproductive system and breast: scrotal edema (1.6%)

Respiratory, thoracic and mediastinal: pleural effusion (6.3%), upper respiratory tract infection (5.6%), cough* (4.8%), hemoptysis (1.6%), nasal congestion (1.6%), oropharyngeal pain (1.6%), pneumothorax (1.6%), pulmonary hypertension (1.6%), pulmonary edema (1.6%), rhinorrhea (1.6%), throat irritation (1.6%)

Skin and subcutaneous tissue: alopecia (7.9%), night sweats (4.0%), petechia (3.2%), hyperhidrosis (2.4%), pruritus generalized (2.4%), blood blister (1.6%), dermatitis contact (1.6%), dryness* (1.6%), erythema (1.6%), skin hemorrhage (1.6%), skin lesion (1.6%), photosensitivity reaction (0.8%)

Vascular: flushing (6.3%), hypertension* (5.6%), hypotension (4.8%), hot flush (2.4%), hemorrhage (1.6%)

*Comprises pooled terms representing similar medical concepts.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 5 summarizes the laboratory abnormalities observed in patients with AdvSM who received the recommended starting dose of 200 mg once daily in Studies EXPLORER and PATHFINDER.

Common (≥ 10%) Grade ≥ 3 laboratory abnormalities were decreased platelets, decreased hemoglobin, decreased neutrophils, decreased lymphocytes and decreased leukocytes.

Table 5: Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients with AdvSM in EXPLORER and PATHFINDER

Laboratory Abnormality	AYVAKYT (200 mg Once Daily) N=126[a]	
	All Grades (%)	Grade ≥ 3 (%)
Hematology		
Decreased platelets	68	25
Decreased hemoglobin	65	25
Decreased neutrophils	57	25
Decreased leukocytes	57	12
Decreased lymphocytes	49	17
Increased activated partial thromboplastin time	13	<1
Chemistry		
Decreased calcium	53	2
Decreased phosphate	48	5
Increased bilirubin	44	6
Increased aspartate aminotransferase	39	<1
Increased creatinine	35	2
Increased alkaline phosphatase	32	6
Decreased potassium	24	6

Laboratory Abnormality	AYVAKYT (200 mg Once Daily) N=126[a]	
	All Grades (%)	Grade ≥ 3 (%)
Decreased albumin	22	3
Increased alanine aminotransferase	18	<1
Decreased sodium	16	<1
Decreased magnesium	16	<1
Increased potassium	11	0

[a] The denominator used to calculate the rate varied from 122 to 125 based on the number of patients with a baseline value and at least one post-treatment value

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Strong and Moderate CYP3A Inhibitors

Coadministration of AYVAKYT with a strong or moderate CYP3A inhibitor increases avapritinib plasma concentrations (see 10 CLINICAL PHARMACOLOGY), which may increase the incidence and severity of adverse reactions of AYVAKYT. Avoid coadministration of AYVAKYT with strong or moderate CYP3A inhibitors. If coadministration of AYVAKYT with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of AYVAKYT (see 4 DOSAGE AND ADMINISTRATION).

Strong and Moderate CYP3A Inducers

Coadministration of AYVAKYT with a strong or moderate CYP3A inducer decreases avapritinib plasma concentrations (see 10 CLINICAL PHARMACOLOGY), which may decrease efficacy of AYVAKYT. Avoid coadministration of AYVAKYT with strong or moderate CYP3A inducers.

CYP Substrates

Avapritinib is a time-dependent inhibitor as well as an inducer of CYP3A at clinically relevant concentrations. Avapritinib is also an inhibitor of CYP2C9. M499, a metabolite of avapritinib, is an inhibitor of CYP3A, CYP2C8, and CYP2C9 at clinically relevant concentrations. Caution should be exercised with co-administration of AYVAKYT with sensitive CYP3A and CYP2C9 substrates as their plasma concentrations may be altered.

Transporter Substrates

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

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6: Established or Potential Drug-Drug Interactions

[Proper/Common Name]	Source of Evidence	Effect	Clinical Comment
Effects of other drugs on avapritinib			
Strong CYP3A inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, conivaptan, hyponatremia, boceprevir, grapefruit or grapefruit juice)	CT	Coadministration of a strong CYP3A inhibitor itraconazole (200 mg twice daily on Day 1 followed by 200 mg once daily for 13 days) with a single 200 mg dose of AYVAKYT on Day 4 in healthy subjects increased avapritinib maximum concentration (C_{max}) by 38% and the area under the concentration-time curve (AUC_{0-inf}) by 321%, relative to a 200 mg dose of AYVAKYT administered alone.	Coadministration of AYVAKYT with a strong CYP3A inhibitor increased avapritinib plasma concentrations and may result in increased adverse reactions. Avoid coadministration of AYVAKYT with strong or moderate CYP3A inhibitors, including grapefruit or grapefruit juice (see 9.5 Drug-Food Interactions). If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of AYVAKYT should be reduced to 50 mg once daily (see 4 DOSAGE AND ADMINISTRATION).
	T	Based on PBPK modelling and simulation, coadministration of AYVAKYT 300 mg once daily with itraconazole 200 mg once daily is predicted to increase avapritinib AUC_{tau} by 600% at steady state.	
Moderate CYP3A inhibitors (such as erythromycin, fluconazole, crizotinib, dronedarone, imatinib, diltiazem)	T	Based on PBPK modelling and simulation, coadministration of AYVAKYT at 300 mg once daily with fluconazole 200 mg once daily (a moderate CYP3A inhibitor) is predicted to increase avapritinib AUC_{tau} by 205% at steady state.	
Strong CYP3A inducers (such as carbamazepine, phenytoin, rifampin, St. John's wort, phenobarbital)	CT	Coadministration of the strong CYP3A inducer rifampin (600 mg once daily for 18 days) with a single 400 mg dose of AYVAKYT on Day 9 in healthy subjects decreased avapritinib C_{max} by 74% and AUC_{0-inf} by 92%.	Coadministration of AYVAKYT with a strong CYP3A inducer decreased avapritinib plasma concentrations and may result in decreased efficacy of AYVAKYT. Avoid coadministration of AYVAKYT with strong and moderate CYP3A inducers, including St. John's wort.
Moderate CYP3A inducers (such as bosentan, efavirenz, etravirine, modafinil, dabrafenib)	T	Based on PBPK modeling and simulation, the decrease in avapritinib AUC_{tau} with 300 mg once daily is estimated to be 62% at steady state with concomitant use of a moderate CYP3A inducer (efavirenz).	

[Proper/Common Name]	Source of Evidence	Effect	Clinical Comment
Effects of Avapritinib on other drugs			
CYP substrates (such as alfentanil, simvastatin, atazanavir, midazolam, sirolimus, tacrolimus, warfarin)	T	In vitro studies indicated that avapritinib is a time-dependent inhibitor as well as an inducer of CYP3A at clinically relevant concentrations. Avapritinib is also an inhibitor of CYP2C9. M499, a metabolite of avapritinib, is an inhibitor of CYP3A, CYP2C8, and CYP2C9 at clinically relevant concentrations.	Avapritinib is a time-dependent inhibitor of CYP3A and an inducer of CYP3A in vitro. Caution should be exercised with coadministration of AYVAKYT with sensitive CYP3A substrates as their plasma concentrations may be altered. Coadministration of AYVAKYT with CYP2C9 substrates may increase their plasma concentrations, e.g. warfarin. Caution should be exercised with coadministration of AYVAKYT with CYP2C9 substrates.
Transporter Substrates	T	Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP in vitro.	Avapritinib has the potential to increase concentrations of co-administered substrates of P-gp, BCRP, MATE1, MATE2-K and BSEP.

Legend: CT = Clinical Trial; T = Theoretical

Effects of other drugs on avapritinib

Gastric Acid Reducing Agents

Based on population PK analysis and non-compartmental PK analysis, no clinically significant differences in the pharmacokinetics of avapritinib were identified when co-administered with gastric acid reducing agents in patients.

Effect of Transporters on Avapritinib

Based on in vitro studies, avapritinib is not a substrate of P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OAT1PB1, OAT1P1B3, MATE1, MATE2-K and BSEP at clinically relevant concentrations.

Effects of Avapritinib on other drugs

CYP Substrates

Based in vitro studies, avapritinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6 at clinically relevant concentrations. Avapritinib is not an inducer of CYP1A2 or CYP2B6. M499, a metabolite of avapritinib, is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Substrates

Based on in vitro studies, avapritinib is not expected to inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2 at clinically relevant concentrations.

9.5 Drug-Food Interactions

Avapritinib C_{max} and $AUC_{0\text{-}inf}$ were increased by 59% and 29%, respectively in healthy subjects administered AYVAKYT after a high fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to the C_{max} and $AUC_{0\text{-}inf}$ after overnight fasting.

AYVAKYT is recommended to be administered on an empty stomach.

Avoid coadministration of AYVAKYT with strong or moderate CYP3A inhibitors, including grapefruit or grapefruit juice (See 9.4 Drug-Drug Interactions).

9.6 Drug-Herb Interactions

Avoid coadministration of AYVAKYT with strong and moderate CYP3A inducers, including St. John's wort (See 9.4 Drug-Drug Interactions).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Avapritinib is a tyrosine kinase inhibitor that targets KIT D816V, PDGFRA, and PDGFRA D842 mutants as well as multiple KIT exon 11, KIT exon 11/17, and KIT exon 17 mutants with half maximal inhibitory concentrations (IC_{50}) below 28 nM in biochemical assays. Constitutive activation of KIT and PDGFRA receptor tyrosine kinases have been implicated in the pathogenesis of a number of oncology malignancies and rare hematologic diseases.

In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V with IC_{50} of 4 nM and 30 nM, respectively, and was less potent against wild-type KIT. Further, avapritinib inhibited the proliferation in KIT mutant cell lines, including a murine mastocytoma cell line and a human mast cell leukemia cell line.

Avapritinib also showed growth inhibitory activity in a xenograft model of murine mastocytoma with KIT exon 17 mutation.

10.2 Pharmacodynamics

Cardiac Electrophysiology

The ability of avapritinib to prolong the QT interval was assessed in a pharmacokinetic-pharmacodynamic analysis of 27 patients administered AYVAKYT at a starting dose of 300 or 400 mg once daily in an open-label, single-arm study in patients with gastrointestinal stromal tumor. Large mean increases from baseline in QTc interval (i.e.> 20 ms) were not predicted for the reported mean steady state maximum concentration (C_{max}) of 899 ng/mL.

10.3 Pharmacokinetics

After repeat dosing of AYVAKYT, systemic exposure (C_{max} and AUC) of avapritinib was approximately dose proportional over the dose range of 30 to 400 mg once daily. Steady state concentrations of avapritinib were reached by day 15 following daily dosing. Pharmacokinetic parameters following 200 mg QD recommended dosing regimen are described in Table 7.

Table 7: Summary of AYVAKYT Pharmacokinetic Parameters in Patients with AdvSM Received 200 mg Once Daily

	$C_{max, ss}$ (ng/mL) Geometric Mean (CV%)	$T_{max, ss}$ (h) Median (Min-Max)	$AUC_{0-24, ss}$ (hr*ng/mL) Geometric Mean (CV%)	CL, ss/F (L/h) Geometric Mean (CV%)	Vz/F[a] (L) Geometric Mean (CV%)	t1/2[a] (h) Median (Min-Max)
Steady-State 200 mg Once Daily Mean	377 (62%, n=18)	4.03 (1.05-8.00, n=18)	6600 (54%, n=16)	29.7 (104%, n=7)	1780 (36.3%, n=12)	39.4 (17.5-53.0, n=12)

[a] Vz/F and t1/2 were estimated following a single dose of AYVAKYT in patients with AdvSM

Absorption

The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of avapritinib 30 mg to 400 mg in patients with AdvSM.

Effect of Food

The C_{max} of avapritinib was increased by 59% and the AUC_{0-inf} was increased by 29% when AYVAKYT was taken with a high-calorie, high-fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to those in the fasted state.

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. The mean (% CV) apparent volume of distribution (V_z/F) of avapritinib following a single 200 mg oral dose was 1900L (43%) in patients with AdvSM.

Metabolism:

Avapritinib is primarily metabolized by CYP3A4, CYP3A5 and to a lesser extent by CYP2C9 in vitro. Following a single oral dose of approximately 310 mg of radiolabeled avapritinib to healthy subjects, unchanged avapritinib (49%) and its metabolites M690 (hydroxy glucuronide; 35%) and M499

(oxidative deamination; 14%) were the major circulating compounds. The formation of the glucuronide M690 is catalyzed mainly by UGT1A3. Following oral administration of AYVAKYT 200 mg once daily in patients with AdvSM, the steady state AUC of the constitutive enantiomers of M499, BLU111207 and BLU111208 are approximately 21% and 26% of the AUC of avapritinib. Compared to avapritinib (IC50 = 4 nM), BLU111207 (IC50 = 41.8 nM) and BLU111208 (IC50 = 12.4 nM) are 10.5- and 3.1-fold less potent against KIT D816V in vitro. M499 is not likely to contribute to efficacy at the recommended dose of avapritinib.

Elimination

Following administration of single oral doses of AYVAKYT ranging from 30 to 400 mg, the mean plasma elimination half-life of avapritinib was 20 to 39 hours in patients with AdvSM. The steady state mean (CV%) apparent oral clearance of avapritinib was 40.3 L/h (86.0%) at 200 mg in patients with AdvSM.

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

Special Populations and Conditions

Population pharmacokinetic analyses indicate that age (18-90 years), body weight (39.5 to 156 kg), race (White, Black, or Asian) and sex, have no clinically meaningful effect on the pharmacokinetics of avapritinib.

- **Hepatic Insufficiency**

  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 clearance was similar between 72 subjects with mild hepatic impairment (total bilirubin within ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST), 13 subjects with moderate hepatic impairment (total bilirubin >1.5 to 3.0 times ULN and any AST), and 402 subjects with normal hepatic function (total bilirubin and AST within ULN). In a clinical study of severe hepatic impairment following a single oral dose administration of 100 mg avapritinib, the mean unbound $AUC_{0\text{-inf}}$ was 61% higher in subjects with severe hepatic impairment (Child-Pugh class C) as compared to matched healthy subjects with normal hepatic function. A lower starting dose is recommended in patients with severe hepatic impairment (see 4 DOSAGE AND AMINISTRATION).

- **Renal Insufficiency**

  Based on a population pharmacokinetic analysis, avapritinib clearance was similar among 136 subjects with mild renal impairment (CLcr 60-89 mL/min; estimated by Cockcroft-Gault), 52 subjects with moderate renal impairment (CLcr 30-59 mL/min) and 298 subjects with normal renal function (CLcr ≥ 90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. The pharmacokinetics of avapritinib in patients with severe renal impairment (CLcr 15-29 mL/min) or end-stage renal disease (CLcr <15 mL/min) have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store AYVAKYT at room temperature (15^{o}C to 30^{o}C) in the original container closure system.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

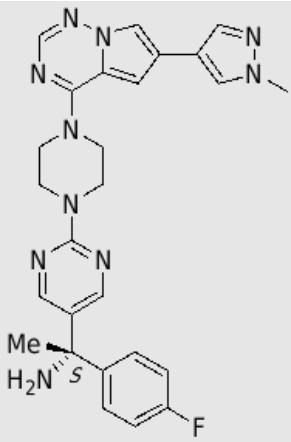
Drug Substance

Proper/Common name: avapritinib

Chemical name: (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine

Molecular formula and molecular mass: $C_{26}H_{27}FN_{10}$, and the molecular weight is 498.57 g/mol

Structural formula:



Physicochemical properties: The solubility of avapritinib in 0.1N HCl (pH 1.0), buffer solutions at pH 2.5, 4.0, and 7.0 (at 25°C) is 3.64 mg/mL, 0.14 mg/mL, 0.07 mg/ml and <0.001 mg/mL, respectively, indicating a decrease in solubility with increasing pH.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Advanced Systemic Mastocytosis (AdvSM)

Table 8: Summary of Patient Demographics for Clinical Trials in AdvSM

Study #	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
EXPLORER (BLU-285-2101; NCT02561988)	multi-centre, single-arm, open-label clinical trial in adult patients with AdvSM and other relapsed or refractory myeloid malignancies	Oral; 30 to 400 mg once daily	Centrally evaluable AdvSM patients treated with the 200 mg daily starting dose: 16	66.5 (31 – 88)	Female:33 Male: 55
PATHFINDER (BLU-285-2202; NCT03580655)	multi-centre, single-arm, open-label clinical trial in adult patients with AdvSM	Oral; 200 mg once daily	Centrally evaluable AdvSM patients treated with the 200 mg daily starting dose: 72		

The efficacy of AYVAKYT was demonstrated in EXPLORER and PATHFINDER, two multi-centre, single-arm, open-label clinical trials. Response-evaluable patients include those with a confirmed diagnosis of AdvSM per the World Health Organization (WHO) and deemed evaluable by modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (mIWG-MRT-ECNM) criteria at baseline as adjudicated by an independent central committee, who received at least 1 dose of AYVAKYT, had at least 2 post-baseline bone marrow assessments and had been on study for at least 24 weeks, or had end of study visit. Eligible patients were required to have an ECOG performance status (PS) of 0 to 3.

The major efficacy outcome measure was overall response rate (ORR) per modified IWG-MRT-ECNM criteria as evaluated by the central committee in 88 patients with AdvSM enrolled in EXPLORER and PATHFINDER, who were evaluable for response and had received a starting dose of 200 mg once daily.

Additional efficacy outcome measures included duration of response (DOR), time to response, and changes in individual measures of mast cell burden. The median duration of follow-up for these patients was 15.4 months (95% confidence interval 13.9 to 17.2 months).

The population characteristics for patients included in the primary efficacy analysis were median age of 68 years (range: 31 to 88 years), 63% were male, 90% were White, 67% had an ECOG PS of 0-1, 33% had an ECOG PS of 2-3, 50% had ongoing corticosteroid therapy use for systemic mastocytosis at baseline, 89% of patients had a D816V mutation, 64% had prior antineoplastic therapy, and 50% had received prior midostaurin. The median bone marrow mast cell infiltrate was 40%, the median serum tryptase level was 204.50 ng/mL, 91% had a platelet count of ≥ 50 X 10^9/L prior to initiation of therapy and the median KIT D816V mutant allele fraction was 10%.

Efficacy results in patients with AdvSM enrolled in EXPLORER and PATHFINDER who received the 200 mg starting dose of AYVAKYT once daily are summarized in Table 9.

Table 9: Results of Studies EXPLORER and PATHFINDER in AdvSM per Modified IWG-MRT-ECNM Criteria

Efficacy Parameter	All Evaluable AdvSM Patients N=88	ASM Patients N=13	SM-AHN Patients N=57	MCL Patients N=18
ORR[a], n (%) (95% CI)[a]	60 (68.2) (57.4, 77.7)	9 (69.2) (38.6, 90.9)	42 (73.7) (60.3, 84.5)	9 (50.0) (26.0, 74.0)
CR, n (%)	4 (4.5)	1 (7.7)	3 (5.3)	0
CRh, n (%)	12 (13.6)	3 (23.1)	9 (15.8)	0
PR, n (%)	39 (44.3)	5 (38.5)	26 (45.6)	8 (44.4)
Clinical Improvement, n (%)	5 (5.7)	0	4 (7.0)	1 (5.6)
Median DOR[b] (months), (95% CI)	N=60 NE (NE, NE)	N=9 NE (NE, NE)	N=42 NE (NE, NE)	N=9 NE (21.6, NE)

Abbreviations: IWG-MRT-ECNM= international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis; ASM=aggressive systemic mastocytosis; SM-AHN=systemic mastocytosis with hematological neoplasm; MCL=mast cell leukemia; CI=confidence interval; CR=complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR=duration of response; NE=not estimable; ORR=overall response rate; PR=partial remission

[a] ORR is defined as the proportion of patients who achieved a CR, CRh, PR or Clinical Improvement.

[b] DOR is defined as the time from first documented response (CR/CRh/PR/Clinical Improvement) to the date of first documented progressive disease (PD), loss of response (LoR), or death due to any cause, whichever occurred first. Determination of PD or LoR was based on the comparison with baseline values. DOR is estimated from Kaplan-Meyer analysis.

In all evaluable patients with a response (N=60) the median time to response CR/CRh/PR/ Clinical Improvement was 1.96 months (range: 0.3, 26.7).

The assessment of the following secondary efficacy endpoints was based on AdvSM patients with baseline and post-baseline values for mast cell burden. 86% of patients had a decrease in bone marrow infiltration that exceeded 50% with 58.5% of patients having complete elimination of bone marrow mast cell aggregates; 92% had a decrease in serum tryptase levels that exceeded 50%, with 49.3% reducing serum tryptase <20 ng/mL; and 76% of patients had a decrease in KIT D816V variant allele fraction in blood that exceeded 50% with decrease to <1% in 48.9% of patients and 65% of patients had a reduction of ≥35% in spleen volume, which correlates with a 50% decrease by palpation.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Repeat-dose Toxicology studies were conducted for up to 6 months in rats and up to 9 months in dogs following daily administration of avapritinib. Most toxicologic effects were mechanism based and similar between rat and dogs with some exceptions.

In a 6-month study in rats, avapritinib was administered at doses of 1, 3 and 10 mg/kg/day, followed by an 8-week recovery period. Target organs of toxicity included bone marrow (decreased cellularity in the sternum, corresponding to decreased red and white blood cells and reticulocytes parameters), bone (increased thickness of the physis in the femur), adrenal gland (cortical hypertrophy, cystic degeneration, angiectasis and 2 incidences of thrombus in 2 females, one of which from the recovery group), thymus (decreased cellularity), spleen (increased extramedullary hematopoiesis and pigmented macrophages), ovary (hemorrhagic and cystic degeneration of the corpora lutea, also present following recovery), vagina (increased mucification), prostate gland (increased incidence of mixed cell inflammation). Elevated serum bilirubin levels were observed at doses $\geq$ 3 mg/kg/day. Most hematology changes and histology findings were observable at doses $\geq$ 3 mg/kg/day (corresponding to 1.5 and 3 times human AUC at the 200 mg dose in males and females, respectively). In studies with higher doses of avapritinib, rats manifested convulsions which was potentially secondary to inhibition of Nav 1.2 (IC50 = 280 nM) at systemic exposures ≥ 14 higher than the exposure at the clinical dose of 200 mg.

In a 9-month study in dogs with an 8-week recovery period at doses of 0.5, 1 and 5 mg/kg/day, target organs of toxicity included bone marrow (decreased hematopoiesis corresponding to decreased red and white blood cells and reticulocytes parameters), spleen (increased extramedullary hematopoiesis and increased pigmented macrophages, also present in recovery animals), and testis at 5 mg/kg/day, the highest dose tested (hypospermatogenesis, also observed in recovery animals). Following administration of avapritinib for 3 months at doses of 7.5, 15 and 30 mg/kg/day, tremors were observed at the highest dose of 30 mg/kg/day, hemorrhage in the brain and spinal cord were observed at ≥ 15 mg/kg/day and choroid plexus edema in the brain at ≥ 7.5 mg/kg/day, corresponding to approximately 3.4 times, 1.8 times and 1 time the human AUC at the 200 mg dose, but these effects were not observed in the 9-month study at 5 mg/kg/day. Decreased cellularity in the thymus and lymph nodes, and angiectasis and hemorrhage in the adrenal gland were observed at ≥ 15 mg/kg/day.

Carcinogenicity: The carcinogenic potential of avapritinib was evaluated in a 6-month transgenic mouse study where there were no effects on carcinogenicity up to the highest dose evaluated of 20 mg/kg/day (corresponding to roughly 11 times human AUC at the 200 mg dose). A long-term carcinogenicity study with avapritinib is ongoing.

Genotoxicity: Avapritinib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test). Avapritinib 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 rat comet test and thus overall non-genotoxic.

Reproductive and Developmental Toxicology: In a fertility and early embryonic development study, rats were exposed to avapritinib daily from 28 and 14 days prior to mating in males and females, respectively, through Gestation Day (GD) 7, at doses of 3, 10 and 30 mg/kg/day for males and 3, 10 and 20 mg/kg/day for females. There were no direct effects on fertility in rats of either sex at the highest doses tested (20.3 and 9.5 times the human AUC at the 200 mg dose). Lower sperm production and

testicular weight were observed at doses ≥10 mg/kg/day (7.5 times the human AUC at the 200 mg dose). Dark red areas in the uterus and cystic ovaries, along with dose-dependent increases in pre- and post-implantation loss and lower number of viable embryos were observed at ≥10 mg/kg/day and enlarged ovaries containing dark red areas at 20 mg/kg/day (roughly 4.5 times and 9.5 times the human AUC at the 200 mg dose, respectively). Avapritinib partitioned into seminal fluids at concentrations roughly 2-4% the observed serum levels and was detected up to 0.5 times the concentration found in human plasma at 200 mg.

In an embryo-fetal development study, avapritinib was administered to pregnant rats at daily doses of 5, 10, 20 and 30 mg/kg/day during GD 6 through 17 and showed embryotoxic and teratogenic effects. Dose-dependent decreased number of viable embryos, decreased fetal body weight, increased incidence of visceral and skeletal malformations were observed at doses ≥10 mg/kg/day (roughly 6.3 times the human AUC at the 200 mg dose). The NOAEL for maternal and embryo-fetal toxicity was considered to be 5 mg/kg/day in this study corresponding to approximately 2.9 times the human AUC at the 200 mg dose (see 7 WARNINGS AND PRECAUTIONS – Teratogenic Risk).

Photosensitivity: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAYVAKYT®

Avapritinib tablets

Read this carefully before you start taking **AYVAKYT** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AYVAKYT**.

What is AYVAKYT used for?

AYVAKYT is used to treat adults with:

- aggressive systemic mastocytosis (ASM),
- systemic mastocytosis with associated hematological neoplasm (SM-AHN), or
- mast cell leukaemia (MCL).

These are disorders in which the body produces too many mast cells, a type of white blood cell. ASM, SM-AHN and MCL are collectively referred to as advanced systemic mastocytosis (AdvSM).

How does AYVAKYT work?

In patients with AdvSM, the overproduced mast cells can build up in different parts of the body, such as liver, bone marrow or spleen. These mast cells also release substances (such as histamine) which can cause various symptoms and damage to involved organs.

AYVAKYT stops the activity of a group of proteins in the body called kinases. It works by targeting a specific change in the gene (mutation) to slow down the growth of masts cells.

What are the ingredients in AYVAKYT?

Medicinal ingredients: avapritinib

Non-medicinal ingredients:

Tablet: copovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose

Tablet coating: Polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide

Blue printing ink (100 mg and 200 mg tablets): ammonium hydroxide 28%, FD&C blue #1/brilliant blue FCF, ferrosoferric oxide/ black iron oxide, isopropyl alcohol, N-butyl alcohol, propylene glycol, shellac glaze 45% (20% esterfied) in ethanol, titanium dioxide

AYVAKYT comes in the following dosage forms:

Tablets: 25 mg, 50 mg, 100 mg and 200 mg

Do not use AYVAKYT if:

- you are allergic to avapritinib or any other ingredients in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AYVAKYT. Talk about any health conditions or problems you may have, including if you:

- have had a bulging and weakening of a blood vessel wall (vascular aneurysm) or bleeding in your brain
- have a history of stroke in the last year.

- have low platelet counts.
- have liver problems.

Other warnings you should know about:

- AYVAKYT may cause:
  - **Bleeding in your brain.** This **may** lead to death. If you have low platelet counts, you may be at a greater risk of bleeding in the brain. Your healthcare professional will check your platelet counts before you start treatment and monitor them as needed during treatment with AYVAKYT.
  - **Cognitive effects** (problems with thinking and how you remember information). This includes memory loss, changes in memory, or confusion. Contact your healthcare professional if you, your caregiver or family member notices that you are getting forgetful or confused.
  - **Sensitivity to sunlight.** 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).
- **Check-ups and testing**
  - While you are taking AYVAKYT, your healthcare professional will ask you to have regular blood tests and weigh you regularly.
- **Children and adolescents (under 18 years of age)**
  - You should not take AYVAKYT if you are under 18 years of age. AYVAKYT has not been studied in children and adolescents under 18 years of age.
- **Female patients**

  Pregnancy and birth control
  - If you are pregnant or planning to become pregnant, there are risks you should discuss with your healthcare professional. This medicine is not recommended for use during pregnancy unless clearly necessary.
  - Do NOT become pregnant during treatment with AYVAKYT. It may harm your unborn baby.
  - If you are able to become pregnant:
    - Your healthcare professional should check if you are pregnant before you start treatment with this medicine.
    - Use effective method of birth control during treatment and for 6 weeks after completion of treatment. Talk to your healthcare professional about birth control methods that may be right for you
    - Tell your healthcare professional right away if you become pregnant or think you may be pregnant.

  Breastfeeding
  - Tell your healthcare professional if you are breastfeeding or planning to breastfeed. It is not known if AYVAKYT passes into breast milk.
  - Do NOT breastfeed during treatment with this AYVAKYT and for at least 2 weeks following the last dose. Talk to your healthcare professional about the best way to feed your baby during this time.

- **Male patients**

  Birth control
  - If you have a female partner who are able to become pregnant, use effective method of birth control during treatment and for 2 weeks after completion of treatment. Talk to your healthcare professional about birth control methods that may be right for you.
  - Tell your healthcare professional right away if your partner becomes pregnant during treatment with AYVAKYT.

- **Driving and using machines**

  - AYVAKYT may affect your ability to concentrate and react. You should avoid or take special care when driving a car or using machines if you experience these side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AYVAKYT:

- Boceprevir – used to treat hepatitis C
- Atazanavir, cobicistat, efavirenz, etravirine, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir – used to treat HIV infections/AIDS
- Clarithromycin, erythromycin, telithromycin – used to treat bacterial infections
- Itraconazole, ketoconazole, posaconazole, voriconazole, fluconazole – used to treat serious fungal infections
- Conivaptan – used to treat low blood sodium levels (hyponatraemia)
- 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) – a herbal medicine used for depression
- Bosentan – used to treat high blood pressure
- Modafinil – used to treat sleep disorders
- Dabrafenib – used to treat certain cancers
- Nafcillin – used to treat certain bacterial infections
- Dexamethasone – used to reduce inflammation
- Alfentanil – used to control pain during operations and medical procedures
- Midazolam – used for anaesthesia, sedation or to decrease anxiety
- Simvastatin – used to treat high cholesterol
- Sirolimus, tacrolimus – used to prevent organ transplant rejection

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

How to take AYVAKYT:

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- 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.

Usual dose:

Adult dose: The recommended dose is 200 mg by mouth once daily.

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

Overdose:

If you think you, or a person you are caring for, have taken too much AYVAKYT, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of AYVAKYT, take it as soon as you remember. If your next dose is within 8 hours, skip the missed dose and take the next dose at your regular time.
- Do NOT take two doses within 8 hours to make up for a forgotten dose
- If you vomit after taking a dose of AYVAKYT, do NOT take an extra dose. Take your next dose at your scheduled time.

What are possible side effects from using AYVAKYT?

These are not all the possible side effects you may have when taking AYVAKYT. If you experience any side effects not listed here, tell your healthcare professional.

- altered taste
- diarrhea
- nausea, retching and vomiting
- change in hair colour
- tiredness
- headache
- dizziness
- decreased sensation, numbness, tingling, or increased sensitivity to pain in arms and legs
- increased tear production
- nose bleed
- dryness affecting eyes, lips, mouth and skin
- constipation, flatulence (gas)
- abdominal (belly) pain
- rash
- hair loss
- pain in the joint, bone, or muscle
- weight gain
- bruising
- cough
- blurry vision

AYVAKYT may cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Low blood platelets, red blood cells or white blood cells: feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		X	
Generalized edema: swelling in parts of your body (e.g. feet, ankle, face, eye, joint), weight gain		X	
COMMON			
Ascites (fluid in the abdomen): abdominal pain, feeling of fullness, flat or pushed out navel, increase in weight, shortness of breath		X	
Cardiac failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		X	
Pleural effusion (fluid around the lungs): chest pain, difficult or painful breathing, cough		X	
Signs of bleeding events including in your brain: severe headache, vision problems, severe sleepiness, severe weakness on one side of your body, nausea, vomiting and altered mental status			X
Signs of cognitive effect: memory loss, changes in memory, or confusion		X	
Gastrointestinal hemorrhage (bleeding in the digestive system such as stomach, rectum, or intestine) symptoms include passing blood in the stools or passing black stools, stomach pain, coughing/vomiting up blood		X	
Acute Kidney injury: Blood tests showing decreased kidney function		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store AYVAKYT at room temperature (15°C to 30°C)
- Keep out of reach and sight of children

If you want more information about AYVAKYT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the Importer and Distributor's website www.medisonpharma.com, or by calling 1-800-696-1341.

This leaflet was prepared by Blueprint Medicines Corporation

Last Revised SEP 18, 2024