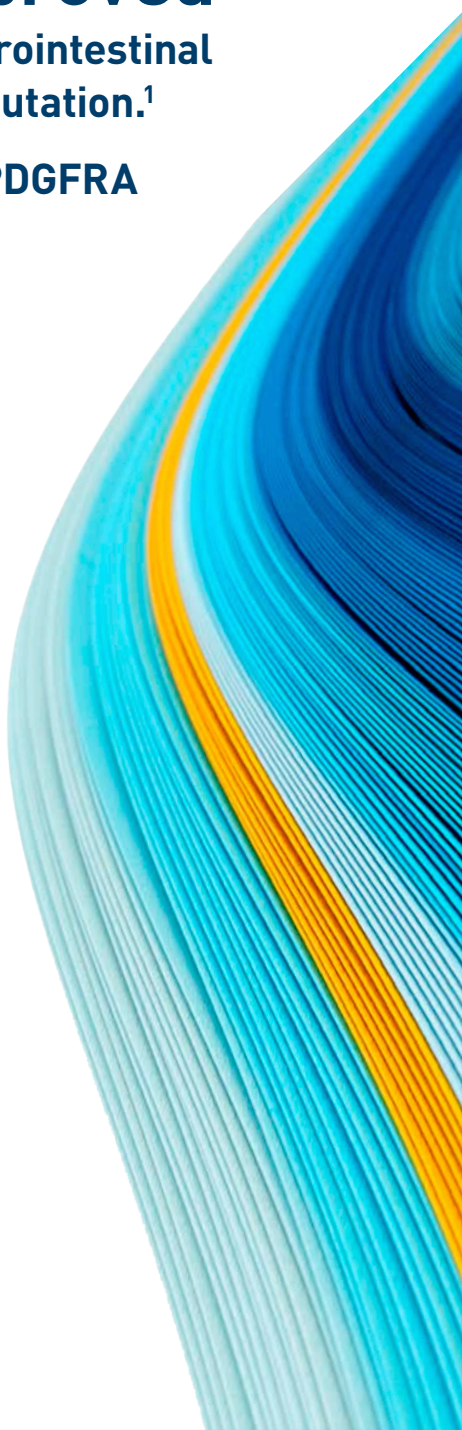
AYVAKIT™
avapritinib | tablets

Introducing the first FDA-approved

tyrosine kinase inhibitor (TKI) for people with a gastrointestinal stromal tumor (GIST) who have a PDGFRA exon 18 mutation.[1]

AYVAKIT™ (avapritinib) selectively targets KIT and PDGFRA mutant kinases, the primary drivers of GIST.[1,2]

FDA Breakthrough Therapy Designation for the treatment of patients with metastatic GIST harboring PDGFRA D842V mutations.[3]



INDICATIONS AND USAGE

AYVAKIT is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 1% of 267 patients (0.7% Grade 3 or 4) with GIST and overall in 3% of 335 patients (1.2% Grade 3 or 4) who received AYVAKIT. Overall, 0.9% of patients receiving AYVAKIT required permanent discontinuation for an intracranial hemorrhage. Withhold AYVAKIT and then resume at a reduced dose upon resolution, or permanently discontinue AYVAKIT based on severity.

Please see additional Important Safety Information and click here to see the full Prescribing Information for AYVAKIT.

Until now, no effective treatment options for unresectable or metastatic PDGFRA D842V GIST[2]

The PDGFRA D842V mutation shifts the kinase into an active state that makes it insensitive to previously approved agents for GIST.[2,4]

- Preclinical studies have shown resistance of PDGFRA D842V GIST to imatinib[5]

A retrospective study demonstrated poor clinical outcomes in patients with advanced PDGFRA D842V GIST treated with imatinib, including a median progression-free survival (PFS) of 2.8 months (95% CI, 2.4-3.2; n=32) and an overall response rate (ORR) of 0% (n=31).[6]

2.8 MONTHS
MEDIAN PFS[6]

0% ORR[6]

Study Background: A retrospective survey collected data from 12 European GIST referral centers and 2 European Organisation for Research and Treatment of Cancer studies on patients with advanced PDGFRA-mutant GISTs treated with imatinib at 400 or 800 mg daily (N=58) (excluding those who had previously taken imatinib in the adjuvant setting). ORR was based on partial responses (PR) and complete responses (CR) as defined by RECIST 1.0 criteria, and PFS was calculated as the time from the date imatinib was started to the date of disease progression or death, whichever occurred first.[6]

Mutational testing is strongly recommended in patients with GIST[7,8]

IF MUTATION STATUS IS UNKNOWN, THERE ARE INDICATORS THAT MAY TRIGGER MUTATIONAL TESTING:

IHC-NEGATIVE FOR KIT

One study has shown nearly 80% of GIST biopsies that stain negative for KIT (CD117) via immunohistochemistry harbor a PDGFRA mutation[9]

GIST HAS EPITHELIOID PHENOTYPE, AND LOCATION IS IN THE STOMACH

Approximately 20% of primary GIST of the stomach harbor the PDGFRA D842V mutation, and almost all have an epithelioid phenotype[5,10,11]

LACK OF RESPONSE TO IMATINIB

Patients with unknown mutational status who exhibit primary resistance to imatinib may have the PDGFRA D842V mutation[6]

The demonstrated safety and efficacy of AYVAKIT™ (avapritinib)[1]

The NAVIGATOR study (NCT02508532) is a multi-center, single-arm, open-label clinical trial.[1]

PRIMARY ENDPOINT: Overall response rate (ORR) as defined by patients who achieved a complete response (CR) or partial response (PR).[1]

STUDY DESIGN:

Eligible patients were required to have a confirmed diagnosis of GIST and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. Patients received AYVAKIT 300 mg or 400 mg orally once daily until disease progression or unacceptable toxicity. The trial initially enrolled patients at a starting dose of 400 mg, which was later reduced to the recommended dose of 300 mg due to toxicity. As there was no apparent difference in ORR between patients who received 300 mg daily compared to those who received 400 mg daily, these patients were pooled for the efficacy evaluation. The major efficacy outcome measure was ORR based on disease assessment by independent radiological review using modified RECIST v1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodules within a pre-existing tumor mass was progression. An additional efficacy outcome measure was duration of response (DOR).[1]

BASELINE CHARACTERISTICS OF PDGFRA EXON 18 MUTATION POPULATION[1]

Population characteristics (N=43)	
Subgroup who had a PDGFRA D842V mutation	38
Duration of follow up, median (range)	10.6 (0.3-24.9) months
Age, median (range)	64 (29-90) years
Male	67%
White	67%
ECOG PS of 0-1	93%
Metastatic disease	98%
Largest target lesion size >5 cm	53%
Prior surgical reduction	86%
Number of prior kinase inhibitors, median (range)	1 (0-5)

Exon 18 mutations other than D842V included in this population: deletion of D842_H845 (n=3); D842Y (n=1); and deletion of D842_H845 with insertion of V (n=1).[1]

IMPORTANT SAFETY INFORMATION

In 335 patients receiving AYVAKIT, CNS adverse reactions occurred overall in 58% of patients including cognitive impairment (41%; 3.6% Grade 3 or 4), dizziness (20%; 0.6% Grade 3 or 4), sleep disorders (15%; 0.3% Grade 3 or 4), mood disorders (13%; 1.5% Grade 3 or 4), speech disorders (6%; none Grade 3 or 4), and hallucinations (2.1%; none Grade 3 or 4). Overall, 3.9% of patients required permanent discontinuation of AYVAKIT for a CNS adverse reaction. Depending on severity, withhold AYVAKIT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKIT.

Groundbreaking data in patients with PDGFRA exon 18 GIST[1]

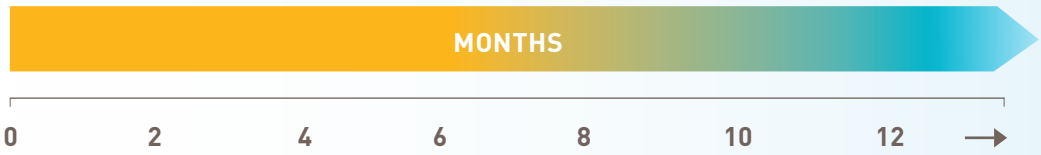
84% ORR*

in 43 patients with GIST harboring a PDGFRA exon 18 mutation.[1]

***(95% CI: 69%, 93%) (77% PR, 7% CR)**

In a subset of patients with the PDGFRA D842V mutation (n=38 of 43), the ORR was 89% (95% CI: 75%, 97%) (82% PR, 8% CR).[1]

MEDIAN DURATION OF RESPONSE NOT REACHED



At the time of analysis, median DOR for PDGFRA exon 18 (n=36) and PDGFRA D842V (n=34) GIST patients was not reached (range: 1.9+ to 20.3+).[1]

DOR ≥ 6-months was reached by 22 patients (61%) with PDGFRA exon 18 and 20 patients (59%) with PDGFRA D842V GIST. 11 patients with an ongoing response were followed < 6 months from onset of response.
CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response
+ Denotes ongoing response at time of analysis

AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential and pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Advise women not to breastfeed during treatment with AYVAKIT and for two weeks after the final dose. Advise females and males of reproductive potential that AYVAKIT may impair fertility.

Please see additional Important Safety Information and click here to see the full Prescribing Information for AYVAKIT.

AYVAKIT™ avapritinib | tablets

Adverse Reactions

The safety of AYVAKIT was evaluated in patients with unresectable or metastatic GIST enrolled in NAVIGATOR. Patients received AYVAKIT 300 mg or 400 mg orally once daily (N=204). Among patients receiving AYVAKIT, 56% were exposed for 6 months or longer and 44% were exposed for greater than 1 year.[1]

Table 1: Adverse Reactions (≥10%) in Patients Receiving AYVAKIT in NAVIGATOR[1]*

Adverse Reactions	AYVAKIT, N=204	
General	**All Grades (%)**	**Grade ≥3 (%)**
Edema[a]	72	2
Fatigue/asthenia	61	9
Pyrexia	14	0.5
Gastrointestinal		
Nausea	64	2.5
Vomiting	38	2
Diarrhea	37	4.9
Abdominal pain[b]	31	6
Constipation	23	1.5
Dyspepsia	16	0
Nervous System		
Cognitive impairment[c]	48	4.9
Dizziness	22	0.5
Headache	17	0.5
Sleep disorders[d]	16	0
Taste effects[e]	15	0
Mood disorders[f]	13	1
Metabolism and nutrition		
Decreased appetite	38	2.9
Eye		
Increased lacrimation	33	0
Skin and subcutaneous tissue		
Rash[g]	23	2.1
Hair color changes	21	0.5
Alopecia	13	-
Respiratory, thoracic and mediastinal		
Dyspnea	17	2.5
Pleural effusion	12	2
Investigations		
Weight decreased	13	1

Hand-Foot Syndrome (HFS) was reported in 1% of patients treated with AYVAKIT.[1]

The median age of patients who received AYVAKIT was 62 years (range: 29 to 90), 60% were <65 years, 62% were male, and 69% were White. Patients had received a median of 3 prior kinase inhibitors (range 0 to 7).[1]

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

[a] Edema includes face swelling, conjunctival edema, eye edema, eyelid edema, orbital edema, periorbital edema, face edema, mouth edema, pharyngeal edema, peripheral edema, edema, generalized edema, localized edema, peripheral swelling, testicular edema.

[b] Abdominal pain includes abdominal pain, upper abdominal pain, abdominal discomfort, lower abdominal pain, abdominal tenderness, and epigastric discomfort.

[c] Cognitive impairment includes memory impairment, cognitive disorder, confusional state, disturbance in attention, amnesia, mental impairment, mental status changes, encephalopathy, dementia, abnormal thinking, mental disorder, and retrograde amnesia.

[d] Sleep disorders includes insomnia, somnolence, and sleep disorder.

[e] Taste effects includes dysgeusia and ageusia.

[f] Mood disorders includes agitation, anxiety, depression, depressed mood, dysphoria, irritability, mood altered, nervousness, personality change, and suicidal ideation.

[g] Rash includes rash, rash maculo-papular, rash erythematous, rash macular, rash generalized, and rash papular.

It is common to modify AYVAKIT™ (avapritinib) dose for each individual patient[1]

Dose strengths of NAVIGATOR trial patients (n=36) still receiving AYVAKIT at 6 months[12]

*400 mg is not an approved dose of AYVAKIT.

The recommended starting dose of AYVAKIT is 300 mg orally once daily.[1]

Recommended Dosage Modifications for AYVAKIT for Adverse Reactions[1]

Recommend 200 mg once daily for first dose reduction and 100 mg once daily for second dose reduction.[1,a]

Adverse Reaction	Severity*	Dosage Modification
Intracranial Hemorrhage	Grade 1 or Grade 2	**First Occurrence:** Withhold AYVAKIT until resolution. Resume at reduced dose. **Subsequent Occurrence:** Permanently discontinue.
	Grade 3 or Grade 4	Permanently discontinue AYVAKIT.
Central Nervous System Effects	Grade 1	Continue AYVAKIT at same dose or withhold until improvement to baseline or resolution. Resume at same dose or reduced dose.
	Grade 2 or Grade 3	Withhold AYVAKIT until improvement to baseline, Grade 1, or resolution. Resume at same dose or reduced dose.
	Grade 4	Permanently discontinue AYVAKIT.
Other	Grade 3 or Grade 4	Withhold AYVAKIT until improvement to less than or equal to Grade 2. Resume at same dose or reduced dose, as clinically appropriate.

[a]Permanently discontinue AYVAKIT in patients who are unable to tolerate a dose of 100 mg once daily.
*Severity as defined by the CTCAE version 5.0.

In patients with unresectable or metastatic GIST, the most common (≥10%) worsening laboratory abnormalities from baseline were decreased hemoglobin (81% all grades, 28% ≥ Grade 3), decreased leukocytes (62% all grades, 5% ≥ Grade 3), decreased neutrophils (43% all grades, 6% ≥ Grade 3), decreased platelets (27% all grades, 0.5% ≥ Grade 3), increased INR (24% all grades, 0.6% ≥ Grade 3), increased activated partial thromboplastin time (13% all grades, 0% ≥ Grade 3), increased bilirubin (69% all grades, 9% ≥ Grade 3), increased aspartate aminotransferase (51% all grades, 1.5% ≥ Grade 3), decreased phosphate (49% all grades, 13% ≥ Grade 3), decreased potassium (34% all grades, 6% ≥ Grade 3), decreased albumin (31% all grades, 2% ≥ Grade 3), decreased magnesium (29% all grades, 1% ≥ Grade 3), increased creatinine (29% all grades, 0% ≥ Grade 3), decreased sodium (28% all grades, 7% ≥ Grade 3), increased alanine aminotransferase (19% all grades, 0.5% ≥ Grade 3), and increased alkaline phosphatase (14% all grades, 1% ≥ Grade 3).[1]

To report suspected adverse reactions, contact Blueprint Medicines Corporation at 1-888-258-7768 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see additional Important Safety Information and click here to see the full Prescribing Information for AYVAKIT.

AYVAKIT™ avapritinib | tablets

AYVAKIT™ (avapritinib) dosing recommendations and patient monitoring

PATIENTS SHOULD TAKE:

1 AYVAKIT tablet[1]

1 time each day[1]

on an empty stomach at least 1 hour before and 2 hours after a meal[1]

The recommended starting dose of AYVAKIT is 300 mg orally once daily.[1]
AYVAKIT is available in 100 mg, 200 mg, and 300 mg dose strengths.[1]

Select patients for treatment with AYVAKIT based on the presence of a PDGFRA exon 18 mutation.[1]

Additional instructions:

- Treatment should be continued until disease progression or unacceptable toxicity.[1]
- Do not make up for a missed dose within 8 hours of the next scheduled dose.[1]
- If your patient vomits after taking a dose of AYVAKIT, an extra dose should not be taken. Patients should continue with the next scheduled dose.[1]

PATIENT MONITORING MATTERS

- Dose modifications are often required for individual AYVAKIT patients. AYVAKIT patients should be monitored closely for signs of CNS effects, including forgetfulness, confusion, getting lost, trouble thinking, drowsiness, dizziness, trouble sleeping, word finding problems, hallucinations, or change in mood or behavior.[1]
    - Consider noting patient's baseline cognitive status to help detect their changes.
    - The median time to onset of the first CNS adverse reaction was 6.1 weeks (range 1 day to 1.9 years). Overall, 3.9% of patients required permanent discontinuation of AYVAKIT for a CNS adverse reaction.[1]
- Patients should be counseled to report any signs of possible intracranial hemorrhage (ICH), including severe headache, vision problems, severe sleepiness, or severe weakness on one side of the body.[1]
- Please see full Prescribing Information for instructions on when to reduce dose, withhold AYVAKIT, or permanently discontinue AYVAKIT.[1]

IMPORTANT SAFETY INFORMATION

Avoid coadministration of AYVAKIT with strong and moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce dose of AYVAKIT. Avoid coadministration of AYVAKIT with strong and moderate CYP3A inducers.

AYVAKIT selectively targets KIT and PDGFRA mutant kinases[1,2]

AYVAKIT BINDS DIRECTLY TO THE ACTIVE CONFORMATION OF PDGFRA AND PDGFRA D842 MUTANTS AS WELL AS MULTIPLE KIT EXON 11, 11/17 AND 17 MUTANTS.[1,2]

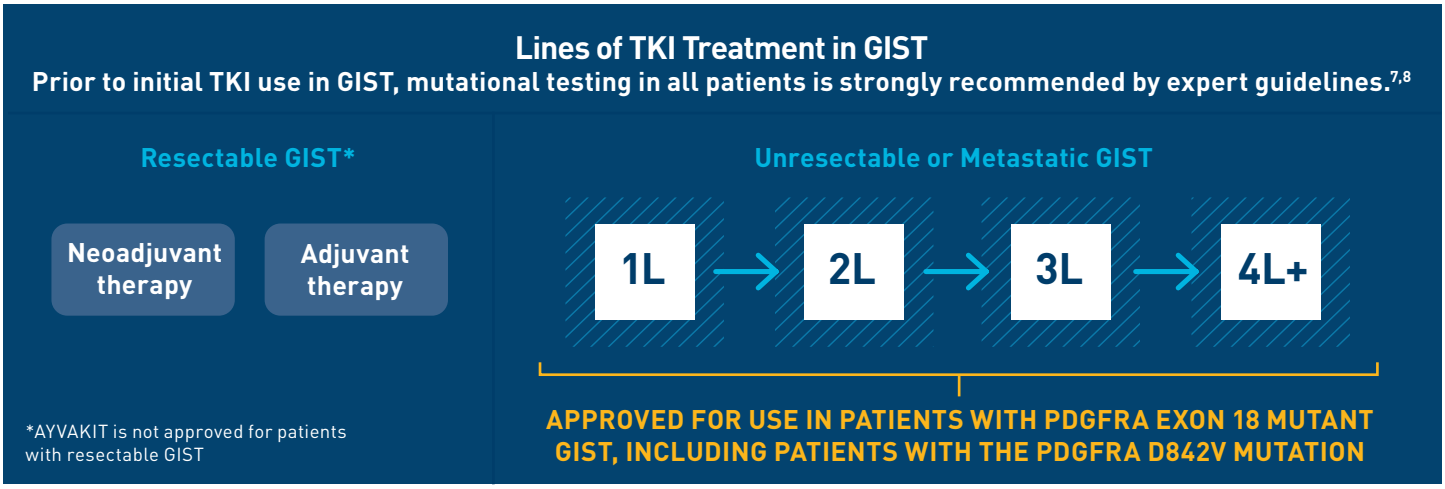
- In in vitro assays, AYVAKIT was shown to be a selective KIT/PDGFRA kinase inhibitor.[1,2]
- AYVAKIT demonstrated potent cellular in vitro activity on PDGFRA D842V mutants associated with resistance to approved kinase inhibitors.[1]
- AYVAKIT exhibited anti-tumor activity in an imatinib-resistant patient-derived xenograft model of human GIST with activating KIT exon 11/17 mutations.[1]

In 204 patients with unresectable or metastatic GIST, the most common adverse reactions (≥20%) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness.

Please see additional Important Safety Information and click here to see the full Prescribing Information for AYVAKIT.

AYVAKIT™ avapritinib | tablets

AYVAKIT™ (avapritinib): FDA approved for PDGFRA exon 18 GIST[1]



84% of GIST patients harboring PDGFRA exon 18 mutations in the NAVIGATOR trial achieved a response[1*]

*(N=43) (95% CI: 69%, 93%) (77% PR, 7% CR)

Important Safety Information

The most common adverse reactions (≥20%) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness.[1]

your blueprint™

YourBlueprint™ is a patient support program that offers benefits investigation, prior authorization support, financial assistance options, and other helpful resources.

To enroll your patients, visit **YourBlueprint.com/HCP** today.

References:
1. AYVAKIT Prescribing Information. Blueprint Medicines Corporation, Cambridge, MA. January 2020. **2.** Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by *KIT/PDGFRA* mutations. *Sci Transl Med.* 2017;(9)414;2017:1-11. **3.** Data on file (DOF-REF-00206). Blueprint Medicines Corporation, Cambridge, MA. 2019. **4.** Liang L, Yan, X-E, Yin Y, Yun C-H. Structural and biochemical studies of the PDGFRA kinase domain. *Biochem Biophys Res Commun.* 2016; doi:10.1016/j.bbrc.2016.06.117 **5.** Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol* 2005;23(23):5357-5364. **6.** Cassier PA, Fumagalli E, Rutkowski P. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin Cancer Res.* 2012;18(16):4458-4464. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.4.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 12, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **8.** Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29(4):iv68-iv78. **9.** Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol.* 2004;28(7):889-894. **10.** Lasota J, Miettinen M. Clinical significance of oncogenic *KIT* and *PDGFRA* mutations in gastrointestinal stromal tumours. *Histopathology.* 2008;53(3):245-266. **11.** Downs-Kelly E, Rubin BP. Gastrointestinal stromal tumors: molecular mechanisms and targeted therapies. *Patholog Res Int.* 2011; doi:10.4061/2011/708596. **12.** Data on file (DOF-REF-00465). Blueprint Medicines Corporation, Cambridge, MA. 2020.

Please see additional Important Safety Information and click here to see the full Prescribing Information for AYVAKIT.
For more information, visit AYVAKIT.com/HCP.

01/2020 USBP-PRA-19.046.1

blueprint™ MEDICINES

AYVAKIT™ avapritinib | tablets