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# Dosing and Patient Management Guide

**An educational resource about AYVAKIT® (avapritinib) for healthcare professionals, including patient and caregiver counseling information.**

**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

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## INDICATION

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

## SELECT SAFETY INFORMATION

Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT. In GIST patients, ICH occurred in 3 of 267 patients (1.1%) and two (0.7%) of the events were Grade ≥3 and resulted in discontinuation. Monitor patients closely for risk of ICH including those with thrombocytopenia, vascular aneurysm or a history of ICH or cerebrovascular accident within the prior year. Permanently discontinue AYVAKIT if ICH of any grade occurs.



**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

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# Dosing[1]

The recommended starting dose of AYVAKIT is 300 mg orally once daily in patients with GIST.

## PATIENTS SHOULD TAKE:

- 1 AYVAKIT tablet
- 1 time each day
- on an empty stomach at least 1 hour before or 2 hours after a meal

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

**Additional instructions:**

- Treatment should be continued until disease progression or unacceptable toxicity.
- Do not make up for a missed dose of AYVAKIT within 8 hours of the next scheduled dose.
- Do not repeat dose if vomiting occurs after AYVAKIT but continue with the next scheduled dose.

### SELECT SAFETY INFORMATION

Cognitive adverse reactions can occur in patients receiving AYVAKIT. Cognitive adverse reactions occurred in 39% of 749 patients and in 41% of 601 GIST patients (5% were Grade >3). Memory impairment occurred in 21% of patients; <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; 1.2% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Amnesia occurred in 3% of patients; <1% of these events were Grade 3. Somnolence and speech disorder occurred in 2% of patients; none of these events were Grade 3. Other events occurred in less than 2% of patients. Depending on the severity, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.



# Dose strengths[1]

AYVAKIT is available in 100 mg, 200 mg, and 300 mg dose strengths. If your patient experiences any adverse reactions while taking AYVAKIT, consider interrupting dose, reducing dose, or permanently discontinuing AYVAKIT.

Available in bottles of 30 tablets.

| Dose Strength | Description |
|---|---|
| 100 mg tablet | Round, white, film-coated tablet, printed with blue ink "BLU" on 1 side and "100" on the other side |
| 200 mg tablet | Capsule-shaped, white, film-coated tablet, printed with blue ink "BLU" on 1 side and "200" on the other side |
| 300 mg tablet | Capsule-shaped, white, film-coated tablet, printed with blue ink "BLU" on 1 side and "300" on the other side |

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# In the NAVIGATOR Study, it was common to modify AYVAKIT doses[1]

Approximately 50% patients in the clinical trial experienced dose reduction and/or interruption due to an adverse reaction.[1] Sixteen percent of patients who received AYVAKIT permanently discontinued due to adverse reactions.

**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[b] | Dosage Modification |
|---|---|---|
| **Intracranial Hemorrhage** | Any grade | Permanently discontinue AYVAKIT. |
| **Cognitive Effects** | Grade 1 | Continue AYVAKIT 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 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.
[b] Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

## SELECT SAFETY INFORMATION

AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise 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 2 weeks after the final dose.

**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

# Dosing considerations for PDGFRA exon 18 GIST

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend avapritinib (AYVAKIT) as a treatment option for unresectable, recurrent or metastatic GIST with PDGFRA exon 18 mutation and also recommend continued use of avapritinib (AYVAKIT) at the same dose in cases of limited progression.[2]

Post hoc analyses of the NAVIGATOR trial showed that each studied dose of AYVAKIT is associated with variable exposure levels across individual patients, supporting need for clinically guided dose adjustments based on adverse reactions.[3]

# Dose strengths of NAVIGATOR PDGFRA exon 18 trial patients (n=36) still receiving AYVAKIT at 6 months[4]


The recommended starting dose of AYVAKIT is 300 mg orally once daily.[1]
*400 mg is not an approved dose of AYVAKIT.
Data cutoff date: November 2018

your blueprint®

The **YourBlueprint® Dose Exchange Program** is available to help ensure continuity of care for patients whose dose has been reduced. Through this program, eligible patients can exchange remaining tablets for tablets at a new dose at no cost.

See page 17 for more information about YourBlueprint.

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# Adverse reactions observed in the NAVIGATOR trial[1,4]

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

**Adverse Reactions (≥10%) in Patients Receiving AYVAKIT***

| Adverse Reactions | AYVAKIT 300 mg n=154 | | AYVAKIT 300/400 mg N=204 | |
|---|---|---|---|---|
| **General** | **All Grades %** | **Grade ≥3 %** | **All Grades %** | **Grade ≥3 %** |
| Edema[a] | 71 | 1.3 | 72 | 2 |
| Fatigue/asthenia | 58 | 6 | 61 | 9 |
| Pyrexia | 12 | 0 | 14 | 0.5 |
| **Gastrointestinal** | | | | |
| Nausea | 60 | 1.3 | 64 | 2.5 |
| Vomiting | 33 | 1.9 | 38 | 2 |
| Diarrhea | 37 | 4.5 | 37 | 4.9 |
| Abdominal pain[b] | 32 | 7 | 31 | 6 |
| Constipation | 22 | 1.9 | 23 | 1.5 |
| Dyspepsia | 16 | - | 16 | 0 |
| **Nervous system** | | | | |
| Cognitive impairment[c] | 44 | 3.9 | 48 | 4.9 |
| Dizziness | 16 | 0.6 | 22 | 0.5 |
| Headache | 16 | 0.6 | 17 | 0.5 |
| Sleep disorders[d] | 15 | 0 | 16 | 0 |
| Taste effects[e] | 18 | 0 | 15 | 0 |
| Mood disorders[f] | 11 | 0 | 13 | 1 |
| **Metabolism and nutrition** | | | | |
| Decreased appetite | 36 | 1.9 | 38 | 2.9 |
| **Eye** | | | | |
| Increased lacrimation | 30 | - | 33 | 0 |
| **Skin and subcutaneous tissue** | | | | |
| Rash[g] | 18 | 1.3 | 23 | 2.1 |
| Hair color changes | 19 | 0 | 21 | 0.5 |
| Alopecia | 11 | - | 13 | - |
| **Respiratory, thoracic and mediastinal** | | | | |
| Dyspnea | 14 | 1.9 | 17 | 2.5 |
| Pleural effusion | 12 | 1.3 | 12 | 2 |
| **Investigations** | | | | |
| Weight decreased | 14 | 1.3 | 13 | 1 |

The safety profile to the left reflects exposure to AYVAKIT in patients with unresectable or metastatic GIST enrolled in NAVIGATOR. Patients received a starting dose of 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]

The median age of patients who received AYVAKIT was 62 years (range: 29 to 90 years), 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).

Clinically relevant adverse reactions occurring in <10% of patients were[1]:
Vascular: hypertension (8%)
Endocrine: thyroid disorders (hyperthyroid, hypothyroid) (3%)
Skin and subcutaneous: palmar-plantar erythrodysesthesia (1%)

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

*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.

**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

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# Select warnings and precautions

## Intracranial hemorrhage is a possible effect of AYVAKIT[1]

Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT. In GIST patients, ICH occurred in 3 of 267 patients (1.1%) and two (0.7%) of the events were Grade ≥3 and resulted in discontinuation. Monitor patients closely for risk of ICH including those with thrombocytopenia, vascular aneurysm or a history of ICH or cerebrovascular accident within the prior year. Permanently discontinue AYVAKIT if ICH of any grade occurs.

Advise patients to contact their healthcare provider immediately if experiencing neurological signs and symptoms that may be associated with intracranial hemorrhage (ie, severe headache, vomiting, drowsiness, dizziness, confusion, slurred speech, or paralysis).

## Cognitive effects can occur when taking AYVAKIT[1]

Cognitive adverse reactions can occur in patients receiving AYVAKIT. Cognitive adverse reactions occurred in 39% of 749 patients and in 41% of 601 GIST patients (5% were Grade >3). Memory impairment occurred in 21% of patients; <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; 1.2% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Amnesia occurred in 3% of patients; <1% of these events were Grade 3. Somnolence and speech disorder occurred in 2% of patients; none of these events were Grade 3. Other events occurred in less than 2% of patients. Depending on the severity, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

The median time to onset of the first cognitive adverse reaction was 8.4 weeks (range: 1 day to 4 years).

Depending on severity, withhold AYVAKIT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKIT.

## Information regarding cognitive effects:

- Among patients who experienced a cognitive effect of Grade 2 or worse (impacting activities of daily living), the median time to improvement to Grade 1 or complete resolution was 7.9 weeks.[1]

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus.[1]

**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**





# Make a monitoring plan with your patients and their caregivers

Help your patients and their caregivers understand that they should be looking out for cognitive effects such as forgetfulness, confusion, getting lost, trouble thinking, drowsiness, trouble staying awake (somnolence), word finding problems, seeing objects or hearing things that are not there (hallucinations), or changes in mood or behavior. Advise patients not to drive or operate hazardous machinery if they are experiencing cognitive adverse reactions.[1]

For example, create a list of questions to help your patients identify any changes in cognitive effects if they arise. Use the questions to educate patients and their caregivers about how to identify changes quickly and notify you as soon as possible to enable timely dose modifications.[5]

Work with your patients and their caregivers to establish a baseline, then set a schedule for periodic monitoring.[5]

**Caregivers can ask patients taking AYVAKIT how often within the prior week they experienced difficulty with the following[5]:**

1. Finding their way to familiar places, like places of work
2. Remembering where they put commonly used personal items (eg, phone, keys)
3. Recalling the name of an object during conversation
4. Keeping track of why they walked into a room
5. Speaking or thinking clearly
6. Completing a task without losing track of what they were doing

Although not comprehensive, this list can help guide the plan you make with your patient and their caregiver to monitor for cognitive effects.*

*These discussion points were adapted from FACT-Cog V3, Copyright 2006, 2016 by David Cella, PhD.[5]

**Be sure to tell your patient and their caregiver how important it is that they monitor for and inform you about any adverse reactions, including possible CNS effects. Help them understand that sharing this information enables timely dose modifications.**

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# IMPORTANT SAFETY INFORMATION

There are no contraindications for AYVAKIT.

Serious intracranial hemorrhage (ICH) may occur with AYVAKIT treatment; fatal events occurred in <1% of patients. Overall, ICH (eg, subdural hematoma, ICH, and cerebral hemorrhage) occurred in 2.9% of 749 patients who received AYVAKIT. In GIST patients, ICH occurred in 3 of 267 patients (1.1%) and two (0.7%) of the events were Grade ≥3 and resulted in discontinuation. Monitor patients closely for risk of ICH including those with thrombocytopenia, vascular aneurysm or a history of ICH or cerebrovascular accident within the prior year. Permanently discontinue AYVAKIT if ICH of any grade occurs.

Cognitive adverse reactions can occur in patients receiving AYVAKIT. Cognitive adverse reactions occurred in 39% of 749 patients and in 41% of 601 GIST patients (5% were Grade >3). Memory impairment occurred in 21% of patients; <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; 1.2% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Amnesia occurred in 3% of patients; <1% of these events were Grade 3. Somnolence and speech disorder occurred in 2% of patients; none of these events were Grade 3. Other events occurred in less than 2% of patients. Depending on the severity, withhold AYVAKIT and then resume at same dose or at a reduced dose upon improvement, or permanently discontinue.

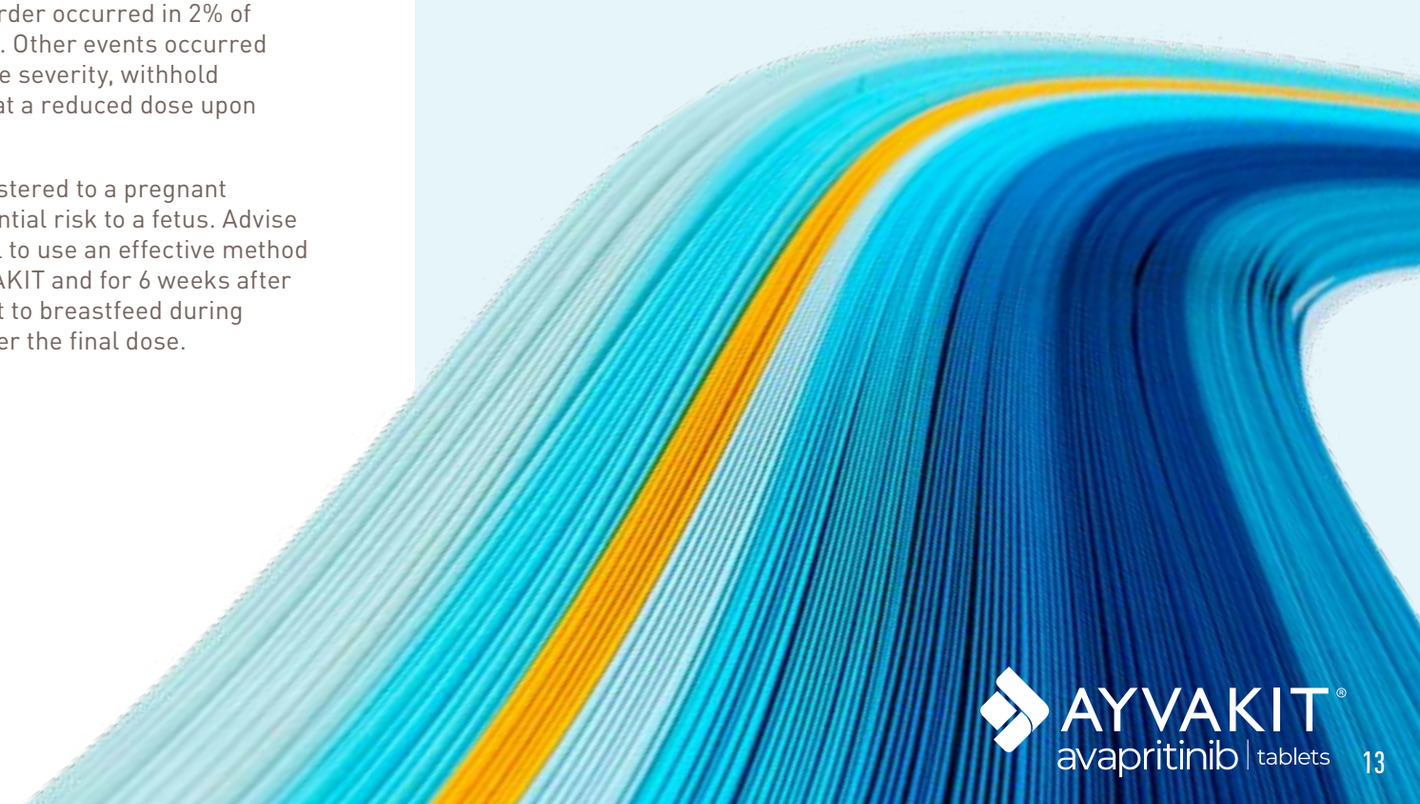
AYVAKIT can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use an effective method of contraception during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks after the final dose.

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.

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.

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

**See the full Prescribing Information for AYVAKIT.**



The following case studies are fictional but based on clinical trial experience with avapritinib. Healthcare providers should make all treatment decisions based on the prescribing information, individual patient profile, and their clinical judgment. Individual results may vary.

## 64-year-old female diagnosed with GIST

### INITIAL TREATMENT

- Patient undergoes resection of a primary GIST of the stomach (9 cm).
- Mutational testing confirms patient's tumor harbors the PDGFRA D842V mutation; imatinib considered not an appropriate adjuvant treatment.
- Patient is considered intermediate risk for relapse.
- One year after initial resection, patient relapses and metastatic disease is confirmed.

### INTRODUCTION OF AYVAKIT

- Patient is prescribed AYVAKIT 300 mg once daily.
- Approximately 1 month into treatment, patient's husband notices she keeps misplacing her keys.
- Patient is determined to have Grade 1 memory impairment.
- Per dosing guidelines, dosage is interrupted until improvement. After a 5-day break, patient resumes at 200 mg once daily while monitoring continues.

### CONTINUED TREATMENT

- After 3 months of therapy at 200 mg daily, patient's spouse notifies nurse practitioner that the patient has been experiencing forgetfulness and word-finding difficulty.
- Patient's memory impairment is determined to have progressed to Grade 2.
- Per dosing guidelines, dosage is once again interrupted until resolution and eventually lowered to 100 mg; monitoring continues.
- After 1 year of treatment, patient continues to be maintained on therapy at 100 mg daily and is tolerating it well without any new signs of cognitive impairment.

## 71-year-old male with metastatic GIST

### PATIENT HISTORY AND INTRODUCTION OF AYVAKIT

- Patient harbors the PDGFRA exon 18 mutation.
- Previously treated with imatinib and sunitinib.
- Patient is prescribed AYVAKIT 300 mg once daily.

### ADVERSE EVENTS

- After 3 months of treatment, patient is tolerating the drug despite a mild periorbital edema.
- Patient experienced a similar adverse event during previous treatment with imatinib.
- Patient noted to have Grade 1 periorbital edema. No dose adjustment required; care team proceeds with continued monitoring.

### CONTINUED TREATMENT

- After 6 months of therapy, patient presents with worsening periorbital edema (now Grade 2) and Grade 3 anemia.
- Per dosing guidelines, dose is interrupted due to onset of Grade 3 anemia.
- Patient takes a break from dosing for 7 days.
- Hemoglobin improves to 9.8 g/dL (Grade 2).
- Patient then resumes at 200 mg once daily.
- Patient continues regimen of AYVAKIT 200 mg daily; no new notable adverse events reported.

**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

# It is important to review the benefits and risks associated with AYVAKIT before initiating patients on therapy

- **In the NAVIGATOR Study it was common to modify AYVAKIT doses[1]**
  The recommended starting dose of AYVAKIT is 300 mg orally once daily. Dosage may be lowered to 200 mg once daily for first dose reduction and 100 mg once daily for second dose reduction for adverse reactions.

- **Side effects**
  Recognizing any changes in how your patient is tolerating AYVAKIT, early and throughout treatment, is important. AYVAKIT may cause certain side effects that the patient did not experience while on other medicines. Ensure your patients are discussing any potential side effects of AYVAKIT with their family or caregiver. Encourage patients and their caregivers to contact you if they experience side effects.

- **Resources**
  There are various resources for patients starting AYVAKIT that are available in print, online, or over the phone. Review these with your patient or contact your local Blueprint Medicines representative if you need help accessing them.



**Please see Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**



# Support and financial assistance options for your patients taking AYVAKIT

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YourBlueprint is a patient support program designed with your patients' care in mind. YourBlueprint assists patients throughout many aspects of treatment by providing:

- Benefits investigation
- Prior authorization support
- Financial assistance options
- Helpful resources

## EXPLORE THE WAYS WE CAN HELP

CALL **1-888-BLUPRNT (1-888-258-7768)**
Monday-Friday 8 AM-8 PM Eastern Time (ET)
**OR**
Visit **www.YourBlueprint.com/HCP**

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# Managing your patients taking AYVAKIT

## INITIATE

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

## MONITOR

Note your patient's baseline signs and symptoms and observe them for early signs of adverse reactions to determine if dose modifications may be appropriate.[1]

## OPTIMIZE

In the NAVIGATOR Study it was common to modify AYVAKIT doses. Modify dose as needed for each individual patient and see the detailed dose modification information within this guide and the AYVAKIT prescribing information.[1,3]

**For additional information about AYVAKIT, visit AYVAKIT.COM/HCP.**

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 Important Safety Information on pages 12 and 13 and the full Prescribing Information for AYVAKIT.**

**References: 1.** AYVAKIT [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; June 2021. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs) V.1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed July 15, 2021. 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. **3.** Joseph CP, et al. *Oncologist*. 2021;26(4):e622-e631. **4.** Data on file. Blueprint Medicines Corporation, Cambridge, MA. 2021. **5.** Cella D. FACIT Measurement System. FACT-Cog: For patients with Cognitive function issues. FACIT. Accessed July 16, 2021. https://www.facit.org/FACITOrg/Questionnaires

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