

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212608Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AYYAKIT safely and effectively. See full prescribing information for AYYAKIT.

AYYAKIT (avapritinib) tablets, for oral use

Initial U.S. Approval: 2020

INDICATIONS AND USAGE

AYYAKIT 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.

DOSAGE AND ADMINISTRATION

- Select patients for treatment with AYYAKIT based on the presence of a PDGFRA exon 18 mutation. (2.1)
- The recommended dosage is 300 mg orally once daily on an empty stomach, at least one hour before and two hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg, 200 mg and 300 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Intracranial Hemorrhage:** Withhold AYYAKIT for Grade 1 or 2 reactions until resolution and then resume at a reduced dose. Permanently discontinue for recurrent Grade 1 or 2 reactions or first occurrence of Grade 3 or 4 reactions. (2.3, 5.1)

- **Central Nervous System (CNS) Effects:** CNS adverse reactions include cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations. Depending on the severity, continue AYYAKIT at same dose, withhold and then resume at same or reduced dose upon improvement, or permanently discontinue. (2.3, 5.2)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 20\%$) are edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness. (6)

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.

DRUG INTERACTIONS

- **Strong and Moderate CYP3A Inhibitors:** Avoid coadministration of AYYAKIT with strong and moderate CYP3A inhibitors. If coadministration of AYYAKIT with a moderate inhibitor cannot be avoided, reduce dose of AYYAKIT. (2.4, 7.1)
- **Strong and Moderate CYP3A Inducers:** Avoid coadministration of AYYAKIT with strong and moderate CYP3A inducers. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection for GIST Harboring PDGFRA Exon 18 Mutations
- 2.2 Recommended Dosage
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Concomitant Use of Strong or Moderate CYP3A Inhibitors

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Intracranial Hemorrhage
- 5.2 Central Nervous System Effects
- 5.3 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on AYYAKIT

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Gastrointestinal Stromal Tumors

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

AYVAKIT is 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 [see *Dosage and Administration* (2.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for GIST Harboring PDGFRA Exon 18 Mutations

Select patients for treatment with AYVAKIT based on the presence of a PDGFRA exon 18 mutation [see *Clinical Studies* (14.1)]. An FDA-approved test for the detection of exon 18 mutations is not currently available.

2.2 Recommended Dosage

The recommended dosage of AYVAKIT is 300 mg orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal [see *Clinical Pharmacology* (12.3)]. Continue treatment until disease progression or unacceptable toxicity. Do not make up for a missed dose within 8 hours of the next scheduled dose.

Do not take an additional dose if vomiting occurs after AYVAKIT, but continue with the next scheduled dose.

2.3 Dosage Modifications for Adverse Reactions

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

Table 1. Recommended Dose Reductions for AYVAKIT for Adverse Reactions

Dose Reduction	Recommended Dosage
First	200 mg once daily
Second	100 mg once daily

*Permanently discontinue AYVAKIT in patients who are unable to tolerate a dose of 100 mg once daily.

Table 2. Recommended Dosage Modifications for AYVAKIT for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Intracranial Hemorrhage [see Warnings and Precautions (5.1)]	Grade 1 or Grade 2	<u>First Occurrence</u> : Withhold AYVAKIT until resolution. Resume at reduced dose. <u>Subsequent Occurrence</u> : Permanently discontinue.
	Grade 3 or Grade 4	Permanently discontinue AYVAKIT.
Central Nervous System Effects [see Warnings and Precautions (5.2)]	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 [see Adverse Reactions (6.1)]	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.

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

2.4. Concomitant Use of Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of AYVAKIT with strong or moderate CYP3A inhibitors. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, reduce the starting dose of AYVAKIT from 300 mg orally once daily to 100 mg orally once daily [see Drug Interactions (7.1)].

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 100 mg, round, white film-coated, printed with blue ink “BLU” on one side and “100” on the other side.
- 200 mg, capsule shaped, white film-coated, printed with blue ink “BLU” on one side and “200” on the other side.
- 300 mg, capsule shaped, white film-coated, printed with blue ink “BLU” on one side and “300” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Intracranial Hemorrhage

Intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 1% of the 267 patients with GIST and overall in 3% of the 335 patients who received AYVAKIT. Events of intracranial hemorrhage occurred in a range from 1.7 months to 19.3 months after

initiating AYVAKIT. Overall, 0.9% of patients receiving AYVAKIT required permanent discontinuation for an intracranial hemorrhage; 1.2% required dosage interruption followed by dose reduction.

Withhold AYVAKIT and then resume at a reduced dose upon resolution, or permanently discontinue AYVAKIT based on severity [see *Dosage and Administration* (2.3)].

5.2 Central Nervous System Effects

A broad spectrum of central nervous system (CNS) adverse reactions can occur in patients receiving AYVAKIT. These include cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations. CNS adverse reactions overall occurred in 58% of 335 patients who received AYVAKIT [see *Adverse Reactions* (6.1)]. Cognitive impairment occurred in 41% of the 335 patients who received AYVAKIT; 3.6% of these were severe (Grade 3 or 4). Dizziness occurred in 20% of patients; 0.6% of these events were severe. Sleep disorders occurred in 15% of patients; 0.3% of these events were severe. Mood disorders occurred in 13% of patients; 1.5% of these events were severe. Speech disorders occurred in 6% of patients; none of these events were severe. Hallucinations occurred in 2.1% of patients; none of these events were severe. 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, 17% required a dosage interruption, and 10% required dose reduction.

Depending on the severity, withhold AYVAKIT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKIT [see *Dosage and Administration* (2.3)].

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, AYVAKIT can 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 2.7 times the human exposure based on area under the curve (AUC) at the 300 mg dose. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Intracranial hemorrhage [see *Warnings and Precautions* (5.1)]
- Central nervous system effects [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to AYVAKIT at 30 mg to 600 mg orally once daily in 335 patients enrolled in one of three clinical trials conducted in patients with advanced malignancies, including NAVIGATOR [see *Clinical Studies* (14.1)]. Among the 335 patients receiving AYVAKIT, 49% were exposed for 6 months or longer and 23% were exposed for greater than 1 year.

Gastrointestinal Stromal Tumors

Unresectable or Metastatic GIST

The safety of AYVAKIT in patients with unresectable or metastatic GIST was evaluated in NAVIGATOR [see *Clinical Studies (14.1)*]. The trial excluded patients with history of cerebrovascular accident or transient ischemic attacks, known risk of intracranial bleeding, and metastases to the brain. 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 one year.

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).

Serious adverse reactions occurred in 52% of patients receiving AYVAKIT. Serious adverse reactions occurring in $\geq 1\%$ of patients who received AYVAKIT were anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%) and tumor hemorrhage (1%). Fatal adverse reactions occurred in 3.4% of patients. Fatal adverse reactions that occurred in more than one patient were sepsis and tumor hemorrhage (1% each).

Permanent discontinuation due to adverse reactions occurred in 16% of patients who received AYVAKIT. Adverse reactions requiring permanent discontinuation in more than one patient were fatigue, abdominal pain, vomiting, sepsis, anemia, acute kidney injury, and encephalopathy.

Dosage interruptions due to an adverse reaction occurred in 57% of patients who received AYVAKIT. Adverse reactions requiring dosage interruption in $>2\%$ of patients who received AYVAKIT were anemia, fatigue, nausea, vomiting, hyperbilirubinemia, memory impairment, diarrhea, cognitive disorder, and abdominal pain.

Dose reduction due to an adverse reaction occurred in 49% of patients who received AYVAKIT. Median time to dose reduction was 9 weeks. Adverse reactions requiring dosage reduction in more than 2% of patients who received AYVAKIT were fatigue, anemia, hyperbilirubinemia, memory impairment, nausea and periorbital edema.

The most common adverse reactions ($\geq 20\%$) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness. Table 3 summarizes the adverse reactions observed in NAVIGATOR.

Table 3. Adverse Reactions ($\geq 10\%$) in Patients Receiving AYVAKIT in NAVIGATOR

Adverse Reactions	AYVAKIT N=204	
	All Grades %	Grade ≥ 3 %
General		
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

*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 include 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.

Clinically relevant adverse reactions occurring in <10% of patients were:

Vascular: hypertension (8%)

Endocrine: thyroid disorders (hyperthyroid, hypothyroid) (3%)

Skin and subcutaneous: palmar-plantar erythrodysesthesia (1%)

Table 4 summarizes the laboratory abnormalities observed in NAVIGATOR.

Table 4. Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients Receiving AYVAKIT in NAVIGATOR

Laboratory Abnormality	AYVAKIT ^a N=204	
	All Grades (%)	Grade ≥ 3 (%)
Hematology		
Decreased hemoglobin	81	28
Decreased leukocytes	62	5
Decreased neutrophils	43	6
Decreased platelets	27	0.5
Increased INR	24	0.6
Increased activated partial thromboplastin time	13	0
Chemistry		
Increased bilirubin	69	9
Increased aspartate aminotransferase	51	1.5
Decreased phosphate	49	13
Decreases potassium	34	6
Decreased albumin	31	2
Decreased magnesium	29	1
Increased creatinine	29	0
Decreased sodium	28	7
Increased alanine aminotransferase	19	0.5
Increased alkaline phosphatase	14	1

^a The denominator used to calculate the rate varied from 154 to 201 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on AYVAKIT

Strong and Moderate CYP3A Inhibitors

Coadministration of AYVAKIT with a strong or moderate CYP3A inhibitor increases avapritinib plasma concentrations [see *Clinical Pharmacology* (12.3)], which may increase the incidence and severity of adverse reactions of AYVAKIT. Avoid coadministration of AYVAKIT with strong or moderate CYP3A inhibitors. If coadministration of AYVAKIT with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of AYVAKIT [see *Dosage and Administration* (2.4)].

Strong and Moderate CYP3A Inducers

Coadministration of AYVAKIT with a strong or moderate CYP3A inducer decreases avapritinib plasma concentrations [see *Clinical Pharmacology* (12.3)], which may decrease efficacy of AYVAKIT. Avoid coadministration of AYVAKIT with strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology* (12.1)], AYVAKIT can cause fetal harm when administered to a pregnant woman. There are no available data on AYVAKIT use in pregnant women. Oral administration of avapritinib to pregnant animals during the period of organogenesis was teratogenic and embryotoxic in rats at exposure levels approximately 2.7 times the human exposure based on AUC at the 300 mg dose (see *Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a reproductive toxicity study, administration of avapritinib to rats during the period of organogenesis resulted in decreased fetal body weights, post-implantation loss, and increases in visceral (hydrocephaly, septal defect, and stenosis of the pulmonary trunk) and skeletal (sternum) malformations at doses greater than or equal to 10 mg/kg/day (approximately 2.7 times the human exposure based on AUC at the 300 mg dose).

8.2 Lactation

Risk Summary

There are no data on the presence of avapritinib or its metabolites in human milk or the effects of avapritinib on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating AYVAKIT [see *Use in Specific Populations* (8.1)].

Contraception

AYVAKIT can cause fetal harm when administered to pregnant women [see *Use in Specific Populations (8.1)*].

Females

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

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose.

Infertility

Based on findings from animal studies, AYVAKIT may impair both male and female fertility [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of AYVAKIT in pediatric patients have not been established.

8.5 Geriatric Use

Of the 204 patients who received AYVAKIT in NAVIGATOR, 40% were 65 years or older, while 6% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger adult patients.

8.6 Renal Impairment

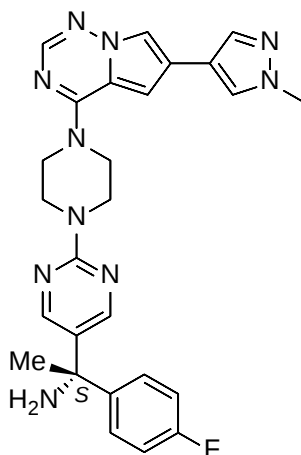
No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CL_{cr}) 30 to 89 mL/min estimated by Cockcroft-Gault]. The recommended dose of AYVAKIT has not been established for patients with severe renal impairment (CL_{cr} 15 to 29 mL/min) or end-stage renal disease (CL_{cr} <15 mL/min) [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild [total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 times ULN and any AST] or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. The recommended dose of AYVAKIT has not been established for patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Avapritinib is a kinase inhibitor with the 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. The molecular formula is C₂₆H₂₇FN₁₀, and the molecular weight is 498.57 g/mol. Avapritinib has the following chemical structure:



The solubility of avapritinib in 0.1N HCl (pH 1.0) and buffer solutions at pH 2.5, 4.0, and 7.0 (at 25°C) is 3.6 mg/mL, 0.14 mg/mL, 0.07 mg/mL and <0.001 mg/mL respectively, indicating a decrease in solubility with increasing pH.

AYVAKIT (avapritinib) film-coated tablets for oral use are supplied with three strengths that contain 100 mg, 200 mg or 300 mg of avapritinib. The tablets also contain inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet coating consists of polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The blue printing ink contains ammonium hydroxide, black iron oxide, esterified shellac, FD&C blue 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Avapritinib is a tyrosine kinase inhibitor that targets PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC_{50} s) less than 25 nM. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumor cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1.

In in vitro cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V, mutants associated with resistance to approved kinase inhibitors, with IC_{50} of 4 nM and 30 nM, respectively. Avapritinib also had anti-tumor activity in mice implanted with an imatinib-resistant patient-derived xenograft model of human GIST with activating KIT exon 11/17 mutations.

12.2 Pharmacodynamics

Exposure-Response Relationships

Based on the data from NAVIGATOR, exposure-response relationships for any Grade 3 or 4 adverse reaction were observed at higher exposures with a faster time to onset for adverse reactions with increasing avapritinib exposure.

Cardiac Electrophysiology

The effect of AYVAKIT on the QTc interval was evaluated in an open-label, single-arm study in 27 patients administered dose of 300 mg or 400 mg (1.3 times the approved recommended dose) once daily. No large mean increase in QTc (i.e. > 20 ms) was detected at the mean steady state maximum concentration (C_{max}) of 899 ng/mL.

12.3 Pharmacokinetics

Avapritinib $C_{\max}$ and AUC increased proportionally over the dose range of 30 mg to 400 mg once daily (0.1 to 1.33 times the recommended dose).

At the recommended dosage of 300 mg once daily, the mean (CV%) steady state $C_{\max}$ of avapritinib was 813 ng/mL (52%) and the mean steady state area under the concentration-time curve (AUC_{0-24h}) was 15400 h•ng/mL (48%). Steady state concentration of avapritinib was reached by day 15 following daily dosing and the mean accumulation ratio was 3.1 to 4.6 after repeated dosing.

Absorption

The median time to peak concentration ($T_{\max}$) ranged from 2.0 to 4.1 hours following single doses of avapritinib 30 mg to 400 mg (0.1 to 1.33 times the approved recommended dose).

Effect of Food

The $C_{\max}$ of avapritinib was increased by 59% and the AUC_{0-INF} was increased by 29% when AYWAKIT 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

The mean apparent volume of distribution of avapritinib is 1200 L (43%). In vitro protein binding of avapritinib is 98.8% and is independent of concentration. The blood-to-plasma ratio is 0.95.

Elimination

The mean plasma elimination half-life of avapritinib was 32 hours to 57 hours following single doses of avapritinib 30 mg to 400 mg (0.1 to 1.33 times the approved recommended dose). The steady state mean apparent oral clearance of avapritinib is 19.5 L/h (48%).

Metabolism

Avapritinib is primarily metabolized by CYP3A4 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. Following oral administration of AYWAKIT 300 mg once daily in patients, the steady state AUC of M499 is approximately 80% of the AUC of avapritinib. M499 is not likely to contribute to efficacy at the recommended dose of avapritinib.

Excretion

Following a single oral dose of approximately 310 mg of radiolabeled avapritinib to healthy subjects, 70% of the radioactive dose was recovered in feces (11% unchanged) and 18% in urine (0.23% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of avapritinib were observed based on age (18 to 90 years), sex, race (White, Black, or Asian), body weight (39.5 to 156.3 kg), mild to moderate (CL_{cr} 30 to 89 mL/min estimated by Cockcroft-Gault) renal impairment, or mild (total bilirubin $\leq$ ULN and AST $>$ ULN or total bilirubin $>$ 1 to 1.5 times ULN and any AST) to moderate (total bilirubin $>$ 1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe renal impairment (CL_{cr} 15 to 29 mL/min), end-stage renal disease ($CL_{cr} <$ 15 mL/min), or severe hepatic impairment (total bilirubin $>$ 3 times ULN and any AST) on the pharmacokinetics of avapritinib is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Strong and Moderate CYP3A Inhibitors on Avapritinib: Coadministration of AYVAKIT 300 mg once daily with itraconazole 200 mg once daily (a strong CYP3A inhibitor) is predicted to increase avapritinib AUC by 600% at steady state.

Coadministration of AYVAKIT 300 mg once daily with fluconazole 200 mg once daily (a moderate CYP3A inhibitor) is predicted to increase avapritinib AUC by 210% at steady state [see *Drug Interactions (7.1)*].

Effect of Strong and Moderate CYP3A Inducers on Avapritinib: Coadministration of AYVAKIT 400 mg as a single dose with rifampin 600 mg once daily (a strong CYP3A inducer) decreased avapritinib C_{max} by 74% and AUC_{0-INF} by 92%.

Coadministration of AYVAKIT 300 mg once daily with efavirenz 600 mg once daily (a moderate CYP3A inducer) is predicted to decrease avapritinib C_{max} by 55% and AUC by 62% at steady-state [see *Drug Interactions (7.1)*].

Effect of Acid-Reducing Agents on Avapritinib: No clinically significant differences in the pharmacokinetics of avapritinib were identified when coadministered with gastric acid reducing agents in patients with GIST.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: In vitro studies indicate that avapritinib is a time-dependent inhibitor as well as an inducer of CYP3A at clinically relevant concentrations.

Avapritinib is an inhibitor of CYP2C9 at clinically relevant concentrations. 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. Avapritinib is a substrate of CYP3A.

M499 is an inhibitor of CYP3A, CYP2C8, or CYP2C9 at clinically relevant concentrations. M499 is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Avapritinib is an inhibitor of P-glycoprotein (P-gp), intestinal BCRP, MATE1, MATE2-K, and BSEP, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2. Avapritinib is not a substrate of P-gp or BCRP. The effect of M499 on transporter systems is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with avapritinib have not been conducted. Avapritinib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test). Avapritinib was clastogenic in the in vitro chromosome aberration test in human peripheral blood lymphocytes but not clastogenic in the in vivo rat bone marrow micronucleus test.

Avapritinib may impair fertility in humans. Administration of avapritinib to female rats for up to 3 months resulted in cystic degeneration of corpora lutea at doses greater than or equal to 5 mg/kg/day (approximately 1.3 times the human exposure based on AUC at the 300 mg dose). Administration of avapritinib to male dogs for up to 3 months resulted in hypo-spermatogenesis at doses greater than or equal to 7.5 mg/kg/day (approximately 0.4 times the human exposure based on AUC at the 300 mg dose).

13.2 Animal Toxicology and/or Pharmacology

In repeat dose toxicology studies, administration of avapritinib to rats and dogs for up to 3 months resulted in tremors at doses greater than or equal to 30 mg/kg/day (approximately 1.5 times the human exposure based on AUC at the 300 mg dose). Hemorrhage in the brain and spinal cord and choroid plexus edema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 0.4 times the human exposure based on AUC at the 300 mg dose).

An in vitro phototoxicity study in 3T3 mouse fibroblasts and an in vivo phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity.

14 CLINICAL STUDIES

14.1 Gastrointestinal Stromal Tumors

The efficacy of AYVAKIT was demonstrated in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label clinical trial. Eligible patients were required to have a confirmed diagnosis of GIST and an 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 overall response rate (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).

Patients with GIST Harboring a PDGFRA Exon 18 Mutation

Patients with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation were identified by local or central assessment using a PCR- or NGS-based assay. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA exon 18 mutations was 10.6 months (range: 0.3 to 24.9 months).

The study population characteristics were median age of 64 years (range: 29 to 90 years), 67% were male, 67% were White, 93% had an ECOG PS of 0-1, 98% had metastatic disease, 53% had largest target lesion >5 cm, and 86% had prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 5).

Efficacy results in patients with GIST harboring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations enrolled in NAVIGATOR are summarized in Table 5.

Table 5. Efficacy Results for Patients with GIST Harboring PDGFRA exon 18 mutations in NAVIGATOR

Efficacy Parameter	PDGFRA exon 18¹ N = 43	PDGFRA D842V N = 38
Overall Response Rate (95% CI)	84% (69%, 93%)	89% (75%, 97%)
Complete Response, n (%)	3 (7%)	3 (8%)
Partial Response, n (%)	33 (77%)	31 (82%)
Duration of Response	n=36	n=34
Median in months (range)	NR (1.9+, 20.3+)	NR (1.9+, 20.3+)
Patients with DOR ≥ 6-months, n (%) [*]	22 (61%)	20 (59%)

Abbreviations: CI=confidence interval; NR=not reached; NE=not estimable

+ Denotes ongoing response

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

* 11 patients with an ongoing response were followed < 6 months from onset of response.

16 HOW SUPPLIED/STORAGE AND HANDLING

AYVAKIT (avapritinib) tablets are supplied as follows:

- 100 mg, round, white film-coated tablet, printed with blue ink “BLU” on one side and “100” on the other side; available in bottles of 30 tablets (NDC 72064-110-30).
- 200 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “200” on the other side; available in bottles of 30 tablets (NDC 72064-120-30).
- 300 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “300” on the other side; available in bottles of 30 tablets (NDC 72064-130-30).

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Intracranial Hemorrhage

Advise patients to contact their healthcare provider immediately if experiencing neurological signs and symptoms that may be associated with intracranial hemorrhage [see *Warnings and Precautions* (5.1)].

Central Nervous System Effects

Advise patients and caretakers to notify their healthcare provider if they experience new or worsening CNS symptoms. Advise patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions [see *Warnings and Precautions* (5.2)].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [see *Use in Specific Populations* (8.3)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose [see *Use in Specific Populations* (8.3), *Nonclinical Toxicology* (13.1)].

Lactation

Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise females and males of reproductive potential that AYVAKIT may impair fertility [see *Use in Specific Populations* (8.3)].

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see *Drug Interactions* (7.1)].

Administration

Advise patients to take AYVAKIT on an empty stomach, at least 1 hour before and at least 2 hours after a meal [see *Dosage and Administration* (2.2)].

Manufactured for:

Blueprint Medicines Corporation, Cambridge, MA 02139, USA

PATIENT INFORMATION
AYVAKIT™ (aye' vah kit)
(avapritinib)
tablets, for oral use

What is AYVAKIT?

AYVAKIT is a prescription medicine used to treat adults with a certain type of stomach, bowel, or esophagus cancer called gastrointestinal stromal tumor (GIST) that cannot be treated with surgery or that has spread to other parts of the body (metastatic), and that is caused by certain abnormal platelet-derived growth factor receptor alpha (PDGFRA) genes. Your healthcare provider will perform a test to make sure that you have this abnormal PDGFRA gene and that AYVAKIT is right for you.

It is not known if AYVAKIT is safe and effective in children.

Before taking AYVAKIT, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. AYVAKIT can cause harm to your unborn baby.
Females who are able to become pregnant:
 - o Your healthcare provider should do a pregnancy test before you start treatment with AYVAKIT.
 - o You should use effective birth control (contraception) during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Talk to your healthcare provider about birth control methods that may be right for you.
 - o Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with AYVAKIT.
- **Males** with female partners who are able to become pregnant should use effective birth control (contraception) during treatment and for 6 weeks after the final dose of AYVAKIT.
- are breastfeeding or plan to breastfeed. It is not known if AYVAKIT passes into your breast milk. Do not breastfeed during treatment with AYVAKIT and for at least 2 weeks after the final dose of AYVAKIT. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. AYVAKIT may affect the way other medicines work, and certain other medicines may affect how AYVAKIT works. Talk to your healthcare provider prior to starting a new medicine.

How should I take AYVAKIT?

- Take AYVAKIT exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking AYVAKIT unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with AYVAKIT if you develop side effects.
- Take AYVAKIT 1 time each day.
- Take AYVAKIT tablet(s) on an empty stomach at least 1 hour before and at least 2 hours after a meal.
- If you miss a dose of AYVAKIT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.
- If you vomit after taking a dose of AYVAKIT, do not take an extra dose. Take your next dose at your next scheduled time.

What should I avoid while taking AYVAKIT?

- **Do not** drive or operate heavy machinery, if you have confusion or trouble thinking during treatment with AYVAKIT.

What are the possible side effects of AYVAKIT?**AYVAKIT may cause serious side effects, including:**

- **Bleeding in your brain.** Stop taking AYVAKIT and tell your healthcare provider if you develop any symptoms such as severe headache, vision problems, severe sleepiness, severe weakness on one side of your body.
- **Central nervous system (CNS) effects.** CNS side effects are common with AYVAKIT and can be severe. Tell your healthcare provider if you develop any new or worsening CNS symptoms including:
 - o forgetfulness
 - o confusion
 - o getting lost
 - o trouble thinking
 - o drowsiness
 - o dizziness
 - o trouble sleeping
 - o word finding problems
 - o seeing objects or hearing things that are not there (hallucinations)
 - o change in mood or behavior

Your healthcare provider may temporarily stop treatment or decrease your dose which may help your symptoms improve. If symptoms do not improve, your healthcare provider may permanently stop treatment with AYVAKIT.

The most common side effects of AYVAKIT include:

- fluid retention or swelling
- nausea
- tiredness
- muscle weakness
- vomiting
- diarrhea
- decreased appetite
- stomach area (abdominal) pain
- increased eye tearing
- constipation
- rash
- dizziness
- hair color changes

These are not all of the possible side effects of AYVAKIT.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AYVAKIT?

- Store AYVAKIT tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep AYVAKIT and all medicines out of the reach of children.**General information about the safe and effective use of AYVAKIT.**

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not take AYVAKIT for a condition for which it was not prescribed. Do not give AYVAKIT to other people, even if they have the same condition that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about AYVAKIT that is written for health professionals.

What are the ingredients in AYVAKIT?

Active ingredient: avapritinib

Inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

Film coat: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Blue printing ink: ammonium hydroxide, black iron oxide, esterified shellac, FD&C blue 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, and titanium dioxide.

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA

© 2020 Blueprint Medicines Corporation. All rights reserved.

For more information, go to www.AYVAKIT.com or call 1-888-258-7768.



100 72064-110-30

Each tablet contains 100 mg of avapritinib.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) (see USP Controlled Room Temperature).
Recommended Dosage: see Prescribing Information.
KEEP AWAY FROM CHILDREN

NDC 72064-110-30 30 Tablets

AYVAKIT™
(avapritinib) tablets

100 mg

For Oral Use

Rx only

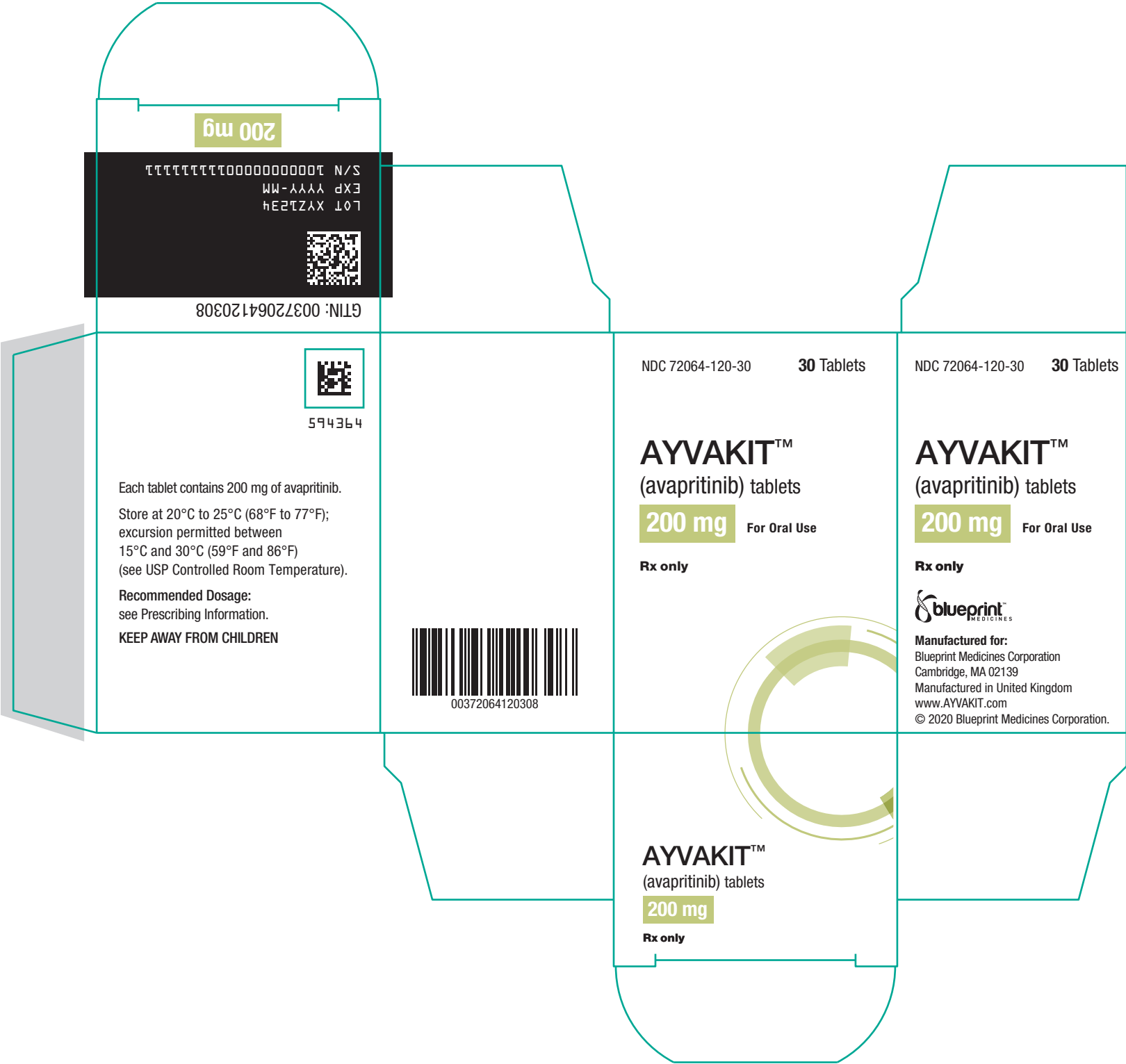


Manufacturer:
Boehringer Ingelheim Corp.
Chemical Development
10000 Boehringer Ingelheim Corp.

Manufacturer:
Boehringer Ingelheim Corp.
Chemical Development
10000 Boehringer Ingelheim Corp.

594356

LOT XYZ1234
EXP YYYY-MM





03372064120308

Each tablet contains 200 mg of avapritinib.
Store at 20° to 25° C (68° to 77° F); excursions permitted between 15° and 30° C (59° F and 86° F) [see USP Controlled Room Temperature].
Recommended Dosage: see Prescribing Information.
KEEP AWAY FROM CHILDREN

NDC 72064-120-30 30 Tablets

AYVAKIT™
(avapritinib) tablets

200 mg

For Oral Use

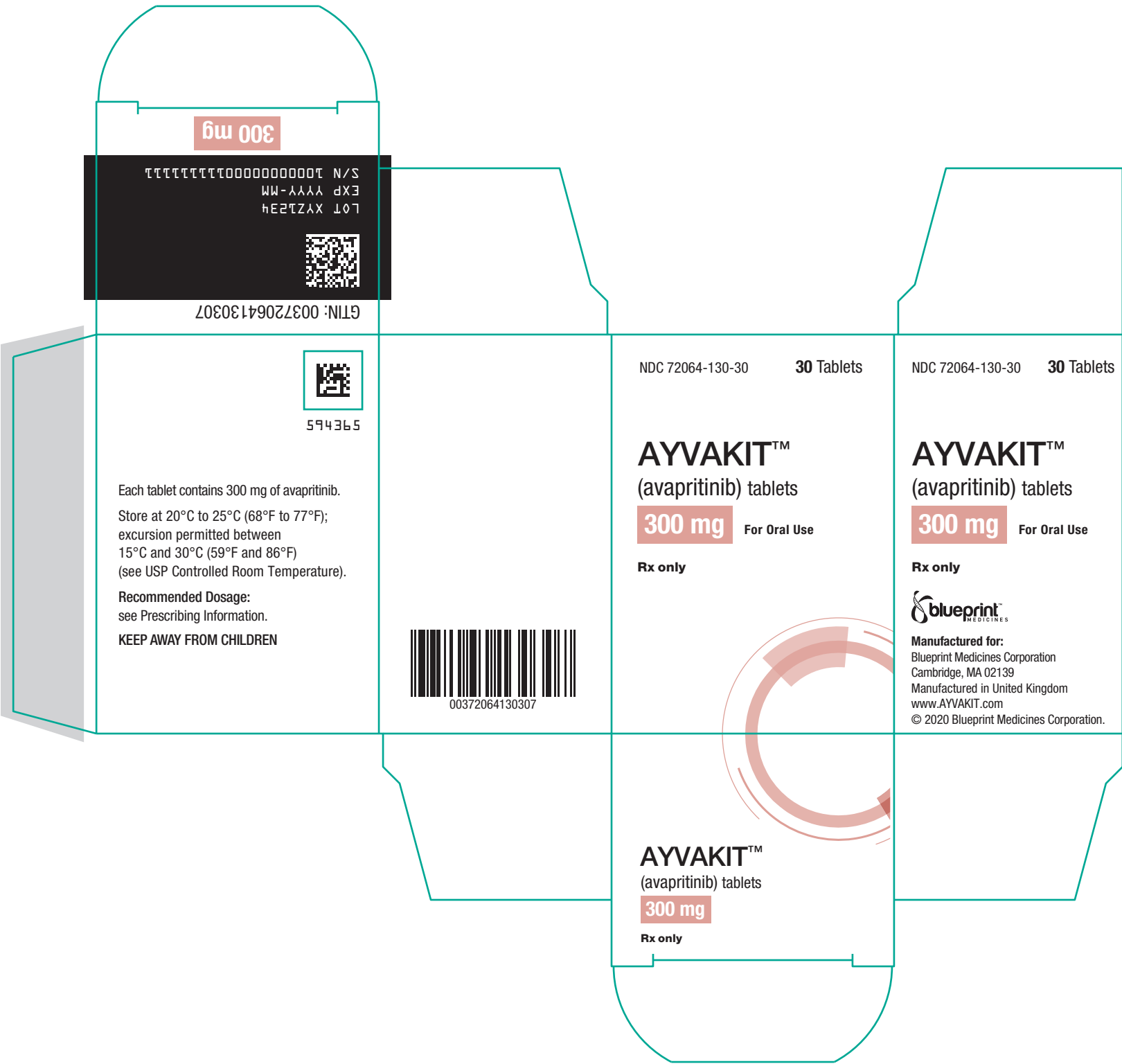
Rx only



Manufactured by: **Maruho Co. Ltd.** (USA) Inc. (Maruho)
1000 Main Street, Suite 200
Cambridge, MA 02142
© 2020 Maruho Co. Ltd. All rights reserved.

594359

LOT XYZ1234
EXP YYYY-MM





00372064-130-307
Each tablet contains 300 mg of avapritinib.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) as shown on the USP Controlled Room Temperature label.
Recommended Dosage: see Prescribing Information.
KEEP AWAY FROM CHILDREN

NDC 72064-130-30 30 Tablets
AYVAKIT™
(avapritinib) tablets
300 mg For Oral Use
Rx only



Manufactured for:
Avapritinib (AYVAKIT) Tablets
Dartmouth College, MA 02139
© 2020 by Avapritinib Pharmaceuticals, Inc.

594361

LOT XYZ1234
EXP YYYY-MM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC R THEORET
01/09/2020 02:20:11 PM