HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EKITNA safely and effectively. See full prescribing information for EKITNA.

EKITNA™ (bezuclastinib) tablets, for oral use
Initial U.S. Approval: 2026

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.

EKITNA, in combination with sunitinib, can cause hepatotoxicity. Monitor AST, ALT, and bilirubin before initiating and during treatment with, EKITNA. Interrupt, reduce the dose, or discontinue EKITNA based on severity *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

----------INDICATIONS AND USAGE----------
EKITNA is a kinase inhibitor indicated in combination with sunitinib for the treatment of adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- The recommended dosage of EKITNA is 600 mg orally once daily, in combination with sunitinib. (2.1)
- Administer EKITNA on an empty stomach at least 1 hour before or 2 hours after food. (2.1)
- See Full Prescribing Information for dosage modifications for adverse reactions. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Tablets: 75 mg (3)

----------CONTRAINDICATIONS----------
- None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of the potential risk to a fetus and to use effective non-hormonal contraception. (5.2, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions, (incidence ≥20%) including laboratory abnormalities are diarrhea, increased liver transaminases, hypertension, dysgeusia, nausea, hair color changes, fatigue, abdominal pain, vomiting, decreased appetite, stomatitis, gastroesophageal reflux disease, rash, dyspepsia, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities (≥5%) were increased alanine aminotransferase, decreased leukocytes, decreased neutrophils, decreased lymphocytes, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cogent Biosciences, Inc. at 1-844-264-3688 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- UGT1A1 Inhibitors: Avoid concomitant use. (7.1)
- UGT1A1 Inducers: Avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 11/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HEPATOTOXICITY

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

EKITNA, in combination with sunitinib, can cause hepatotoxicity. Monitor AST, ALT, and bilirubin before initiating, and during treatment with, EKITNA. Interrupt, reduce the dose, or discontinue EKITNA based on severity *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

EKITNA™, in combination with sunitinib, is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration

The recommended dosage of EKITNA is 600 mg orally once daily, in combination with sunitinib 37.5 mg orally once daily until disease progression or unacceptable toxicity occurs.

Administer EKITNA on an empty stomach at least 1 hour before or 2 hours after food.

Swallow tablets whole. Do not crush, break, or dissolve the tablets.

Missed Dose

If a dose is missed, skip the missed dose and take the next dose at the next scheduled time. Do not take 2 doses to make up for a missed dose.

Vomited Dose

If vomiting occurs after taking a dose, do not take another dose. Resume dosing at the next scheduled time.

2.2 Dosage Modifications for Adverse Reactions

The recommended dose reductions are provided in Table 1. Permanently discontinue EKITNA if patients are unable to tolerate a dosage of 300 mg once daily.

Table 1: Recommended Dose Reductions for EKITNA

Dose Reduction	Recommended Dosage
First	450 mg once daily
Second	300 mg once daily

The recommended dosage modifications for EKITNA for adverse reactions are provided in Table 2. Refer to the Prescribing Information for sunitinib for information about dosage modifications for adverse reactions associated with sunitinib.

Table 2: Recommended Dosage Modifications for EKITNA for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	ALT/AST >3 to 5 × ULN, or bilirubin >1.5 to 3 × ULN	Increase laboratory monitoring to once weekly and monitor for signs and symptoms of liver injury until recovered to baseline.
	ALT/AST 5 to 20 × ULN or bilirubin 3 to 10 × ULN	Withhold EKITNA until improvement to ≤Grade 1. If resolves in ≤28 days, resume at reduced dose. If not resolved within 28 days, permanently discontinue.
	ALT/AST >20 × ULN or bilirubin >10 × ULN	Permanently discontinue EKITNA.
	AST and/or ALT increases >3 × ULN and total bilirubin	Withhold EKITNA until resolved to ≤Grade 1 or baseline. If alternative

	increases >2 × ULN or INR >1.5 × ULN	cause is identified, resume EKITNA at a reduced dose after improvement to ≤Grade 1.
Other *[see Adverse Reactions (6.1)]*	Grade 3 or Grade 4	Withhold EKITNA until improvement to ≤Grade 1. Resume at same dose or reduced dose, as clinically appropriate.

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

3 DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg white, capsule-shaped tablet, debossed with "CGT" on one side and "75" on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

EKITNA, in combination with sunitinib, can cause hepatotoxicity.

In patients with GIST who received EKITNA at 600 mg orally once daily in combination with sunitinib at 37.5 mg orally once daily in PEAK (n=387), increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 43% of patients, including 8% Grade 3. Increased AST occurred in 38% of patients, including 3% Grade 3; increased ALT occurred in 40%, including 7% Grade 3; and increased bilirubin occurred in 13%, including 0.5% Grade 3. Of patients who experienced increased transaminases of any grade, 93% experienced their first increase within the first 4 months. Dose interruptions occurred in 13% of patients, dose reductions in 9% of patients, and discontinuations occurred in 1% of patients due to hepatotoxicity.

Monitor liver function tests (ALT, AST, and bilirubin) at baseline, during each four-week cycle, and as clinically indicated.

Interrupt, reduce the dose, or permanently discontinue EKITNA, in combination with sunitinib, based on the severity of liver transaminase elevations *[see Dosage and Administration (2.2)]*.

The safety of EKITNA in patients with baseline ALT or AST >2.5 × ULN or with >5.0 × ULN and liver metastases, or patients with total bilirubin >1.5 × ULN (or for patients with confirmed Gilbert's syndrome, direct bilirubin >1.5 × ULN and indirect bilirubin >3 × ULN) has not been established.

5.2 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, EKITNA can cause fetal harm when administered to pregnant women. Oral administration of bezuclastinib to pregnant animals during the period of organogenesis resulted in embryo-fetal mortality and structural abnormalities at or above the human exposure at the recommended dose based on the area under the curve (AUC).

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EKITNA and for 2 weeks after the last dose, since EKITNA can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with EKITNA and for 2 weeks after the last 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:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*.

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 pooled safety population described in Warnings and Precautions reflects exposure to EKITNA in combination with sunitinib in 387 patients who received EKITNA in combination with sunitinib, including 204 patients who received combination therapy during the randomized portion of PEAK Part 2, 128 additional patients who received EKITNA plus sunitinib during the crossover portion of PEAK Part 2, and an additional 55 patients who received combination therapy in other parts of the PEAK trial. Among 387 patients who received EKITNA with sunitinib, 67% were exposed for 6 months or longer, and 42% were exposed for greater than 1 year.

The safety of EKITNA in patients with GIST was evaluated in Part 2 of PEAK *[see Clinical Studies (14)]*. Patients received EKITNA 600 mg orally once daily with sunitinib 37.5 mg once daily (n=204) or sunitinib 37.5 mg once daily as a single agent (n=208).

Serious adverse reactions occurred in 34% of patients who received EKITNA in combination with sunitinib. Serious adverse reactions occurring in ≥2% of patients who received EKITNA in combination with sunitinib were anemia, ALT increase, pneumonia, and hemorrhage. Fatal adverse reactions occurred in 6 patients (1.5%), including hemorrhage (0.3%), abdominal sepsis (0.3%), cardiac arrest (0.3%), pneumonia (0.3%), sepsis (0.3%), and small intestinal obstruction (0.3%).

Permanent discontinuation due to an adverse reaction of EKITNA occurred in 15% of patients. Adverse reactions requiring permanent discontinuation of EKITNA which occurred in at least 2 patients are diarrhea (3 patients), decreased neutrophil count (3 patients), increased ALT (3 patients), increased AST (2 patients), and chronic kidney disease (2 patients).

Dosage interruptions due to adverse reactions of EKITNA occurred in 75% of patients. Adverse reactions requiring dosage interruption of EKITNA in ≥2% of patients were diarrhea, increased ALT, fatigue, rash, increased AST, nausea, vomiting, decreased neutrophil count, anemia, hypertension, abdominal pain, hemorrhage, pyrexia, increased bilirubin, COVID-19, stomatitis, musculoskeletal pain, dyspepsia, and decreased appetite.

Dosage reductions due to an adverse reaction of EKITNA occurred in 44% of patients. Adverse reactions requiring dosage reductions of EKITNA in ≥2% of patients were diarrhea, increased ALT, increased AST, fatigue, hypertension, rash, anemia, increased bilirubin, and neutropenia.

The most common adverse reactions (reported in ≥20% of patients) were diarrhea, increased liver transaminases, hypertension, dysgeusia, nausea, hair color changes, fatigue, abdominal pain, vomiting, decreased appetite, stomatitis, gastroesophageal reflux disease, rash, dyspepsia, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities (reported in ≥5% of patients) were increased ALT, decreased leukocytes, decreased neutrophils, decreased lymphocytes, and decreased hemoglobin.

Table 3 lists the adverse reactions that occurred in ≥20% of patients treated with EKITNA in combination with sunitinib in Part 2 of PEAK.

Table 3: Adverse Reactions Occurring in ≥20% of Patients with GIST Receiving EKITNA in Combination with Sunitinib with a Difference Between Arms of at ≥5% Compared to Sunitinib Alone in PEAK Part 2

Adverse Reactions*	**EKITNA (600 mg once daily) + sunitinib 37.5 mg once daily N=204 (%)**		**Sunitinib 37.5 mg once daily N=208 (%)**	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	78	8	66	7

Nausea	40	1	27	1
Vomiting	28	1	22	2
Gastroesophageal reflux disease	22	0	14	0
Dyspepsia	21	3	14	0
Nervous system disorders				
Dysgeusia†	48	0	25	0
Skin and subcutaneous tissue disorders				
Hair color changes	39	0	18	0
General disorders and administration site conditions				
Pyrexia	20	0	10	1
Edema†	21	1	14	0
Metabolism and nutrition disorders				
Decreased appetite	27	3	22	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
†Included related group terms.

Table 4 lists the laboratory abnormalities that occurred in at least 10% of patients treated with EKITNA in combination with sunitinib in Part 2 of PEAK.

Table 4: Laboratory Abnormalities Worsening From Baseline in ≥10% of Patients with GIST Receiving EKITNA in Combination with Sunitinib with a Difference Between Arms of ≥5% Compared to Sunitinib Alone in PEAK Part 2

Laboratory Abnormality	EKITNA (600 mg once daily) + sunitinib 37.5 mg once daily* (%)		Sunitinib 37.5 mg once daily* (%)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Aspartate aminotransferase increased	91	3	40	1
Alanine aminotransferase increased	88	10	26	1
Lactate dehydrogenase increased	53	0	39	0
Alkaline phosphatase increased	53	1	14	1
Albumin decreased	39	1	21	1
Total bilirubin increased	39	2	17	0
Creatinine increased	36	1	31	1
Potassium decreased	33	3	22	1
Magnesium decreased	32	1	17	1
Sodium decreased	30	3	21	1
Bicarbonate decreased	23	0	15	0
Hematology				
Lymphocytes decreased	55	12	38	7
Hemoglobin decreased	42	8	36	5
Eosinophils increased	17	0	8	0

*The denominator used to calculate the rate varied from 190 to 203 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 EKITNA

UGT1A1 Inhibitors

Avoid concomitant use of UGT1A1 inhibitors with EKITNA.

Bezuclastinib is a UGT1A1 substrate. Concomitant use with UGT1A1 inhibitors may increase bezuclastinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase EKITNA adverse reactions.

UGT1A1 Inducers

Avoid concomitant use of UGT1A1 inducers with EKITNA.

Bezuclastinib is a UGT1A1 substrate. Concomitant use with UGT1A1 inducers decreases bezuclastinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the effectiveness of EKITNA.

7.2 Effect of EKITNA on Other Drugs

Hormonal Contraceptives

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EKITNA and for 2 weeks after the last dose.

Bezuclastinib is a weak CYP3A inducer. Concomitant use of EKITNA with hormonal contraceptives may decrease their plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may lead to therapeutic failure.

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)]*, EKITNA can cause fetal harm when administered to pregnant women. There are no available data on the use of EKITNA in pregnant women to inform a drug-associated risk. Oral administration of bezuclastinib to pregnant animals during the period of organogenesis resulted in embryo-fetal mortality and structural abnormalities at or above the human exposure at the recommended dose based on AUC (*see Data*). Advise pregnant women and females of reproductive potential 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal toxicity study, oral administration of bezuclastinib to pregnant rats during the period of organogenesis resulted in embryo mortality (increased post-implantation loss) and embryo-fetal toxicities including visceral malformations in the abdomen (situs inversus), heart (dilation of the ductus arteriosus and pulmonary trunk, transposition of the great vessels, and membranous ventricular septal defect), and lung (fused left lobe) at 250 mg/kg/day (2.8 times the human exposure at the recommended dose based on AUC), as well as skeletal variations at doses ≥100 mg/kg/day (1.9 times the human exposure at the recommended dose based on AUC).

In an embryo-fetal toxicity study, oral administration of bezuclastinib to pregnant rabbits during the period of organogenesis resulted in fetal toxicities including visceral malformations in the heart (dilation of aorta and aortic arch, small right and misshapen A-V valves, and narrow pulmonary arch) at doses ≥35 mg/kg/day (0.8 times the human exposure at the recommended dose based on AUC).

In a pre- and postnatal study in rats, no adverse effects were observed in dams or offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of bezuclastinib or its metabolites in human milk or their effects on the breastfed child or milk production. When administered to lactating rats, bezuclastinib was detected in the plasma of nursing pups at low levels, suggestive of bezuclastinib in rat milk (*see Data*). When a drug is present in animal milk, it will likely be present in human milk. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EKITNA and for 2 weeks following the final dose.

Data

Animal Data

In a pre- and postnatal developmental study in rats, bezuclastinib was orally administered to lactating rats at doses of 20, 60, or 125 mg/kg/day. Bezuclastinib was detected in the plasma of nursing pups on postnatal Day 10, indicating the presence of bezuclastinib in rat milk.

8.3 Females and Males of Reproductive Potential

Based on animal data and mechanism of action, EKITNA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating EKITNA.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EKITNA and for 2 weeks after the final dose. EKITNA may render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with EKITNA and for 2 weeks after the final dose.

Infertility

Females

Based on results of animal studies, EKITNA may impair fertility in females. The reversibility of the effects on female fertility was not assessed *[see Nonclinical Toxicology (13.1)]*.

Males

Based on results of animal studies, EKITNA may impair fertility in males. The reversibility of the effects on male fertility was not assessed *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 204 patients in PEAK who received EKITNA in combination with sunitinib, 34% were between 65 to 74 years of age and 10% were 75 years of age or older. There were insufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

8.6 Use in Genomic Subgroups

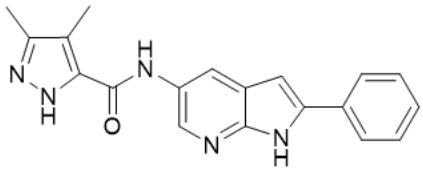
Bezuclastinib plasma concentrations are predicted to be elevated in UGT1A1 poor metabolizers *[see Clinical Pharmacology (12.5)]*, which may increase the risk of EKITNA adverse reactions. Avoid use in patients who are known poor metabolizers of UGT1A1.

The prevalence of UGT1A1 poor metabolizers is estimated to be 18% to 20% in Black or African American populations, 10% to 16% in White populations, and 9% to 19% in Asian populations.

11 DESCRIPTION

Bezuclastinib is a kinase inhibitor. The chemical name of bezuclastinib is 3,4-dimethyl-N-(2-phenyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazole-5-carboxamide. The molecular formula is: $C_{19}H_{17}N_5O$ and the molecular weight is 331.38 g/mol. It is a white to light yellow to light brown solid and has a pKa value of 2.86. Bezuclastinib is practically insoluble in water (at 37°C), ethanol, and isopropanol but soluble in dimethyl sulfoxide. The solubility of bezuclastinib is less than 0.003 mg/mL (at 37°C) and does not exhibit pH-dependent solubility over the physiological range in buffer solutions at pH 1 (0.1N HCl), 4.5 (acetate buffer), and 6.8 (phosphate buffer).

The chemical structure is:



EKITNA is intended for oral administration and is supplied as 75 mg tablets. The tablets contain the following inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bezuclastinib is a kinase inhibitor that inhibits mutated KIT proto-oncogene receptor tyrosine kinase (KIT), including exon 11, 17, and 18 KIT mutations. Bezuclastinib does not inhibit PDGFR alpha, FLT3, or kinase mutations in KIT exon 14.

12.2 Pharmacodynamics

Exposure-Response Relationships

An increased incidence in elevated liver transaminases was observed at higher bezuclastinib plasma concentrations.

Cardiac Electrophysiology

At the recommended EKITNA dose, a mean increase in the QTc interval >20 ms is unlikely.

12.3 Pharmacokinetics

Bezuclastinib pharmacokinetics were observed at steady state in patients with GIST at the approved recommended dosage and are presented as mean (coefficient of variation (CV%)) unless otherwise specified.

Bezuclastinib maximum concentration (C_{max}) is 1,220 ng/mL (82%) and total systemic exposure (AUC) is 26,900 ng•hr/mL (92%). Bezuclastinib steady-state C_{max} and AUC increase in a less than dose proportional manner over the dosage range of 300 mg (0.5 times the approved recommended dosage) to 600 mg once daily. Steady state is reached within 14 days and accumulation is approximately 3- to 4-fold.

Absorption

Bezuclastinib median (min, max) time to maximum plasma concentration (T_{max}) is 3 hours (1, 9 hours).

Effect of Food

Bezuclastinib AUC and C_{max} each increased 1.6-fold following administration with a high-fat meal (800 to 1000 calories, >50% fat) or a low-fat meal (400 to 500 calories, 25% fat).

Distribution

Bezuclastinib estimated steady-state apparent volume of distribution is 944 L (31%). Bezuclastinib plasma protein binding is greater than 99% and is not concentration dependent *in vitro*. Bezuclastinib blood-to-plasma ratio is approximately 0.4 to 0.8 *in vitro*.

Elimination

Bezuclastinib estimated elimination half-life is 53.4 (37%) hours with an apparent (oral) clearance of 12.4 L/h (45%).

Metabolism

Bezuclastinib is primarily metabolized by UGT1A1 with minor contribution from CYP3A4.

Excretion

Following a single oral dose of radiolabeled bezuclastinib 200 mg to healthy subjects, approximately 91% of the dose was recovered in the feces (76.5% unchanged) and 3.5% in the urine (0.0002% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of bezuclastinib were observed based on age (20 to 87 years), sex (41% female), race (60% White, 6% Black, 5.3% Asian), body weight (39 to 177 kg), eGFR 30 to 89 mL/min (estimated by the Chronic Kidney Disease Epidemiology Collaboration), and mild hepatic impairment (total bilirubin ≤ULN and AST>ULN or total bilirubin >1 to 1.5 times ULN and any AST). The effect of eGFR 15 to 29 mL/min and moderate (total bilirubin >1.5 to 3 times ULN and any AST) and severe (total bilirubin >3 times ULN and any AST) hepatic impairment on the bezuclastinib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

EKITNA with Sunitinib: No clinically significant differences in bezuclastinib AUC were observed when used concomitantly with sunitinib 37.5 mg orally once daily.

The combined AUC of sunitinib and its active metabolite decreased to 69% following concomitant use of EKITNA 600 mg once daily.

UGT1A1 Inducers: Bezuclastinib AUC decreased to 57% following concomitant use of rifampin (UGT1A1 inducer) 600 mg once daily for 28 days.

Acid Reducing Agents: No clinically significant differences in bezuclastinib pharmacokinetics were predicted following concomitant use of proton pump inhibitors, H2 antagonists, and antacids.

Other Drugs: No clinically significant differences in bezuclastinib pharmacokinetics were observed following concomitant use of itraconazole (strong CYP3A4 inhibitor).

CYP3A Substrates: Midazolam AUC decreased to 72% following concomitant use of EKITNA 600 mg once daily for 14 days.

In Vitro Studies

CYP450 Enzymes: Bezuclastinib does not induce CYP1A2 or CYP2B6. Bezuclastinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

UGT Enzymes: Bezuclastinib does not inhibit UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, UGT2B15, or UGT2B17.

Transporter Systems: Bezuclastinib is a substrate of BCRP but not of P-gp, OATP1B1, or OATP1B3. Bezuclastinib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, MATE1, or MATE2-K.

12.5 Pharmacogenomics

EKITNA is primarily metabolized by UGT1A1 *[see Clinical Pharmacology (12.3)]*. The gene encoding UGT1A1 has variants that affect UGT1A1 function. UGT1A1 poor metabolizers are individuals with

2 nonfunctional alleles (*e.g.*, *UGT1A1**28/*28, *UGT1A1**6/*6, *UGT1A1**37/*28), and as a result, little or no UGT1A1 enzyme activity. Administration of EKITNA 600 mg is likely to result in higher AUC and C_{max} in UGT1A1 poor metabolizers compared to that of UGT1A1 normal metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Bezuclastinib was not carcinogenic in a 6-month transgenic mouse study up to the highest dose evaluated at 90 mg/kg/day.

Mutagenesis

Bezuclastinib was not genotoxic in the bacterial reverse mutation (Ames) assay, an *in vitro* chromosome aberration assay, or an *in vivo* micronucleus assay in rats.

Impairment of Fertility

In a fertility and early embryonic development study, no effects on fertility or reproductive capacities were observed in male or female rats.

In a repeat-dose, 4-week study in mice, oral administration of bezuclastinib caused decreased sperm in the epididymis and atrophy in testes at 800 mg/kg/day (7.4 times the human exposure at the recommended dose based on AUC) as well as decreased number of corpora lutea and degeneration in the ovaries and atrophy of the uterus at doses as low as 200 mg/kg/day (5.5 times the human exposure at the recommended dose based on AUC).

14 CLINICAL STUDIES

The efficacy of EKITNA in combination with sunitinib was evaluated in the PEAK study [NCT05208047], a multipart, open-label, randomized, international, multicenter trial in patients with histologically confirmed, locally advanced, unresectable, or metastatic GIST with documented disease progression on or intolerance to imatinib. Patients were randomized to receive bezuclastinib 600 mg once daily in combination with sunitinib 37.5 mg once daily or sunitinib 37.5 mg once daily alone until disease progression. Randomization was stratified by imatinib intolerance and by *KIT* exon 9 mutation status.

The major efficacy endpoint was progression-free survival (PFS) as determined by blinded independent central review (BICR) using mRECIST v1.1. Additional efficacy endpoints included objective response rate (ORR) and overall survival (OS). Crossover to EKITNA in combination with sunitinib was allowed following BICR-confirmed progressive disease for patients randomized to sunitinib alone.

A total of 413 patients were randomized: 204 patients to EKITNA in combination with sunitinib arm and 209 to sunitinib. The median age of randomized patients was 63 years (range: 30 to 88 years); 64% of patients were male; 40% were White, 9% were Asian, 2.7% were Black, 0.2% were American Indian or Alaska Native, 1.0% identified as other, 0.7% were reported as unknown, and 46% were not reported; and 43% were not Hispanic or Latino, 10% were Hispanic or Latino, 0.7% reported as unknown, and 46% were not reported. Of patients randomized to sunitinib alone, 61% crossed over to receive EKITNA in combination with sunitinib after disease progression.

The trial demonstrated a statistically significant improvement in PFS and ORR for patients randomized to EKITNA in combination with sunitinib compared to those randomized to sunitinib alone. Efficacy results from PEAK are summarized in Table 5 and Figure 1. OS data were not mature at the time of the PFS analysis.

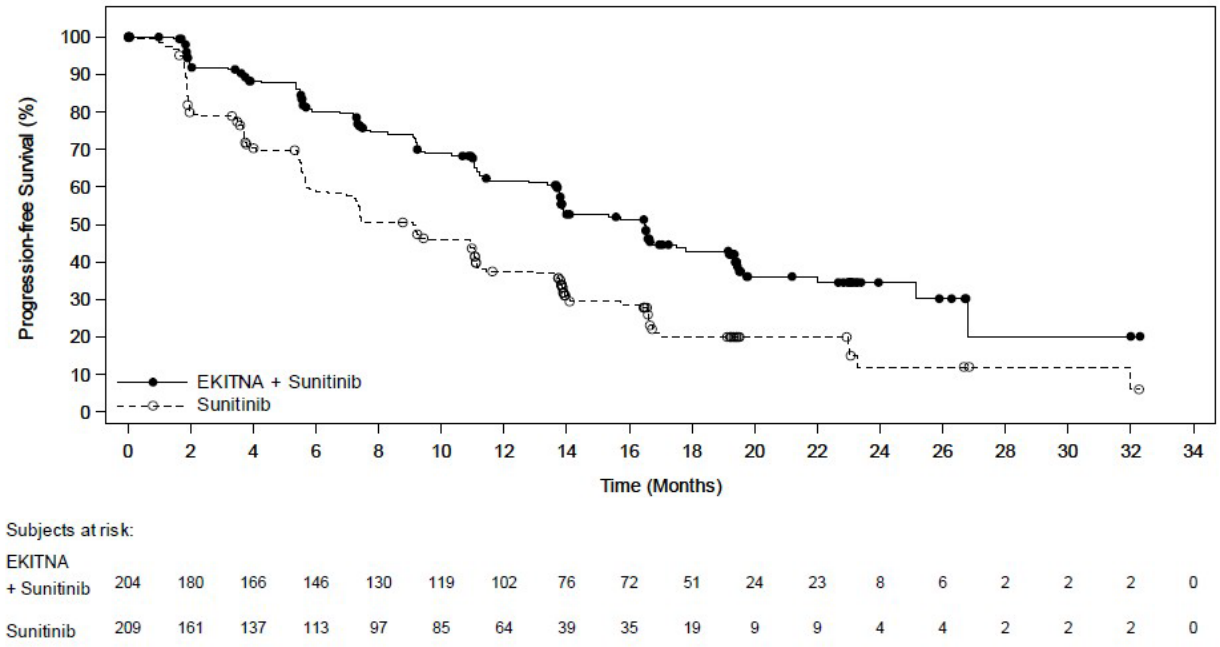
Table 5: Efficacy Results in PEAK

	EKITNA (N=204)	**Sunitinib (N=209)**
Progression-Free Survival*		
Number of patients with event (%)	106 (52)	148 (71)
Median, months (95% CI)	16.5 (13.8, 19.2)	9.2 (7.2, 11.0)

Hazard ratio (95% CI)†	0.50 (0.39, 0.65)	
2-sided p-value‡	<0.0001	
Overall Response Rate*		
ORR (%)	46	26
(95% CI)	(39, 53)	(20, 32)
Complete response, n (%)	13 (6)	4 (1.9)
Partial response, n (%)	80 (39)	50 (24)
2-sided p-value§	<0.0001	

CI = confidence interval; ORR = objective response rate
*Assessed per blinded independent central review.
†Based on a stratified Cox proportional hazards model.
‡Based on a stratified log-rank test.
§Based on a stratified Cochran-Mantel-Haenszel test.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival in PEAK



16 HOW SUPPLIED/STORAGE AND HANDLING

EKITNA (bezuclastinib) tablets are supplied in the following dose strength:

- 75 mg bezuclastinib, white, capsule-shaped, debossed with “CGT” on one side and “75” on the other.

EKITNA tablets are available as described below:

Tablet Strength (bezuclastinib)	Pack Configuration Description	NDC Number
75 mg	2 x 120-count bottle with child-resistant closure in a carton	84825-102-60
75 mg	2 x 90-count bottle with child-resistant closure in a carton	84825-102-61

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].

Store and dispense in the original bottle with desiccant. Keep bottle tightly closed to protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

Hepatotoxicity

Advise patients that hepatotoxicity can occur and that they will be monitored before starting treatment with EKITNA, during each four-week cycle and as clinically indicated *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EKITNA and for 2 weeks after the last dose *[see Use in Specific Populations (8.3)]*, since EKITNA can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with EKITNA and for 2 weeks after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

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

Infertility

Advise females and males of reproductive potential that EKITNA may impair fertility *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Administration

Advise patients to take EKITNA on an empty stomach, at least 1 hour before or 2 hours after a meal *[see Dosage and Administration (2.1)]*.

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PATIENT INFORMATION
EKITNA™ (ee kit' nah)
(bezuclastinib)
tablets, for oral use

What is the most important information I should know about EKITNA?
EKITNA can cause serious side effects, including:

- **Liver problems.** EKITNA in combination with sunitinib can cause liver problems that can be severe. Your healthcare provider will do blood tests to check your liver before you start and during treatment with EKITNA.

See **"What are the possible side effects of EKITNA?"** for more information about side effects.

What is EKITNA?
EKITNA is a prescription medicine used in combination with a medicine called sunitinib, to treat adults with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib.
It is not known if EKITNA is safe and effective in children.

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

- are pregnant or plan to become pregnant. EKITNA can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with EKITNA.
  - Use effective non-hormonal birth control (contraception) during treatment with EKITNA and for 2 weeks after your last dose.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with EKITNA.

  Males with female partners who are able to become pregnant:
  - Use effective birth control (contraception) during treatment with EKITNA and for 2 weeks after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if EKITNA passes into your breast milk. **Do not** breastfeed during treatment with EKITNA and for 2 weeks after your last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
EKITNA and certain other medicines can affect each other causing side effects and affect how the medicines work.

How should I take EKITNA?

- Take EKITNA exactly as your healthcare provider tells you to take it.
- Take EKITNA 1 time a day.
- Take EKITNA on an empty stomach, at least 1 hour before or 2 hours after food.
- Swallow EKITNA tablets whole. Do not crush, break, or dissolve the tablets.
- If you miss a dose, skip the missed dose and take your next dose at your scheduled time. **Do not** take 2 doses to make up the missed dose.
- If you vomit after taking a dose, do not take another dose. Take your next dose at your scheduled time.

What are the possible side effects of EKITNA?
EKITNA can cause serious side effects, including:

- See **"What is the most important information I should know about EKITNA?"**

The most common side effects of EKITNA include:

- diarrhea
- increase in liver function tests
- high blood pressure
- change in taste
- nausea
- change in hair color
- tiredness
- stomach area (abdominal) pain
- vomiting
- decreased appetite
- sores in the mouth
- heartburn (GERD)
- rash
- indigestion
- fever

The most common severe abnormal blood tests include increased liver enzymes, decreased white blood cell counts, and decreased red blood cell counts.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with EKITNA if you develop certain side effects.
EKITNA may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.
These are not all of the possible side effects of EKITNA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Cogent Biosciences, Inc. by calling 1-844-264-3688.

How should I store EKITNA?

- Store EKITNA at room temperature between 68°F to 77°F (20°C to 25°C).
- Close the bottle tightly after each dose.
- The bottle contains a desiccant to help keep the tablets dry (protect from humidity). Keep the desiccant in the bottle.
- EKITNA bottle comes with a child-resistant closure.

Keep EKITNA and all medicines out of the reach of children.

General information about the safe and effective use of EKITNA.

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

What are the ingredients in EKITNA?

Active ingredient: bezuclastinib

Inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, mannitol, microcrystalline cellulose, and sodium stearyl fumarate

Distributed by Cogent Biosciences, Inc., 180 Third Avenue, 4th Floor, Waltham, MA 02451
Made in Spain.
For more information, call 1-844-264-3688 or visit www.EKITNA.com.
This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 11/2026

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