QUIZAR

Quizartinib Dihydrochloride INN

Everest

COMPOSITION

QUIZAR 17.7 tablet: Each film coated tablet contains Quizartinib Dihydrochloride INN equivalent to Quizartinib 17.7 mg.

QUIZAR 26.5 tablet: Each film coated tablet contains Quizartinib Dihydrochloride INN equivalent to Quizartinib 26.5 mg.

PHARMACOLOGY

Quizartinib is a small molecule inhibitor of the receptor tyrosine kinase FLT3. Quizartinib and its major active metabolite AC886 bind to the adenosine triphosphate (ATP) binding domain of FLT3 with comparable affinity, and both had 10-fold lower affinity towards FLT3-ITD mutation compared to FLT3 in a binding assay. Quizartinib and AC886 inhibited FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting downstream FLT3 receptor signaling and blocking FLT3-ITD-dependent cell proliferation. Quizartinib showed antitumor activity in a mouse model of FLT3-ITD-dependent leukemia.

INDICATION

Quizartinib is a kinase inhibitor indicated in combination with standard Cytarabine and Anthracycline induction and Cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive.

Limitations of Use

Quizartinib is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with Quizartinib in this setting has not been demonstrated.

DOSAGE AND ADMINISTRATION

Patients Selection

Select patients for the treatment of AML with Quizartinib based on the presence of FLT3-ITD mutation positivity.

Recommended Dosage

A treatment course consists of up to 2 cycles of Quizartinib in combination with induction Cytarabine and Anthracycline, up to 4 cycles of Quizartinib in combination with high-dose Cytarabine consolidation, and up to 36 cycles of Quizartinib as maintenance therapy or until disease progression or unacceptable toxicity. Quizartinib maintenance therapy should be initiated following consolidation chemotherapy upon blood count recovery of absolute neutrophil count >500/mm3 and platelet count >50,000/mm3.

• See Table 1 for the recommended dosage of Quizartinib by phase of therapy.

Table 1: Quizartinib Dosage Regimen

Quizartinib Initiation	Induction*	Consolidation†	Maintenance
	Starting on Day 8 (for 7+3 regimen)‡	Starting on Day 6	Starting on Day 1
Dose	35.4 mg orally once daily	35.4 mg orally once daily	• Administer 26.5 mg orally once daily Days 1 through 14 of the first cycle if QTcF is less than or equal to 450 ms. • Increase the dose to 53 mg once daily on Day 15 of the first cycle if QTcF is less than or equal to 450 ms. Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration (28-day cycles)	Two weeks in each cycle (Days 8 to 21)	Two weeks in each cycle (Days 6 to 19)	• Once daily with no break between cycles for up to 36 cycles

* Patients can receive up to 2 cycles of induction.
† Patients can receive up to 4 cycles of consolidation.
‡ For 5 + 2 regimen as the second induction cycle, Quizartinib will be given on Days 6 to 19.

For patients who proceed to hematopoietic stem cell transplantation (HSCT), Quizartinib should be stopped 7 days before the start of a conditioning regimen.

Administer Quizartinib orally with or without food at approximately the same time each day. Swallow tablets whole. Do not cut, crush, or chew the tablets. If a dose of Quizartinib is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of Quizartinib is missed or not taken at the usual time, administer the dose as soon as possible on the same day and return to the usual schedule the following day. The patient should not take two doses on the same day.

Monitoring and Dosage Modifications for Adverse Reactions

Initiate Quizartinib only if QTcF is less than or equal to 450 ms.

During induction and consolidation, perform ECGs prior to initiation and then once weekly during Quizartinib treatment or more frequently as clinically indicated.

During maintenance, perform ECGs prior to initiation, once weekly for at least the first month following dose initiation and escalation, and thereafter as clinically indicated. Escalate the dose only if QTcF is less than or equal to 450 ms.

Correct electrolyte abnormalities (hypokalemia and hypomagnesemia), and if possible, avoid concomitant administration of drugs that prolong the QT interval.

For recommended dosage modifications due to adverse reactions, see Table 2. For dosage adjustments due to adverse reactions, see Table 3.

Table 2: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Recommended Action
QTcF between 450 ms and 480 ms (Grade 1)	• Continue Quizartinib dose.
QTcF between 481 ms and 500 ms (Grade 2)	• Reduce the dose of Quizartinib (see Table 3) without interruption. • Resume Quizartinib at the previous dose in the next cycle if QTcF has decreased to less than 450 ms. Monitor the patient closely for QT prolongation during the first cycle at the increased dose.
QTcF greater than 500 ms (Grade 3)	• Interrupt Quizartinib. • Resume Quizartinib at a reduced dose (see Table 3) when QTcF returns to less than 450 ms. • Maintain the 26.5 mg once daily dose during maintenance if QTcF greater than 500 ms was observed during induction or consolidation.
Recurrent QTcF greater than 500 ms (Grade 3)	• Permanently discontinue Quizartinib if QTcF greater than 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medications).
Torsades de pointes, polymorphic ventricular tachycardia, signs/symptoms of lifethreatening arrhythmia (Grade 4)	• Permanently discontinue Quizartinib.
Grade 3 or 4 nonhematologic adverse reactions	• Interrupt Quizartinib. • Resume treatment at the previous dose if adverse reaction improves to Grade 1 or less. • Resume treatment at a reduced dose (see Table 3) if adverse reaction improves to Grade 2. • Discontinue if Grade 3 or 4 adverse reaction persists beyond 28 days.
Grade 3 or 4 hypokalemia (<3 mmol/L) or hypomagnesemia (<0.4 mmol/L or <0.9 mg/dL)	• Interrupt Quizartinib. • Correct hypokalemia and hypomagnesemia according to institutional guidelines. • Quizartinib may be restarted at the previous dose when the adverse reaction improves to Grade 2 or less without symptoms.
Grade 4 neutropenia or thrombocytopenia after achieving remission*	• Reduce Quizartinib dose (see Table 3).

Grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

* Recommend bone marrow evaluation.

Table 3: Recommended Dosage Adjustments for Adverse Reactions for Quizartinib

Current Dosages	Modified Dosages
53 mg once daily	35.4 mg once daily
35.4 mg once daily	26.5 mg once daily
26.5 mg once daily	Interrupt
17.7 mg once daily	Interrupt

Dosage Modifications for Strong CYP3A Inhibitors
Reduce the dosage of Quizartinib when used concomitantly with strong CYP3A inhibitors as shown in Table 4. If the current dosage is 17.7 mg once daily, interrupt Quizartinib treatment for the duration of strong CYP3A inhibitor use. After discontinuation of a strong CYP3A inhibitor for 5 half-lives, resume the Quizartinib dose that was taken before initiating the strong inhibitor.

Table 4: Dosage Adjustments for Concomitant Use with Strong CYP3A Inhibitors

Current Dosages	Modified Dosages
53 mg once daily	26.5 mg once daily
35.4 mg once daily	17.7 mg once daily
26.5 mg once daily	17.7 mg once daily

CONTRAINDICATIONS
Quizartinib is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes.

WARNINGS AND PRECAUTIONS
QT Prolongation, Torsades de Pointes, and Cardiac Arrest Monitor electrocardiograms and levels of serum electrolytes. Reduce, interrupt, or permanently discontinue Quizartinib as appropriate.

Embryo-Fetal Toxicity
Quizartinib can cause fetal harm. Advise females of reproductive potential and males with female partners of reproductive potential of potential risk to a fetus and to use effective contraception.

Quizartinib REMS
Quizartinib is available only through a restricted distribution program under a REMS called the Quizartinib REMS because of the serious risk of QT prolongation, torsades de pointes, and cardiac arrest.

Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, Quizartinib can cause fetal harm when administered to a pregnant woman.

ADVERSE REACTIONS
The most common (>20%) adverse reactions, including laboratory abnormalities, are lymphocytes decreased, potassium decreased, albumin decreased, phosphorus decreased, alkaline phosphatase increased, magnesium decreased, febrile neutropenia, diarrhea, mucositis, nausea, calcium decreased, abdominal pain, sepsis, neutropenia, headache, creatine phosphokinase increased, vomiting, and upper respiratory tract infection.

USE IN SPECIFIC POPULATIONS
Pregnancy
Based on findings from animal studies and its mechanism of action, Quizartinib can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on Quizartinib use in pregnant women to evaluate for a drug-associated risk.

Lactation
There are no data on the presence of quizartinib or its metabolites in human milk, or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Quizartinib and for one month after the last dose.

Females and Males of Reproductive Potential
Quizartinib can cause embryo-fetal harm when administered to pregnant women.

Pregnancy Testing
Verify pregnancy status in females of reproductive potential within seven days before starting treatment with Quizartinib.

Contraception
Females
Advise female patients of reproductive potential to use effective contraception during treatment with Quizartinib and for 7 months after the last dose.

Males
Based on genotoxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment with Quizartinib and for 4 months after the last dose.

Infertility
Females
Based on findings from animal studies, Quizartinib may impair female fertility. These effects on fertility were reversible.

Males
Based on findings from animal studies, Quizartinib may impair male fertility. These effects on fertility were reversible.

Pediatric Use
Safety and effectiveness of Quizartinib have not been established in pediatric patients.

Geriatric Use
No overall differences in safety or efficacy were observed between patients 65 years of age and older and younger adult patients in the clinical study.

Renal Impairment
No dosage adjustment is recommended in patients with mild to moderate renal impairment (i.e., estimated creatinine clearance [CLcr] by Cockcroft-Gault equation: CLcr 30 to 89 mL/min). Quizartinib has not been studied in patients with severe renal impairment (CLcr <30 mL/min).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Class A or total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1 to 1.5 times ULN and any value for AST) or moderate hepatic impairment (Child-Pugh Class B or total bilirubin >1.5 to 3 times ULN and any value for AST). Quizartinib has not been studied in patients with severe (Child-Pugh Class C or total bilirubin >3 times ULN and any value for AST) hepatic impairment.

OVERDOSE
In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS
Strong CYP3A Inhibitors
Quizartinib is a CYP3A substrate. Concomitant use of Quizartinib with a strong CYP3A inhibitor increases Quizartinib systemic exposure which may increase the risk of Quizartinib adverse reactions.

QT Interval Prolonging Drugs
Quizartinib Prolongs the QT/QTc interval.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30^0 C in a cool and dry place. Keep away from light. Keep out of the reach of children.

How Supplied
QUIZAR 17.7 tablet: Each HDPE container contains 28 tablets (Each film coated tablet contains Quizartinib Dihydrochloride INN equivalent to Quizartinib 17.7 mg), a silica gel desiccant and polyester coil with child resistant closure.

QUIZAR 26.5 tablet: Each HDPE container contains 28 tablets (Each film coated tablet contains Quizartinib Dihydrochloride INN equivalent to Quizartinib 26.5 mg), a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
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