Gilternib

Gilteritinib 40 mg tablets

Everest

COMPOSITION

Gilternib tablet: Each film coated tablet contains Gilteritinib Fumarate INN equivalent to Gilteritinib 40 mg.

PHARMACOLOGY

Mechanism of Action

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

Pharmacodynamics In patients with relapsed or refractory AML administered Gilteritinib 120 mg, substantial (>90%) inhibition of FLT3 phosphorylation was rapid (within 24 hours after first dose) and sustained, as characterized by an ex vivo plasma inhibitory activity (PIA) assay.

Cardiac Electrophysiology

The effect of GILTERITINIB 120 mg once a day on the QTc interval has been evaluated in patients, which showed an absence of large mean increases (i.e., 20 msec) in the QTc interval. Of 317 patients with a post-baseline QTc measurement on treatment with Gilteritinib at 120 mg in clinical trials, 4 patients (1.3%) experienced a QTcF >500 msec. Additionally, across all doses 2.3% of patients with relapse/refractory AML had a maximum post-baseline QTcF interval >500 msec.

Pharmacokinetics

The following pharmacokinetic parameters were observed following administration of Gilteritinib 120 mg once daily, unless otherwise specified. Gilteritinib exposure (Cmax and AUC24) increases proportionally with once daily doses ranging from 20 mg to 450 mg (0.17 to 3.75 times the recommended dosage) in patients with relapsed or refractory AML. Gilteritinib mean (±SD) steady-state Cmax is 374 ng/mL (±190) and AUC24 is 6943 ng.hr/mL (±3221). Steady-state plasma levels are reached within 15 days of dosing with an approximate 10-fold accumulation.

Absorption

The time to maximum Gilteritinib concentration (tmax) observed is approximately between 4 and 6 hours postdose in the fasted state.

Effect of Food

In healthy adults administered a single Gilteritinib 40 mg dose (0.3 times the recommended dosage), Gilteritinib Cmax decreased by 26% and AUC decreased by less than 10% when co-administered with a high-fat meal (approximately 800 to 1,000 total calories with 500 to 600 fat calories, 250 carbohydrate calories, 150 protein calories) compared to a fasted state. Median tmax was delayed 2 hours when Gilteritinib was administered with a high-fat meal.

Distribution

The population mean (%CV) estimates of apparent central and peripheral volume of distribution were 1092 L (9.22%) and 1100 L (4.99%), respectively, which may indicate extensive tissue distribution. In vivo, Gilteritinib is approximately 94% bound to human plasma proteins. In vitro, Gilteritinib is primarily bound to human serum albumin.

Elimination

The estimated half-life of Gilteritinib is 113 hours, and the estimated apparent clearance is 14.85 L/h.

Metabolism

Gilteritinib is primarily metabolized via CYP3A4 in vitro. At steady state, the primary metabolites in humans include M17 (formed via N-dealkylation and oxidation), M16 and M10 (both formed via N-dealkylation). None of these 3 metabolites exceeded 10% of overall parent exposure.

Excretion

After a single radiolabeled dose, Gilteritinib is excreted in feces with 64.5% of the total administered dose recovered in feces. Of the total radiolabeled dose of Gilteritinib, 16.4% was recovered in urine as unchanged drug and metabolites.

Specific Populations

Pregnancy

Based on findings from animal studies and its mechanism of action, Gilteritinib can cause fetal harm when administered to a pregnant woman. There are no available data on Gilteritinib use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of Gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC24) approximately 0.4 times the AUC24 in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

Lactation

Risk Summary

There are no data on the presence of Gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled Gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, Gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with Gilteritinib and for at least 2 months after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating Gilteritinib treatment. Contraception Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of Gilteritinib.

Males

Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of Gilteritinib.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 319 patients in clinical studies of Gilteritinib, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

Drug Interaction Studies

Clinical Studies

Combined P-gp and Strong CYP3A Inducers: Gilteritinib Cmax decreased approximately 30% and AUC decreased approximately 70% when co-administered with rifampin (a combined P-gp and strong CYP3A inducer).

Strong CYP3A Inhibitors: Gilteritinib Cmax increased approximately 20% and AUC increased approximately 120% when co-administered with itraconazole (a strong CYP3A inhibitor).

Moderate CYP3A Inhibitors: Gilteritinib Cmax increased approximately 16% and AUC increased approximately 40% when co-administered with fluconazole (a moderate CYP3A inhibitor).

CYP3A Substrates: Midazolam (a CYP3A substrate) Cmax and AUC increased approximately 10% when co-administered with Gilteritinib. MATE1 Substrates: Cephalexin (a MATE1 substrate) Cmax and AUC decreased by less than 10% when co-administered with Gilteritinib.

In Vitro Studies

Gilteritinib inhibits human 5HT2B receptor or sigma nonspecific receptors, which may reduce the effects of drugs that target these receptors such as escitalopram, fluoxetine and sertraline. Gilteritinib is a substrate of P-gp transporter and has the potential to inhibit breast cancer resistance protein (BCRP) and organic cation transporter 1 (OCT1) transporters.

INDICATIONS AND USAGE

Gilteritinib is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the treatment of AML with Gilteritinib based on the presence of FLT3 mutations in the blood or bone marrow. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available.

Recommended Dosage

The recommended starting dose of Gilteritinib is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response. Do not break or crush Gilteritinib tablets. Administer Gilteritinib tablets orally about the same time each day. If a dose of Gilteritinib is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

Dose Modification

Assess blood counts and blood chemistries, including creatine phosphokinase, prior to the initiation of Gilteritinib, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with Gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles.

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CONTRAINDICATIONS
Gilteritinib is contraindicated in patients with hypersensitivity to Gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials.

WARNINGS AND PRECAUTIONS
Differentiation Syndrome.
Of 319 patients treated with Gilteritinib in the clinical trials, 3% experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with Gilteritinib included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after Gilteritinib initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of Gilteritinib. If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt Gilteritinib until signs and symptoms are no longer severe.

Posterior Reversible Encephalopathy Syndrome
Of 319 patients treated with Gilteritinib in the clinical trials, 1% experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of Gilteritinib. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue Gilteritinib in patients who develop PRES.

Prolonged QT Interval
Gilteritinib has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with Gilteritinib in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with Gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce Gilteritinib dosage in patients who have a QTcF >500 msec. Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during Gilteritinib administration.

Pancreatitis
Of 319 patients treated with Gilteritinib in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of Gilteritinib in patients who develop pancreatitis.

Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, Gilteritinib can cause embryo-fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of Gilteritinib to pregnant rats during organogenesis caused embryo-fetal lethality, suppressed fetal growth and teratogenicity at maternal exposures (AUC24) approximately 0.4 times the AUC24 in patients receiving the recommended dose. Advise females of reproductive potential to use effective contraception during treatment with Gilteritinib and for at least 6 months after the last dose of Gilteritinib. Advise males with female partners of reproductive potential to use effective contraception during treatment with Gilteritinib and for at least 4 months after the last dose of Gilteritinib. Pregnant women, patients becoming pregnant while receiving Gilteritinib or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

SIDE EFFECTS
The following adverse drug reactions are described elsewhere in the labeling:

- Fever
- Cough
- Trouble breathing
- Rash
- Dizziness or lightheadedness
- Rapid weight gain
- Swelling of your arms or legs
- Decreased urination

DRUG INTERACTIONS
Effect of Other Drugs on Gilteritinib.
Combined P-gp and Strong CYP3A Inducers Concomitant use of Gilteritinib with a combined P-gp and strong CYP3A inducer decreases Gilteritinib exposure which may decrease Gilteritinib efficacy. Avoid concomitant use of Gilteritinib with combined P-gp and strong CYP3A inducers.

Strong CYP3A Inhibitors
Concomitant use of Gilteritinib with a strong CYP3A inhibitor increases Gilteritinib exposure. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for Gilteritinib adverse reactions. Interrupt and reduce Gilteritinib dosage in patients with serious or life-threatening toxicity.

Effect of GILTERITINIB on Other Drugs
Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor Concomitant use of Gilteritinib may reduce the effects of drugs that target the 5HT2B receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with Gilteritinib unless their use is considered essential for the care of the patient.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action, Gilteritinib can cause fetal harm when administered to a pregnant woman.

There are no available data on Gilteritinib use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of Gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC24) approximately 0.4 times the AUC24 in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

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Females and Males of Reproductive Potential

Pregnancy testing
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Contraception Females
Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of Gilteritinib.

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

PHARMACEUTICAL INFORMATION
How Supplied
Gilternib tablet: Each HDPE container contains 90 film-coated tablets (each tablet contains 40 mg Gilteritinib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com

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