Biganib

Brigatinib INN 90 mg & 180 mg Tablet

COMPOSITION

Biganib: Each film coated tablet contains Brigatinib INN 90 mg.

Biganib-180: Each film coated tablet contains Brigatinib INN 180 mg.

PHARMACOLOGY

Mechanism of Action: Brigatinib is a tyrosine kinase inhibitor with in vitro activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1 R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. Brigatinib also inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.

Pharmacodynamics: Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Pharmacokinetics:

Absorption: Following administration of single oral doses of Brigatinib of 30 to 240 mg, the median time to peak concentration (Tmax) ranged from 1 to 4 hours.

Distribution: Brigatinib is 91% bound to human plasma proteins and the binding is not concentration-dependent in vitro. The blood-to-plasma concentration ratio is 0.69. Following oral administration of Brigatinib 180 mg once daily, the mean apparent volume of distribution (Vz/F) of Brigatinib at steady-state was 307L.

Elimination: Following oral administration of Brigatinib 180 mg once daily, the mean apparent oral clearance (CL/F) of Brigatinib at steady-state is 8.9L/h and the mean plasma elimination half-life is 25 hours.

Metabolism: Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 in vitro. Following oral administration of a single 180 mg dose of radiolabeled Brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged Brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components.

Excretion: Following oral administration of a single 180 mg dose of radiolabeled Brigatinib to healthy subjects, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged Brigatinib represented 41 % and 86% of the total radioactivity in feces and urine, respectively.

INDICATIONS

Brigatinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC).

Dosage and Administration: The recommended dosing regimen for Brigatinib is: 90 mg orally once daily for the first 7 days; If 90 mg is tolerated during the first 7 days, the dose should be increased to 180 mg orally once daily. Brigatinib should be administered until disease progression or unacceptable toxicity. If Brigatinib is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. Brigatinib may be taken with or without food. Patients should be instructed to swallow tablets whole. Tablets should not be crushed or chewed. If a dose of Brigatinib is missed or vomiting occurs after taking a dose, an additional dose should not be administered and take the next dose of Brigatinib should be taken at the scheduled time. Or, as directed by the registered physician.

Dose Modification for Adverse Reactions:

Dosage	Dosage Reduction		
	First	Second	Third
90 mg once daily	60 mg once daily	permanently discontinue	N/A
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

SIDE EFFECTS

- Interstitial Lung Disease (ILD)/Pneumonitis
- Hypertension
- Bradycardia
- Visual Disturbance
- Creatine Phosphokinase (CPK) Elevation
- Pancreatic Enzyme Elevation
- Hyperglycemia
- Hepatotoxicity
- Photosensitivity

CONTRAINDICATION

It is contraindicated in patients with known hypersensitivity to Brigatinib or any other components of this product.

USE IN PREGNANCY AND LACTATION

Brigatinib can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of Brigatinib in pregnant women. Pregnant women should be advised of the potential risk to a fetus.

Lactation: There are no data regarding the secretion of Brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, lactating women should not advise to breastfeed during treatment with Brigatinib and for 1 week following the final dose.

Females and Males of Reproductive Potential: Pregnancy Testing: Pregnancy status should be verified in females of reproductive potential prior to initiating Brigatinib.

Females: Females of reproductive potential should be advised to use effective contraception during treatment with Brigatinib and for at least 4 months after the final dose.

Males: Because of the potential for genotoxicity, males with female partners of reproductive potential should be advised to use effective contraception during treatment with Brigatinib and for at least 3 months after the final dose.

Infertility: Based on findings in male reproductive organs in animals, Brigatinib may cause reduced fertility in males.

PEDIATRIC USE

The safety and efficacy of Brigatinib in pediatric patients have not been established.

DRUG INTERACTION

Effect of Other Drugs on Brigatinib

Strong or Moderate CYP3A Inhibitors: Coadministration of Brigatinib with a strong or moderate CYP3A inhibitor increased Brigatinib plasma concentrations, which may increase the incidence of adverse reactions. So coadministration of Brigatinib with strong or moderate CYP3A inhibitors should be avoided. If coadministration of strong or moderate CYP3A inhibitors cannot be avoided, modify dose as recommended.

Strong or Moderate CYP3A Inducers: Coadministration of Brigatinib with a strong or moderate CYP3A inducer decreased Brigatinib plasma concentrations, which may decrease the efficacy of Brigatinib. So coadministration of Brigatinib with strong or moderate CYP3A inducers should be avoided. If coadministration of moderate CYP3A inducers cannot be avoided, modify dose as recommended.

PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with Brigatinib. It should be withheld in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). Brigatinib should be discontinued permanently for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

Hypertension: Hypertension was reported in 11% of patients in the 90 mg group who received Brigatinib and 21% of patients in the 90mg→180mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Blood pressure should be controlled prior to treatment with Brigatinib. Blood pressure should be monitored after 2 weeks and at least monthly thereafter during treatment with Brigatinib. It should be withheld for Grade 3 hypertension despite optimal antihypertensive therapy. Permanent discontinuation of treatment should be considered with Brigatinib for Grade 4 hypertension or recurrence of Grade 3 hypertension. Caution should be used when administering Brigatinib in combination with antihypertensive agents that cause bradycardia.

Bradycardia: Bradycardia can occur with Brigatinib. Heart rate and blood pressure should be monitored during treatment with Brigatinib. Patients should be monitored more frequently if concomitant use of drug known to cause bradycardia cannot be avoided.

Visual Disturbance: Adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving Brigatinib in the 90 mg group and 10% of patients in the 90mg→180mg group. Patients should be advised to report any visual symptoms. Brigatinib should be withheld and obtained an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, Brigatinib should be resumed at a reduced dose. Treatment with Brigatinib should be permanently discontinued for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: Creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving Brigatinib in the 90 mg group and 48% of patients in the 90mg→180mg group. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored during Brigatinib treatment. Brigatinib should be withheld for Grade 3 or 4 CPK elevation.

Pancreatic Enzyme Elevation: Amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90mg→180mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90mg→180mg group. Lipase and amylase should be monitored during treatment with Brigatinib. Brigatinib should be withheld for Grade 3 or 4 pancreatic enzyme elevation.

Hyperglycemia: 43% of patients who received Brigatinib experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes Brigatinib or glucose intolerance at baseline required initiation of insulin while receiving Brigatinib. Fasting serum glucose should be assessed prior to initiation of Brigatinib and monitored periodically thereafter. Antihyperglycemic medications should be initiated or optimized as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, Brigatinib should be withheld until adequate hyperglycemic control is achieved and considered reducing the dose of Brigatinib.

Photosensitivity

0.9% of patients who received Brigatinib in the 90 mg group experienced photosensitivity and 0.9% of patients in the 90mg →180mg group. Grade 3 to 4 photosensitivity was not reported in patients in the 90 mg group or in the 90mg→180mg group. Patients should be advised to limit sun exposure while taking Brigatinib, and for at least 5 days after discontinuation of treatment. Patients should be advised to wear a hat and protective clothing when outdoors, and use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sunscreen and lip balm (SPF ≥30) to help protect against sunburn. Based on the severity Brigatinib should be withheld, then resume at the same dose, or reduce the dose, or permanently discontinued.

OVERDOSE: No data available.

STORAGE: Store below 30°C in a cool and dry place, away from sunlight. Keep out of the reach of children.

PACKING:

Biganib: Each box contains 10 tablets in a blister pack.

Biganib-180: Each box contains 7 tablets in blister pack.

Manufactured by
DRUG INTERNATIONAL LTD.
Tongi, Gazipur, Bangladesh