Briganix
Brigatinib

COMPOSITION

Briganix 30 Tablet: Each film-coated tablet contains Brigatinib INN 30 mg

Briganix 90 Tablet: Each film-coated tablet contains Brigatinib INN 90 mg

Briganix 180 Tablet: Each film-coated tablet contains Brigatinib INN 180 mg

PHARMACOLOGICAL INFORMATION

Therapeutic Class: Anti-Cancer agent.

PHARMACOLOGICAL ACTION

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-1R), 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. At clinically achievable concentrations (500 nM), brigatinib inhibited the in vitro viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including Crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y.

Brigatinib exhibited in vivo anti-tumor activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on Crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

Pharmacodynamics

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

Cardiac Electrophysiology

The QT interval prolongation potential of Brigatinib was assessed in 123 patients following once daily Brigatinib doses of 30 mg (1/6th of the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose). Brigatinib did not prolong the QT interval to a clinically relevant extent.

PHARMACOKINETICS

The geometric mean (CV%) steady-state maximum concentration (C_{max}) of Brigatinib at Brigatinib doses of 90 mg and 180 mg once daily was 552 (65%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve (AUC0-Tau) was 8165 (57%) ng h/mL and 20276 (56%) ng h/mL. After a single dose and repeat dosing of Brigatinib, systemic exposure of Brigatinib was dose proportional over the dose range of 60 mg (0.3 times the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Absorption

Following administration of single oral doses of Brigatinib of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours.

Effect of Food

Brigatinib Cmax was reduced by 13% with no effect on AUC in healthy subjects administered Brigatinib after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the Cmax and AUC after overnight fasting.

Distribution

Brigatinib is 66% 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 153 L.

Elimination

Following oral administration of Brigatinib 180 mg once daily, the mean apparent oral clearance (CL/F) of Brigatinib at steady-state is 12.7 L/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. The steady-state AUC of AP26123 was less than 10% of AUC of Brigatinib exposure in patients. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than Brigatinib in vitro.

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.

THERAPEUTIC INDICATION

Brigatinib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to Crizotinib.

DOSAGE & 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, increase the dose to 180 mg orally once daily.

Administer Brigatinib until disease progression or unacceptable toxicity. If Brigatinib is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose.

Brigatinib may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets. If a dose of Brigatinib is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of Brigatinib at the scheduled time.

Dose Modifications for Adverse Reactions

Brigatinib dose modification levels are summarized in Table 1.

Dose	*Dose Reduction Levels*		
	First	*Second*	*Third*
90 mg once daily	60 mg once daily	Permanently discontinue	Not Applicable
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

Once reduced for adverse reactions, do not subsequently increase the dose of Brigatinib. Permanently discontinue Brigatinib if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dose modifications of Brigatinib for the management of adverse reactions are provided in Table 2

Adverse Reaction	Severity*	Dose Modification
Interstitial Lung Disease (ILD) /Pneumonitis	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold Brigatinib until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold Brigatinib until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue Brigatinib.
	Grade 2	• If new pulmonary symptoms occur during the first 7 daysof treatment, withhold Brigatinib until recovery to baseline. Resume at next lower dose (Table 1) and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold Brigatinib until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose (Table 1); otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue Brigatinib.
	Grade 3 or 4	Permanently discontinue Brigatinib for ILD/pneumonitis.
Hypertension	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	• Withhold Brigatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume Brigatinib at next lower dose (Table 1). • Recurrence: withhold Brigatinib until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment.
	Grade 4 hypertension (lifethreatening consequences, urgent intervention indicated)	• Withhold Brigatinib until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment. • Recurrence: permanently discontinue Brigatinib for recurrence of Grade 4 hypertension.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	• Withhold Brigatinib until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume Brigatinib at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume Brigatinib at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life threatening consequences, urgent intervention indicated	• Permanently discontinue Brigatinib if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume Brigatinib at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue Brigatinib.
Visual Disturbance	Grade 2 or 3 visual disturbance	Withhold Brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue Brigatinib.
Creatine Phosphokinase (CPK) Elevation	Grade 3 CPK elevation (greaterthan 5.0 ULN)	Withhold Brigatinib until recovery to Grade 1 or less (lessthan or equal to 2.5 ULN) or to baseline, then resume Brigatinib at same dose.
	Grade 4 CPK elevation (greater than 10.0 ULN) or recurrence of Grade 3 elevation	Withhold Brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 ULN) or to baseline, then resume Brigatinib at next lower dose (Table 1).
Lipase/Amylase Elevation	Grade 3 lipase or amylase elevation (greater than 2.0 ULN)	Withhold Brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 ULN) or to baseline, then resume BRIGATINIB at same dose.
	Grade 4 lipase or amylase elevation (greater than 5.0 x ULN) or recurrence of Grade 3 elevation	Withhold Brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 ULN) or to baseline, then resume Brigatinib at next lower dose (Table 1).
Hyperglycemia	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold Brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next dose (Table 1) or permanently discontinue Brigatinib.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		
*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).		

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on its mechanism of action and findings in animals, Brigatinib can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of Brigatinib in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased postimplantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient 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, advise lactating women not to breastfeed during treatment with Brigatinib and for 1 week following the final dose.

Females and Males of Reproductive Potential

Contraception

Brigatinib can cause fetal harm

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with Brigatinib and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since Brigatinib can render some hormonal contraceptives ineffective.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential 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.

Geriatric Use

Clinical studies of Brigatinib did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients 65 years and younger patients.

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than 1 and up to 1.5 times ULN and any AST). The pharmacokinetics and safety of Brigatinib in patients with moderate or severe hepatic impairment have not been studied.

Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min estimated by Cockcroft-Gault)]. The pharmacokinetics and safety of Brigatinib in patients with severe renal impairment (CLcr 15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied.

ADVERSE REACTIONS

The following adverse reactions were in common in Clinical Trails.

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

CONTRAINDICATIONS

None.

DRUG INTERECTIONS

Drugs That May Increase Brigatinib Plasma Concentrations

Strong CYP3A Inhibitors

Coadministration of Itraconazole, a strong CYP3A inhibitor, increased Brigatinib plasma concentrations and may result in increased adverse reactions. Avoid the concomitant use of strong CYP3A inhibitors with Brigatinib, including but not limited to certain antivirals (e.g., Boceprevir, Cobicistat, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir), macrolide antibiotics (e.g., Clarithromycin), antifungals (e.g., Itraconazole, Ketoconazole, Posaconazole, Voriconazole), and conivaptan. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the dose of Brigatinib by approximately 50%.

Drugs That May Decrease Brigatinib Plasma Concentrations

Strong CYP3A Inducers

Coadministration of Brigatinib with rifampin, a strong CYP3A inducer, decreased Brigatinib plasma concentrations and may result in decreased efficacy. Avoid the concomitant use of strong CYP3A inducers with Brigatinib, including but not limited to Rifampin, Carbamazepine, Phenytoin, and St. John's Wort.

Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

CYP3A Substrates

Brigatinib induces CYP3A in vitro and may decrease concentrations of CYP3A substrates. Coadministration of Brigatinib with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates.

PHARMACEUTICAL INFORMATION

Storage Condition

Store at below 30°C, dry place and away from light. Keep out of the reach of children.

Presentation & Packing

Briganix 30 Tablet: Each commercial box contain 30 tablets in a HDPE Pot.

Briganix 90 Tablet: Each commercial box contain 30 tablets in a HDPE Pot.

Briganix 180 Tablet: Each commercial box contain 30 tablets in a HDPE Pot.

Only for Export

LF25501

Manufactured By
Beacon Pharmaceuticals Limited
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Marketed By
BEACON®
Medicare Limited
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