TREPMAC

Brigatinib INN 90 mg tablet

"Please Carefully Read the Full Leaflet"

COMPOSITION
TREPMAC 90 mg tablet: Each film coated tablet contains Brigatinib INN 90 mg.

DESCRIPTION
Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 5-chloro-N4-[2-(dimethylphosphoryl)phenyl]-N2-{2-methoxy-4[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine. The molecular formula is $C_{29}H_{39}ClN_7O_2P$ which corresponds to a formula weight of 584.10 g/mol. Brigatinib has no chiral centers. Brigatinib is an off-white to beige/tan solid. The pKas were determined to be: 1.73 ± 0.02 (base), 3.65 ± 0.01 (base), 4.72 ± 0.01 (base), and 8.04 ± 0.01 (base).

PHARMACEUTICAL FORM AND STRENGTHS
TREPMAC is available as 90 mg film coated tablet for oral administration.

THERAPEUTIC INDICATIONS
TREPMAC is a kinase inhibitor 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. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION
The recommended dosing regimen for TREPMAC 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 TREPMAC until disease progression or unacceptable toxicity.
If TREPMAC 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.
TREPMAC may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.
If a dose of TREPMAC is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of TREPMAC at the scheduled time.

Recommended Dose Modifications for TREPMAC
TREPMAC dose modification levels are summarized in Table 1.

Table 1: Recommended TREPMAC Dose Reduction Levels

Dose	Dose Reduction Levels		
	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

*Not applicable
Once reduced for adverse reactions, do not subsequently increase the dose of TREPMAC. Permanently discontinue TREPMAC if patients are unable to tolerate the 60 mg once daily dose.
Recommendations for dose modifications of TREPMAC for the management of adverse reactions are provided in Table 2.

Table 2: Recommended TREPMAC Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold TREPMAC 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 TREPMAC until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue TREPMAC.
	Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold TREPMAC 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 TREPMAC 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 TREPMAC.
	Grade 3 or 4	Permanently discontinue TREPMAC 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 TREPMAC until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume TREPMAC at next lower dose (Table 1). • Recurrence: withhold TREPMAC until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment.
	Grade 4 hypertension (life- threatening consequences, urgent intervention indicated)	• Withhold TREPMAC until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment. • Recurrence: permanently discontinue TREPMAC for recurrence of Grade 4 hypertension.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	• Withhold TREPMAC until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment. • Recurrence: permanently discontinue TREPMAC for recurrence of Grade 4 hypertension.
		• Withhold TREPMAC 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 TREPMAC 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 TREPMAC 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 TREPMAC if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume TREPMAC 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 TREPMAC.
Visual Disturbance	Grade 2 or 3 visual disturbance	Withhold TREPMAC until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1).
	Grade 4 visual disturbance	Permanently discontinue TREPMAC.
Creatine Phosphokinase (CPK) Elevation	Grade 3 CPK elevation (greater than 5.0 × ULN)	Withhold TREPMAC until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume TREPMAC at same dose.
	Grade 4 CPK elevation (greater than 10.0 × ULN) or recurrence of Grade 3 elevation	Withhold TREPMAC until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume TREPMAC at next lower dose (Table 1).
Lipase/Amylase Elevation	Grade 3 lipase or amylase elevation (greater than 2.0 × ULN)	Withhold TREPMAC until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume TREPMAC at same dose.
	Grade 4 lipase or amylase elevation (greater than 5.0 x ULN) or recurrence of Grade 3 elevation	Withhold TREPMAC until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume TREPMAC 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 TREPMAC until adequate hyperglycemic control is achieved and consider reduction to the next dose (Table 1) or permanently discontinue TREPMAC.
Other	Grade 3	• Withhold TREPMAC until recovery to baseline, then resume at same dose. • Recurrence: withhold TREPMAC until recovery to baseline, then resume at next lower dose or discontinue TREPMAC (Table 1).
	Grade 4	• First occurrence: either withhold TREPMAC until recovery to baseline and resume at next lower dose (Table 1) or permanently discontinue. • Permanently discontinue TREPMAC for recurrence.
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).

Dose Modification for Strong CYP3A Inhibitors
Avoid concomitant use of strong CYP3A inhibitors during treatment with TREPMAC. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the TREPMAC once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A

inhibitor, resume the TREPMAC dose that was tolerated prior to initiating the strong CYP3A inhibitor.

CLINICAL 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-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 TREPMAC was assessed in 123 patients following once daily TREPMAC doses of 30 mg (1/6th of the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose). TREPMAC 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 TREPMAC 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 (AUC_{0-Tau}) was 8165 (57%) ng·h/mL and 20276 (56%) ng·h/mL. After a single dose and repeat dosing of TREPMAC, 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 TREPMAC of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from 1 to 4 hours.

Effect of Food

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered TREPMAC after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the C_{max} 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 TREPMAC 180 mg once daily, the mean apparent volume of distribution (Vz/F) of brigatinib at steady-state was 153 L.

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.

Elimination

Following oral administration of TREPMAC 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.

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.

Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

Hepatic Impairment

As hepatic elimination is a major route of excretion for brigatinib, hepatic impairment may result in increased plasma brigatinib concentrations. Based on a population pharmacokinetic analysis, brigatinib exposures were similar between 49 subjects 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) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of brigatinib in patients with moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) to severe (total bilirubin greater than 3.0 times ULN and any AST) hepatic impairment has not been studied.

Renal Impairment

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CLcr 60 to less than 90 mL/min), 34 subjects with moderate renal impairment (CLcr 30 to less than 60 mL/min) and 270 subjects with normal renal function (CLcr greater than or equal to 90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CLcr less than 30 mL/min) were not included in clinical trials.

DRUG INTERACTIONS

Effects of Other Drugs on Brigatinib:

Strong CYP3A Inhibitors: Coadministration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg dose of TREPMAC increased brigatinib C_{max} by 21% and AUC_{0-INF} by 101%, relative to a 90 mg dose of TREPMAC administered alone.

Strong CYP2C8 Inhibitors: Coadministration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of TREPMAC decreased brigatinib C_{max} by 41% and AUC_{0-INF} by 12%, relative to a 90 mg dose of TREPMAC administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

Strong CYP3A Inducers: Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of TREPMAC decreased brigatinib C_{max} by 60% and AUC_{0-INF} by 80%, relative to a 180 mg dose of TREPMAC administered alone.

P-gp and BCRP Inhibitors: In vitro studies suggest that brigatinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability in vitro, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

Other Transporters: Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).

Effects of Brigatinib on Other Drugs Transporter Substrates: Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K in vitro. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

CYP Substrates: Brigatinib and its primary metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations.

NONCLINICAL TOXICOLOGY

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an in vivo mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or in vitro mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the 2-month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

CONTRAINDICATIONS

None

SPECIAL WARNINGS AND PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 9.1% of patients at the recommended dose. Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold TREPMAC for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue TREPMAC.
- Hypertension: Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold TREPMAC, then dose reduce or permanently discontinue.)
- Bradycardia: Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold TREPMAC, then dose reduce or permanently discontinue.
- Visual Disturbance: Advise patients to report visual symptoms. Withhold TREPMAC and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue TREPMAC.
- Creatine Phosphokinase (CPK) Elevation: Monitor CPK levels regularly during treatment. Based on the severity, withhold TREPMAC, then resume or reduce dose.
- Pancreatic Enzyme Elevation: Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold TREPMAC, then resume or reduce dose.
- Hyperglycemia: Assess fasting serum glucose prior to starting TREPMAC and regularly during treatment. If not adequately controlled with optimal medical management, withhold TREPMAC, then consider dose reduction or permanently discontinue, based on severity.
- Embryo-Fetal Toxicity: Can cause fetal harm when administered to pregnant women. Advise females of reproductive potential of the potential risk to a fetus and to use a non- hormonal method of effective contraception.

ADVERSE REACTIONS

The most common adverse reactions (≥25%) with TREPMAC were nausea, diarrhea, fatigue, cough, and headache.

DRUG INTERACTIONS

- CYP3A Inhibitors: Avoid concomitant use of TREPMAC with strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of TREPMAC.
- CYP3A Inducers: Avoid concomitant use of TREPMAC with strong CYP3A inducers
- CYP3A Substrates: Hormonal contraceptives may be ineffective due to decreased exposure.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed.

PHARMACEUTICAL INFORMATIONS

Storage condition

Store below 30° C.

Keep away from light, store in a cool & dry place. Keep out of the reach of children.

HOW SUPPLIED

TREPMAC 90 mg: Each commercial box contains 3X10's tablets in Alu-Alu blister.

TREPMAC 90 mg: Each commercial box contains 6X10's tablets in Alu-Alu blister.

Manufactured by

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