Daconib

Dacomitinib 15 mg & 45 mg tablets

Everest

COMPOSITION

DACONIB 15 tablet: Each film coated tablet contains Dacomitinib Monohydrate INN equivalent to Dacomitinib 15 mg.

DACONIB 45 tablet: Each film coated tablet contains Dacomitinib Monohydrate INN equivalent to Dacomitinib 45 mg.

PHARMACOLOGY

Mechanism of Action

Dacomitinib is an irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, and HER4) and certain EGFR activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation). In vitro Dacomitinib also inhibited the activity of DDR1, EPHA6, LCK, DDR2, and MNK1 at clinically relevant concentrations.

Dacomitinib demonstrated dose-dependent inhibition of EGFR and HER2 autophosphorylation and tumor growth in mice bearing subcutaneously implanted human tumor xenografts driven by HER family targets including mutated EGFR. Dacomitinib also exhibited antitumor activity in orally-dosed mice bearing intracranial human tumor xenografts driven by EGFR amplifications.

Pharmacokinetic properties

The maximum Dacomitinib plasma concentration (C_{max}) and AUC at steady state increased proportionally over the dose range of Dacomitinib 2 mg to 60 mg orally once daily (0.04 to 1.3 times the recommended dose) across Dacomitinib studies in patients with cancer. At a dose of 45 mg orally once daily, the geometric mean [coefficient of variation (CV%)] Cmax was 108 ng/mL (35%) and the $AUC_{0\text{-}24h}$ was 2213 ng•h/mL (35%) at steady state in a dose-finding clinical study conducted in patients with solid tumors. Steady state was achieved within 14 days following repeated dosing and the estimated geometric mean (CV%) accumulation ratio was 5.7 (28%) based on AUC.

Absorption

The mean absolute bioavailability of Dacomitinib is 80% after oral administration. The median Dacomitinib time to reach maximum concentration (T_{max}) occurred at approximately 6.0 hours (range 2.0 to 24 hours) after a single oral dose of Dacomitinib 45 mg in patients with cancer.

Effect of food

Administration of Dacomitinib with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) had no clinically meaningful effect on Dacomitinib pharmacokinetics.

Distribution

The geometric mean (CV%) volume of distribution of Dacomitinib (Vss) was 1889 L (18%). In vitro binding of Dacomitinib to human plasma proteins is approximately 98% and is independent of drug concentrations from 250 ng/mL to 1000 ng/mL.

Elimination

Following a single 45 mg oral dose of Dacomitinib in patients with cancer, the mean (CV%) plasma half-life of Dacomitinib was 70 hours (21%), and the geometric mean (CV%) apparent plasma clearance of Dacomitinib was 24.9 L/h (36%).

Metabolism

Hepatic metabolism is the main route of clearance of Dacomitinib, with oxidation and glutathione conjugation as the major pathways. Following oral administration of a single 45 mg dose of [^{14}C] Dacomitinib, the most abundant circulating metabolite was O-desmethyl Dacomitinib, which had similar in vitro pharmacologic activity as Dacomitinib. The steady-state plasma trough concentration of O-desmethyl Dacomitinib ranges from 7.4% to 19% of the parent. In vitro studies indicated that cytochrome P450 (CYP) 2D6 was the major isozyme involved in the formation of O-desmethyl Dacomitinib, while CYP3A4 contributed to the formation of other minor oxidative metabolites.

Excretion

Following a single oral 45 mg dose of [^{14}C] radiolabeled Dacomitinib, 79% of the radioactivity was recovered in feces (20% as Dacomitinib) and 3% in urine (<1% as Dacomitinib)

Specific Populations

Patients with Renal Impairment

Based on population pharmacokinetic analyses, mild (60 mL/min ≤ CLcr <90 mL/min; N=590) and moderate (30 mL/min ≤ CLcr <60 mL/min; N=218) renal impairment did not alter Dacomitinib pharmacokinetics, relative to the pharmacokinetics in patients with normal renal function (CLcr ≥90 mL/min; N=567). The pharmacokinetics of Dacomitinib has not been adequately characterized in patients with severe renal impairment (CLcr <30 mL/min) (N=4) or studied in patients requiring hemodialysis.

Patients with Hepatic Impairment

In a dedicated hepatic impairment trial, following a single oral dose of 30 mg Dacomitinib, Dacomitinib exposure (AUCinf and Cmax) was unchanged in subjects with mild hepatic impairment (Child-Pugh A; N=8) and decreased by 15% and 20%, respectively in subjects with moderate hepatic impairment (Child-Pugh B; N=9) when compared to subjects with normal hepatic function (N=8). Based on this trial, mild and moderate hepatic impairment had no clinically important effects on pharmacokinetics of Dacomitinib. In addition, based on a population pharmacokinetic analysis of 1381 patients, in which 158 patients had mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1 to 1.5 × ULN with any AST) and 5 patients had moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN and any AST), no effects on pharmacokinetics of Dacomitinib were observed. The effect of severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST) on Dacomitinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies.

Effect of Acid-Reducing Agents on Dacomitinib

Coadministration of a single 45 mg dose of Dacomitinib with multiple doses of rabeprazole (a proton pump inhibitor) decreased Dacomitinib C_{max} by 51% and $AUC_{0\text{-}96h}$ by 39%.

Coadministration of Dacomitinib with a local antacid (Maalox® Maximum Strength, 400 mg/5 mL) did not cause clinically relevant changes Dacomitinib concentrations.

The effect of H2 receptor antagonists on Dacomitinib pharmacokinetics has not been studied.

Effect of Strong CYP2D6 Inhibitors on Dacomitinib

Coadministration of a single 45 mg dose of Dacomitinib with multiple doses of paroxetine (a strong CYP2D6 inhibitor) in healthy subjects increased the total AUC_{last} of Dacomitinib plus its active metabolite (O-desmethyl Dacomitinib) in plasma by approximately 6%, which is not considered clinically relevant.

Effect of Dacomitinib on CYP2D6 Substrates

Coadministration of a single 45 mg oral dose of Dacomitinib increased dextromethorphan (a CYP2D6 substrate) C_{max} by 9.7-fold and AUC_{last} by 9.6-fold.

In Vitro Studies

Effect of Dacomitinib and O-desmethyl Dacomitinib on CYP Enzymes: Dacomitinib and its metabolite O-desmethyl Dacomitinib do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Dacomitinib does not induce CYP1A2, CYP2B6, or CYP3A4.

Effect of Dacomitinib on Uridine 5' diphospho-glucuronosyltransferase (UGT) Enzymes: Dacomitinib inhibits UGT1A1. Dacomitinib does not inhibit UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15.

Effect of Dacomitinib on Transporter Systems: Dacomitinib is a substrate for the membrane transport protein P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Dacomitinib inhibits P-gp, BCRP, and organic cation transporter (OCT)1. Dacomitinib does not inhibit organic anion transporters (OAT)1 and OAT3, OCT2, organic anion transporting polypeptide (OATP)1B1, and OATP1B3

INDICATIONS AND USAGE

Dacomitinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with Dacomitinib based on the presence of an EGFR exon 19 deletion or exon 21 L858R substitution mutation in tumor specimens.

Recommended Dosage

The recommended dosage of Dacomitinib is 45 mg taken orally once daily, until disease progression or unacceptable toxicity occurs. Dacomitinib can be taken with or without food.

Take Dacomitinib the same time each day. If the patient vomits or misses a dose, do not take an additional dose or make up a missed dose but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions

Reduce the dose of Dacomitinib for adverse reactions as described in Table.

Table: Dacomitinib Recommended Dose Reductions for Adverse Reactions

Dose Level	Dose (Once Daily)
First dose reduction	30 mg
Second dose reduction	15 mg

Dosage Modifications for Acid-Reducing Agents
Avoid the concomitant use of proton pump inhibitors (PPIs) while taking Dacomitinib. As an alternative to PPIs, use locally-acting antacids or if using an histamine 2 (H2)-receptor antagonist, administer Dacomitinib at least 6 hours before or 10 hours after taking an H2-receptor antagonist.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease (ILD)
Severe and fatal ILD/pneumonitis occurred in patients treated with Dacomitinib and occurred in 0.5% of the 394 Dacomitinib-treated patients; 0.3% of cases were fatal.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Withhold Dacomitinib and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Permanently discontinue Dacomitinib if ILD is confirmed.

Diarrhea
Severe and fatal diarrhea occurred in patients treated with Dacomitinib. Diarrhea occurred in 86% of the 394 Dacomitinib- treated patients; Grade 3 or 4 diarrhea was reported in 11% of patients and 0.3% of cases were fatal.

Withhold Dacomitinib for Grade 2 or greater diarrhea until recovery to less than or equal to Grade 1 severity, then resume Dacomitinib at the same or a reduced dose depending on the severity of diarrhea. Promptly initiate anti-diarrheal treatment (loperamide or diphenoxylate hydrochloride with atropine sulfate) for diarrhea.

Dermatologic Adverse Reactions
Rash and exfoliative skin reactions occurred in patients treated with Dacomitinib. Rash occurred in 78% of the 394 Dacomitinib-treated patients; Grade 3 or 4 rash was reported in 21% of patients. Exfoliative skin reactions of any severity were reported in 7% of patients. Grade 3 or 4 exfoliative skin reactions were reported in 1.8% of patients.

Withhold Dacomitinib for persistent Grade 2 or any Grade 3 or 4 dermatologic adverse reaction until recovery to less than or equal to Grade 1 severity, then resume Dacomitinib at the same or a reduced dose depending on the severity of the dermatologic adverse reaction. The incidence and severity of rash and exfoliative skin reactions may increase with sun exposure. At the time of initiation of Dacomitinib, initiate use of moisturizers and appropriate measures to limit sun exposure. Upon development of Grade 1 rash, initiate treatment with topical antibiotics and topical steroids. Initiate oral antibiotics for Grade 2 or more severe dermatologic adverse reactions.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, Dacomitinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of Dacomitinib to pregnant rats during the period of organogenesis resulted in an increased incidence of post-implantation loss and reduced fetal body weight at doses resulting in exposures near the exposure at the 45 mg human dose. The absence of EGFR signaling has been shown to result in embryolethality as well as post-natal death in animals. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with Dacomitinib and for at least 17 days after the final dose.

SIDE EFFECTS
The following adverse drug reactions are described elsewhere in the labeling:
- Interstitial Lung Disease
- Diarrhea
- Dermatologic Adverse Reactions

DRUG INTERACTIONS
Effect of Other Drugs on Dacomitinib
Concomitant use with a PPI decreases Dacomitinib concentrations, which may reduce Dacomitinib efficacy. Avoid the concomitant use of PPIs with Dacomitinib. As an alternative to PPIs, use locally-acting antacids or an H2-receptor antagonist. Administer Dacomitinib at least 6 hours before or 10 hours after taking an H2-receptor antagonist.

Effect of Dacomitinib on CYP2D6 Substrates
Concomitant use of Dacomitinib increases the concentration of drugs that are CYP2D6 substrates which may increase the risk of toxicities of these drugs. Avoid concomitant use of Dacomitinib with CYP2D6 substrates where minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities.

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

Lactation
There is no information regarding the presence of Dacomitinib or its metabolites in human milk or their effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Dacomitinib, advise women not to breastfeed during treatment with Dacomitinib and for at least 17 days after the last dose.

Females and Males of Reproductive Potential
Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating Dacomitinib.

Contraception
Dacomitinib can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with Dacomitinib and for at least 17 days after the final dose.

Pediatric Use
The safety and effectiveness of Dacomitinib in pediatrics have not been established.

Geriatric Use
Of the total number of patients (N=394) in five clinical studies with EGFR mutation-positive NSCLC who received Dacomitinib at a dose of 45 mg orally once daily [ARCHER 1050 (N=227), Study A7471009 (N=38), Study A7471011 (N=83), Study A7471028 (N=16), and Study A7471017 (N=30)] 40% were 65 years of age and older.

Exploratory analyses across this population suggest a higher incidence of Grade 3 and 4 adverse reactions (67% versus 56%, respectively), more frequent dose interruptions (53% versus 45%, respectively), and more frequent discontinuations (24% versus 10%, respectively) for adverse reactions in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault). The recommended dose of Dacomitinib has not been established for patients with severe renal impairment (CLcr <30 mL/min).

Hepatic Impairment
No dose adjustment is recommended in patients with mild (total bilirubin ≤ upper limit of normal [ULN] with AST > ULN or total bilirubin > 1 to 1.5 × ULN with any AST) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment. The recommended dose of Dacomitinib has not been established for patients with severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST).

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

HOW SUPPLIED
DACONIB 15 tablet: Each HDPE container contains 30 film coated tablets, a silica gel desiccant and polyester coil with a child-resistant closure.

DACONIB 45 tablet: Each HDPE container contains 30 film coated tablets, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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