Adakras
Adagrasib INN

Everest

COMPOSITION
ADAKRAS Tablet: Each film coated tablet contains Adagrasib INN 200 mg.

DESCRIPTION
Adagrasib is an irreversible inhibitor of KRAS G12C and belongs to the RAS GTPase family. The molecular formula is $C_{32}H_{35}ClFN_7O_2$ and the molecular weight is 604.1 g/mol. The chemical name is {(2S)-4-[7-(8-chloronaphthalen-1-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]-methoxy}-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2- yl}acetonitrile.

PHARMACOLOGY
Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting wild-type KRAS protein. Adagrasib inhibits tumor cell growth and viability in cells harboring KRAS G12C mutations and results in tumor regression in KRAS G12C-mutated tumor xenograft models with minimal off-target activity.

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

Cardiac Electrophysiology
Adagrasib increased QTc in a concentration-dependent manner. Based on the concentration QTcF relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (15, 21) ms at the mean steady-state maximum concentration ($C_{max,ss}$) in patients after administration of Adagrasib 600 mg twice daily

Pharmacokinetics
The pharmacokinetics of Adagrasib were studied in healthy subjects and in patients with KRAS G12C-mutated NSCLC and are presented as mean (percent coefficient of variation) unless otherwise specified.

Adagrasib AUC and C_{max} increase dose proportionally over the dose range of 400 mg to 600 mg (0.67 to 1 times the approved recommended dose). Adagrasib steady-state was reached within 8 days following administration of the approved recommended dosage and accumulation was approximately 6-fold.

Absorption
The median (min, max) T_{max} of Adagrasib is approximately 6 (6, 12) hours.

Distribution
The apparent volume of distribution of Adagrasib is 942 L (57%). Human plasma protein binding of Adagrasib is approximately 98% in vitro.

Elimination
The Adagrasib terminal elimination half-life is 23 hours (16%) and the apparent oral clearance (CL/F) is 37 L/h (54%) in patients.

Effect of Food
No clinically significant differences in the pharmacokinetics of Adagrasib were observed following administration of a high-fat and high-calorie meal (containing approximately 900 to 1000 calories, 50% from fat).

Metabolism
Adagrasib is metabolized primarily by CYP3A4 following single dose administration. Adagrasib inhibits its own CYP3A4 metabolism following multiple dosing to steady-state which permits CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2D6 to contribute to its metabolism at steady-state.

Excretion
Following a single oral dose of radiolabeled Adagrasib, approximately 75% of the dose was recovered in feces (14% as unchanged) and 4.5% recovered in urine (2% as unchanged).

Specific Populations
No clinically significant differences in the pharmacokinetics of Adagrasib based on age (19 to 89 years), sex, race (White, Black or African American, or Asian), body weight (36 to 139 kg), ECOG PS (0, 1), or tumor burden. No clinically significant differences in the pharmacokinetics of Adagrasib are expected in patients with mild to severe renal impairment (CLcr 15 to < 90 mL/min estimated by Cockcroft-Gault equation) or in patients with mild to severe hepatic impairment (Child-Pugh classes A to C).

Drug Interaction Studies
The following table describes the effect of other drugs on the pharmacokinetics of Adagrasib.

Table:01 Effect of Other Drugs on Adagrasib

Concomitant Drug	Adagrasib Dosage	Changes in Cmax or AUC of Adagrasib	
		Cmax % Decrease	AUC % Decrease
Rifampin (a strong CYP3A inducer)	600 mg single dose	88%	95%
	600 mg multiple doses	>61%a	>66%a

C_{max} = maximum plasma concentration; AUC = area under the plasma concentration-time curve a Predicted changes in C_{max} or AUC of Adagrasib

Strong CYP3A Inhibitors:
Adagrasib C_{max} increased by 2.4-fold and AUC increased by 4-fold following concomitant use of a single dose of 200 mg (0.33 times the approved recommended dose) with Itraconazole (a strong CYP3A inhibitor). No clinically significant differences in the pharmacokinetics of Adagrasib at steady state were predicted when used concomitantly with Itraconazole.

No clinically significant differences in the pharmacokinetics of Adagrasib were predicted or observed when used concomitantly with Efavirenz (a moderate CYP3A inducer), pantoprazole (a proton pump inhibitor), or Rosuvastatin (a BCRP/OATP substrate).

The following table describes the effect of Adagrasib on the pharmacokinetics of other drugs.

Table: 02 Effect of Adagrasib on Other Drugs

Concomitant Drug	Adagrasib Dosage	Fold Increase of Concomitant Drug	
		C_{max}	AUC
Midazolam (a sensitive CYP3A substrate)	400 mg[a] twice daily 600 mg twice daily	4.8-fold 3.1-fold[b]	21-fold 31-fold[b]
Warfarin (a sensitive CYP2C9 substrate)	600 mg twice daily	1.1-fold[b]	2.9-fold[b]
Dextromethorphan (a sensitive CYP2D6 substrate)	400 mg[a] twice daily 600 mg twice daily	1.9-fold 1.7-fold[b]	1.8-fold 2.4-fold[b]
Digoxin (a P-gp substrate)	600 mg twice daily	1.9-fold[b]	1.5-fold[b]

C_{max} = maximum plasma concentration; AUC = area under the plasma concentration-time curve
a 0.66 times the approved recommended dosage
b Predicted changes in C_{max} or AUC of concomitant drug
In Vitro Studies
Cytochrome P450 (CYP) Enzymes: Adagrasib may inhibit CYP2B6. Transporter Systems: Adagrasib may be a substrate of BCRP and may inhibit MATE-1/MATE2K.

INDICATIONS AND USAGE
Adagrasib is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

DOSAGE AND ADMINISTRATION
The recommended dosage of Adagrasib is 600 mg orally twice daily until disease progression or unacceptable toxicity.

Adagrasib should be taken with or without food at a same time every day. Tablet should be swallowed whole. It shouldn't be crushed, chewed, splitted or dissolved into water.

If vomiting occurs after taking Adagrasib, do not take an additional dose. Resume dosing at the next scheduled time.

If a dose is inadvertently missed, it should be skipped if greater than 4 hours have elapsed from the expected dosing time. Resume dosing at the next scheduled time.

Dosage Modifications for Adverse Reactions
Recommended dose reductions for adverse reactions are outlined in Table 3. If adverse reactions occur, a maximum of two dose reductions are permitted. Permanently discontinue Adagrasib in patients who are unable to tolerate 600 mg once daily.

Table 3: Recommended Adagrasib Dosage Reductions for Adverse Reactions

Dose Reduction	Dosage
First dose reduction	400 mg twice daily
Second dose reduction	600 mg once daily

The recommended dosage modifications for adverse reactions are provided in Table 4

Table 4: Recommended Adagrasib Dosage Modifications for Adverse Reactions

Adverse reaction	Severity[a]	Dosage Modification
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 or 4	• Withhold Adagrasib until recovery to ≤ Grade 1 or return to baseline. • Resume Adagrasib at the next lower dose level.

Diarrhea despite appropriate supportive care (including antidiarrheal therapy)	Grade 3 or 4	• Withhold Adagrasib until recovery to ≤ Grade 1 or return to baseline. • Resume Adagrasib at the next lower dose level.
QTc Interval Prolongation	QTc absolute value greater than 500 ms Or Greater than an increase of 60 ms from baseline	• Withhold Adagrasib until QTc interval less than 481 ms or return to baseline. • Resume Adagrasib at the next lower dose level.
	Torsade de pointes, polymorphic ventricular tachycardia or signs or symptoms of serious or life threatening arrhythmia	• Permanently discontinue Adagrasib.
Hepatotoxicity	Grade 2 AST or ALT	• Decrease Adagrasib to the next lower dose level.
	Grade 3 or 4 AST or ALT	• Withhold Adagrasib until recovery to ≤ Grade 1 or return to baseline. • Resume Adagrasib at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	• Permanently discontinue Adagrasib.
Interstitial Lung Disease / Pneumonitis	Any Grade	• Withhold Adagrasib TI if ILD/pneumonitis is suspected. • Permanently discontinue Adagrasib if ILD/pneumonitis is confirmed.
Other Adverse Reactions	Grade 3 or 4	• Withhold Adagrasib until ≤ Grade 1 or return to baseline. • Resume Adagrasib at the next lower dose level.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Gastrointestinal Adverse Reactions
Adagrasib can cause severe gastrointestinal adverse reactions including nausea, diarrhea, or vomiting. Patient should be monitored and manage with supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. With hold, reduce the dose, or permanently discontinue Adagrasib based on severity.

QTc Interval Prolongation
Adagrasib can cause QTc interval prolongation, which can increase the risk for ventricular Tachyarrhythmias or sudden death.

Concomitant use of Adagrasib should be avoided with other products with a known potential to prolong the QTc interval.

Hepatotoxicity
Adagrasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis.

Patients should be monitored for liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) prior to the start of Adagrasib and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue Adagrasib based on severity.

SIDE EFFECT
The most common side effects are nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, and decreased appetite. lymphocytes, decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils and increased alkaline phosphatase.

DRUG INTERACTIONS
Effects of Other Drugs on Adagrasib
Strong CYP3A4 Inducers
Concomitant use of Adagrasib with strong CYP3A inducers should be avoided.
Adagrasib is a CYP3A4 substrate. Concomitant use of Adagrasib with a strong CYP3A inducer reduces Adagrasib exposure, which may reduce the effectiveness of Adagrasib.

Strong CYP3A4 Inhibitors
Concomitant use of Adagrasib with strong CYP3A inhibitors until Adagrasib concentrations have reached steady state (after approximately 8 days). Adagrasib is a CYP3A4 substrate. If Adagrasib concentrations have not reached steady state, concomitant use of a strong CYP3A inhibitor will increase Adagrasib concentrations, which may increase the risk of Adagrasib adverse reactions.

Effects of Adakras on Other Drugs
Sensitive CYP3A Substrates
Concomitant use of Adagrasib should be avoided with sensitive CYP3A substrates unless otherwise recommended in the prescribing information for these substrates.
Adagrasib is a CYP3A inhibitor. Concomitant use with Adagrasib increases exposure of CYP3A substrates, which may increase the risk of adverse reactions related to these substrates.

Sensitive CYP2C9 Substrates
Avoid Concomitant use of Adagrasib should be avoided with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.
Adagrasib is a CYP2C9 inhibitor. Concomitant use with Adagrasib increases exposure of CYP2C9 substrates, which may increase the risk of adverse reactions related to these substrates.

Sensitive CYP2D6 Substrates
Concomitant use of Adagrasib should be avoided with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.
Adagrasib is a CYP2D6 inhibitor. Concomitant use with Adagrasib increases exposure of CYP2D6 substrates, which may increase the risk of adverse reactions related to these substrates.

P-gp Substrates
Concomitant use of Adagrasib should be avoided with P-gp substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates. Adagrasib is a P-gp inhibitor. Concomitant use with Adagrasib increases exposure of P-gp substrates, which may increase the risk of adverse reactions related to these substrates.

Drugs That Prolong QTc Interval
Concomitant use of Adagrasib with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, monitor electrocardiogram and electrolytes prior to starting Adagrasib, during concomitant use, and as clinically indicated. Adagrasib should be withhold if the QTc interval is > 500 ms or the change from baseline is > 60 ms.

Adagrasib causes QTc interval prolongation. Concomitant use of Adagrasib with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrythmias, and sudden death.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on the use of Adagrasib in pregnant women. In animal reproduction studies, oral administration of Adagrasib to pregnant rats and rabbits during the period of organogenesis did not cause adverse development effects or embryo-fetal lethality at exposures below the human exposure at the recommended dose of 600 mg twice daily.

Lactation
There are no data on the presence of Adagrasib or its metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, women should be advised not to breastfeed during treatment with Adagrasib and for 1 week after the last dose.

Females and Males of Reproductive Potential

Infertility
Based on findings from animal studies, Adagrasib may impair fertility in females and males of reproductive potential.

Pediatric Use
The safety and effectiveness of Adagrasib has not been established in pediatric patients.

Geriatric Use
No overall differences in safety or effectiveness were observed between older and younger patients.

PHARMACEUTICAL INFORMATION

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

HOW SUPPLIED
ADAKRAS Tablet: Each HDPE container contains 42 film coated tablets, each of which contains Adagrasib INN 200 mg, a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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