Ribolib

Ribociclib Succinate INN

COMPOSITION
Ribolib Tablet: Each Film coated tablet contains Ribociclib Succinate INN equivalent to Ribociclib 200 mg.

Therapeutic Class: Anti Cancer Agent.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Cardiac Electrophysiology
Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of Ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 267 patients treated with Ribociclib at doses ranging from 50 to 1200 mg, including 193 patients treated with Ribociclib 600 mg. The analysis suggested that Ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF was 22.9 ms (90% CI: 21.6, 24.1) at the mean observed C_{max} at steady-state following administration at the recommended 600 mg dose.

Mechanism of Action
Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D- cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, Ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. In vivo, treatment with single agent Ribociclib in a rat xenograft model with human tumor cells led to decreased tumor volumes, which correlated with inhibition of pRb phosphorylation. In studies using patient-derived estrogen receptor positive breast cancer xenograft models, combination of Ribociclib and antiestrogen (e.g. letrozole) resulted in increased tumor growth inhibition compared to each drug alone.

Pharmacokinetics
Ribociclib exhibited over-proportional increases in exposure (peak plasma concentrations (Cmax) and area under the time concentration curve (AUC)) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and Ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.972 to 6.40).

Absorption: The time to reach C_{max} (T_{max}) following Ribociclib administration was between 1 and 4 hours.

Food Effect: Compared to the fasted state, oral administration of a single 600 mg dose of Ribociclib film-coated tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no effect on the rate and extent of absorption of Ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUCinf GMR: 1.06; 90% CI: 1.01, 1.12).

Distribution: Binding of Ribociclib to human plasma proteins in vitro was approximately 70% and independent of concentration (10 to 10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.04. The pparent volume of distribution at steady-state (Vss/F) was 1090 L based on population PK analysis.

Metabolism: In vitro and in vivo studies indicated Ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled Ribociclib to humans, the primary metabolic pathways for Ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of Ribociclib Phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of Ribociclib exposure. Clinical activity (pharmacological and safety) of Ribociclib was due primarily to parent drug, with negligible contribution from circulating metabolites. Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

Elimination: The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life ($t_{1/2}$) of Ribociclib ranged from 29.7 to 54.7 hours and geometric mean CL/F of Ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects. Ribociclib is eliminated mainly via feces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of radio-labeled Ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; feces was the major route of excretion (69%), with 23% of the dose recovered in urine.

INDICATIONS

Ribociclib is a kinase inhibitor indicated in combination with:

- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or

- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine based therapy or following disease progression on endocrine therapy.

DOSAGE AND ADMINISTRATION

Ribociclib tablets are taken orally with or without food in combination with an aromatase inhibitor or fulvestrant.

Recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment.

Dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability.

DOSE MODIFICATIONS FOR ADVERSE REACTIONS

Level	Dose	Number of Tablets
Starting dose	600 mg/Day	Three 200 mg Tablets
First dose reduction	400 mg/Day	Two 200 mg Tablets
Second dose reduction	200 mg/Day	One 200 mg Tablet
*If further dose reduction below 200 mg/day is required, discontinue the treatment		

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings from animal studies and the mechanism of action, Ribociclib can cause fetal harm when administered to a pregnant woman.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of Ribociclib to pregnant animals during organogenesis resulted in increased incidences of postimplantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies in the U.S. general population.

Lactation
It is not known if Ribociclib is present in human milk. There are no data on the effects of Ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from Ribociclib, advise lactating women not to breastfeed while taking Ribociclib and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing
Based on animal studies, Ribociclib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with Ribociclib.

Contraception
Based on animal studies, Ribociclib can cause fetal harm when administered to a pregnant woman. females of reproductive potential are advised to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Ribociclib and for at least 3 weeks after the last dose.

Infertility
Based on animal studies, Ribociclib may impair fertility in males of reproductive potential.

Pediatric Use
The safety and efficacy of Ribociclib in pediatric patients has not been established

Geriatric Use
Of 334 patients who received Ribociclib in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients who received Ribociclib in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. No overall differences in safety or effectiveness of Ribociclib were observed between these patients and younger patients.

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of Ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.50 for C_{max}; 1.32 for AUC_{inf}) and severe (GMR: 1.34 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment.

Renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73m2≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m2) or moderate (30 mL/min/1.73m2≤ eGFR <60 mL/min/1.73m2) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73m2), a starting dose of 200 mg is recommended. Ribociclib has not been studied in breast cancer patients with severe renal impairment.

CONTRAINDICATIONS
None

WARNING AND PRECAUTIONS
Interstitial Lung Disease (ILD)/Pneumonitis: Patients treated with CDK 4/6 inhibitors should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Interrupt and evaluate patients with new or worsening respiratory symptoms suspected to be due to ILD/pneumonitis. Permanently discontinue Ribociclib in patients with recurrent symptomatic or severe ILD/pneumonitis.

Severe Cutaneous Adverse Reactions (SCARs): Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), and drug-reaction with eosinophilia and systemic symptoms (DRESS) can occur with Ribociclib treatment. Permanently discontinue Ribociclib in patients with SCARs or other life-threatening cutaneous reactions

Neutropenia: Perform complete blood count (CBC) before initiating therapy with Ribocicilib. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

QT interval prolongation: Monitor electrocardiograms (ECGs) and electrolytes prior to initiation of treatment with Ribociclib. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated. Avoid using Ribociclib with drugs known to prolong QT interval and/or strong CYP3A inhibitors.

Increased QT Prolongation with Concomitant Use of Tamoxifen: Ribociclib is not indicated for concomitant use with tamoxifen.

Hepatobiliary Toxicity: Increases in serum transaminase levels have been observed. Perform Liver Function Tests (LFTs) before initiating treatment with Ribociclib. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception during therapy.

SIDE EFFECTS
Most common side effects (incidence ≥ 20%) are neutropenia, nausea, infections, fatigue, diarrhea, leukopenia, vomiting, alopecia, headache, constipation, rash and cough. Serious side effects are heart rhythm problem (QT prolongation) and liver problems.

DRUG INTERACTIONS

Drugs That Affect Ribocicilib Plasma Concentrations

CYP3A4 Inhibitors: A drug interaction trial in healthy subjects was conducted with Ritonavir (a strong CYP3A inhibitor). Compared to Ribociclib alone, Ritonavir (100 mg twice a day for 14 days) increased Ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg Ribociclib dose. C_{max} and AUC for LEQ803 (a prominent metabolite of LEE011, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. A moderate CYP3A4 inhibitor (erythromycin) is predicted to increase Ribociclib C_{max} and AUC by 1.3-fold and 1.9-fold, respectively.

CYP3A4 Inducers: A drug interaction trial in healthy subjects was conducted with Rifampicin (a strong CYP3A4 inducer). Compared to Ribociclib alone, rifampicin (600 mg daily for 14 days) decreased Ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg Ribociclib dose. LEQ803 Cmax increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. A moderate CYP3A inducer (Efavirenz) is predicted to decrease Ribociclib C_{max} and AUC by 37% and 60%, respectively.

Drugs That are Affected by Ribocicilib

CYP3A4 and CYP1A2 Substrates:
A drug interaction trial in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of Ribociclib (400 mg once daily for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Administration of Ribociclib at 600 mg once daily is predicted to increase midazolam C_{max} and AUC by 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of 400 mg Ribociclib on caffeine was minimal, with C_{max} decreased by 10% and AUC_{inf} increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at 600 mg Ribociclib once daily dose.

Gastric pH-elevating Agents: Coadministration of Ribociclib with drugs that elevate the gastric pH was not evaluated in a clinical trial; however, altered Ribociclib absorption was not identified in a population PK analysis and was not predicted using physiology based PK models.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between Ribociclib and letrozole following coadministration of the drugs.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between Ribociclib and anastrozole following coadministration of the drugs.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between Ribociclib and exemestane following coadministration of the drugs.

Fulvestrant: Data from a clinical trial in patients with breast cancer indicated no clinically relevant effect of Fulvestrant on Ribociclib exposure following coadministration of the drugs.

Tamoxifen: Ribociclib is not indicated for concomitant use with tamoxifen. Data from a clinical trial in patients with breast cancer indicated that tamoxifen Cmax and AUC increased approximately 2-fold following coadministration of 600 mg Ribociclib.

In vitro Studies Effect of Ribociclib on CYP Enzymes: In vitro, Ribociclib was a reversible inhibitor of CYP1A2, CYP2E1 and CYP3A4/5 and a time-dependent inhibitor of CYP3A4/5, at clinically relevant concentrations. In vitro evaluations indicated that Ribociclib has no potential to inhibit the activities of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 at clinically relevant concentrations. It has no potential for time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6, and no induction of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 at clinically relevant concentrations.

Effect of Ribociclib on Transporters: In vitro evaluations indicated that Ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations.

Effect of Transporters on Ribociclib: Based on in vitro data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 in vitro.

OVERDOSAGE
There is limited experience with reported cases of overdose with Ribociclib in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

PHARMACEUTICAL INFORMATION
Storage condition
Store below 30° C and dry place, away from light and moisture. Keep out of the reach of children.

Packaging
Ribolib Tablet: Each commercial box contains 21 tablets in HDPE bottle.

LF40501

Manufactured by-
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

রিবোলিব

রিবোসিক্লিব সাক্সিনেট আইএনএন

উপাদান ঃ

রিবোসিক্লিব ট্যাবলেট ঃ প্রতিটি ফিল্ম কোটেড ট্যাবলেটে আছে রিবোসিক্লিব সাক্সিনেট আই এন এন যা রিবোসিক্লিব ২০০ মি গ্রা এর সমতুল্য।

নির্দেশনা ঃ

রিবোসিক্লিব মেনোপোজ পূর্ববর্তী , মেনোপোজ মধ্যবর্তী এবং মেনোপোজ পরবর্তী মহিলাদের হরমোন পজিটিভ হার টু নেগেতিভ এডভান্সড / মেটাস্টাটিক স্তন ক্যান্সারে অ্যারোমাটেজ ইনহিবিটর অথবা ফুলভেস্ট্রান্টের সাথে নির্দেশিত।

সেবনমাত্রা ও বিধি ঃ

রিবোসিক্লিব খালি পেটে অথবা খাওয়ার পর ৬০০ মিগ্রা প্রতিদিন একবার (তিনটি ২০০ মি গ্রা ট্যাবলেট) ২১ দিনের জন্য সেবন করতে হবে এবং পরবর্তী ৭ দিন বন্ধ রাখতে হবে।

রোগীর শারীরিক অবস্থার উপর বিবেচনা করে সেবনমাত্রা স্থগিত/বিরত অথবা কমাতে হবে।

নির্দিষ্ট জনসংখ্যার উপর ব্যবহার

গর্ভাবস্থায় ব্যবহার ঃ গর্ভকালীন অবস্থায় রিবোসিক্লিব ব্যবহার ভ্রুনের ক্ষতির কারণ হতে পারে।

স্তন্যদানকালীন সময় ব্যবহার ঃ স্তন্যদানকালীন নারীদের ক্ষেত্রে রিবোসিক্লিব নির্দেশিত নয়।

প্রতিনির্দেশনা ঃ

নাই

পার্শ্বপ্রতিক্রিয়া ঃ

- নিউট্রোপেনিয়া
- বমি বমি ভাব
- সংক্রমণ
- ক্লান্তি
- ডায়রিয়া
- লিউকোপেনিয়া
- চুল পরে যাওয়া
- মাথা ব্যথা
- কোষ্ঠকাঠিন্য
- কফ
- ফুসকুড়ি
- হৃৎপিণ্ডের সমস্যা
- যকৃতের সমস্যা

সংরক্ষণ ঃ

৩০° সে তাপমাত্রার নিচে, শুকনো স্থানে, আলো ও আদ্রতা থেকে দূরে রাখুন। সকল ওষুধ শিশুদের নাগালের বাইরে রাখুন ।

সরবরাহ ঃ

প্রতিটি বানিজ্যিক মোড়কে ২১ টি ট্যাবলেট এইচডিপিই বোতলে রয়েছে।

বিস্তারিত ইংরেজী অংশে দেখুন

প্রস্তুতকারক
বীকন ফার্মাসিউটিক্যালস্ লিমিটেড
ভালুকা, ময়মনসিংহ, বাংলাদেশ