COMPOSITION

RIBOKIS tablet: Each film coated tablet contains Ribociclib Succinate INN equivalent to Ribociclib 200 mg.

PHARMACOLOGY

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and are downstream of 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).

INDICATION

Early Breast Cancer

Ribociclib is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

Advanced or Metastatic Breast Cancer

Ribociclib is indicated for the treatment of adults with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- Fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Important Administration Instructions

Ribociclib can be taken with or without food preferably in the morning. Pre/perimenopausal women, or men, treated with the combination Ribociclib plus an aromatase inhibitor or Fulvestrant, should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist according to current clinical practice standards.

Patients should take their dose of Ribociclib at approximately the same time each day, preferably in the morning. If the patient vomits after taking the dose, or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

Early Breast Cancer

The recommended dosage of Ribociclib is 400 mg (two 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. Ribociclib should be given in combination with an aromatase inhibitor.

In patients with early breast cancer, treatment with Ribociclib should continue for 3 years or until disease recurrence or unacceptable toxicity occurs.

Advanced or Metastatic Breast Cancer

The recommended dosage of Ribociclib is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off in 28-day treatment cycles. Ribociclib should be given in combination with endocrine therapy (Fulvestrant or an aromatase inhibitor).

Dosage Modifications for Adverse Reactions:

The recommended dose modifications for adverse reactions are listed in Table 1.

Table 1: Recommended Dose Modification for Adverse Reactions

Level	Ribociclib Dose	Number of Tablets
Early breast cancer		
Starting dose	400 mg/day	two 200 mg tablets
Dose reduction	200 mg/day*	one 200 mg tablet
Advanced or metastatic breast cancer		
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 dose reduction below 200 mg/day is required, discontinue Ribociclib.

Table 2: Dose Modification and Management for Interstitial Lung Disease/Pneumonitis

	Grade 1 (asymptomatic)	Grade 2 (symptomatic)	Grade 3 (severe symptomatic) or 4 (life-threatening)
ILD/Pneumonitis	No dose interruption or adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade ≤ 1 then consider resuming Ribociclib at the next lower dose level*. If Grade 2 recurs, discontinue Ribociclib.	Discontinue Ribociclib.

Abbreviation: ILD, interstitial lung disease.

*An individualized benefit-risk assessment should be performed when considering resuming Ribociclib.

Table 3: Dose Modification and Management for Cutaneous Adverse Reactions, Including SCARs

	Grade 1 (< 10% body surface area (BSA) with active skin toxicity, no signs of systemic involvement)	**Grade 2** (10%-30% BSA with active skin toxicity, no signs of systemic involvement)	**Grade 3** (severe rash not responsive to medical management; > 30% BSA with active skin toxicity, signs of systemic involvement present; SJS*)	**Grade 4** (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life threatening consequences; TEN**)
Cutaneous adverse reactions, including SCARs	**Grade 1 & 2** No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.		**Grade 3** Interrupt Ribociclib until the etiology of the reaction has been determined. If the etiology is a SCAR, permanently discontinue Ribociclib. If the etiology is not a SCAR, interrupt dose until recovery to Grade ≤ 1, then resume Ribociclib at same dose level. If the cutaneous adverse reaction still recurs at Grade 3, resume Ribociclib at the next lower dose level.	**Grade 4** Permanently discontinue Ribociclib.

Abbreviations: BSA, body surface area; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*SJS (Grade 3 and 4) is defined as skin sloughing covering < 10% BSA and 10%-30% BSA, respectively, with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

**TEN (Grade 4) is defined as skin sloughing covering ≥ 30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment).

Table 4: Dose Modification and Management for QT Prolongation

QTcF* prolongation	Early breast cancer	Advanced or metastatic breast cancer
> 480 ms and ≤ 500 ms	Interrupt Ribociclib treatment and wait until QTcF resolves to < 480 ms	
	Resume at the same dose	Reduce to the next lower dose level
	If QTcF > 480 ms recurs, interrupt Ribociclib treatment and wait until QTcF resolves to < 480 ms, then resume at next lower dose level.	
> 500 ms	Interrupt Ribociclib treatment and wait until QTcF resolves to < 480 ms, then resume at next lower dose level. If QTcF > 500 ms recurs, discontinue Ribociclib.	

Permanently discontinue Ribociclib if QTcF interval prolongation is either > 500 ms or > 60 ms change from baseline and associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, syncope, or signs/symptoms of serious arrhythmia.

Note: If dose reduction below 200 mg/day is required, discontinue Ribociclib. Electrocardiograms (ECGs) should be assessed prior to initiation of treatment in all patients. Repeat ECGs at approximately Day 14 of the first cycle, and as clinically indicated.

In case of QTcF prolongation at any given time during treatment, monitor ECG more frequently, and as clinically indicated.

*QTcF = QT interval corrected by Fridericia's formula.

Table 5: Dose Modification and Management for Hepatobiliary Toxicity

	Grade 1 (> ULN – 3 x ULN)	**Grade 2 (> 3 to 5 x ULN)**	**Grade 3 (> 5 to 20 x ULN)**	**Grade 4 (> 20 x ULN)**
AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN	No dose adjustment is required.	Baseline* at < Grade 2: Dose interruption until recovery to ≤ baseline grade, then resume Ribociclib at same dose level. If Grade 2 recurs, resume Ribociclib at next lower dose level.	Dose interruption until recovery to ≤ baseline* grade, then resume at next lower dose level. If Grade 3 recurs, discontinue Ribociclib.	Discontinue Ribociclib.
		Baseline* at Grade 2: No dose interruption.		
Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue Ribociclib.			

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.

If Grade ≥ 2 abnormalities are noted, monitor more frequently, and as clinically indicated.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

*Baseline = prior to treatment initiation.

Table 6: Dose Modification and Management for Neutropenia

	Grade 1 or 2 (ANC 1000/mm^3 ≤ LLN)	Grade 3 (ANC 500 ≤ 1000/mm^3)	Grade 3 febrile* neutropenia	Grade 4 (ANC < 500/mm^3)
Neutropenia	No dose adjustment is required.	Dose interruption until recovery to Grade ≤ 2. Resume Ribociclib at the same dose level. If toxicity recurs at Grade 3, dose interruption until recovery, then resume Ribociclib at the next lower dose level.	Dose interruption until recovery of neutropenia to Grade ≤ 2. Resume Ribociclib at the next lower dose level.	Dose interruption until recovery to Grade ≤ 2. Resume Ribociclib at the next lower dose level.
	Perform complete blood counts (CBCs) before initiating treatment with Ribociclib. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.			

Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal.

*Grade 3 neutropenia with single episode of fever > 38.3°C (or) 38°C or above for more than one hour and/or concurrent infection.

Table 7: Dose Modification and Management for Other Toxicities*

	Grade 1 or 2	Grade 3	Grade 4
Other Toxicities	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to Grade ≤ 1 then resume Ribociclib at same dose level. If Grade 3 recurs, resume Ribociclib at the next lower dose level.	Discontinue Ribociclib.

*Excluding interstitial lung disease (ILD)/pneumonitis, cutaneous adverse reactions, including severe cutaneous adverse reactions (SCARs), QT interval prolongation, hepatobiliary toxicity, and neutropenia.

Dose Modification for Use with Strong CYP3A Inhibitors
Avoid concomitant use of Ribociclib with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential for CYP3A inhibition.

If a strong CYP3A inhibitor must be coadministered, reduce the Ribociclib dose as shown in Table 8.

Table 8: Dose Modification for Use with Strong CYP3A Inhibitors

Indication	Co-administration with Strong CYP3A Inhibitors
Early breast cancer	Reduce the Ribociclib dose to 200 mg once daily
Advanced or metastatic breast cancer	Reduce the Ribociclib dose to 400 mg once daily

If the strong inhibitor is discontinued, change the Ribociclib dose (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Dose Modification for Hepatic Impairment
The recommended dose modifications for patients with hepatic impairment are shown in Table 9.

Table 9: Dose Modification for Hepatic Impairment

Indication	Mild hepatic impairment (Child-Pugh class A)	Moderate and severe hepatic impairment (Child-Pugh class B or C)
Early breast cancer	No dose adjustment is necessary	No dose adjustment is necessary
Advanced or metastatic breast cancer	No dose adjustment is necessary	Ribociclib 400 mg once daily

Dose Modification for Severe Renal Impairment
The recommended starting dose is 200 mg Ribociclib once daily for patients with severe renal impairment.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Interstitial Lung Disease (ILD)/Pneumonitis
Patients treated with CDK 4/6 inhibitors should be monitored for pulmonary symptoms indicative of 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.

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 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.

Hepatotoxicity
Increases in serum transaminase and bilirubin 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.

Neutropenia
Perform complete blood count (CBC) before initiating therapy with Ribociclib. Monitor CBC 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 females to use effective contraception during therapy.

ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Interstitial Lung Disease/Pneumonitis
- Severe Cutaneous Adverse Reactions
- QT Interval Prolongation
- Hepatotoxicity
- Neutropenia

USE IN SPECIFIC POPULATIONS
Pregnancy
Ribociclib can cause fetal harm when administered to a pregnant woman.

Lactation
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
Ribociclib can cause fetal harm when administered to a pregnant woman.

Females
Advise females of reproductive potential to use effective contraception during treatment with Ribociclib and for at least 3 weeks after the last dose.

Males
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
No overall differences in safety or effectiveness of Ribociclib were observed between older and younger adults with early breast cancer & advanced or metastatic breast cancer.

Hepatic Impairment
No dose adjustment is necessary in patients with breast cancer who have mild hepatic impairment (Child-Pugh class A). A reduced starting dose of 400 mg is recommended in patients with advanced or metastatic breast cancer who have moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C).

Renal Impairment
No dose adjustment is necessary in patients with breast cancer who have mild to moderate (30 mL/min to 89 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR)) renal impairment. A reduced starting dose of 200 mg is recommended in patients with breast cancer who have severe renal impairment.

DRUG INTERACTIONS
CYP3A Inhibitors: Avoid concomitant use of Ribociclib with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce Ribociclib dose.

CYP3A4 Inducers: Avoid concomitant use of Ribociclib with strong CYP3A inducers.

CYP3A Substrates: The dose of CYP3A substrates may need to be reduced when given concurrently with Ribociclib.

Drugs Known to Prolong QT Interval: Avoid concomitant use of drugs known to prolong QT interval, such as anti-arrhythmic medicines.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 25^0 C in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
RIBOKIS tablet: Each HDPE container contains 63 tablets, a silica gel desiccant and polyester coil with child resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com

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