Indication	Ribociclib in combination with an aromatase inhibitor as adjuvant treatment for high risk hormone receptor-positive and HER2-negative early breast cancer. NB: The patient has currently received no more than 12 months of adjuvant or neoadjuvant endocrine therapy. NB: Patients must have had no prior treatment with a CDK 4/6 inhibitor unless either the patient is transferring from a company early access scheme and meets all the commissioning criteria for adjuvant ribociclib or the patient has suffered unacceptable toxicity on adjuvant abemaciclib plus endocrine therapy without any evidence of disease progression and is transferring to treatment with adjuvant ribociclib plus an aromatase inhibitor. If the latter, the treatment plan should be for a maximum CDK4/6 inhibitor treatment duration of 3 calendar years in all (time on abemaciclib plus that on ribociclib).
Treatment Intent	Adjuvant
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression or excessive toxicity or until the patient chooses to discontinue or for a maximum of 3 calendar years, whichever is the sooner.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • If patient is pre- or peri-menopausal they must have undergone ovarian ablation or suppression with LHRH agonist treatment. • Monitor **FBC**, **U&E** and **LFT** at baseline then every 2 weeks for the first two cycles and then at the beginning of the next four cycles, then every 2 months and more frequently if clinically indicated. If grade >/=2 hepatic abnormalities are noted (see table 2 below), more frequent monitoring is recommended. • Correct abnormalities in potassium, calcium, phosphorus and magnesium prior to initiating treatment. • If neuts >/= 1 and PLT >/= 100 proceed with treatment. • If neuts <1 or PLT <100 withhold ribociclib and alert consultant. • **Cardiac monitoring and guidance:** o ECG before starting treatment and then on day ~14 of cycle 1, then as clinically indicated. o Treatment should only be initiated in patients with QTcF values less than 450 msec. o In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended and treatment may have to be interrupted, reduced or discontinued see Table 3. o The use of ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation including; patients with long QT syndrome, with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias, and patients with electrolyte abnormalities. • **Hepatic impairment**: no dose adjustment required. • **Renal impairment:** No dose adjustment is necessary in mild or moderate impairment. In patients with severe renal impairment (CrCl <30 mL/min) a starting dose of 200mg/day is recommended, with close monitoring for signs of toxicity.

	• **Management of adverse reactions and dose adjustments:**
	  ○ **Dose Modification:** First and only dose reduction to 200mg/day, if further dose reduction required, discontinue treatment.
	  ○ **Haematological and non-haematological toxicities of ribociclib,** see tables below, for thrombocytopenia discuss with consultant.
	  ○ Adverse drug reactions include neutropenia, leukopenia, headache, back pain, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia, abnormal liver function test, lymphopenia, hypophosphataemia.
	  ○ **Interstitial lung disease/pneumonitis:** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). See table 5 below for dose modification and guidance in patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis.
	  ○ **Cases of toxic epidermal necrolysis (TEN)** have been reported with ribociclib treatment. If signs and symptoms suggestive of severe cutaneous reactions (e.g. progressive widespread skin rash often with blisters or mucosal lesions) appear, ribociclib should be discontinued immediately.
	• **Common drug and food interactions (for comprehensive list refer to BNF/SPC):**
	  ○ Avoid concomitant use with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) and consider an alternative medication with no or minimal CYP3A4 inhibition. If patients must be co-administered a strong CYP3A4 inhibitor, reduce ribociclib dose to 200mg/day, if patients have already been dose reduced to 200mg/day and initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided ribociclib treatment should be interrupted. If the strong inhibitor is discontinued, the ribociclib dose should be changed to the dose used prior to the initiation of the strong CYP3A44 inhibitor after at least 5 half-lives of the strong CYP3A44 inhibitor.
	  ○ Concomitant use with medicinal products known to prolong QTc interval (e.g. amiodarone, disopyramide, procainamide, quinidine, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol) should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval.
	  ○ Caution with CYP3A4 substrates with a narrow therapeutic index (e.g. ciclosporin, fentanyl, tacrolimus); the dose may need to be reduced as ribociclib may increase their exposure. Concomitant use of the following CYP3A44 substrates should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.
	  ○ Concomitant use of ribociclib with strong CYP3A44 inducers (carbamazepine, phenytoin, rifampicin, St John's Wort) should be avoided as it may lead to reduced ribociclib exposure.
	  ○ Contraindicated in patients with a peanut or soya allergy.
	  ○ Do not take with grapefruit juice / fruit.
	• **Missed dose:** If a dose is missed or vomiting occurs, an additional dose should not be taken that day.
	• **Driving and machinery:** Patients should be advised to be cautious when driving or using machines in case they experience fatigue, dizziness or vertigo during treatment.
	• For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.

References	SPC accessed online 15.05.2025 CDF list accessed online V1.362 15.05.2025 KMCC protocol BRE-063 V4

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modification of ribociclib – Neutropenia

	Grade 1 or 2 Neuts 1 - ≤LLN	**Grade 3** Neuts 0.5 - <1	**Grade 3 febrile neutropenia** Neuts 0.5 - <1 and single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection)	**Grade 4** Neuts < 0.5
Neutropenia	No dose adjustment is required	Dose interruption until recovery to grade ≤2. Resume at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery to grade ≤2, then resume and reduce by 1 dose level.	Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level	Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level.

Grading according to CTCAE Version 4.03

Table 2 Dose modification of ribociclib – 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 grade <2: Dose interruption until recovery to ≤ baseline grade, then resume at same dose level. If grade 2 recurs, resume at next lower dose level. Baseline grade = 2: No dose interruption.	Dose interruption until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue.	Discontinue
Combined elevations in AST and/or ALT together 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.			

Grading according to CTCAE Version 4.03

Table 3 Dose modification of ribociclib – QT prolongation

>480 msec and </=500 msec	Dose interrupt until QTcF resolves to <481 msec and resume at the same dose level. If QTcF >/=481 msec recurs, interrupt treatment until QTcF resolves to <481 msec, then resume at next lower dose level.
>500 msec	Dose interrupt until QTcF resolves to <481 msec and resume at the next lower dose level. If QTcF >500 msec recurs, discontinue.
If QTcF interval is greater than 500 msec or shows a greater than 60 msec change from baseline in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue.	

Table 4 Dose modification of ribociclib and management – ILD/pneumonitis

	Grade 1* (asymptomatic)	**Grade 2*** (symptomatic)	**Grade 3 or 4*** (severe)
ILD/pneumonitis	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume at the next lower dose level**.	Discontinue
***Grading according to CTCAE Version 4.03 ****An individualised benefit-risk assessment should be performed when considering resuming ribociclib.			

Table 5 Dose modification and management - Other toxicities*

Other toxicities	**Grade 1 or 2****	**Grade 3****	**Grade 4****
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Dose interruption until recovery to grade ≤1, then resume at the same dose level. If grade 3 recurs, resume at the next lower dose level.	Discontinue
* Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis. ** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)			

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**RIBOCICLIB**	**400mg**	PO	OD for 21 days followed by a 7-day break. Swallow whole, do not chew, crush or split tablets prior to swallowing. Take the dose at approximately the same time each day. Available as 200mg tablets Store in the original package, do not use after 2 months after dispensing date. Return any remaining tablets to the pharmacy for disposal.
	LETROZOLE	**2.5mg**	PO	OD *An alternative aromatase inhibitor may be prescribed.*
	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously. Dispense with cycle 1 only.