Ribociclib Therapy (Adjuvant) - 28 day

- **Note: This regimen relates to the use of ribociclib in the ADJUVANT setting only**
- **For use in the metastatic setting, please refer to NCCP Regimen 525 Ribociclib Therapy (Metastatic) -28 Day**

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
In combination with an aromatase inhibitor (AI) is indicated for the adjuvant treatment of patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence.	C50	00892a	N/A

*For post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ribociclib is taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise of a complete cycle of 28 days. Treatment is continued for up to three years, or until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route and Method of Administration	Cycle
1-21	Ribociclib	400mg daily	PO with or without food	Every 28 days
Please note ribociclib should be administered in combination with an aromatase inhibitor which should be taken orally once daily continuously throughout the 28-day cycle.				
In pre or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone releasing hormone (LHRH) agonist.				
Ribociclib should not be taken with grapefruit or grapefruit juice. If the patient vomits after taking a dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.				

ELIGIBILITY:

- Indication as above
- ECOG 0-1
- Anatomic Stage Group II disease that is either:
  - N1, or
  - N0 (T2-3, N0) with G2-3 and/or Ki67 ≥20%, excluding G1
- Anatomic Stage Group III disease
- QTcF interval <450ms
- Adequate bone marrow and organ function

CAUTION:

- Active cardiac disease or a history of cardiac dysfunction
- Impaired gastrointestinal function that alters drug absorption

EXCLUSIONS:

- Hypersensitivity to ribociclib or to peanut, soya or any of the excipients
- Metastatic disease, node negative breast cancer, inflammatory breast cancer
- Prior treatment with CDK4 or CDK6 inhibitors
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Serum electrolytes (including potassium, calcium, phosphorus and magnesium)
- ECG

Regular tests:

- FBC, renal and liver profile every two weeks for the first 2 cycles
- FBC, renal and liver profile prior to each cycle for the subsequent 4 cycles then as clinically indicated
    - If grade ≥2 liver abnormalities are noted, more frequent monitoring is recommended
- Serum electrolytes (including potassium, calcium, phosphorus and magnesium) prior to each cycle for 6 cycles and then as clinically indicated
- ECG should be repeated at day 14 of the first cycle and then as clinically indicated

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in Tables 1-7

Table 1: Recommended dose modifications of ribociclib for adverse reactions

Dose Level	Dose
Recommended dose	400mg/day
Dose reduction	200mg*/day
***If further dose reduction below 200mg/day is required, discontinue treatment**	

Haematological

Table 2: Dose modification and management of ribociclib for neutropenia

Grade 1 or 2*	Grade 3*	Grade 3*	Grade 4*
ANC 1.0x10^9/L - ≤LLN	**ANC 0.5 – <1.0x10^9/L**	**febrile neutropenia****	**ANC <0.5 x10^9/L**
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 to grade ≤2, then resume ribociclib and reduce by 1 dose level.	Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level	Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level.
* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) ** Grade 3 neutropenia with a single fever >38.3°C (or above 38°C for more than one hour and/or concurrent infection) ANC = absolute neutrophil count; LLN = lower limit of normal			

Renal and Hepatic Impairment:

Table 3: Dose modification of ribociclib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment
Mild/moderate	No dose adjustment is necessary	No dose adjustment is necessary in patients with early breast cancer with hepatic impairment
Severe	A starting dose of 200mg is recommended	
Renal and hepatic - SmPC		

Non-haematological Adverse events

Table 4: Dose modification and management of ribociclib 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 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. Baseline grade = 2: No dose interruption.	Dose interruption of ribociclib until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue ribociclib	Discontinue ribociclib
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 ribociclib			

* Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)
** Baseline = prior to treatment initiation

Table 5: Dose modification and management of ribociclib for QT prolongation

ECGs with QTcF >480 msec and ≤500 msec	• The dose should be interrupted until QTcF resolves to <481 msec • Resume at same dose level • If QTcF ≥481 msec recurs, interrupt treatment until QTcF resolves to <481 msec, then resume at next lower dose level
ECGs with QTcF >500 msec	• Dose interruption until QTcF resolves to <481 msec, then resume at next lower dose level • If QTcF >500 msec recurs, discontinue treatment
If QTcF interval prolongation to greater than 500 msec or greater than 60 msec change from baseline occurs in combination with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue ribociclib. Note: If further dose reductions are required at the 200 mg dose, treatment should be discontinued.	

Table 6: Dose modification and management of ribociclib for ILD/pneumonitis

ILD/pneumonitis	Grade 1* (asymptomatic)	Grade 2* (asymptomatic)	Grade 3 or 4* (severe)
	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 the next lower dose level**.	Discontinue ribociclib
*Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events) **An individualised benefit-risk assessment should be performed when considering resuming ribociclib ILD = interstitial lung disease			

Table 7: Dose modification and management of ribociclib for 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 ribociclib at the same dose level. If grade 3 recurs, resume ribociclib at the next lower dose level.	Discontinue ribociclib
* Excluding neutropenia, hepatotoxicity, QT interval prolongation and ILD/pneumonitis ** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events)			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Moderate to High (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists.
Information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: Not usually required

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **QT interval prolongation:** ECG should be assessed before initiating treatment. Any abnormality should be corrected before initiating treatment with ribociclib. The use of ribociclib should be avoided in patients who already have or at significant risk of developing QTc prolongation. This includes patients:
  - With long QT syndrome
  - With uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias.
  - With electrolyte abnormalities
  - The use of ribociclib with medicinal products known to prolong QTc interval should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Slamon D, et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. N Engl J Med 2024;390:1080-1091
2. FDA Special Alerts: Cyclin-Dependent Kinase 4/6 Inhibitors Safety Alert September 2019 available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Ribociclib (KISQALI®) Summary of Product Characteristics Accessed January 2025 .Available at: https://backend-prod.medicines.ie/uploads/files/66d78d84efad8.pdf

Version	Date	Amendment	Approved By
1	27/01/2025		Prof Michaela Higgins

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.