Ribociclib Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of **postmenopausal** women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer as **initial** endocrine-based therapy in combination with an aromatase inhibitor.	C50	00525a	CDS 01/02/2019
Treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine based therapy or in women who have received prior endocrine therapy. In pre or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone releasing hormone (LHRH) agonist	C50	00525b	CDS 01/09/2020

*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 once daily for 21 consecutive days followed by 7 days off treatment to comprise of a complete cycle of 28 days until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route and Method of Administration	Cycle
1-21	*Ribociclib	600mg 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 or fulvestrant 500mg which is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter				
*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:

- Indications as above
- Post menopausal woman with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy
- No prior systemic anti-cancer therapy for advanced disease
- ECOG 0-1
- Adequate bone marrow and organ function

CAUTION:

- Use with caution in patients with inflammatory breast cancer
- Active cardiac disease or a history of cardiac dysfunction
- Central nervous system metastases
- Impaired gastrointestinal function that alters drug absorption

EXCLUSIONS:

- Hypersensitivity to ribociclib or to peanut, soya or any of the excipients
- Prior treatment with any CDK4/6 inhibitor

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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
- 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	600mg/day
First dose reduction (Dose level -1)	400mg/day
Second dose reduction (Dose level -2)	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**	
CrCl (mL/min)	**Dose**	**Mild (Child Pugh Class A)**	No dose adjustment is needed
≥ 30 mL/min	No dose adjustment is needed	**Moderate and severe (Child Pugh Class B and C)**	67% of the original dose
< 30 mL/min	33% of the original starting dose		
Haemodialysis	Not recommended		

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	The dose should be interrupted. 1. If QTcF prolongation resolves to <481 msec, resume treatment at the same dose level. 2. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume ribociclib at the next lower dose level.
ECGs with QTcF >500 msec	If QTcF is greater than 500 msec on at least 2 separate ECGs, interrupt ribociclib until QTcF is <481 msec then resume ribociclib at next lower dose level. 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.

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

Minimal to Low (**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:

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2. Hurvitz, S et al Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2− advanced breast cancer (ABC) treated with endocrine therapy ± ribociclib: Overall survival (OS) results**.** JCO.2019.37.18_suppl.LBA1008
3. Tripathy, D et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. The lancet oncology: Volume 19, Issue 7, p904-915 July 2018
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6. Hortobagyi G N, Stemmer S M et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Annals of Oncology 29: 1541–1547, 2018
7. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
8. 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
9. 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
10. Ribociclib (KISQALI®) Summary of Product Characteristics Accessed October 2024 .Available at: https://backend-prod.medicines.ie/uploads/files/66d78d84efad8.pdf

Version	Date	Amendment	Approved By
1	30/01/2019		Prof Seamus O'Reilly
2	23/10/2019	Updated renal impairment recommendations as per SmPC update.Updated adverse events/regimen specific complications as per FDA Safety alert regarding ILD/pneumonitis .Addition of new indication	Prof Maccon Keane
3	22/04/2020	Updated adverse events/regimen specific complications as per SPC update regarding severe cutaneous reactions	Prof Maccon Keane
4	19/08/2020	Reimbursement status updated.Addition of dose modification table for ILD/pneumonitis	Prof Maccon Keane
5	29/11/2024	Reviewed. Updated exclusions and cautions sections. Updated regular testing section as per SmPC update. Updated renal and hepatic dose modifications table to align with Giraud et al 2023. Updated regimen in line with NCCP standardisation.	Prof Seamus O'Reilly

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.