Ribociclib Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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

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 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

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

EXCLUSIONS:

- Hypersensitivity to ribociclib or to peanut, soya or any of the excipients
- Active cardiac disease or a history of cardiac dysfunction
- Prior treatment with any CDK4/6 inhibitor
- Central nervous system metastases
- Impaired gastrointestinal function that alters drug absorption

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, prior to the second 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	

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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:

Table3: Dose modification of ribociclib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Mild to moderate	No dose adjustment required	**Mild (Child Pugh Class A)**	No dose adjustment required
Severe	Starting dose of 400mg Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity	**Moderate (Child Pugh Class B)**	Starting dose 400mg
		Severe (Child Pugh Class C)	

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE: Not usually required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Ribociclib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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 information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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.

- **Hepatobiliary toxicity:** Liver function tests should be performed before initiating treatment with ribociclib. After initiating treatment, liver function should be monitored. Based on the severity of the transaminase elevations, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in table 4.
- **Infections:** Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.
- **Interstitial lung disease (ILD) and/or pneumonitis:** Patients should be regularly monitored for pulmonary symptoms indicative of ILD and/or pneumonitis. Patients with new or worsening respiratory symptoms should have treatment interrupted for further evaluation. Patients found to have severe ILD or pneumonitis should have CDK 4/6 inhibitor therapy permanently discontinued.
- **Concomitant treatment with inhibitors of CYP3A4:** Strong inhibitors of CYP3A4 may lead to increased toxicity. Concomitant use of strong CYP3A inhibitors during treatment with ribociclib should be avoided.
  - If co-administration with a strong CYP3A inhibitor is unavoidable, reduce the ribociclib dose to 400mg once daily.
  - In patients who have had their dose reduced to 400mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced to 200mg.
  - In patients who have had their dose reduced to 200mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, ribociclib treatment should be interrupted.

  Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring of signs of toxicity is recommended. When the strong inhibitor is discontinued, increase the ribociclib dose (after at least 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.
- **Severe cutaneous reactions:** Toxic epidermal necrolysis (TEN) has 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.
- **Concomitant treatment with inducers of CYP3A4:** May lead to decreased ribociclib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of ribociclib with strong CYP3A4 inducers should be avoided. There is insufficient data to establish whether dose adjustments are required for co-administration of ribociclib with moderate CYP3A inducers.
- **CYP3A4 substrates:** Ribociclib is a strong CYP3A4 inhibitor at the 600mg dose and a moderate CYP3A4 inhibitor at the 400mg dose. Thus, ribociclib may interact with medicinal products which are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates. Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index and the SmPC of the other product should be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

DRUG INTERACTIONS:

- The concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers and ribociclib should be avoided - see adverse effects/ regimen specific complications for further details.
- Current drug interaction databases should be consulted for more information.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

REFERENCES:

1. Salmon, D et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3. *Journal of Clinical Oncology* 36, no. 24 (August 20 2018) 2465-2472.
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
4. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016;375:1738-48
5. Slamon D, Neven P et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472
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. KISQALI® Summary of Product Characteristics Accessed April 2020 Available at https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_en.pdf
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

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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens