Systemic Anti-Cancer Treatment Protocol

Ribociclib

PROTOCOL REF: MPHARIBOBR
(Version No: 1.0)

Approved for use in:

Ribociclib in combination with an aromatase inhibitor is indicated for the treatment of previously untreated, oestrogen receptor-positive, HER2- negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy.

Blueteq form is required and includes the following criteria:

- Previous hormone therapy whether as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval ≥ 12 months.
- Female patients are either post-menopausal or if pre- or peri-menopausal have undergone ovarian ablation or suppression with LHRH agonist treatment.
- ECOG status 0-2.

Dosage:

Drug	Dosage	Route	Frequency
Ribociclib	600mg once daily	Oral	Days 1 to 21 followed by 7 days rest 28 day cycle
Letrozole or alternative Aromatase Inhibitor		Oral	Days 1 to 28 continuously

Treatment to continue until progression or unacceptable toxicity.

Aromatase inhibitor to be initiated at CCC, 1 month's supply given then further supply to be obtained from the GP.

Extravasation risk:

Not applicable

Contra-indications to treatment with Ribociclib:

Hypersensitivity to the active substance or to peanut, soya or any of the excipients listed in the SmPC.

Administration:

Ribociclib is available as 200 mg film-coated tablets.

It can be taken with or without food. Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patient vomits after taking the 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.

Ribociclib tablets should be swallowed whole and should not be chewed, crushed or split prior to swallowing.

Ribociclib should be used together with letrozole or another aromatase inhibitor. The aromatase inhibitor is taken orally, once daily, continuously throughout the 28‑day cycle. Please refer to the Summary of Product Characteristics (SmPC) of the aromatase inhibitor for additional details.

Patients should be instructed to avoid pomegranates, pomegranate juice, grapefruit or grapefruit juice. These are known to inhibit CYP3A4 enzymes and may increase exposure to ribociclib.

Drug Interactions

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter its pharmacokinetics.

CYP3A4 inhibitors	The concomitant use of strong CYP3A4 inhibitors must be avoided, list includes but is not exhaustive; **clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, verapamil and voriconazole**. Alternative concomitant medicinal products with less potential to inhibit CYP3A4 should be considered and patients should be monitored for ribociclib related adverse events. If co-administration of ribociclib with a strong CYP3A4 inhibitor cannot be avoided, the **dose of ribociclib should be reduced by one dose level** (see Table 1.0). In patients who have had their dose reduced to 200mg ribociclib daily and in whom initiation of a strong CYP3A4 inhibitor cannot be avoided, ribociclib treatment should be interrupted.
CYP3A4 inducers	The concomitant use of strong CYP3A4 inducers should be avoided, including, but not limited to, **phenytoin, rifampicin, carbamazepine and St John's Wort**. An alternative concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered. The concomitant use of moderate CYP3A4 inducers may lead to decreased exposure and consequently a risk for impaired efficacy, in particular in patients treated with ribociclib at 400 mg or 200 mg once daily.
CYP3A4 substrates	Ribociclib is a moderate to strong CYP3A4 inhibitor and may interact with medicinal substrates that are metabolised via CYP3A4, which can lead to increased serum concentrations of the concomitantly used medicinal product. Concomitant administration of ribociclib at the 600 mg dose with the following CYP3A4 substrates should be avoided: **alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.**
	Caution is recommended in case of concomitant use with sensitive CYP3A4 substrates with a narrow therapeutic index including but not limited to **alfentanil, ciclosporin, everolimus, fentanyl, sirolimus and tacrolimus**. The dose of a sensitive CYP3A4 substrate with a narrow therapeutic index may need to be reduced as ribociclib can increase their exposure.
Substrates of transporters	Caution and monitoring for toxicity are advised during concomitant treatment with sensitive substrates of these transporters which exhibit a narrow therapeutic index, including but not limited to **digoxin, pitavastatin, pravastatin, rosuvastatin and metformin.**
Medical products with potential to prolong QT interval	Co-administration of ribociclib with medicinal products with a known potential to prolong the QT interval such as anti-arrhythmic medicinal products (including, but not limited to, **amiodarone, disopyramide, procainamide, quinidine and sotalol**), and other medicinal products that are known to prolong the QT interval (including, but not limited to, **chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron**) should be avoided.

Investigations and Treatment Plan:

	Pre	C1	C1D14	C2	C2D14	C3	Ongoing
Medical Assessment	X	X		X		X	Every cycle
Nursing Assessment		X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	Every cycle
LFT	X		X	X	X	X	Every cycle
U&E	X			X		X	
Bone profile	X						After C1 as clinically indicted
ECG	X		X	X			After C2 as clinically indicated
CT scan	X					X	3 monthly
Informed Consent	X						
PS recorded	X	X	X	X	X	X	
Toxicities documented	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

The most common grade 3/4 adverse drug reactions (ADRs), reported at a frequency ≥ 20% and ≥ 2% respectively for the ribociclib and letrozole combination are listed below (this list is not exhaustive, please refer to SmPC for full details):

- Neutropenia
- Leukopenia
- Infections- UTIs very common
- Headache
- Back Pain
- Nausea and vomiting
- Fatigue
- Diarrhoea/ constipation
- Alopecia, rash (maculopapular), pruritis
- Hepatobilliary toxicity- raised LFTs (ALT, AST and serum bilirubin)
- Electrolyte disturbances- **hypocalcaemia, hypokalaemia, hypophosphataemia**

Special Warnings and Precautions

Neutropenia

- Based on the severity of the neutropenia, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in Table 2.0.

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 3.0. Recommendations for patients who have elevated AST/ALT grade ≥ 3 at baseline have not been established.

QT interval prolongation

- ECG should be assessed before initiating treatment. Treatment with ribociclib should be initiated only in patients with QTcF values less than 450 msec. ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.
- Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with ribociclib.
- The use of ribociclib should be avoided in patients who already have or who are 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 brady-arrhythmias;
    - with electrolyte abnormalities.
- The use of ribociclib with medicinal products known to prolong QTc interval and/or strong CYP3A4 inhibitors should be avoided as this may lead to clinically meaningful prolongation of the QTcF interval. If treatment with a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg once daily.

- Based on the observed QT prolongation during treatment, treatment with ribociclib may have to be interrupted, reduced or discontinued as described in Table 4.0.

Table 1.0: Dose modification guidelines

Dose level	Ribociclib dose	Number of 200 mg tablets
Starting dose	600 mg once daily	3
1st dose reduction	400 mg once daily	2
2nd dose reduction	200 mg* once daily	1
* If further dose reduction below 200 mg/day is required, the treatment should be permanently discontinued.		

Table 2.0: Dose modification and management- Neutropenia

Toxicities	Grade 1 or 2* (ANC 1000/mm^3 to ≤LLN)	Grade 3* (ANC 500 to < 1000/mm^3)	Grade 4* (ANC <500/mm^3)
Neutropenia	No dose adjustment is required.	Dose interruption until recovery to grade ≤2, then resume at the same dose level. If toxicity recurs at grade 3: dose interruption until recovery ≤ 2, then resume and reduce by 1 dose level***. For grade 3 febrile neutropenia**: Dose interruption until recovery to grade ≤2. Resume and reduce by 1 dose level***.	Dose interruption until recovery to grade ≤2, then resume 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). ***See Table 1.0 for dose modification levels. ANC = absolute neutrophil count; LLN = lower limit of normal			

Table 3.0: Dose modification and management- Hepatobiliary toxicity

Toxicities	Grade 1* (>ULN - 3xULN)	Grade 2* (>3 - 5xULN)	Grade 3* (>5 - 20xULN)	Grade 4* (>20xULN)
AST and/or ALT elevations from baseline**, without increase in total bilirubin > 2 x ULN	No dose adjustment is required.	Baseline at <grade 2: Dose interruption until recovery to ≤ baseline grade, resume ribociclib at same dose level. If grade 2 recurs, resume and reduce by 1 dose level***. Baseline at grade 2: No dose interruption.	Dose interruption of ribociclib until recovery to ≤ baseline grade, resume and reduce by 1 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 >3xULN along with total bilirubin >2xULN 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. ***See Table 1.0 for dose modification levels. ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal	

Table 4.0: Dose modification and management- QT Prolongation

ECGs with QTcF >480 msec	1. The dose should be interrupted. 2. If QTcF prolongation resolves to <481 msec, resume and reduce by 1 dose level. 3. If QTcF ≥481 msec recurs, interrupt dose until QTcF resolves to <481 msec and then resume and reduce by 1 dose level*.
ECGs with QTcF >500 msec	If QTcF >500 msec on at least 2 separate ECGs, interrupt ribociclib until QTcF is <481 msec then resume and reduce by 1 dose level. If QTcF interval prolongation to >500 msec or >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.
* See Table 1.0 for dose modification levels. QTcF = QT interval corrected using Fridericia's formula	

Table 5.0: Dose modification and management of 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 the same dose level. If grade 3 recurs, resume ribociclib and reduce by 1 dose level***.	Discontinue ribociclib.
* Excluding neutropenia, hepatotoxicity and QT interval prolongation. ** Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events). ***See Table 1.0 for dose modification levels.			

Haematological toxicity

Proceed rules for Cycle 1* day 1:

ANC ≥ 1.5 x 10^9/L	Platelets ≥ 100 x 10^9/L

Proceed on day 1 of each subsequent cycle:

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L

*Based on MonaLEEsa 2 clinical trial inclusion criteria.

Hepatic impairment

Mild Child-Pugh class A) - No dose adjustment

Moderate (Child-Pugh class B) to severe (Child-Pugh class C) – starting dose of 400 mg once daily is recommended.

Renal impairment

CrCl ≥ 30ml/min- no dose reduction.

CrCl < 30ml/min- close monitoring of signs of toxicity. No experience with ribociclib in this population.

References:

Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J (2016) Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med*. 3;375(18):1738-1748.

KISQALI® (ribociclib): Treatment Protocol Proforma1 .Novartis.September 2017

SmPC Ribociclib. Novartis. Available via electronic medicines compendium at https://www.medicines.org.uk/emc/product/8110 (accessed 01/10/18)