RIBOCICLIB (KISQALI®)
(in combination with an aromatase inhibitor)

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Cycle length</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1 to 21</td>
<td>4 weeks</td>
<td>Ribociclib</td>
<td>600 mg</td>
<td>Oral</td>
<td>ONCE daily</td>
</tr>
</tbody>
</table>

Ribociclib should be given along with continuous therapy with an aromatase inhibitor (such as letrozole 2.5mg daily). This should continue even in the case of treatment delays due to neutropenia and can be supplied by primary care.

NUMBER OF DAYS PER CYCLE
28 days

APPROVED INDICATIONS
Ribociclib, with an aromatase inhibitor, is recommended, as an option for treating hormone receptor positive, HER2 negative, locally advanced or metastatic breast cancer as initial endocrine based therapy in adults.

ELIGIBILITY CRITERIA
For patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate haematological, coagulation, hepatic, renal, and cardiac function.

EXCLUSION CRITERIA
No prior treatment with a CDK 4/6 inhibitor, unless palbociclib which has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity.

PREMEDICATION: None

RECOMMENDED TAKE HOME MEDICATION
Metoclopramide 10mg three times daily as required
*Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details*

INVESTIGATIONS / MONITORING REQUIRED
- FBC, U&E, LFT’s & tumour markers as appropriate prior to each cycle
- FBC every two weeks of the first two cycles
- ECG should be assessed before initiating treatment with Ribociclib. After initiating treatment, ECG should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.

REVIEW BY CLINICIAN
Day 28 of each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES
- Ribociclib can be taken with or without food (see section 4.5). 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 dose should be taken at the usual time.
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- Patients should be instructed to avoid pomegranates or pomegranate juice and grapefruit or grapefruit juice. These are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib.
  - Ribociclib is metabolised by CYP3A. Strong CYP3A inhibitors (such as clarithromycin, ketoconazole, verapamil, etc.) should be avoided during ribociclib treatment.
  - No dose modification is required for mild/moderate CYP3A inhibitors, but increased monitoring is advised.
  - Strong CYP3A inducers (such as rifampicin, carbamazepine, phenytoin, etc.) should be avoided due to decrease in ribociclib exposure.
  - Concomitant administration of a moderate CYP3A inducer may still reduce ribociclib exposure by a significant amount which may lead to treatment failure, particularly in patients who have already had a dose reduction however this has not been studied.
  - Ribociclib is also moderate to strong CYP3A inhibitor. Doses of CYP3A substrates with narrow therapeutic indexes may need to be reduced (such as cyclosporin, tacrolimus, fentanyl, etc.). The combination of 600mg ribociclib with the following drugs should be avoided: alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam.
  - Ribociclib has a potential to inhibit the activities of drug transporters P-gp, BCRP, OATP1B1/1B3, OCT1, OCT2, MATE1 and BSEP. 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.
  - Co-administration of Kisqali 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.
  - Patients should be made aware of the risks and symptoms of neutropenia and neutropenic sepsis and advised to stop taking ribociclib and contact the chemotherapy unit if they have any signs of infection.

EXTRAVASATION Not Applicable

TOXICITIES
- Neutropenia (59.6% of patients in trials experienced grade 3 neutropenia)
- Infections
- Hepatotoxicity
- QTcF prolongation
- Fatigue
- Nausea
- Decreased appetite
- Stomatitis
- Anaemia
- Alopecia
- Diarrhoea

DOSE MODIFICATION
**RIBOCICLIB (KISQALI®)**
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<table>
<thead>
<tr>
<th>Starting dose</th>
<th>600 mg/day</th>
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<tbody>
<tr>
<td>First dose reduction</td>
<td>400 mg/day</td>
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<tr>
<td>Second dose reduction</td>
<td>200 mg/day</td>
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**Haematological toxicity - Neutropenia**

<table>
<thead>
<tr>
<th>Grade 1 or 2* (ANC &gt; 1.0)</th>
<th>Grade 3* (ANC 0.5 – 1.0)</th>
<th>Grade 3* febrile neutropenia**</th>
<th>Grade 4* (ANC &lt;0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose adjustment is required</td>
<td>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.</td>
<td>Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level.</td>
<td>Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level.</td>
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**Table 3 Dose modification and management – Hepatobiliary toxicity**

<table>
<thead>
<tr>
<th>AST and/or ALT elevations from baseline**, without increase in total bilirubin above 2 x ULN</th>
<th>Grade 1* (&gt; ULN – 3 x ULN)</th>
<th>Grade 2* (&gt;3 to 5 x ULN)</th>
<th>Grade 3* (&gt;5 to 20 x ULN)</th>
<th>Grade 4* (&gt;20 x ULN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose adjustment is required.</td>
<td>Baseline grade &lt;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.</td>
<td>Dose interruption of ribociclib until recovery to ≤ baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue ribociclib.</td>
<td>Discontinue ribociclib.</td>
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**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.
Table 4 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 treatment at the same dose level.
|                         | 3. 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 5 Dose modification and management – Other toxicities*

<table>
<thead>
<tr>
<th>Other toxicities</th>
<th>Grade 1 or 2**</th>
<th>Grade 3**</th>
<th>Grade 4**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.</td>
<td>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.</td>
<td>Discontinue Ribociclib.</td>
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* Excluding neutropenia, hepatotoxicity and QT interval prolongation.

TREATMENT LOCATION
Cancer Centre or Cancer Unit

REFERENCES:

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>Ribociclib</th>
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<tbody>
<tr>
<td>Document No:</td>
<td>CRP13 B034</td>
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<tr>
<td>Current Version:</td>
<td>1.0</td>
</tr>
<tr>
<td>Author:</td>
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<td>Date Approved:</td>
<td>28.02.18</td>
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<td>Approved by:</td>
<td>Steve Williamson Consultant Pharmacist Northern Cancer Alliance</td>
</tr>
<tr>
<td>Due for Review</td>
<td>01.03.21</td>
</tr>
<tr>
<td>Summary of Changes</td>
<td>V1.0 First edition</td>
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