RIBOCICLIB (Kisqali) (with aromatase inhibitor)

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (RIB2) (RIB3)

1. The treatment of previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic, not amenable to curative treatment, breast cancer, without prior CDK 4/6 inhibitor treatment, without previous hormone therapy for locally advanced or metastatic disease (previous hormone therapy with anastrazole or letrozole whether as adjuvant therapy or as neoadjuvant treatment is allowed as long as the patient has had a disease-free interval of 12 months or more since completing treatment with neoadjuvant or adjuvant anastrazole or letrozole). PS 0, 1 or 2. (TA496)
2. Ribociclib in combination with an aromatase inhibitor as adjuvant treatment for high risk hormone receptor-positive and HER2-negative early breast cancer, has completed definitive locoregional therapy (surgery with or without radiotherapy) and completed any adjuvant or neoadjuvant chemotherapy (no prior treatment with a CDK 4/6 inhibitor) but has currently received no more than 12 months of adjuvant or neoadjuvant endocrine therapy. PS 0 or 1.

REGIMEN

Metastatic disease

Days 1 to 21 RIBOCICLIB 600mg tablet oral once daily (then 7 days off)
Aromatase inhibitor (prescribe appropriate support regimen)

Adjuvant disease

Days 1 to 21 RIBOCICLIB 400mg tablet oral once daily (then 7 days off)
Aromatase inhibitor (prescribe appropriate support regimen)

CYCLE FREQUENCY AND NUMBER OF CYCLES

Metastatic disease - every 28 days whilst deriving benefit or until unacceptable toxicity.
Adjuvant high risk disease - every 28 days for maximum 3 calendar years from date of first dose of a CDK4/6 inhibitor.

ADMINISTRATION

Available as 200mg tablets
Swallow whole with or without food.
Grapefruit and grapefruit juice should be avoided while on ribociclib.
Not allowed if allergic to soya or peanuts.

ANTI-EMETICS

Low risk all days

CONCURRENT MEDICATION REQUIRED

Aromatase inhibitor (letrozole or anastrazole (or exemestane but exemestane would make patients ineligible for 2nd line everolimus)) must be prescribed (may be by GP).
Ovarian suppression for pre or peri-menopausal women.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Not applicable

INVESTIGATIONS

Blood results required before ribociclib administration
FBC baseline, every 2 weeks for 2 cycles, then every 4 weeks for 4 cycles, then may be reduced to every 2–3 months in patients with stable disease
Platelets x 10^9/L >50
LFTs baseline, every 2 weeks for 2 cycles, then every 4 weeks for 4 cycles, then as indicated
U&Es every 4 weeks, then may be reduced in line with FBC monitoring
ECG to include QT interval (baseline QTcF <450msec), at 2 weeks, at 4 weeks, then only as indicated

MAIN TOXICITES AND ADVERSE REACTIONS

Ribociclib	Neutropenia Abnormal liver function tests Electrocardiogram QT prolongation leukopenia, anaemia, lymphopenia, Thrombocytopenia, febrile neutropenia Hypocalcaemia, hypokalaemia, hypophosphataemia Respiratory disorders Skin rashes Fatigue, peripheral oedema, asthenia, pyrexia UTI Blood creatinine increased, weight decreased

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS (not exhaustive list check SPC/BNF/Stockleys)

Ribociclib	Ribociclib is a strong CYP3A4 inhibitor at the 600mg dose and a moderate CYP3A4 inhibitor at the 400mg dose. Ribociclib may interact with medicinal products which are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrates. Strong CYP3A4 inhibitors (eg clarithromycin, itraconazole, posaconazole, voriconazole) should be avoided. CYP3A4 inducers (eg carbamazepine, phenytoin) should be avoided. Grapefruit and grapefruit juice should be avoided. Tamoxifen – avoid. Drugs that prolong QT interval – caution with adding drugs that prolong QT interval after the initiation period with ribociclib without further ECG monitoring.

DOSE MODIFICATIONS

Ribociclib dose combination therapy
Recommended dose 600mg once daily
First dose adjustment 400mg once daily
Second dose adjustment 200mg once daily
If further dose reduction below 200mg/day is required, the treatment should be permanently discontinued.

Haematological

Ribociclib

Neutropenia grade 1 or 2 (ANC 1.0x10^9/l - ≤LLN)	No dose adjustment is required
Neutropenia grade 3 (ANC 0.5-<1.0x10^9/l)	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.
Neutropenia grade 3 febrile neutropenia (with a single fever >38.0°C (or concurrent infection)	Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level
Neutropenia grade 4	Dose interruption until recovery to grade ≤2. Resume ribociclib and reduce by 1 dose level.

Non-haematological

Ribociclib

Hepatobiliary toxicity

AST and/or ALT elevations from baseline, without increase in total bilirubin above 2xULN Grade 1 (>ULN–3xULN)	No dose adjustment is required.
AST and/or ALT elevations from baseline, without increase in total bilirubin above 2xULN Grade 2 (>3 to 5xULN) Baseline grade <2 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. No dose interruption.
AST and/or ALT elevations from baseline, without increase in total bilirubin above 2xULN Grade 3 (>5 to 20xULN)	Dose interruption of ribociclib until recovery to ≤baseline grade, then resume at next lower dose level. If grade 3 recurs, discontinue ribociclib.
AST and/or ALT elevations from baseline, without increase in total bilirubin above 2xULN Grade 4 (>20xULN)	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.

QT prolongation

ECGs with QTcF >480msec - 1	The dose should be interrupted.
If QTcF prolongation resolves to <481msec,	Resume treatment at the next lower dose level.
If QTcF ≥481msec recurs	Interrupt dose until QTcF resolves to <481 msec and then resume ribociclib at the next lower dose level.
ECGs with QTcF >500msec	
If QTcF is greater than 500msec,	Interrupt ribociclib until QTcF is <481msec then resume ribociclib at next lower dose level.
interrupt ribociclib until QTcF is <481msec then resume ribociclib at next lower dose level.	Permanently discontinue ribociclib.

Other toxicities

Grade 1 or 2	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3	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.
Grade 4	Discontinue ribociclib.

Hepatic impairment

Ribociclib

Child-Pugh scores are based on ascites, encephalopathy, INR, albumin, total bilirubin

Mild hepatic impairment (Child-Pugh A)	No dose adjustment is required
Moderate hepatic impairment (Child-Pugh B) and severe hepatic impairment (Child-Pugh C)	Can have increased (less than 2-fold) exposure to ribociclib and the starting dose of 400mg ribociclib once daily is recommended.

Renal impairment

Ribociclib

Mild or moderate renal impairment	No dose adjustment is necessary
Severe renal impairment	A starting dose of 400mg is recommended Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity.

REFERENCES

1. SPC November 2019
2. CDF list
3. Hortobagyi, G et al; NEJM 2016; 375: 1738–1748
4. Im, S-A et al; NEJM 2019; published online DOI: 10.1056/NEJMoa1903765