Ribociclib

Indication

In combination with letrozole (plus ovarian suppression if pre/peri-menopausal) for the initial treatment of postmenopausal women with ER positive, HER2 negative advanced breast cancer
In combination with fulvestrant for patients with ER positive, HER2 negative advanced breast cancer, in patients who have progressed on an aromatase inhibitor

In combination with an aromatase inhibitor (plus ovarian suppression if pre/peri-menpausal) for adjuvant treatment of hormone receptor-positive HER2-negative early breast cancer at high risk of recurrence defined as:
- ≥4 positive axillary lymph nodes or
- 1-3 positive axillary lymph nodes and a primary tumour size ≥5cm or
- 1-3 positive axillary lymph nodes and histological grade 3 disease or
- 1-3 positive axillary lymph nodes and a primary tumour size ≥5cm and histological grade 3 disease

via Novartis FOC scheme In combination with an aromatase inhibitor (plus ovarian suppression if pre/peri-menpausal) for the adjuvant treatment of patients with ER positive, HER-2 negative early breast cancer at high risk of recurrence as defined by the NATALEE registration trial

Regimen details

ADVANCED	Ribociclib	**600mg** OD for 21 days
ADJUVANT	Ribociclib	**400mg** OD for 21 days

Cycle frequency

28 days

Number of cycles

Advanced- continue until disease progression
Adjuvant- maximum of 3 years (39 cycles if no delays)

Administration

Ribociclib 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. No tablet should be ingested if it is broken, cracked or otherwise not intact.
Patients should be instructed to avoid grapefruit or grapefruit juice. Also see further sections for drug interactions and dose considerations

Additional supportive medication

Metoclopramide with cycle 1

Investigations – pre first cycle

Investigation	Validity period

FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
ECG	

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) – if bloods have been normal can consider bloods 12 weekly from cycle 7

Also check on day 14 of the first 2 cycles

ECG at baseline, on day 14 of first cycle, and then as clinically indicated

Clinical toxicity assessment for infection, bleeding, thromboembolism, fatigue, GI effects and neuropathy

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

No dose adjustments necessary in patients with early breast cancer with hepatic impairment. Reduce starting dose to 400mg in patients with moderate or severe hepatic impairment in advanced breast cancer.
Reduce starting dose to 200mg in patients with severe renal impairment
Concomitant use of strong CYP3A4 inhibitors (see dose modifications)
Avoid concomitant use of strong CYP3A4 inducers
Concomitant use of drugs that prolong QT interval
Ribociclib is a moderate/strong CYP3A4 inhibitor and may interact with drugs metabolized by CYP3A4 (see Drug Interactions section)

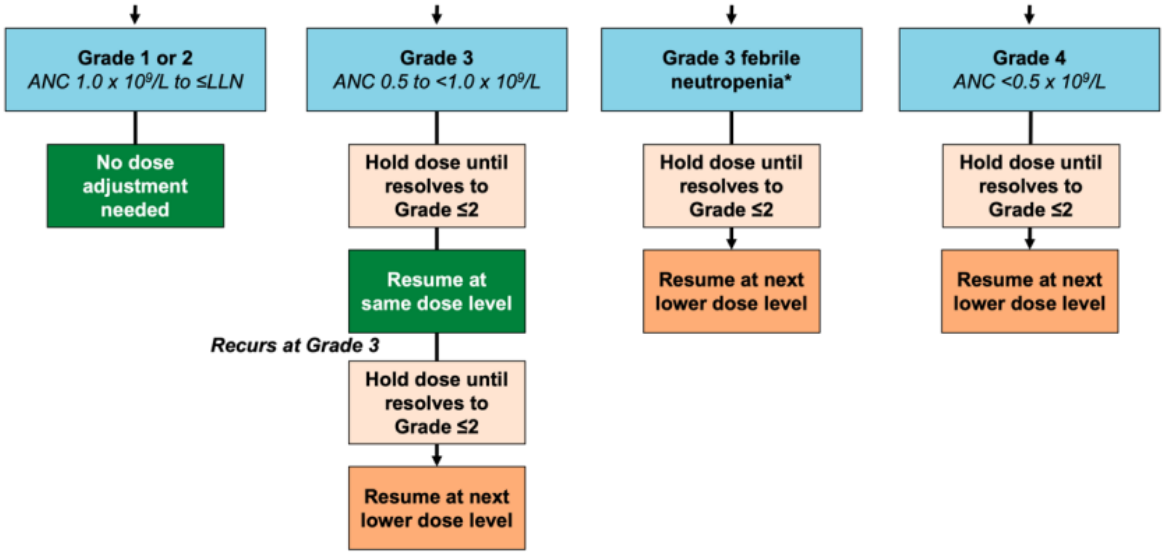
Adverse effects –

for full details consult product literature/ reference texts

Dosing levels

Dose level	Ribociclib Dose
Starting dose ABC	600mg
Starting dose EBC/Dose reduction 1 ABC	400mg
Dose reduction 1 EBC/ Dose reduction 2 ABC	200mg

Neutropenia

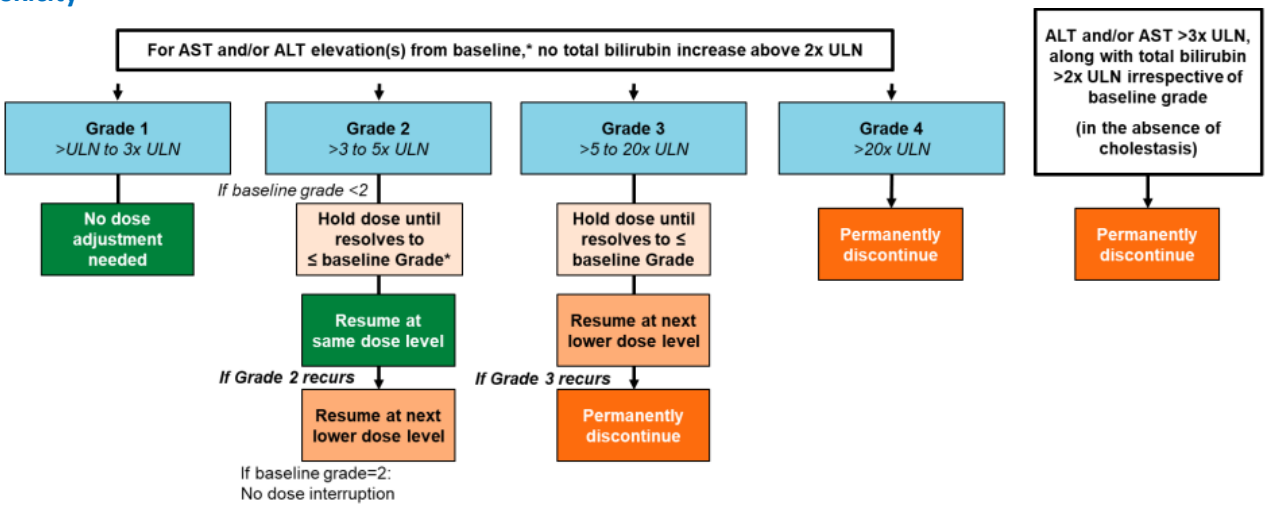


*Grade 3 neutropenia with a single fever >38.3°C (or 38°C and above for more than one hour and/or concurrent infection).

Grading according to CTCAE Version 4.03.

ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.

Hepatotoxicity

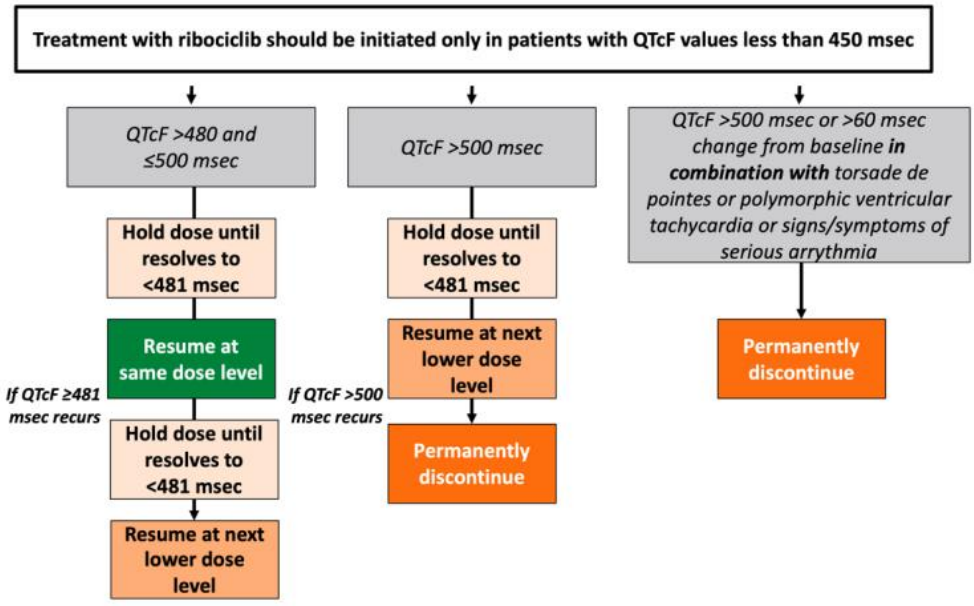


*Baseline = prior to treatment initiation.

Grading according to CTCAE Version 4.03.

ALT=alanine transaminase; AST=aspartate transaminase; CTCAE=Common Terminology Criteria for Adverse Events; ULN=upper limit of normal.

QT Prolongation



Interstitial lung disease

Significant drug interactions

Ribociclib is primarily metabolised by CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter its pharmacokinetics. For more detailed interaction information, please refer to the Ribociclib SmPC. **Ribociclib is not recommended to be used with tamoxifen.**

CYP3A4 inhibitors	The concomitant use of strong CYP3A4 inhibitors must be avoided, including, but not limited to, **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 400 mg ribociclib daily with a strong CYP3A4 inhibitor cannot be avoided, the dose of ribociclib should be reduced by one dose level (to 200 mg). In patients who have had their dose reduced to 200 mg ribociclib daily and in whom initiation of a strong CYP3A4 inhibitor cannot be avoided, ribociclib treatment should be interrupted. There are no clinical data with these dose adjustments. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ribociclib-related adverse reactions is recommended. In the event of ribociclib-related toxicity, the dose should be modified or treatment should be interrupted until toxicity is resolved. If the strong inhibitor is discontinued, the ribociclib dose should be changed to the dose used prior to the initiation of the strong CYP3A4 inhibitor after at least 5 half-lives of the strong CYP3A4 inhibitor (refer to the SmPC of the CYP3A4 inhibitor in question).
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 with the following CYP3A4 substrates should also be avoided: **alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam and 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	In vitro evaluations indicated that 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 that exhibit a narrow therapeutic index, including, but not limited to, **digoxin, pitavastatin, pravastatin, rosuvastatin and metformin**.
Medicinal 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, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and intravenous ondansetron**) should be avoided.

Additional comments

Pharmacy: Store in a refrigerator (2°C - 8°C) for up to 10 months.

Patient: Store below 25°C for up to 2 months. Store in the original package.

References

https://www.medicines.org.uk/emc/product/8110/smpc#gref

Novartis systemic anti-cancer therapy protocol: Ribociclib and aromatase inhibitor in early breast cancer. Feb 2025

THIS PROTOCOL HAS BEEN DIRECTED BY DR MOON, DESIGNATED LEAD CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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