KISQALI® (ribociclib) in combination with an aromatase inhibitor (AI) in early breast cancer (eBC)

Formulary application support pack

The purpose of this document is to provide information to support healthcare professionals in producing their own formulary applications for ribociclib as a treatment option for patients with eBC, in line with the National Institute for Health and Care Excellence (NICE) recommendation (TA1086).[1]

Scan or click the QR code to view Prescribing Information.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report or alternatively email medinfo.uk@novartis.com or call 01276 698370.

KISQALI (ribociclib) is indicated for the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) locally advanced or metastatic breast cancer in combination with an AI 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.*,[2]

KISQALI (ribociclib) in combination with an AI is indicated for the adjuvant treatment of patients with HR+/HER2– eBC at high risk of recurrence (see section 5.1 of the SmPC for selection criteria). In pre- or perimenopausal women, or in men, the AI should be combined with an LHRH agonist.*,[2]

*KISQALI is not recommended to be used in combination with tamoxifen.

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Background

Breast cancer is the second most common cancer globally, with female breast cancer accounting for 11.6% of all cancers diagnosed in 2022.[3] HR+/HER2− breast cancer is the most common type of breast cancer.[4] It is predicted that 64.5% of people with early or locally advanced breast cancer will have HR+/HER2− disease by 2026/2027.[5]

In 2021, 85% of breast cancers in women were diagnosed at an early stage (Stages I and II) in England.[6] eBC describes cancer that has not spread beyond the breast or lymph nodes in the armpit on the same side of the body.[7]

For most patients diagnosed with HR+/HER2− eBC, current practice guidelines recommend surgical excision, radiotherapy and adjuvant endocrine therapy.[8]

Reason for request

The licence for ribociclib has been further extended to include patients with eBC, when given in combination with an AI as adjuvant treatment[2]

Ribociclib is indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.* The marketing authorisation for ribociclib has been extended to include patients with eBC at a high risk of recurrence when given alongside an AI;* NICE has also recommended ribociclib + AI in this population. This formulary application support pack is required to provide current and accurate information on ribociclib + AI in eBC.[2]

*In pre- or perimenopausal women, the endocrine therapy should be combined with an LHRH agonist. Ribociclib is not recommended for use in combination with tamoxifen.[2]

Despite current standard of care treatment in HR+/HER2− eBC, patients remain at risk of recurrence[9–11]

Current standard of care treatment for patients with HR+/HER2− eBC does not eliminate the risk of disease recurrence.[9–11] Within 5 years, up to 12% of patients with HR+/HER2− eBC may experience a recurrence, despite standard of care. A meta-analysis of data for risk of recurrence from 14 Phase III clinical trials was performed (n=30,139), including four trials of adjuvant cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy, in patients with Stage I–III HR+/HER2– eBC with any nodal involvement, who had received 5 years of standard of care adjuvant endocrine therapy and chemotherapy. Invasive disease-free survival (iDFS) or disease-free survival (DFS) were reported at 3 and 5 years post-randomisation. The meta-analysis performed on pooled 5-year data revealed a 12% risk of invasive recurrence for the overall population, regardless of stage or nodal status.[12]

Across two trials in HR+ eBC, around 75% of breast cancer recurrences were shown to be incurable metastases, despite standard of care. This is based on results from two trials:[13,14]

- A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group of AIs vs tamoxifen in 7,030 premenopausal women with oestrogen receptor-positive eBC. In both treatment arms at 0–4 years, 74% of recurrences were metastatic (423/569 recurrence events)[13]
- A Phase III randomised Breast International Group 1-98 trial of letrozole and tamoxifen in postmenopausal women with HR+ eBC (N=8,010). In both treatment arms at 5 years, 76% of recurrences were metastatic (409/535 recurrences)[14]

Patients with eBC may experience metastatic recurrences regardless of endocrine therapy or nodal status.[15]

Ribociclib + non-steroidal aromatase inhibitor (NSAI) demonstrated a reduction in the risk of invasive disease, recurrence or death following 3 years of treatment vs NSAI in the Phase III NATALEE trial[16]

The randomised, open-label NATALEE trial (N=5,101) assessed the efficacy and tolerability of adjuvant ribociclib + NSAI in patients with HR+/HER2− eBC. The primary endpoint was iDFS according to Standardised Definitions for Efficacy End Points criteria as assessed by the investigator.[16] iDFS includes invasive, ipsilateral breast tumour recurrence, local or regional invasive recurrence, distant recurrence, death (from breast cancer, non-breast cancer or unknown cause), invasive, contralateral breast cancer or second primary invasive cancer (non-breast cancer).[17]

The primary endpoint of the study was met at the primary analysis (data cutoff 11 January 2023). There was a statistically significant improvement in iDFS (hazard ratio [HR] 0.75; 95% confidence interval [CI]: 0.62–0.91; two-sided P-value=0.003).[11]

In a prespecified final analysis (data cutoff 21 July 2023), patients treated with ribociclib + NSAI demonstrated a 25.1% reduction in the risk of iDFS events vs NSAI over 3 years (HR 0.749; 95% CI: 0.628–0.892; two-sided nominal P-value=0.0012), with an absolute risk reduction of 3.1%.[16]

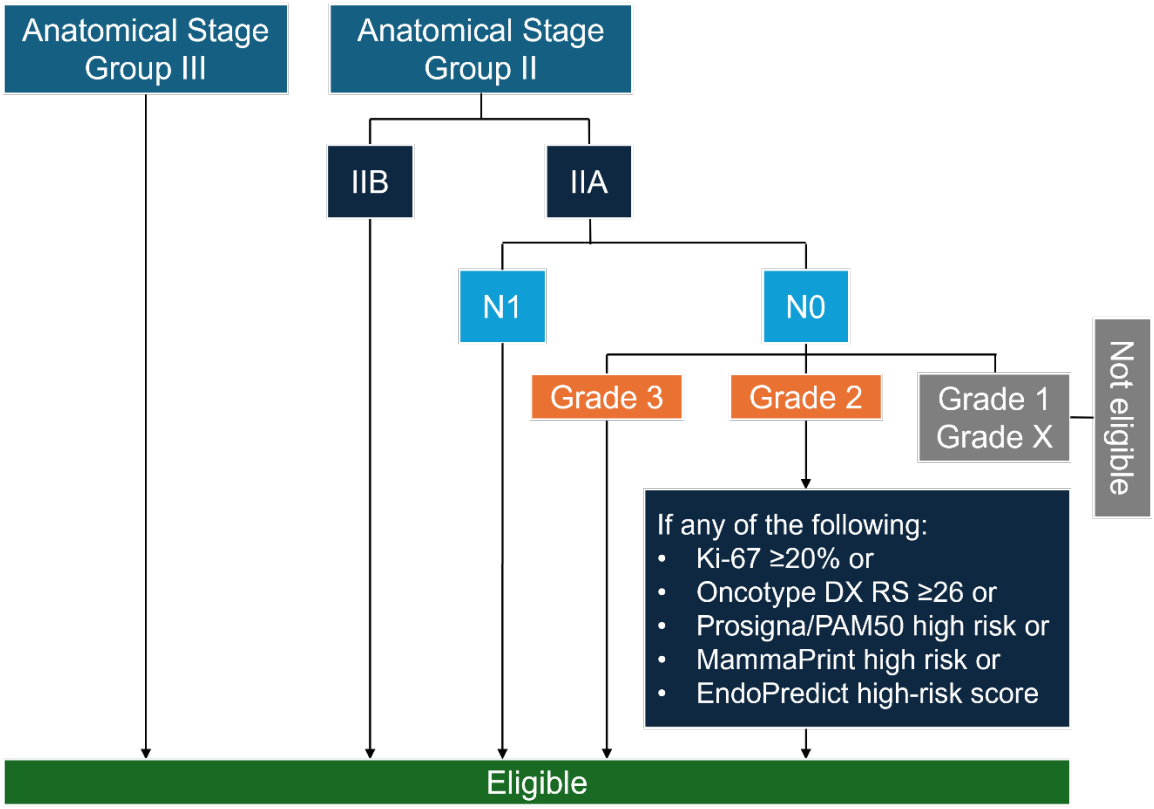
A benefit in recurrence-free survival (RFS) (secondary endpoint) was observed with ribociclib + NSAI at 3 years with a 92.1% RFS rate vs 89.1% in NSAI (HR 0.727; 95% CI: 0.602–0.877; two-sided nominal P-value=0.0008). A benefit in distant disease-free survival (DDFS) (secondary endpoint) was also observed with ribociclib + NSAI at 3 years with a 92.9% DDFS rate at 3 years vs 90.2% with NSAI (HR 0.749; 95% CI: 0.623–0.900; two-sided nominal P-value=0.0020) vs NSAI.[16]

During an exploratory analysis, at 4 years (data cutoff 29 April 2024), ribociclib + NSAI was observed to reduce the risk of iDFS events by 28.5% vs NSAI (HR 0.715; 95% CI: 0.609–0.840; nominal P-value <0.0001), with an absolute risk reduction of 4.9% (data cutoff 29 April 2024).[18]

Ribociclib + AI can be offered to a broad range of patients with eBC at a high risk of recurrence[2]

Nodal status may not be restrictive for treatment with ribociclib, and the eligibility criteria is aligned to include patients at high risk of recurrence regardless of nodal status. Ribociclib + AI can be offered to a broad range of patients with HR+/HER2− eBC with:[2]

- Anatomic stage Group IIB–III, or
- Anatomic stage Group IIA that is either:
  - Node positive or
  - Node negative, with:
    - Histological Grade 3, or
    - Histological Grade 2, with any of the following criteria:
      - Antigen Kiel-67 (Ki-67) ≥20%
      - High risk by gene signature testing



Adapted from Tarantino P, et al. 2024.[19]
Ki-67=antigen Kiel-67; N0=no positive lymph nodes; N1=1–3 positive lymph nodes; RS=recurrence score.

Ribociclib + NSAI has a generally manageable and well-characterised safety profile and maintained quality of life (QoL)[2,16,18,20]

In the prespecified final analysis (data cutoff 21 July 2023), no new safety signals were observed in the NATALEE trial. At least one treatment-emergent adverse event (TEAE) occurred in 2,474 patients (98.0%) in the ribociclib + NSAI arm and 2,145 (87.8%) in the NSAI arm. Serious adverse events (AEs) occurred in 14.1% and 10.5% of patients, respectively.[16]

Incidence of AEs remained stable at 4-year follow-up (data cutoff 29 April 2024) from prior analyses (3-year follow-up; data cutoff 21 July 2023). AEs of special interest at 4-year follow-up included neutropenia, liver-related AEs, QT interval prolongation and interstitial lung disease (ILD)/pneumonitis:[16,18]

- Rates of neutropenia of any grade increased from 62.5% to 62.8% with ribociclib + NSAI vs a decrease from 4.6% to 4.5% with NSAI
- Liver-related AEs of any grade, which were predominantly alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) elevations without concomitant bilirubin increase, were reported as 26.7% with ribociclib + NSAI vs 11.4% with NSAI at 4-year follow-up.[18]
  At 3-year follow-up:
  - Rates of increased ALT of any grade were reported as 19.5% with ribociclib + NSAI vs 5.6% with NSAI[16]
  - Rates of increased AST of any grade were reported as 16.9% with ribociclib + NSAI vs 5.7% with NSAI[16]
- Rates of QT interval prolongation of any grade increased from 5.3% to 5.4% with ribociclib + NSAI vs an increase from 1.4% to 1.6% with NSAI
- Rates of ILD/pneumonitis were not reported in the 3-year analysis, but were reported as 1.6% with ribociclib + NSAI vs 0.9% with NSAI in the 4-year follow-up

At 3 years (data cutoff 11 January 2023), health-related quality of life (HRQoL) was maintained with ribociclib + NSAI vs NSAI. Physical functioning and global health scores were maintained over time in both the ribociclib + NSAI and NSAI arms.[20]

Ribociclib details

For full Prescribing Information, consult the SmPC.[2]

Name of medicine[2]

KISQALI (ribociclib)

Mechanism of action[2]

Ribociclib is a selective inhibitor of CDK4/6:

- CDK4/6 are activated upon binding to D-cyclins and play a role in signalling pathways, which lead to cell cycle progression and cellular proliferation
- The cyclin D–CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma (Rb) protein
- Ribociclib decreases Rb protein phosphorylation, resulting in reduced proliferation in breast cancer cells
- Ribociclib has been associated with tumour regressions, delayed tumour regrowth, tumour growth inhibition and immunomodulation

Licensed indications[2]

eBC:

- Ribociclib in combination with an AI is indicated for the adjuvant treatment of patients with HR+/HER2− eBC at high risk of recurrence (see section 5.1 of the SmPC for selection criteria)
- In pre- or perimenopausal women, or in men, the AI should be combined with an LHRH agonist

Advanced breast cancer:

- Ribociclib is indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer in combination with an AI 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 an LHRH agonist

Ribociclib is not recommended to be used in combination with tamoxifen.

Dosing[2]

The recommended dose of ribociclib in eBC is shown below:[2]

Drug	Dose	Route	Frequency
Ribociclib[2]	400 mg once daily (two 200 mg film-coated tablets)	Oral	Days 1 to 21 followed by 7 days off treatment (28-day cycle)
Letrozole or alternative AI[21]	See SmPC for dosing	Oral	Days 1 to 28 continuously

In patients with eBC, ribociclib should be taken until completion of 3 years of treatment or until disease recurrence or unacceptable toxicity occur.[2]

Administration in eBC[2]

- 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
- Ribociclib should be used together with letrozole or another AI. The AI is taken orally, once daily, continuously throughout the 28-day cycle

Special populations[2]

- Renal impairment:
    - Ribociclib has not been studied in patients with breast cancer with severe renal impairment
    - No dose adjustment is necessary in patients with mild or moderate renal impairment
    - A starting dose of 200 mg is recommended in patients with severe renal impairment

- Hepatic impairment:
    - No starting dose adjustment is necessary in patients with hepatic impairment in eBC
    - Liver function tests (LFTs) 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 of the SmPC
    - Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established
- No dose adjustment is required in patients over 65 years of age
- The safety and efficacy of ribociclib in children and adolescents have not been established. No data are available

Contraindications[2]

Hypersensitivity to the active substance or to peanut, soya or excipients.

Special warnings and precautions[2]

For further information on special warnings and precautions, please refer to the ribociclib SmPC.[2]

Critical visceral disease
• The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease
Neutropenia
• Based on the severity of the neutropenia, treatment with ribociclib may have to be interrupted, reduced or discontinued • **Please refer to Table 2 of the ribociclib SmPC for information on dose modification and management in neutropenia**
Hepatobiliary toxicity
• LFTs should be performed before initiating treatment with ribociclib. After initiating treatment, liver function should be monitored • Based on the severity of transaminase elevations, treatment with ribociclib may have to be interrupted, reduced or discontinued • **Please refer to Table 3 of the ribociclib SmPC for information on dose modification and management in hepatobiliary toxicity**

- Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established

QT interval prolongation

- The use of ribociclib should be avoided in patients who already have or who are at significant risk of developing corrected QT interval (QTc) prolongation. This includes patients with:
  - Long QT syndrome
  - Uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
  - Electrolyte abnormalities
- The use of ribociclib with medicinal products known to prolong the QTc interval and/or strong cytochrome P450 3A4 (CYP3A4) inhibitors should be avoided, as this may lead to clinically meaningful prolongation of the QT interval corrected for heart rate using the Fridericia formula (QTcF). If co-administration of ribociclib with a strong CYP3A4 inhibitor cannot be avoided, the ribociclib dose should be changed as described in section 4.2 of the ribociclib SmPC
- Ribociclib is not recommended for use in combination with tamoxifen
- Electrocardiogram (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, then as clinically indicated
- In patients with eBC, appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first six cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with ribociclib and during treatment with ribociclib
- Based on the observed QT prolongation during treatment, treatment with ribociclib may have to be interrupted, reduced or discontinued, as described in Table 4 of the ribociclib SmPC

Severe cutaneous reactions

- Toxic epidermal necrolysis 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

ILD/pneumonitis

- ILD/pneumonitis has been reported with ribociclib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough and dyspnoea, and dose modifications should be managed in accordance with Table 5 of the ribociclib SmPC

• Based on the severity of the ILD/pneumonitis, which may be fatal, ribociclib may require dose interruption, reduction or discontinuation, as described in Table 5 of the ribociclib SmPC
Blood creatinine increase
• Ribociclib may cause blood creatinine increase • In case of blood creatinine increase while on treatment, it is recommended that further assessment of renal function be performed to exclude renal impairment
CYP3A4 substrates
• Ribociclib is a strong CYP3A4 inhibitor at the 600 mg dose and a moderate CYP3A4 inhibitor at the 400 mg dose. Thus, ribociclib may interact with medicinal products that are metabolised via CYP3A4, which may lead to increased serum concentrations of CYP3A4 substrate • 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
Renal impairment
• Caution should be used in patients with severe renal impairment with close monitoring for signs of toxicity
Women of childbearing potential/contraception
• Women of childbearing potential should be advised to use an effective method of contraception while taking ribociclib and for at least 21 days after the last dose
Soya lecithin
• Ribociclib contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take ribociclib

Pregnancy, breastfeeding and fertility[2]

- Ribociclib is not recommended during pregnancy and in women of childbearing potential not using contraception
- Patients receiving ribociclib should not breastfeed for at least 21 days after the last dose
- There are no clinical data available regarding effects of ribociclib on fertility. Based on animal studies, ribociclib may impair fertility in males of reproductive potential

Clinically relevant drug interactions[2]

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. For any interaction queries, please contact your pharmacy.

Ribociclib is not recommended to be used in combination 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 AEs. In patients taking 600 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be reduced to 400 mg. In patients taking 400 mg ribociclib daily and in whom initiation of co-administration of a strong CYP3A4 inhibitor cannot be avoided, the dose should be further reduced 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 interpatient 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 five 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 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**.
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**, **ciprofloxacin**, **levofloxacin**, **azithromycin**, **haloperidol**, **methadone**, **moxifloxacin**, **bepridil**, **pimozide** and **intravenous ondansetron**) should be avoided. Ribociclib is also not recommended to be used in combination with **tamoxifen**.

Proposed place in therapy

Patients[2]

Ribociclib was evaluated in HR+/HER2− eBC in adults with anatomic Stage II or III irrespective of nodal status at high risk of recurrence, in combination with an AI that was:

- Anatomic stage Group IIB–III, or
- Anatomic stage Group IIA that is either:
    - Node positive or
    - Node negative, with:
        - Histological Grade 3, or

- Histological Grade 2, with any of the following criteria:
    - Ki-67 ≥20%
    - High risk by gene signature testing

Ribociclib can be added as adjuvant therapy for eligible patients up to 12 months following endocrine therapy initiation.[17]

Prescribers[2]

Treatment with ribociclib should only be initiated by a physician experienced in the use of anti-cancer therapies.

National guidance

NICE recommendation

Ribociclib with an AI is recommended, within its marketing authorisation, as an option for the adjuvant treatment of HR+/HER2– eBC at high risk of recurrence in adults.[1] In pre- or perimenopausal women, or in men, the AI should be combined with an LHRH agonist.[2]

Therefore, ribociclib is now NICE recommended for the adjunctive treatment of eBC in line with the full licensed population. Ribociclib is recommended only if the company provides it according to the commercial arrangement.[1]

Following the NICE recommendation, the guidance should be adopted by the NHS in Wales and Northern Ireland.

Scottish Medicines Consortium (SMC)

The SMC submission is under review to secure reimbursement of ribociclib to enable patient access via the NHS in Scotland.[22]

Clinical efficacy: NATALEE trial

Objective[16]

The 3-year NATALEE trial aimed to evaluate the efficacy and tolerability of adjuvant ribociclib + NSAI compared with NSAI in a broad population of patients with HR+/HER2− eBC.

Study design[16]

The NATALEE trial was an international, randomised, open-label, Phase III trial conducted across 20 countries (N=5,101).

Patients were randomised 1:1 to receive either ribociclib 400 mg/day once daily (Days 1–21 of a 28-day cycle, over a duration of 36 months) + NSAI (letrozole 2.5 mg or anastrozole 1 mg once daily continuously for 60 months) (n=2,549) or NSAI (n=2,552).

Men and premenopausal women also received subcutaneous goserelin 3.6 mg once every 28 days.

The median duration of exposure to the study treatment was 36.2 months in the ribociclib + NSAI arm and 35.9 months in the NSAI arm.

An exploratory analysis was also conducted at Year 4, which provided an additional 10.9 months of follow-up after the final analysis.[18]

Inclusion and exclusion criteria[17]

Inclusion criteria included but were not limited to:

- Men or pre- or postmenopausal women aged ≥18 years with histologically confirmed unilateral primary invasive HR+/HER2− breast cancer, with a date of initial cytological or histological diagnosis ≤18 months prior to randomisation
- Complete surgical resection with microscopic margins free of tumours with available archival tumour tissue from the surgical specimen or from the diagnostic biopsy for patients who had neoadjuvant therapy and achieved a pathological complete response
- Anatomic Stage II or Stage III disease per the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Completion of (neo)adjuvant chemotherapy (if indicated) and adjuvant radiotherapy (if indicated)
- Permitted to have already received any standard (neo)adjuvant endocrine therapy but must be randomised within 12 months of the initial start date of endocrine therapy

Exclusion criteria included but were not limited to:

- Distant metastases of breast cancer beyond the regional lymph nodes and/or evidence of disease after curative surgery
- Prior treatment with a CDK4/6 inhibitor
- Prior treatment with tamoxifen, raloxifene or NSAIs for reduction in risk of breast cancer and/or prior treatment for osteoporosis in the preceding 2 years
- Prior treatment with anthracyclines at cumulative doses of ≥450 mg/m^2 for doxorubicin or ≥900 mg/m^2 for epirubicin
- Clinically significant, uncontrolled heart disease and/or cardiac repolarisation abnormalities
- Major surgery, chemotherapy or radiotherapy within 14 days prior to randomisation

Statistical analysis[16]

iDFS between the two treatment arms was compared using a stratified log-rank test based on randomisation stratification factors. Primary and secondary endpoints were estimated using the Kaplan–Meier method. The HR was calculated using a stratified Cox proportional hazards model and efficacy analyses were conducted in the intent-to-treat population.

Primary endpoint results[16,17]

The primary endpoint was iDFS and had a median duration follow-up of 27.7 months.[16]

iDFS included invasive, ipsilateral breast tumour recurrence, local or regional invasive recurrence, distant recurrence, death (from breast cancer, non-breast cancer or unknown cause), invasive, contralateral breast cancer or second primary invasive cancer (non-breast cancer).[17]

The primary endpoint of the study was met at the primary analysis (data cutoff 11 January 2023).[11]

Ribociclib + NSAI demonstrated a significant iDFS benefit over NSAI.[11,16]

- There was a statistically significant improvement in iDFS with 3-year iDFS rates of 90.4% with ribociclib + NSAI vs 87.1% with NSAI (HR 0.75; 95% CI: 0.62–0.91; two-sided P-value=0.003)[11]
- Overall, 189/2,549 and 237/2,552 iDFS events occurred with ribociclib + NSAI vs NSAI, respectively[11]

In a final prespecified analysis (data cutoff 21 July 2023):

- The 3-year iDFS rates were 90.7% (95% CI: 89.3–91.8) in the ribociclib + NSAI group vs 87.6% (95% CI: 86.1–88.9) in the NSAI group[16]

- There was a 25.1% reduction in the risk of iDFS events at 3 years in the ribociclib + NSAI arm compared with the NSAI arm (HR 0.749; 95% CI: 0.628–0.892; nominal P-value=0.0012). Absolute risk reduction at 3 years was 3.1%[16]

Secondary endpoint results[16,23]

Key secondary endpoints were RFS, DDFS, overall survival (OS), HRQoL and safety and tolerability.[16]

- RFS was defined as the time from date of randomisation to date of first event of local invasive breast recurrence, regional invasive recurrence, distant recurrence or death (any cause)[23]
- DDFS was defined as the time from date of randomisation to date of first event of distant recurrence, death (any cause) or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin)[23]
- OS was defined as the time from date of randomisation to date of death due to any cause[23]
- HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The EORTC QLQ-C30 contains functional scales, symptom scales, a single-item scale and a global health status/QoL scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level[23]

DDFS and RFS favoured ribociclib + NSAI vs NSAI, and the OS data were immature at the time of analysis (final prespecified analysis; data cutoff: 21 July 2023).[16]

- Ribociclib + NSAI demonstrated a benefit for RFS vs NSAI, with 3-year RFS rates of 92.1% vs 89.1%, respectively (HR 0.727; 95% CI: 0.602–0.877; two-sided nominal P-value=0.0008)
- Ribociclib + NSAI demonstrated a benefit for DDFS vs NSAI, with 3-year DDFS rates of 92.9% vs 90.2%, respectively (HR 0.749; 95% CI: 0.623–0.900; two-sided nominal P-value=0.0020)
- The most common sites of disease recurrence were bone and liver in both treatment arms
- OS events occurred in 172 patients (84 in the ribociclib arm and 88 in the NSAI arm); however, OS data were not mature at the time of analysis
    - 3-year OS rates were 97.0% with ribociclib + NSAI and 96.1% with NSAI (HR 0.892; 95% CI: 0.661–1.203)
- In a prespecified analysis of the NATALEE trial, the HRQoL of patients with HR+/HER2− eBC was maintained in patients treated with ribociclib + NSAI vs NSAI[20]
    - Physical functioning and global health scores were maintained over time in both the ribociclib + NSAI and NSAI arms

    - Following descriptive analysis, physical functioning scores in the ribociclib + NSAI arm were –1.12 at 1 year, –1.62 at 2 years and –1.50 at 3 years from baseline vs –1.35, –1.10 and –1.34 in the NSAI arm, respectively
    - Following model-based analyses, physical functioning scores in the ribociclib + NSAI arm were –1.85 at 1 year, –2.30 at 2 years and –2.75 at 3 years from baseline vs –2.39, –2.84 and –3.29 in the NSAI arm, respectively
    - Following descriptive analysis, global health status scores in the ribociclib + NSAI arm were –2.77 at 1 year, –3.25 at 2 years and –3.10 at 3 years from baseline vs –1.61, –1.91 and –1.96 in the NSAI arm, respectively
    - Following model-based analyses, global health status scores in the ribociclib + NSAI arm were –2.99 at 1 year, –3.65 at 2 years and –4.30 at 3 years from baseline vs –2.40, –3.05 and –3.71 in the NSAI arm, respectively
- Safety and tolerability results are highlighted in the 'Safety and tolerability' section on *Page 19* of this formulary application support pack

Exploratory analysis results[18]

During the 4-year exploratory analysis, the primary endpoint was iDFS and had a median duration follow-up of 44.2 months.

- There was a 28.5% reduction in the risk of iDFS events at 4 years in the ribociclib + NSAI arm compared with the NSAI arm (HR 0.715; 95% CI: 0.609–0.840; nominal P-value <0.0001). Absolute risk reduction at 4 years was 4.9%
- The 4-year iDFS rates were 88.5% in the ribociclib + NSAI arm vs 83.6% in the NSAI arm

Safety and tolerability profiles

AEs

The most common adverse drug reactions (ADRs) (reported at a frequency ≥20%) in the dataset for which the frequency for ribociclib + AI exceeds the frequency for AI were neutropenia, infections, nausea, headache, fatigue, leukopenia and abnormal LFTs.[2]

The most common Grade 3/4 ADRs (reported at a frequency of ≥2%) in the dataset for which the frequency for ribociclib + AI exceeds the frequency for AI were neutropenia, abnormal LFTs and leukopenia.[2]

Dose reduction due to AEs, regardless of causality, occurred in 22.8% of patients receiving ribociclib + AI in the Phase III clinical study. Permanent discontinuation was reported in 19.7% of patients receiving ribociclib + AI.[2]

Please refer to the ribociclib SmPC for further safety and tolerability information.[2]

Summary of key safety results from the NATALEE trial[16]

In a final prespecified analysis (data cutoff 21 July 2023):[16]

- No new safety signals were observed
- At least one TEAE occurred in 98.0% (n=2,474) of patients in the ribociclib + NSAI arm and 87.8% (n=2,145) of patients in the NSAI arm
- Serious AEs occurred in 14.1% (n=357) of patients in the ribociclib + NSAI arm and 10.5% (n=256) of patients in the NSAI arm
- The most common AEs of any grade were:
    - Neutropenia (62.5% with ribociclib + NSAI vs 4.6% with NSAI)
    - Arthralgia (37.3% with ribociclib + NSAI vs 43.3% with NSAI)
    - Nausea (23.3% with ribociclib + NSAI vs 7.8% with NSAI)
- AEs leading to ribociclib discontinuation and dose reduction occurred in 19.5% and 22.8% of patients, respectively

At 4-year follow-up (data cutoff 29 April 2024):[18]

- Incidence of AEs remained stable from prior analyses
- Rates of discontinuation due to AEs (20.0%) remained stable through all the data cuts, with a <1.0% increase from the previous cutoff

- AEs of special interest (of any grade) were:
    - Neutropenia (62.8% with ribociclib + NSAI vs 4.5% with NSAI)
    - Liver-related AEs (26.7% with ribociclib + NSAI vs 11.4% with NSAI)
        - Liver-related AEs were predominantly ALT/AST elevations without concomitant bilirubin increase
    - QT interval prolongation (5.4% with ribociclib + NSAI vs 1.6% with NSAI)
    - ILD/pneumonitis (1.6% with ribociclib + NSAI vs 0.9% with NSAI)

Financial impact

Ribociclib is recommended by NICE for NHS routine commissioning for the adjuvant treatment of HR+/HER2– eBC at high risk of recurrence in adults, and in England must be funded within 90 days of publication of final guidance.[1] Access to ribociclib is available via the Cancer Drugs Fund until routine commissioning at 90 days after final guidance publication and aligned to Blueteq criteria.[24]

Guidance (TA1086) published by NICE in August 2025 concluded that there is enough evidence to show that ribociclib with an AI provides benefit and value for money and therefore can be used routinely across the NHS in the full licensed population.[1]

The list prices of ribociclib 200 mg tablets are:[25]

- £983.33 per 21 pack
- £1,966.67 per 42 pack
- £2,950 per 63 pack

The company has a simple patient access scheme, which makes ribociclib available to the NHS with a confidential commercial discount.

In Scotland, ribociclib is commissioned directly through each of the 14 health boards that are each responsible for drug approval (post-SMC acceptance).[26]

Service impact

Ribociclib is approved as an adjuvant treatment for a broad range of patients with Stage II and III HR+/HER2− eBC, including all node-positive and high-risk node-negative patients (section 5.1 SmPC).[2]

High-risk node negative	N0, T2	**Grade 3 or Grade 2 with high genomic risk of Ki67 ≥20%**
	N0, T3–4	**All eligible patients**
Node positive	N1, N2, N3	**All eligible patients**

Ki-67=antigen Kiel-67; N=lymph node staging; T=tumour staging.

There are around 56,822 new cases of breast cancer each year in the UK (data taken from 2017−2019).[27] The incidence of breast cancer varies across the UK, with around 46,000 people diagnosed in England each year, 4,800 people in Scotland, 2,600 people in Wales and 1,500 people in Northern Ireland.[28] Approximately 64.5% of patients with breast cancer are HR+/HER2–.[5]

Breast cancer staging data at a national level can provide general estimates as shown below, but for accuracy when estimating the number of eligible patients with eBC for ribociclib, local data should be prioritised where available due to local staging and sub-staging variability.

Proportion of all breast cancer cases at Stage II or III at diagnosis, by UK nation (CRUK)[29]

Country	Time (annual average)	% Stage II	% Stage III	Number diagnosed at Stage II/III per annum
England	2021	35%	7.9%	21,147
Scotland	2021–2022	46%	8.1%	2,519
Wales	2019–2021	36.6%	9.8%	1,256
Northern Ireland	2017–2021	39%	11%	745

CRUK=Cancer Research UK.

To appropriately understand the number of patients with eBC eligible for ribociclib, further Stage II subpopulation analysis (based on anatomical features, which define treatment eligibility) needs to be conducted to identify an accurate proportion of patients with Stage II HR+/HER2– eBC who meet the specified anatomical criteria as defined in the SmPC section 5.1. There are no restrictive anatomical criteria for patients with Stage III HR+/HER2– breast cancer when assessing eligibility for ribociclib adjuvant treatment in combination with an AI.[2]

AJCC anatomical staging[30]	TN (M0)	NATALEE[16]
Stage IIA	T1N1 T2N0	T2N0 only if Grade 3; or Grade 2 with Ki-67 ≥20% or high genomic risk
Stage IIB	T2N1 T3N0	
Stage IIIA	T0N2 T1N2 T2N2 T3N1 T3N2	
Stage IIIB	T4N0 T4N1 T4N2	
Stage IIIC	Any T, N3	

AJCC=American Joint Committee on Cancer; Ki-67=antigen Kiel-67; M=metastasis; N=lymph node staging; T=tumour staging.

For further support in understanding the potential impact of treating eligible patients with eBC with adjuvant ribociclib on local breast cancer services, please contact your local Novartis account manager.

Treatment impact on services[2]

Treatment with ribociclib should be initiated by a physician experienced in the use of anti-cancer therapies. Ribociclib is an oral therapy and can be taken at home; however, there are initiation and monitoring requirements to be considered:

- Full blood counts (FBCs) and LFTs should be performed before initiating ribociclib. FBCs and LFTs should then be repeated every 2 weeks for the first two cycles of treatment, and at the beginning of each subsequent four cycles, then as clinically indicated. If Grade ≥2 abnormalities are noted in LFTs, more frequent monitoring is recommended
- Monitoring of serum electrolytes should be performed before treatment initiation and at the beginning of the first six cycles, and then as clinically indicated. Typically, the FBCs (and LFTs) and serum electrolyte tests can be done in the same outpatient appointment and by the same healthcare professional
- ECGs should be performed before treatment initiation with ribociclib and then repeated at approximately Day 14 of the first cycle, then as clinically indicated. Treatment with ribociclib should be initiated only in patients with QTcF values less than 450 msec. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended in patients with eBC

Tests	Pre-initiation	Cycle 1 (Day 14)	Cycle 2 (Day 1)	Cycle 2 (Day 14)	Cycle 3	Cycle 4	Cycle 5	Cycle 6
FBCs and LFTs	1	1	1	1	1	1	1	1
ECG	1	1						
Serum electrolytes	1	1	1	1	1	1	1	1

ECG=electrocardiogram; FBC=full blood count; LFT=liver function test.

Please refer to the ribociclib SmPC for more information on dose modification and management.

The monitoring requirements for ribociclib as detailed within the SmPC relate to the first six cycles of treatment, with subsequent FBC, LFT and serum electrolyte testing as clinically indicated.[2]

The table below estimates the number of testing points required for long-term monitoring of ribociclib, aligned with differing monthly frequencies as could be clinically indicated for that patient (assuming that FBCs, LFTs and serum electrolytes are tested together).

Number of test points*	Year 1 (post-first six cycles)	Year 2	Year 3
Monthly† monitoring	7	13	13
3-monthly† monitoring	2	4	4
6-monthly† monitoring	1	2	2

*Assumes that at a single testing point the FBCs, LFTs and serum electrolytes are done together.
†'Monthly' used as a proxy for a 4-week cycle, therefore within 1 year there would be 13 cycles.

References

1. National Institute for Health and Care Excellence (NICE). Ribociclib with an aromatase inhibitor for adjuvant treatment of hormone receptor-positive, HER2-negative early breast cancer at high risk of recurrence. [TA1086]. August 2025. Available from: https://www.nice.org.uk/guidance/TA1086 [Last accessed: August 2025].
2. KISQALI (ribociclib) Summary of Product Characteristics.
3. Bray F, et al. *CA Cancer J Clin*. 2024;74(3):229–263.
4. Howlader N, et al. *J Natl Cancer Inst*. 2014;106(5):dju055.
5. National Institute for Health and Care Excellence (NICE). Resource impact report: Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (TA810). July 2022. Available from: https://www.nice.org.uk/guidance/ta810/resources/resource-impact-report-pdf-11139447853 [Last accessed: August 2025].
6. NHS Digital. Cancer Registrations Statistics, England 2021 - First release, counts only 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/cancer-registration-statistics/england-2021---summary-counts-only/cancer-incidence-by-stage [Last accessed: August 2025].
7. Cancer Research UK. About breast cancer staging and grades. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-grades/about [Last accessed: August 2025].
8. Loibl S, et al. *Ann Oncol*. 2024;35(2):159–182.
9. Johnston SRD, et al. *Lancet Oncol*. 2023;24(1):77–90.
10. Mayer EL, et al. *Lancet Oncol*. 2021;22(2):212–222.
11. Slamon D, et al. *N Engl J Med*. 2024;390(12):1080–1091.
12. Curigliano G, et al. *J Clin Oncol*. 2024;42(Suppl 16):abstract 541.
13. The Early Breast Cancer Trialists' Collaborative Group. *Lancet Oncol*. 2022;23(3):382–392.
14. The Breast International Group 1-98 Collaborative Group. *N Engl J Med*. 2005;353(26):2747–2757.
15. Pan H, et al. *N Engl J Med*. 2017;377(19):1836−1846.
16. Hortobagyi GN, et al. *Ann Oncol*. 2025;36(2):149–157.
17. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.
18. Fasching PA, et al. *Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial.* Oral late-breaking abstract presentation at the *European Society for Medical Oncology Congress 2024*; 13–17 September 2024; Barcelona, Spain. Oral LBA13.
19. Tarantino P, et al. *Risk of Recurrence in Real-World (RW) NATALEE- and monarchE-Eligible Populations of Patients With HR+/HER2− Early Breast Cancer (EBC) in an Electronic Health*

Record (EHR)–Derived Database. Poster presented at the *San Antonio Breast Cancer Symposium 2024*; 10–13 December 2024; San Antonio, USA. Poster P2-12-02.

20. Fasching PA, et al. *Health-Related Quality of Life in the Phase 3 NATALEE Study of Adjuvant Ribociclib Plus a NSAI vs NSAI Alone in Patients with HR+/HER2- Early Breast Cancer*. Virtual plenary presented at the *European Society for Medical Oncology Virtual Plenary 2023*; 14–15 September 2023; Virtual. Abstract VP3-2023.
21. Femara (letrozole) Summary of Product Characteristics.
22. Scottish Medicines Consortium. Medicines advice. Ribociclib (KISQALI). Available from: https://scottishmedicines.org.uk/medicines-advice/ribociclib-kisqali-full-smc2803/ [Last accessed: August 2025].
23. ClinicalTrials.gov. NCT03701334. Available from: https://clinicaltrials.gov/study/NCT03701334 [Last accessed: August 2025].
24. NHS England. National Cancer Drugs Fund List. Version 1.342. 2025. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/National-Cancer-Drugs-Fund-list-version-1.342.pdf [Last accessed: August 2025].
25. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF). Medicinal forms. Ribociclib. Available from: https://bnf.nice.org.uk/drugs/ribociclib-specialist-drug/medicinal-forms/#oral-tablet [Last accessed: August 2025].
26. Scottish Medicines Consortium. Working with SMC – A Guide for Manufacturers. March 2023. Available from: https://scottishmedicines.org.uk/media/8208/working-with-smc.pdf [Last accessed: August 2025].
27. Cancer Research UK. Breast cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer [Last accessed: August 2025].
28. Breast Cancer Now. Breast cancer facts and statistics. Available from: https://breastcancernow.org/about-us/why-we-do-it/breast-cancer-facts-and-statistics/ [Last accessed: August 2025].
29. Cancer Research UK. Early Cancer Diagnosis Data Hub. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ [Last accessed: August 2025].
30. American Joint Commission on Cancer. AJCC Cancer Staging Manual, Eighth Edition. Springer International Publishing. 2017.