Healthcare Improvement Scotland | SMC Advice on new medicines

Advice from New Drugs Committee

SMC2803

ribociclib (Kisqali®) film-coated tablets

Novartis Pharmaceuticals UK Ltd

10 October 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

ribociclib (Kisqali®) is accepted for use within NHSScotland.

Indication under review: In combination with an aromatase inhibitor for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

In an open-label phase III study in patients with HR-positive, HER2-negative early breast cancer, ribociclib in combination with an aromatase inhibitor was associated with a statistically significant improvement in invasive disease-free survival when compared with aromatase inhibitor monotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) four and six, which play an important role in signalling pathways and lead to cell cycle progression and proliferation. In combination with an aromatase inhibitor, the recommended dose is 400 mg orally once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete cycle of 28 days. Treatment is continued for 36 months or until disease recurrence or unacceptable toxicity. When ribociclib is used in combination with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Summary of Product Characteristics (SPC) of the aromatase inhibitor for additional details. In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.[1]

1.2. Disease background

Breast cancer is the most common cancer among women in Scotland, with around 4,900 new cases diagnosed every year. Approximately 80% of breast cancers are diagnosed at an early stage in Scotland, and most can be cured by multimodality treatment; cure rates vary by clinical stage and subtype. Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most common subtype, accounting for approximately 70% of cases. Patients with stage II/III disease with larger tumour size, metastases in multiple regional lymph nodes, high tumour grade, and high recurrence genomic score are all at higher risk of recurrence.[2-4]

1.3. Treatment pathway and relevant comparators

Patients with HR-positive, HER2-negative early breast cancer undergo surgery, and may receive either neoadjuvant or adjuvant chemotherapy in combination with endocrine therapy, which reduces the risk of local and distant recurrence and improves overall survival[5]; radiotherapy is also commonly used, and certain groups of patients may receive bisphosphonate treatment.

Treatment choice depends on menopausal status at diagnosis, the risk of disease recurrence, toxicity of treatment (alongside patient's age and co-morbidities), and patient choice. Endocrine therapies include tamoxifen and the aromatase inhibitors exemestane or letrozole. Aromatase inhibitors are the preferred choice for those with high-risk disease whilst tamoxifen may be considered in the absence of high-risk features or if aromatase inhibitors are not tolerated, contraindicated or for patient preference. In premenopausal patients, aromatase inhibitors should be offered in combination with ovarian function suppression, using LHRH agonists such as leuprorelin. For patients with HR-positive, HER2-negative, node positive early breast cancer at high risk of recurrence, abemaciclib in combination with endocrine therapy (and LHRH agonist if pre- or perimenopausal) was accepted for use by SMC within NHSScotland (SMC2494).[3, 6, 7]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The evidence to support the efficacy and safety of ribociclib in combination with an aromatase inhibitor for the adjuvant treatment of HR-positive, HER2-negative early breast cancer comes from NATALEE, the details of this study are documented in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	NATALEE[4, 8, 9]
Study design	International, open-label, randomised, phase III study.
Eligible patients	Key inclusion criteria: • Men or pre/postmenopausal women, ≥ 18 years of age, with histologically confirmed HR-positive, HER2-negative early breast cancer according to local assessment • Stage II or III disease regardless of nodal involvement • Stage IIA without nodal involvement either tumour grade 3 or tumour grade 2 with high risk genomic profile or Ki67 ≥20% • Complete surgical resection with free tumour margins • ECOG performance status 0 to 1 and who were deemed eligible for adjuvant endocrine therapy for at least 60 months • Standard neoadjuvant and/or adjuvant endocrine therapy before study enrolment was allowed, but randomisation should occur within 12 months of the initial start date of endocrine therapy.
Treatments	• Ribociclib 400 mg taken orally once daily on days one to 21 of a 28-day cycle for 36 months, plus an aromatase inhibitor (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily) for at least 60 months or, • Aromatase inhibitor (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily) taken for at least 60 months. Treatment with ribociclib was continued for 36 months unless treatment was discontinued due to disease recurrence or unacceptable toxicity. Men and premenopausal patients in both groups also received goserelin subcutaneously 3.6 mg once every 28 days.
Randomisation	Patients were randomised in a 1:1 ratio to treatments and stratified according to anatomical stage II or III, menopausal status (premenopausal women and men or postmenopausal women), previous adjuvant or neoadjuvant chemotherapy (yes or no) and geographic location (North America, Western Europe, Oceania, or the rest of the world).
Primary outcome	Invasive disease-free survival, defined as time from the date of randomisation to the date of the first event of local or regional invasive breast recurrence, distant recurrence, contralateral invasive breast cancer, ipsilateral invasive breast cancer, a second primary non-breast invasive cancer, or death due to any cause (STEEP criteria version 1).
Key secondary outcomes	Distant disease-free survival, overall survival.
Statistical analysis	Efficacy analyses were performed in the intention to treat population which included all patients that were randomised and received a dose of the study treatments. No multiple testing procedure had been planned except for testing the primary outcome at different data-cuts. Therefore, the results reported for secondary outcomes are descriptive only.

Abbreviations: AI = aromatase inhibitor; ECOG = Eastern Cooperative Oncology Group; HER = human epidermal growth factor receptor; HR = hormone receptor; Ki67 = Keil 67; STEEP = standardised definitions for efficacy end points.

At the data-cut April 2024, the addition of ribociclib to aromatase inhibitor treatment was associated with statistically significant improvements in invasive disease-free survival for patients with HR-positive, HER2-negative stage II or III early breast cancer. See Table 2.2 for details.

Table 2.2. Key efficacy results from NATALEE (ITT population; data-cut April 2024).[8]

	Ribociclib plus aromatase inhibitor (n=2,549)	Aromatase inhibitor (n=2,552)
Primary outcome: invasive disease-free survival (STEEP v1 criteria, investigator-assessed)		
Median follow-up	44.2 months	
Events, n	263	340
Median iDFS	NR	NR
Hazard ratio (95% CI)	0.72 (0.61 to 0.84) p<0.001	
4-year iDFS rate	88%	84%
Secondary outcome: distant disease-free survival		
Median follow-up	44.2 months	
Events, n	240	311
Median DDFS	NR	NR
Hazard ratio (95% CI)	0.72 (0.60 to 0.85)	
Secondary outcome: overall survival		
Median follow-up	44.3 months	
Events, n	105	121
Median OS	NR	NR
Hazard ratio (95% CI)	0.83 (0.64 to 1.07)	

Abbreviations: CI = confidence interval; DDFS = distant disease-free survival; iDFS = invasive disease-free survival; ITT – intention to treat; NR = not reached; OS = overall survival; STEEP = standardised definitions for efficacy end points.

At the April 2024 data-cut, results of subgroup analysis of the primary outcome demonstrated a consistent benefit with ribociclib plus aromatase inhibitor across subgroups, including in node negative disease (hazard ratio [HR] = 0.67; 95% confidence interval [CI]: 0.40 to 1.12) and node positive disease (HR = 0.73; 95% CI: 0.62 to 0.87).[8] The company also presented post-hoc subgroup analysis in the subgroup of patients who were node positive, high risk, and eligible for abemaciclib.[10]

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using; the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (EORTC QLQ-C30, version 3.0), the supplementary EORTC breast cancer–specific quality of life questionnaire [EORTC QLQ-BR23 version 1.0 (for women)], the EQ-5D-5L, and the Hospital Anxiety and Depression Scale questionnaire. Overall, no meaningful differences between treatment groups were detected, indicating that quality of life was maintained in both treatment groups.[11]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing ribociclib (in combination with an aromatase inhibitor) with abemaciclib (in combination with endocrine therapy) the submitting company presented an indirect treatment comparison (Table 2.3).

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored matching-adjusted indirect comparison (MAIC). The submitting company presented both unweighted and weighted analyses.

Population	Patients with HR-positive, HER2-negative, node positive, high risk early breast cancer with pathological tumour involvement in:
	• ≥4 ipsilateral axillary lymph nodes, or
	• 1 to 3 axillary lymph nodes with either:
	  ○ grade 3 disease, or
	  ○ primary tumour size ≥5 cm

Comparators	Abemaciclib plus endocrine therapy (letrozole, anastrozole, exemestane, or tamoxifen)
Studies included	NATALEE[12] – randomised controlled, open-label phase III study comparing ribociclib plus aromatase inhibitor with aromatase inhibitor alone monarchE[13] – randomised controlled, open-label phase III study comparing abemaciclib plus endocrine therapy with endocrine therapy alone
Outcomes	Invasive disease-free survival, overall survival, safety
Results	Overall, no statistically significant differences were found between ribociclib (plus aromatase inhibitor) and abemaciclib (plus endocrine therapy) for both invasive disease-free survival and overall survival. Hazard ratio central estimates were close to 1 and 95% confidence intervals (CI) spanned 1, suggesting comparable efficacy between the two treatments. There were differences between ribociclib plus aromatase inhibitor and abemaciclib plus endocrine therapy in select adverse events.

3. Summary of Safety Evidence

Evidence from NATALEE supports the relative safety of ribociclib plus aromatase inhibitor compared with aromatase inhibitor monotherapy for the treatment of patients with HR-positive, HER-2 negative early breast cancer at high risk of recurrence. Aromatase inhibitor monotherapy is considered a relevant comparator in this clinical setting. Published data from the NATALEE study is available from the January 2023 data-cut, where median duration of exposure to study treatment was 30 months in both treatment groups.[9]

Serious adverse events (AE) were reported in 13% (336/2,524) of patients in the ribociclib plus aromatase inhibitor group and in 9.9% (242/2,444) of patients in the aromatase inhibitor group; 63% and 18% of the respective groups had any AE of grade 3 or greater; 19% of patients had an AE that led to early discontinuation of ribociclib; the proportion of patients that discontinued aromatase inhibitor due to AE or any other reason were similar between treatment groups.[9]

The most common AEs of any grade that occurred in ≥20% of patients in either treatment group were neutropenia (62% versus 4.5%), arthralgia (36% versus 42%), nausea (23% versus 7.5%), headache (22% versus 16%), and fatigue (22% versus 13%). The most common AEs grade 3 or above were neutropenia (44% versus 0.8%), alanine aminotransferase increased (7.3% versus 0.7%), and aspartate aminotransferase increased (4.4% versus 0.5%).[9]

Monitoring of liver function, QT interval with electrocardiogram (ECG) plus serum electrolytes, pulmonary symptoms, and complete blood counts is required prior to initiation of ribociclib and at regular intervals during treatment.[1]

Overall, the safety profile of ribociclib in early breast cancer is in line with what has previously been reported in advanced breast cancer and was considered acceptable by regulatory bodies. No new safety concerns were identified.[4]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Ribociclib is the first CDK4/6 inhibitor that is licensed for use in HR-positive, HER2-negative, high risk early breast cancer irrespective of nodal status. Patients with node negative or node positive disease may be eligible to receive ribociclib.
- NATALEE is a large phase III study comparing ribociclib plus aromatase inhibitor with aromatase inhibitor alone which is a relevant comparator in this setting.
- The addition of ribociclib to aromatase inhibitor was associated with statistically significant and clinically relevant improvements in invasive disease-free survival; the hazard ratio of 0.72 (April 2024 data-cut) represents a 28% lower relative risk of invasive disease, recurrence or death; the absolute benefit in invasive disease-free survival was 4.9% at 4 years. Positive trends in secondary outcomes such as distant disease-free survival and overall survival have also been observed.[11]

4.2. Key uncertainties

- There are no direct data comparing ribociclib plus aromatase inhibitor with abemaciclib plus endocrine therapy which is a relevant comparator for patients in this setting with node positive disease. The MAIC had several limitations including potential treatment modifiers not adjusted for, differences between the study populations, and safety outcomes were selectively assessed. Despite these limitations, the conclusion of comparable efficacy between these two CDK4/6 inhibitors seems reasonable.
- Invasive disease-free survival, distant disease-free survival and overall survival data are immature; median survival duration for these outcomes was not reached at the latest data-cut. Additional data are required to further characterise the long-term benefit of ribociclib in this setting.[4]
- Secondary outcomes in NATALEE were not adjusted for multiplicity and should therefore be interpreted with caution.[4] Health-related quality of life outcomes should also be interpreted with caution; the study was open-label, HRQoL outcomes were not adjusted for multiplicity, and questionnaires were completed on day one of every third treatment cycle (this is after one week off ribociclib).[4]
- Tamoxifen was not permitted in the NATALEE study. Although aromatase inhibitors such as the ones included in NATALEE are the preferred initial treatment for patients with high risk features in NHSScotland, some patients may receive tamoxifen, either initially (if aromatase inhibitors are contraindicated for example) or they may switch to tamoxifen if

aromatase inhibitors are not tolerated. Tamoxifen may be less efficacious than aromatase inhibitors however patients in the study were not able to switch to tamoxifen if unable to tolerate aromatase inhibitor which may have improved outcomes for some patients.[9, 14] It is not clear what impact this may have on the generalisability of the study results.

- Black patients may have been underrepresented in the NATALEE population (1.7%) and there may have been a higher proportion of premenopausal patients in the study than expected in the Scottish population.[9]

*Other data were also assessed but remain confidential.**

4.3. Clinical expert input

Clinical experts consulted by SMC considered that ribociclib in combination with aromatase inhibitor fills an unmet need in this therapeutic area, namely for patients with node negative disease. Clinical experts considered that the place in therapy of ribociclib in combination with aromatase inhibitor would be to treat eligible patients with node negative disease or as an alternative to abemaciclib in those with node positive disease (in patients who are contraindicated or cannot tolerate abemaciclib). In patients who are eligible for both abemaciclib and ribociclib, experts suggested that abemaciclib may be preferable due to a shorter treatment duration (two years versus three years).

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine will likely impact on the patient and the service. When compared with abemaciclib, ribociclib has a longer treatment duration which will impact on services. When compared with endocrine therapy (where patients can typically be discharged from the care of oncology), patients taking ribociclib will require additional ongoing care from oncology units.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Breast Cancer Now and METUP UK, both organisations are registered charities.
- Breast Cancer Now has received 0.5% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has received 23% pharmaceutical company funding in the past two years, including from the submitting company.
- A diagnosis of early breast cancer can have a major impact on patients' day to day lives. The physical and psychological impacts of breast cancer can last for many years beyond initial treatment. Fear of recurrence can have a substantial impact on patients' psychological well-being for many years.
- In recent years more treatments have been available at this stage in the treatment pathway, including adjuvant abemaciclib but not all patients are eligible to receive this treatment.

- Patients welcome the introduction of more adjuvant treatment options to help reduce the risk of recurrence. A broader population of patients who currently feel undertreated may be able to access ribociclib. Access to a CDK4/6 inhibitor would be particularly welcomed by patients who cannot have abemaciclib as they are lymph node negative or who cannot tolerate abemaciclib.
- All breast cancer treatments have side effects. The most common adverse effects of ribociclib in the NATALEE study were neutropenia and joint pain. Whilst it is important that patients are informed of potential adverse effects; most find the benefits of a new treatment outweigh the risk of adverse effects.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An overview of the economic analysis is presented in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime (50 years).
Population	Adult patients with HR-positive/HER2-negative early breast cancer at high risk of recurrence. The base case population were all patients (population 1), with sub-group populations defined as node positive (population 2), node negative (population 3), and node positive and eligible for abemaciclib (population 4). All patients were at high risk of recurrence. For population 4, unweighted (4A) and weighted analyses (4B, accounting for the baseline characteristics of the monarchE study for abemaciclib) were performed.
Comparators	Endocrine therapy (ET) in populations 1-4; abemaciclib plus ET in patients eligible for abemaciclib (population 4 only).
Model description	A semi-Markov cohort state-transition model with time-dependent transition matrices and tunnel states was used. Six health states consisting of invasive disease-free survival (iDFS), second primary malignancy (SPM), non-metastatic recurrence (NMR), remission, distant recurrence (DR) and death. SPM and death were absorbing states. There were two sub-states within DR: ET resistant (for patients DR ≤12 months following completion of ET), and ET sensitive (DR >12 months after ET completion). The model had a 28-day cycle length. A partitioned survival modelling approach was used for estimating progression-free survival (PFS) and OS outcomes in the DR state.
Clinical data	The NATALEE clinical study ITT data were used for the population 1 all patient analysis with the aromatase inhibitor (AI) arm used to represent the efficacy of the ET comparator in the economic analysis. As the AI arm of NATALEE did not include use of tamoxifen or exemestane, stated by the company to be used in Scottish clinical practice, the efficacy of the comparator arm was adjusted using a HR of 1.10 for tamoxifen vs AIs for disease recurrence, based on evidence from a published network meta analysis that tamoxifen is less effective than AIs in increasing DFS.[14] The relevant sub-group data from the NATALEE study were used for the node positive (population 2), node negative (population 3) and node positive eligible for abemaciclib (population 4) populations versus ET. Evidence from an indirect treatment comparison in the form of a MAIC was used for the comparison with abemaciclib plus ET in population 4. Based on the MAIC, it was assumed that the iDFS outcomes for ribociclib plus AI vs abemaciclib plus ET are equivalent, hence a HR of one for disease recurrence was applied. Transition probabilities to death were capped at age and sex matched general population mortality (using Scottish life tables). On request an additional analysis was provided by the company for the patient population ineligible for abemaciclib (population 5)

	Treatment waning was assumed for ribociclib plus AI, with an assumption this occurs from 8 years, with waning assumed to have an impact up to the time at which the iDFS event rate equalled general population mortality. Adverse event data used in the economic analysis (grade 3+ with an incidence ≥5%) was derived from the NATALEE study for ribociclib plus AI and ET, and from the MonarchE study for abemaciclib plus ET.[15]
Extrapolation	The iDFS data used in economic analysis were extrapolated by fitting parametric functions to the observed data in the NATALEE study, with the choice of function across each population selected primarily based on best statistical fit and clinical plausibility. For ribociclib there is a maximum treatment duration specified of 3 years, and the observed time on treatment data to permanent discontinuation from the NATALEE study with no extrapolation was used in the economic analysis. Time to treatment discontinuation (TTD) data from the NATALEE study was extrapolated for AI/ET (which could continue beyond ribociclib discontinuation) with a maximum duration of 5 years specified in the base case. The choice of parametric function across each population was based primarily on clinical plausibility. For abemaciclib plus ET the base case TTD used the published Kaplan-Meier plot from the MonarchE study for abemaciclib with a maximum duration of treatment set at 2 years.[15] Subsequent treatments were assumed to be used within the DR sub-states, including re-treatment with CDK4/6 inhibitors with the proportionate use of ribociclib plus ET and abemaciclib plus ET based on clinical expert opinion. PFS, OS and TTD were modelled for each subsequent therapy in the DR ET resistant and DR ET sensitive sub-states. For PFS and OS this used a mixture of fitting parametric functions to available patient level data when available or using a network meta-analysis when patient data not available.[16] TTD was assumed to be the same as PFS in both sub-states.
Quality of life	EQ-5D-5L data collected in the NATALEE study was analysed using generalised estimating equations regression modelling mapped to 3L utility values in order to estimate utilities for the iDFS and NMR health states at 0.7606 and 0.6815 for iDFS and NMR respectively. The remission health state was assumed to have the same utility as for iDFS. The PFS utility for DR ET resistant and sensitive sub-states of 0.6189 was also based on NATALEE EQ 5D-5L analysis. Post progression Survival (PPS) utility estimates for DR sub-states were estimated based on previous technology appraisals and clinical studies of ribociclib in advanced breast cancer. A lower utility was estimated for DR ET resistant disease (0.576) compared to DR ET sensitive disease (0.594), supported by clinical expert opinion stating DR ET resistant as representing more aggressive disease. Disutilities were also included for selected AEs (alanine aminotransferase increased, diarrhoea, leukopenia, lymphopenia, neutropenia) based on published studies/NICE technology appraisals.
Costs and resource use	Medicine acquisition costs were included for all medicines included in the economic analysis, and medicine administration costs for some subsequent therapies. Wastage and relative dose intensity (RDI) were estimated for ribociclib and abemaciclib. RDIs for AI/ET drugs were also estimated. Estimates of the ET treatment mix and subsequent therapies used with proportions of patients receiving each therapy made based on clinical expert opinion. Costs were also included for disease monitoring and follow-up with resource use estimates based on prior NICE early breast cancer technology appraisals. Adverse event and end of life costs were also included. A one-off cost of diagnosis was included for the SPM absorbing state.

PAS	A Patient Access Scheme (PAS) was submitted by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. PAS discounts are in place for abemaciclib, and for fulvestrant and palbociclib as subsequent therapies, and these were included in the results used for decision-making by using estimates of the comparator/subsequent therapies PAS prices.

6.2. Results

The base case results are presented in Table 6.2. The quality adjusted life year (QALY) gains are driven by the greater time spent in the iDFS state and lower probability of being in the DR ET resistant state (worst outcomes). There are higher acquisition costs for ribociclib plus AI with cost offsets associated with a lower probability of being in the DR ET resistant state. SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

Table 6.2: Base case results for Population 1 – all node positive and negative patients at high risk of recurrence

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Ribociclib plus AI versus:	CIC	15.30	CIC	-	-	-	-
ET	CIC	14.70	CIC	CIC	0.60	CIC	CIC

Abbreviations: AI = aromatase inhibitor; CIC = commercial in confidence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

The results for the sub-group populations of node positive and node negative patients are presented in Tables 6.3a and b respectively. Results for sub-group populations 4 eligible for abemaciclib and 5 ineligible for abemaciclib are presented in Tables 6.3c and d respectively.

Table 6.3a: Results for Population 2 – node positive patients at high risk of recurrence

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Ribociclib plus AI versus:	CIC	15.22	CIC	-	-	-	-
ET	CIC	14.62	CIC	CIC	0.60	CIC	CIC

Abbreviations: AI = aromatase inhibitor; CIC = commercial in confidence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

Table 6.3b: Results for Population 3 - node negative patients at high risk of recurrence

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Ribociclib plus AI versus:	CIC	15.27	CIC	-	-	-	-
ET	CIC	14.70	CIC	CIC	0.57	CIC	CIC

Abbreviations: AI = aromatase inhibitor; CIC = commercial in confidence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

Table 6.3c: Results for Population 4 (weighted analysis) – node positive patients at high risk of recurrence eligible for abemaciclib

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Ribociclib plus AI versus:	CIC	15.07	CIC	-	-	-	-
ET	CIC	14.28	CIC	CIC	0.79	CIC	CIC
abemaciclib plus ET	CIC	15.07	CIC	CIC	-0.001	CIC	CIC

Abbreviations: AI = aromatase inhibitor; CIC = commercial in confidence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

Table 6.3d: Results for Population 5 – patients at high risk of recurrence ineligible for abemaciclib

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Ribociclib plus AI versus:	CIC	16.23	CIC	-	-	-	-
ET	CIC	15.70	CIC	CIC	0.53	CIC	CIC

Abbreviations: AI = aromatase inhibitor; CIC = commercial in confidence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality adjusted life years.

6.3. Sensitivity analyses

The one way sensitivity analysis varied various input parameters by ±10% range. The most impactful parameters on the cost-effectiveness results for the all patient population were related to varying PFS and OS outcomes associated with abemaciclib plus ET when used as a post progression therapy in the DR ET resistant sub-state, and for population 4 when varying the RDI estimates for abemaciclib.

A range of sensitivity and scenario analyses were considered and descriptions of these key scenarios are provided in Table 6.4 below. The key scenario analyses performed for the population 1 (all patients) and population 3 are presented in Table 6.5. Population 3, patients who are node negative, was identified from SMC clinical expert feedback as the population in which ribociclib is most likely to be used in clinical practice.

Table 6.4: Selected key scenario analyses for whole population and key sub-group

	Parameter	Base Case	Scenarios
1	Efficacy of tamoxifen in ET	HR=1.10 vs AI applied (less effective)	(a) HR=1.45 (Source: Janni et al 2023)
			(b) HR=1 (no difference)
2	iDFS extrapolation (ribociclib + AI ;ET) – population 1	Exponential	Log logistic (R)

3	iDFS extrapolation (ribociclib + AI ;ET) – population 3	Log logistic	Generalised Gamma
4	Time horizon	50 years	(a) 20 years
			(b) 15 years
5	Extrapolation ribociclib + ET outcomes in DR ET resistant state	PFS extrapolated using log normal (R) function	(a) Extrapolated using log normal
		OS extrapolated using log logistic (R) function	(b) Extrapolated using Weibull (R)
		TTD extrapolated using Gompertz (R) function	(c) Extrapolated using RCS Weibull (R)
			(d) Combined scenario 4 (a), (b), (c)
6	Treatment waning	Waning from year 8	(a) Waning from year 10
			(b) Waning from year 5
			(c) Waning from year 5 with no benefit after year 8
7	Use of CDK4/6i in DR ET resistant (CDK4/6 inhibitor sensitive) sub-state	Estimated re-treatment with a CDK4/6i 30% of patients	CDK4/6i retreatment assumed 60% of patients
8	RDI % for treatment arms, ribociclib (83.4%)	Ribociclib, AI, ET RDIs based on NATALEE study/ assumption	(a) All AI/ET RDIs set to 100%
			(b) RDI for ribociclib based on treatment pauses only (97.2%)

Abbreviations: AI=aromatase inhibitor; CIC = commercial in confidence; DR=distant recurrence; ET=endocrine therapy; HR=hazard ratio; iDFS=invasive disease-free survival; NMR=non-metastatic recurrence; RDI = relative dose intensity; R=restricted model; RCS=restricted cubic spline model; TTD=time to treatment discontinuation.

6.4. Key strengths

- Modelling approach is appropriate, making good use of individual patient data available and provides granularity in using a partitioned survival modelling approach to estimate distant recurrence state outcomes.
- Large EQ-5D-5L data set from the NATALEE study with which to estimate iDFS state utilities using regression modelling.
- Good range of scenario analysis tested.

6.5. Key uncertainties

- The patient populations of most relevance and interest for Scottish clinical practice is likely to be population 3, node negative patients at high risk of recurrence. SMC clinical expert responses suggested a general preference for abemaciclib due to its shorter duration of treatment but indicated an interest in using ribociclib in node negative patients, for whom abemaciclib is not an option. Hence, the cost-effectiveness results in these patients are highly relevant.
- The adjustment applied to reduce the efficacy of the ET comparator arm to allow for tamoxifen use in Scottish clinical practice was uncertain and without the adjustment there was a small upward impact on the cost-effectiveness results (Scenario 1b, Table 6.4).
- The immaturity of data from the NATALEE study for iDFS and survival outcomes meant there was uncertainty over the extrapolations for iDFS for ribociclib plus AI and ET with uncertainty over choice of function to best extrapolate iDFS. Using alternative plausible functions for iDFS has a modest impact on the cost-effectiveness of ribociclib plus AI vs ET (scenarios 2 and 3, Table 6.4). The results showed some sensitivity to applying shorter time horizons to explore the inherent uncertainty with longer term extrapolations (scenario 4, Table 6.4). There was uncertainty over extrapolations of PFS/OS and TTD in the DR ET resistant state, as illustrated by a scenario for PFS, OS and TTD extrapolation for ribociclib plus fulvestrant used as a subsequent therapy in the DR ET resistant state (Scenario 5d, Table 6.4).
- Treatment waning assumptions for ribociclib were highly uncertain with waning assumed to start several years after stopping ribociclib treatment. Scenario analysis demonstrated upward sensitivity in the cost-effectiveness results to a more pessimistic treatment waning assumption that any iDFS benefit for ribociclib over ET ends at year 8 (Scenario 6c, Table 6.5).
- There was a lack of direct clinical evidence for the comparison with abemaciclib plus ET in the patient population eligible for abemaciclib (population 4), and the assumption of equal iDFS efficacy and outcomes based on a MAIC which had limitations is uncertain. The estimate of AE driven utility/cost differences that are favourable for ribociclib vs abemaciclib are uncertain.

7. Conclusion

After considering all the available evidence, the Committee accepted ribociclib for use in NHSScotland.

8. Guidelines and Protocols

Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the treatment of primary breast cancer were published in 2013.[6]

National Institute for Health and Care Excellence (NICE) guidelines for early and locally advanced breast cancer were published in 2018 and updated in 2025.[7]

European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up of early breast cancer were published in 2024.[3]

9. Additional Information

9.1. Product availability date

06 February 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 36-month course (£)
ribociclib	**400 mg orally once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete cycle of 28 days. Treatment is continued for 36 months or until disease recurrence or unacceptable toxicity.**	**£70,800**

Costs from BNF online on 23 July 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 127 patients estimated to receive treatment in year 1 rising to 762 patients in year 3.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 September 2025.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.