Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2198

ribociclib 200mg film-coated tablets (Kisqali®)

Novartis Pharmaceuticals UK Ltd

04 October 2019

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

ADVICE: following a full submission assessed under the end of life and orphan medicine process

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

Indication under review: for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant* as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

SMC restriction: women who have relapsed on or within 12 months of completing (neo) adjuvant endocrine therapy, or those who have progressed on first-line endocrine-based therapy for advanced breast cancer.

Ribociclib in combination with fulvestrant significantly increased progression-free survival compared with endocrine monotherapy in women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

This SMC advice takes account of the benefit of Patient Access Schemes (PAS) that improve the cost effectiveness of ribociclib and fulvestrant. This advice is contingent upon the continuing availability of these PAS in NHSScotland or list prices that are equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

* For SMC advice relating to the use of ribociclib in combination with an aromatase inhibitor in this setting, please refer to SMC 1295/18

Chairman, Scottish Medicines Consortium

Published 11 November 2019

Indication

Ribociclib is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.[1]

Dosing Information

The recommended dose is 600mg (three 200mg film-coated tablets) of ribociclib once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. 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.

When ribociclib is used in combination with fulvestrant, fulvestrant is administered intramuscularly (IM) on days 1, 15 and 29, and once monthly thereafter.

Treatment of pre- and peri-menopausal women with the approved ribociclib combinations should also include an LHRH agonist in accordance with local clinical practice.

Please refer to the Summary of Product Characteristics for details of ribociclib dose modifications.

Treatment with ribociclib should be initiated by a physician experienced in the use of anticancer therapies.[1]

Product availability date

17 December 2018

Ribociclib meets SMC end of life and orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Ribociclib is a cyclin-dependent kinase (CDK) 4 and 6 inhibitor. Oestrogen receptor induced proliferation requires cyclin D and increases with CDK 4 and 6 activity, which may promote cell cycle progression. Inhibition of CDK 4 and 6 disrupts this pathway and diminishes breast cancer cell growth. Continuous inhibition is associated with sustained growth arrest or apoptosis.[1] Ribociclib has previously been accepted by SMC for the treatment of women with HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy, or in women who have received prior endocrine therapy (SMC 1295/18). This submission relates to a new indication in this group of patients permitting use of ribociclib in combination with fulvestrant, and within this the submitting

company has requested that SMC considers ribociclib when positioned for use in women with endocrine-resistant disease, who have relapsed on or within 12 months of completing (neo) adjuvant endocrine therapy, or those who have progressed on first-line endocrine-based therapy for advanced breast cancer (subpopulation B, defined below).

The key evidence for the use of ribociclib in combination with fulvestrant for the treatment of HR-positive/HER2-negative advanced breast cancer (which comprises metastatic and locally advanced disease not amenable to curative surgery) comes from MONALEESA-3, a phase III, double-blind, placebo-controlled, parallel group, international study.[2] The study included postmenopausal women with confirmed HR-positive/HER2-negative advanced breast cancer. Patients had >1 measurable lesion per Response Evaluation Criteria In Solid Tumours (RECIST; version 1.1) or one predominantly lytic bone lesion, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, with adequate organ and bone marrow function.[2] The study included two subpopulations, according to presence or absence of evidence of resistance to prior endocrine therapy:

Subpopulation A:
• Newly diagnosed advanced breast cancer (de novo), treatment naïve.
• Relapsed more than 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.

Subpopulation B
• Relapsed on or within 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.
• Relapsed more than 12 months from completion of (neo) adjuvant endocrine therapy and then subsequently progressed after one line of endocrine therapy (with either an anti-oestrogen or an aromatase inhibitor) for advanced/metastatic disease.
• Advanced/metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy (with either an anti-oestrogen or an aromatase inhibitor).

Patients were randomised 2:1 to receive ribociclib 600mg/day orally (3 weeks on, 1 week off) or placebo, both in addition to fulvestrant 500mg IM on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1. Randomisation was stratified by lung or liver metastases (yes or no) and prior endocrine therapy (subpopulation A or B). Treatment with study medicine continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Ribociclib dose modifications were permitted to manage adverse events, this included treatment interruption and up to two dose reductions. Fulvestrant dose modifications were not permitted.[2]

The primary outcome was investigator-assessed progression-free survival (PFS) in the full analysis set, which included all randomised patients. PFS was defined as the time from randomisation to the date of the first documented disease progression using RECIST version 1.1 or death by any

cause.[2, 3] The study demonstrated that ribociclib plus fulvestrant was superior to placebo plus fulvestrant for PFS in the total study population.[2, 3] The results are detailed in Table 1.

Table 1. Primary outcome, progression-free survival, result from MONALEESA-3.

		Ribociclib plus fulvestrant n=484	**Placebo plus fulvestrant n=242**
median time from randomisation to data cut-off for the PFS analysis was 20.4 months			
Total study population	Number of events	210	150
	K-M median time estimate	20.5 months	12.8 months
		HR 0.59 (95% CI: 0.48 to 0.73) p<0.001	
	K-M 12-month event-free rate	67%	52%
	K-M 24-month event-free rate	40%	18%

PFS = progression-free survival, HR = Hazard ratio, CI = confidence interval, K-M = Kaplan-Meier estimate,

Overall survival data for the ribociclib and placebo groups were immature at the time of this data-cut off and median survival could not be estimated. Other secondary outcomes included overall response rate (ORR), defined as the proportion of patients with the best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1, and clinical benefit rate (CBR), defined as the proportion of patients with a best overall response of CR or PR or stable disease lasting 24 weeks or longer as defined in RECIST 1.1: these comparisons were descriptive only with estimates favouring treatment with ribociclib over placebo. The results are detailed in Table 2.[4]

Table 2. Important secondary outcome results from MONALEESA-3 for the total study population.[2, 4]

		Ribociclib plus fulvestrant n=484	**Placebo plus fulvestrant n=242**
Overall survival	Number of events	70	50
	K-M median time estimate	NE	NE
		HR 0.67 (95% CI:0.46 to 0.96)	
Overall response rate (95% CI)		32% (28 to 37)	22% (16 to 27)
Clinical benefit rate (95% CI)		70% (66 to 74)	63% (57 to 69)

NE = not estimable, HR = Hazard ratio, CI = confidence interval, K-M = Kaplan-Meier estimate

The time from randomisation to progression on next-line therapy or death, whichever occurred first, was added as an exploratory outcome and is also known as PFS2. This outcome provides information on longer-term benefit between PFS and overall survival but is descriptive only. For

the ribociclib and placebo groups respectively, median time to PFS2 was not estimable and 25 months, with event rates of 24% and 34%.[4]

The PFS results for the subgroup relevant to the company's positioning (subpopulation B) were consistent with the results for the overall study population.[4] Detailed results are included in Table 3.

Table 3. Median progression-free survival for selected subpopulations of MONALEESA-3.[4]

Patient subgroup based on treatment history		Ribociclib plus fulvestrant	Placebo plus fulvestrant
Subpopulation A (likely endocrine therapy sensitive disease)	Number of events	76/238	66/129
	Median time	NE	18.3 months
		HR 0.58 (95% CI: 0.42 to 0.80)	
Subpopulation B (likely endocrine therapy resistant disease)	Number of events	131/236	84/109
	Median time	14.6 months	9.1 months
		HR 0.56 (95% CI: 0.43 to 0.74)	

NE = not estimable, CI = confidence interval, HR = Hazard ratio.

Time to 10% deterioration in the global health status/QOL scale score of the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire and change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30 were secondary outcomes of MONALEESA-3. Similar results were reported for both treatment groups for these outcomes.[4]

An updated analysis of the MONALEESA-3 study at 39.4 months follow-up showed that ribociclib resulted in a statistically significant increase in overall survival compared with placebo, median overall survival was still to be reached in the ribociclib group and was 40.0 months in the placebo group (hazard ratio [HR] 0.72; 95% confidence interval [CI]: 0.57 to 0.92; p=0.005). Similar results were shown in Subpopulation B with median overall survival of 40.2 months compared with 32.5 months in the placebo group (HR 0.73; 95% CI: 0.53 to 1.00).[5]

Indirect evidence

The submitting company presented a network meta-analysis (NMA) to compare ribociclib plus fulvestrant with everolimus plus exemestane for PFS in patients with HR-positive/HER2–negative advanced breast cancer whose disease had progressed after prior endocrine therapy. The analysis included patients who had not received any prior systemic anticancer treatment for advanced disease (first-line) and patients whose disease has progressed after prior endocrine therapy (second-line). The network included five studies and applied the Bucher method across multiple comparisons in order to compare the treatments of interest. The analysis indicated there was no evidence of difference between the treatments for PFS.

Summary of evidence on comparative safety

The safety profile for ribociclib plus fulvestrant from MONALEESA-3 is consistent with the known profiles for the two treatments.[4] Safety analyses were conducted in all patients who received at least one dose of a study medicine and had at least one post-baseline safety assessment (n=724).[2] Median duration of exposure in the ribociclib (n=483) and placebo (n=241) groups respectively were 16 months and 12 months.[2]

For the ribociclib and placebo groups, suspected treatment-related AEs were reported for 95% and 68% of patients, suspected serious treatment-related AEs were reported for 11% and 2.5%, and suspected treatment-related AEs leading to discontinuation were 14% and 3.3%.[4] For the same groups the following AEs of any grade were reported: neutropenia (56% and 0.8%), nausea (45% and 28%), fatigue (31% and 33%), diarrhoea (29% and 20%), vomiting (27% and 13%), constipation (25% and 12%), pruritus (20% and 6.6%), alopecia (19% and 4.6 %), rash (18% and 5.8%), anaemia (17% and 5.4%), aminotransferase increased (14% and 4.6%) and QT prolongation (6.2% and 0.8%).[4]

For ribociclib and placebo respectively, dose reductions were reported for 38% and 4.1% of patients; 31% and 3.7% had a single dose reduction. Adverse events (AEs) were the most common reason for dose reductions (33% and 3.3% respectively).[2]

The important safety concerns with ribociclib are myelosuppression (primarily neutropenia), hepatobiliary toxicity and QT interval prolongation.[4]

Summary of clinical effectiveness issues

Locally advanced and metastatic breast cancer are collectively described as advanced breast cancer. The expression of certain receptors, such as HR and HER-2, by breast cancer cells play an important role in determining the therapeutic efficacy of treatments.[1, 4] Women with HR-positive, HER2-negative advanced breast cancer receive first line treatment with an endocrine therapy, most commonly an aromatase inhibitor, with or without a CDK 4/6 inhibitor, unless the disease is imminently life-threatening or requires early relief of symptoms due to significant visceral organ involvement, in which case chemotherapy may be used.

The choice of first-line endocrine therapy depends on which treatment was used in the (neo) adjuvant setting, response to it and its duration as well as the time elapsed from the end of the (neo) adjuvant treatment. In most patients, progressive disease ultimately develops, either as early failure to respond to endocrine therapy (primary or *de novo* resistance) or as relapse/progression following an initial response (acquired resistance).[4, 6] In NHSScotland, for patients who are considered to have aromatase inhibitor resistant disease, fulvestrant alone and everolimus plus exemestane are the main treatment options.

The median overall survival for advanced breast cancer is approximately 3 years. Ribociclib meets SMC end-of-life and orphan equivalent criteria for this indication.[6] Other CDK4/6 inhibitors, abemaciclib (SMC2179) and palbociclib (SMC2149) have recently been accepted for use in this setting.

The submitting company has requested that SMC considers ribociclib in combination with fulvestrant when positioned for use in women who have relapsed on or within 12 months of completing (neo) adjuvant endocrine therapy, or those who have progressed on first-line endocrine-based therapy for advanced breast cancer (that is, subpopulation B, patients who have demonstrated some resistance to prior endocrine therapy).

In the MONALEESA-3 study ribociclib plus fulvestrant demonstrated clinically meaningful superiority over placebo plus fulvestrant, increasing median PFS by approximately 8 months in the total study population and by about 5.6 months in subpopulation B.[2, 4] In the context of advanced breast cancer, the benefits of prolonged improvements in PFS include; a delay in the worsening of disease symptoms and a delay in the time to treatment with chemotherapy.[4]

Overall survival data were immature at the time of the initial data cut-off.[2, 4] In the absence of mature OS data, the EMA considered that the exploratory outcome PFS2, the time from randomisation to progression on next-line therapy or death, provides important supporting evidence of delay in disease progression beyond initial on-treatment progression.[4]

A blinded independent review committee analysis of a random sample of 40% of randomised patients highlighted a degree of bias in investigators assessment. For the ribociclib and placebo groups respectively, progressive disease reported by study investigators was not confirmed in 35% and 23% of cases. This suggests that the potential bias favoured treatment with placebo.[4] Differences in the rate of neutropenia (56% and 0.8%) may have resulted in unblinding which may have influenced the reporting of safety and patient-reported outcomes.

The relative treatment effect was consistent across subgroups based on prior treatment. Notably, response rates were lower in subpopulation B than in the overall study population: this is expected as patients in this group are considered to be endocrine treatment resistant.[4] As the study was not powered for subpopulation B, there is some uncertainty surrounding the size of the treatment-effect in this patient group.[4]

The exclusion of patients with cardiac comorbidities and more severe disease, as indicated by poor performance status may reduce the generalisability of the study results to the Scottish population. The MONALEESA-3 study did not include pre- or peri-menopausal women, however the EMA concluded that results could be extrapolated to include pre- and peri-menopausal women treated with ovarian suppression therapy (LHRH agonist).[4] Study results may not be generalisable to patients who have failed on CDK 4/6 inhibitors as first-line treatment, as this patient group was also excluded from the key study.

Limitations of the indirect evidence include differences in clinical characteristics: whether patients had received prior endocrine treatment in the (neo) adjuvant setting or were endocrine treatment resistant, and differences in study methodologies in terms of tumour assessment and tumour assessment schedules. The network formed a long path with no single common comparator to connect the network, which is likely to increase the uncertainty of the NMA results. The company did not compare treatments for important outcomes such as overall survival, health-related quality of life and safety. Despite these limitations, overall, the indirect evidence is acceptable.

The introduction of ribociclib plus fulvestrant would provide an additional treatment option for patients with endocrine-resistant advanced breast cancer.

The ribociclib summary of product characteristics advises assessment of patient electrocardiogram (ECG) prior to initiating treatment, with assessment repeated at approximately day 14 of the first cycle, at the beginning of the second cycle, and then as clinically indicated. More frequent ECG monitoring may be required for patients with prolonged QTc.[1]

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ribociclib in combination with fulvestrant, as an end of life and orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced breast cancer is incurable and its diagnosis leads to emotional and psychological distress and impacts negatively on the patient's quality of life.

- There is an unmet need for treatments which delay the time to disease progression and death. This is particularly important in endocrine-resistant disease where existing treatments may not be suitable for every patient due to toxic adverse effects.

- Ribociclib plus fulvestrant, compared to fulvestrant monotherapy, delays disease progression and the time to more burdensome and toxic chemotherapy. This may allow patients to maintain their quality of life and remain well for longer, live independently, and contribute to social and financial aspects of family life for longer.

- The ribociclib regimen has a known and manageable adverse event profile which is different to alternative treatment options.

- Ribociclib is an oral treatment with the advantage that it can be taken at home.

Additional Patient and Carer Involvement

We received a patient group submission from Breast Cancer Care and Breast Cancer Now (a new charity formed from a merger between Breast Cancer Care and Breast Cancer Now), which is a registered charity. In the past two years, Breast Cancer Care has received 0.69% pharmaceutical company funding and Breast Cancer Now has received 10% pharmaceutical company funding, both including from the submitting company. A representative from the merged organisation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing ribociclib plus fulvestrant to either fulvestrant alone or exemestane plus everolimus in women who have relapsed on or within 12 months of completed (neo) adjuvant endocrine therapy, or progressed on first-line endocrine-based therapy for advanced breast cancer. The time horizon for the analysis was 40 years.

A semi-Markov model was used in the analysis. This consisted of the following states: PFS, post-progression survival (PPS) and death. PFS data from the key study were used in the analysis for the comparison versus fulvestrant, with extrapolation as necessary. The company investigated a range of possible distributions for the extrapolation, assessed using goodness of fit criteria, expert opinion and visual inspection of the plausibility of the extrapolation. The company selected the restricted log normal distribution for both arms in the base case. For PPS, individual patient failure time data were used to estimate the probabilities for the model. This analysis used the pooled PPS data from subpopulation B rather than the data from the ribociclib and fulvestrant arms individually as the difference in PPS was not statistically significant between the arms. PPS was thus assumed to be the same between ribociclib plus fulvestrant and fulvestrant.

The NMA reported above was used as the source of PFS data to model PFS benefits for ribociclib plus fulvestrant in the comparison with everolimus plus exemestane. The same assumption as above regarding no difference in PPS was used versus everolimus plus exemestane. No specific evidence was presented to support this assumption so it is a source of uncertainty. Individual patient failure time data from subpopulation B of MONALEESA-3 were also used to estimate time to treatment discontinuation (TTD) for ribociclib plus fulvestrant and fulvestrant alone, and restricted Weibull distributions were selected. TTD for exemestane plus everolimus was assumed to be until disease progression.

Utility values were estimated from the MONALEESA-3 study where quality of life was measured using EQ-5D- 5L. Given current issues about the validity of the 5L values, these were cross-walked into the 3L version, as currently recommended by NICE. The same values were used for all treatments (that is, treatment-specific values were not used) on the basis that there were no

significant differences between the arms of the key study in terms of EQ-5D values. The values used were assumed to reflect treatment disutilities.

Costs in the model related to medicines acquisition, monitoring and administration costs (for fulvestrant). Health state costs for the PFS and PPS states were estimated from resource use for packages of care recommended in clinical guidelines, as used in other health technology appraisals.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PAS discounts are also in place for fulvestrant and everolimus these were included in the results used for decision-making SMC by using estimates of the comparator PAS prices.

SMC is unable to present the results provided by the company which used an estimate of the PAS price for fulvestrant and everolimus due to commercial confidentiality and competition law issues. As such the list price results are presented below.

Table 4: Base case cost-effectiveness results at list prices

ribociclib plus fulvestrant versus:	**Incremental cost-effectiveness ratio (ICER)**
fulvestrant	£101,277
everolimus plus exemestane	Dominant

A summary of the variables that produced the greatest upward movement in the ICERs is as shown in tables 5 and 6:

Table 5: Sensitivity analysis results at list prices, versus fulvestrant

	Sensitivity analysis	**ICER**
1	TTD based on unrestricted Gompertz distribution	£124,546
2	25% increase in medication costs	£125,832
3	PFS HR increased by 25%	£118,990
4	TTD based on restricted Gompertz distribution	£118,118
5	25% disutility applied to all health states	£109,924
6	PFS was based on the exponential distribution.	£105,821

ICER = Incremental cost-effectiveness ratio, TTD = time to treatment discontinuation, PFS = progression-free survival. HR = hazard ratio

Table 6: Sensitivity analysis results at list prices, versus everolimus plus exemestane

	Sensitivity analysis	ICER
1	TTD based on unrestricted Gompertz distribution	£108,254
2	TTD based on restricted Gompertz distribution	£86,886
3	PFS was based on the exponential distribution	£90,359
4	No differences in PFS	dominant

ICER = Incremental cost-effectiveness ratio, TTD = time to treatment discontinuation, PFS = progression-free survival

There were a number of weaknesses with the analysis:

- There are weaknesses with the indirect comparison versus everolimus plus exemestane. Differences in PFS were included in the modelled benefits howeverthe submitting company provided additional analysis on request to remove the PFS difference (analysis 4, table 6.
- For both comparisons, the analysis does predict life year gains for ribociclib plus fulvestrant, but as noted above, there is uncertainty associated with this given the immaturity of the data provided within the SMC submission. Following the New Drugs Committee, the submitting company provided additional information relating to updated survival analysis, as noted above.[5] The economic analysis was not updated to reflect these updated data but the company commented that the findings were supportive of the outputs modelled in the economic analysis.
- There is uncertainty associated with the modelling of time to treatment discontinuation and the ICERs were particularly sensitive to the choice of distributions chosen.
- There is uncertainty associated with the assumption of no difference in post-progression survival, particularly with respect to the comparison with everolimus plus exemestane. The impact of this on the ICER is unknown.

The Committee also considered the benefits of ribociclib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as ribociclib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ribociclib for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

In August 2017 the National Institute for Health and Care Excellence (NICE) updated its clinical guideline (CG 81): Advanced breast cancer: diagnosis and treatment. It recommends that an aromatase inhibitor be offered as first line treatment to postmenopausal women with ER-positive advanced breast cancer, unless their disease is imminently life-threatening or needs early symptomatic relief due to significant visceral organ involvement, in which case they should be offered chemotherapy.[7] The guideline predates the licensing of ribociclib.

In 2018 the European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) produced the 4th ESO‑ESMO International Consensus Guidelines for Advanced Breast Cancer. The guideline advises that for ER-positive advanced breast cancer pre-menopausal women should have adequate ovarian function suppression or ovarian function ablation and should then be treated in line with post-menopausal women. For patients with ER-positive/HER2-negative advanced breast cancer the preferred first line treatment in the majority of case is endocrine therapy; for patients with visceral crisis of endocrine resistance other treatments are likely to be preferred. Previous therapies and response to these therapies will guide the choice of endocrine therapy, monotherapy options include; aromatase inhibitors (exemestane, letrozole, anastrozole), tamoxifen, or fulvestrant. The guideline suggests that there is some uncertainty around the optimal role of the CDK inhibitors—palbociclib, ribociclib and abemaciclib, in clinical practice.[5]

Additional information: comparators

Exemestane plus everolimus and fulvestrant. Palbociclib and abemaciclib, both in combination with fulvestrant, have only recently been accepted by SMC for patients groups similar to the patient group under review and are not included as comparators in the economic analysis.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
ribociclib plus fulvestrant	**ribociclib 600mg oral once daily plus fulvestrant 500mg intramuscular every 2 weeks for the first 3 doses, then 500mg every month**	**45,141 (45,664 in year 1)**
abemaciclib plus fulvestrant	abemaciclib 150mg oral twice daily plus fulvestrant 500mg intramuscular every 2 weeks for the first 3 doses, then 500mg every month	45,141 (45,664 in year 1
palbociclib plus fulvestrant	palbociclib 125mg oral once daily for first 21 days of 28-day cycle plus fulvestrant 500mg intramuscular every 2 weeks for the first 3 doses, then 500mg every month	45,141 (45,664 in year 1
exemestane plus everolimus	everolimus 10mg oral once daily plus exemestane 25mg oral once daily	35,519
fulvestrant	500mg intramuscular every 2 weeks for the first 3 doses, then 500mg every month	6,791 (7,314 in year 1)

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 21 June 2019 and eVADIS September 2019. Costs do not take any patient access schemes into consideration. Regimens assume maximum licensed dose for the indication is tolerated.

Additional information: budget impact

The submitting company estimated there would be 359 patients eligible for treatment with ribociclib plus fulvestrant in year 1, falling to 171 by year 5. Estimated treated patient numbers were 7 patients in year 1 rising to 36 patients in year 5.

SMC is unable to publish the with PAS budget impact estimate 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.

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

References

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6. Cardoso F SE, Costa A, Papadopoulos E, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Annals of Oncology. 2018;29(8):1634-57.
7. National Institute for Health Care Excellence. Clinical Guideline 81 Advanced breast cancer: diagnosis and treatment. 2017 [cited; Available from: https://www.nice.org.uk/Guidance/CG81/Resources.

This assessment is based on data submitted by the applicant company up to and including 16 August 2019.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.