

abemaciclib 50mg, 100mg and 150mg tablets (Verzenios®)

Eli Lilly and Company

5 April 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

abemaciclib (Verzenios®) is accepted for 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 an aromatase inhibitor* as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In a phase III randomised study in women with HR-positive, HER2-negative advanced breast cancer, abemaciclib in combination with an aromatase inhibitor significantly increased progression-free survival compared with aromatase inhibitor monotherapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of abemaciclib. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

*For SMC advice relating to the use of abemaciclib in combination with fulvestrant in this setting, please refer to SMC2179.

Chairman
Scottish Medicines Consortium

Indication

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 an aromatase inhibitor 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.¹

Dosing Information

The recommended dose of abemaciclib is 150mg twice daily when used in combination with endocrine therapy. Please refer to the Summary of Product Characteristics of the endocrine therapy combination partner for the recommended posology.

In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

Abemaciclib is given orally at approximately the same times each day as a tablet to be swallowed whole with or without food. It should not be taken with grapefruit or grapefruit juice.

Abemaciclib should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Abemaciclib should only be initiated and supervised by physicians experienced in the use of anti-cancer therapies. Please refer to the summary of product characteristics for further information.¹

Product availability date

October 2018

Abemaciclib meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Abemaciclib is a cyclin-dependent kinase (CDK) 4 and 6 inhibitor. Oestrogen receptor induced proliferation requires cyclin D and increases in 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.²

The licensed indication for abemaciclib includes two distinct populations for use: ‘in combination with an aromatase inhibitor as initial endocrine-based therapy or in women who have received prior endocrine therapy’ and ‘in combination with fulvestrant as initial endocrine-based therapy or in women who have received prior endocrine therapy’. This detailed advice document (DAD) refers to the first of these populations. Patients in this population could have received endocrine therapy prior to progressing to the advanced cancer setting and this is reflected in the MONARCH 3 study inclusion criteria. The second population (abemaciclib in combination with fulvestrant) is covered in a separate DAD (SMC2179).

Key evidence for the use of abemaciclib for this indication comes from MONARCH 3, a double-blind, randomised, controlled phase III study. MONARCH 3 investigated the efficacy and safety of abemaciclib in combination with a non-steroidal aromatase inhibitor (NSAI) in women with HR-positive, HER2-negative advanced breast cancer.^{3, 4}

This study recruited post-menopausal women with confirmed HR-positive, HER2-negative locoregional or metastatic breast cancer not suitable for surgical resection or radiotherapy with curative intent, who had measurable disease or non-measurable bone-only disease as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, and had adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 . Prior endocrine therapy in the neoadjuvant or adjuvant setting was permitted if the patient had a disease-free interval >12 months from the completion of endocrine therapy. Patients were excluded if they had received prior systemic therapy for advanced disease.^{3, 4}

Patients were randomised 2:1 to treatment with abemaciclib 150mg oral twice daily (n=328) or matching placebo (n=165) and were stratified by metastatic site (visceral, bone only, or other) and prior endocrine therapy (aromatase inhibitor, other endocrine therapy or no endocrine therapy).^{3, 4} Patients in both groups received a NSAI which could be either anastrozole 1mg or letrozole 2.5mg oral once daily. Assigned medicines were taken in continuous 28-day cycles and treatment was to continue until disease progression, unacceptable toxicity, patient withdrawal or death. Dose interruptions and reductions of abemaciclib or placebo were permitted in accordance with the study protocol. Patients were allowed to discontinue abemaciclib/placebo or NSAI and continue the other medicine.^{3, 4}

The primary outcome was investigator-assessed progression-free survival (PFS), defined as the time from randomisation until objective disease progression (according to RECIST version 1.1) or death in the intention-to-treat population which included all randomised patients.^{3, 4} Patients were censored at the time of their last tumour assessment or the time of randomisation if baseline or post baseline assessments were missing.^{3, 4} The results of the final PFS analysis are presented in Table 1. PFS was significantly longer in the abemaciclib group compared with the placebo group.^{3, 4}

Table 1. Final analysis of progression-free survival, the primary outcome of MONARCH 3.^{3, 4}

		abemaciclib plus NSAI (n=328)	placebo plus NSAI (n=165)
Final PFS analysis, data cut-off 3 November 2017			
PFS assessed by investigator	PFS events, n (%)	138 (42%)	108 (65%)
	Median PFS, months (95% CI)	28.2	14.8
	HR 0.54, (0.42 to 0.70), p<0.001		

NSAI=non-steroidal aromatase inhibitor, PFS=progression-free survival, CI=confidence interval, NR=not reached, HR=hazard ratio

The results of key secondary outcomes are described in Table 2.

Table 2. Results of key secondary outcomes of MONARCH 3.^{3, 4}

		abemaciclib plus NSAI (n=328)	placebo plus NSAI (n=165)
Overall survival (OS), data cut-off 3 November 2017	OS Events, n (%)	63 (19%)	30 (18%)
	Median OS, months (95% CI)	NR	NR
		HR 1.06 (0.68 to 1.63), p=0.80	
Objective response rate, % (95% CI)		50% (44 to 55)	37% (30 to 44)
	OR 1.7, p=0.005		
Median duration of response, months (95% CI)		27.4 (25.7 to NR)	17.5 (11.2 to 22.2)
Clinical benefit rate, % (95% CI)		78% (74 to 83)	72% (65 to 78)
	OR 1.4, p=0.10		

NSAI=non-steroidal aromatase inhibitor, OS=overall survival, CI=confidence interval, NR=not reached HR=hazard ratio, OR=Odds ratio. Clinical benefit definition includes patients with complete response, partial response, or stable disease for 6 months or more.

Analyses of PFS across pre-specified subgroups were consistent with the results of the final analysis of PFS.^{3, 4} The majority of the overall study population (79%) received letrozole as NSAI treatment.³

MONARCH 3 recorded quality of life data using the following tools: European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC-QLQ-BR23, and EuroQol (EQ) 5D-5L. For the EORTC QLQ-C30 tool, differences in change from baseline between treatment groups was reported for three categories; increases in diarrhoea, which was associated with abemaciclib plus NSAI treatment; and improvements in global health status and fatigue associated with NSAI treatment.⁴ Antidiarrhoeals were required for the majority of patients treated with abemaciclib.³

Other data were also assessed but remain confidential.*

Summary of evidence on comparative safety

The duration of therapy was similar for both treatment groups in MONARCH 3 with a median duration of 16 and 15 months respectively in the abemaciclib and placebo groups. In the safety population the following were reported for patients in the abemaciclib (n=327) and placebo (n=161) groups respectively: adverse events (AEs) related to study treatment 94% versus 57%, serious AEs related to study treatment 13% versus 2.5%, discontinued treatment due to a study treatment related AE 12% versus 0%,⁴ dose reductions due to AEs 43% versus 6.2% and dose interruptions due to AEs 56% versus 19%.³ The most common AEs in the same groups respectively were; diarrhoea (82% and 32%), neutropenia (44% and 1.9%), fatigue (41% and 34%), nausea (41% and 20%), anaemia (32% and 8%), abdominal pain (31% and 13%), vomiting (30% and 13%) and alopecia (28% and 11%).⁴

The European Medicines Agency (EMA) concluded that the safety profile for abemaciclib in combination with a NSAID was consistent with its safety profile when used in combination with other endocrine therapies for the treatment of advanced breast cancer.⁴

Summary of clinical effectiveness issues

Breast cancer is the most common cancer in women. The expression of certain receptors, such as HR and HER-2, by breast cancer cells plays an important role in determining the therapeutic efficacy of treatments.⁴ Most women with HR-positive, HER2-negative advanced breast cancer receive first line treatment with endocrine therapy, with or without a CDK 4/6 inhibitor, unless the disease is considered to be imminently life-threatening or requires early relief of symptoms due to significant visceral organ involvement, in which case chemotherapy may be used. Endocrine therapy options include anastrozole, letrozole, exemestane, fulvestrant and tamoxifen.^{6,7} The choice of first-line endocrine therapy for advanced breast cancer depends on which treatment was used in the (neo) adjuvant setting, the duration of that treatment as well as the time elapsed from the end of the (neo) adjuvant treatment. The CDK inhibitors, palbociclib and ribociclib, are licensed for use as add-on therapies to endocrine therapies, as is everolimus. 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} The median overall survival for advanced breast cancer is approximately 3 years,⁶ and abemaciclib meets SMC end of life criteria.

In MONARCH 3, median progression free survival was 13 months longer in patients treated with abemaciclib plus endocrine therapy compared with endocrine therapy alone. The difference between treatments in progression-free survival was statistically significant and clinically meaningful.⁴ Overall survival data are immature with an event rate of approximately 20% reported at the data cut-off for the final analysis of PFS.^{3,4}

Favourable effects on survival are the most persuasive outcome of a clinical study for an anti-cancer medicine, however prolonged PFS is considered to be of benefit to the patient.⁸ In the context of advanced breast cancer, the possible benefits of improvements in PFS include a delay in the worsening of disease symptoms and a delay in the time to treatment with poorly tolerated chemotherapy.⁴ Diarrhoea had a meaningful adverse impact of quality of life outcomes for patients treated with abemaciclib compared with the control group in MONARCH 3.⁴

The MONARCH 3 study did not include pre- or peri-menopausal women, however study results in post-menopausal should be considered to apply equally to pre- or peri-menopausal women treated with ovarian suppression therapy.^{4,6} Approximately 30% of patients in MONARCH 3 were Asian which is not representative of the overall Scottish population, however a subgroup analysis reported statistically significant improvements in PFS in both white and Asian patients.^{3,4}

In the absence of direct evidence comparing abemaciclib with other CDK 4/6 inhibitors the submitting company presented Bayesian network meta-analyses (NMAs) for the intended population. Data from 18 studies were used to inform the networks for the following outcomes; progression-free survival, overall survival, objective response rate, clinical benefit rate and complete response rate. The comparators of interest were palbociclib 125mg and ribociclib 600mg in combination with anastrozole 1mg or letrozole 2.5mg. The networks also included six other treatments which are considered less relevant for Scottish practice. The results of the NMAs were presented for each CDK 4/6 inhibitor in combination with an aromatase inhibitor relative to anastrozole and letrozole, for which similar efficacy was assumed. The results suggested there was likely to be no difference between abemaciclib, palbociclib and ribociclib when used in combination with an aromatase inhibitor for all efficacy outcomes for which NMAs were conducted. No SUCRA scores or rank probabilities were provided. A sensitivity analysis for progression-free survival was conducted as Bucher method comparisons of abemaciclib versus palbociclib and abemaciclib versus ribociclib, all in combination with an aromatase inhibitor. The results were in line with the NMA results suggesting no difference in efficacy for the CDK 4/6 inhibitors.

Points to consider when interpreting the NMA results include: heterogeneity between studies in terms of study phase, populations, disease characteristics, year of reporting and timings of tumour assessments; the proportional hazards assumption did not hold for all studies included; and overall survival data from some of the studies were immature. Despite these considerations the NMA could support a conclusion of comparable efficacy.

The safety profile of abemaciclib differs from that of palbociclib and ribociclib. Neutropenia is an important concern for the CDK 4/6 inhibitors, and has been reported more frequently for palbociclib and ribociclib than abemaciclib. Diarrhoea causing dose reduction and interruption is an important concern for patients treated with abemaciclib, occurring more frequently than in patients treated with palbociclib or ribociclib.⁴

Abemaciclib administration is continuous compared with palbociclib and ribociclib, which have a 7-day treatment free period every 28 day cycle, and abemaciclib requires twice daily administration compared with palbociclib and ribociclib which require once daily administration. Ribociclib treatment requires electrocardiogram assessment prior to commencing and during treatment.⁹ Clinical experts consulted by SMC considered that the place in therapy of abemaciclib for this indication is as a treatment option within the CDK 4/6 inhibitor class.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing abemaciclib in combination with a NSAID to palbociclib plus NSAID or ribociclib plus NSAID, as initial endocrine-based therapy in woman with HR positive, HER2 negative locally advanced or metastatic breast cancer.

To support the cost-minimisation analysis, a Bayesian NMA was conducted to compare abemaciclib with palbociclib and ribociclib. Outcomes included PFS, overall survival, objective response rate, clinical benefit rate and complete response. As noted above, the company concluded that the treatment effects for each outcome were similar between abemaciclib and comparators indicating efficacy is comparable across the CDK 4/6 inhibitors. Safety was not included as an outcome in the NMA but differences in adverse events were included in the cost-minimisation analysis based on the rates observed in the MONARCH 3 study for abemaciclib and the primary publications used in the NMA for the comparators.

The analysis included medicine acquisition and administration costs, best supportive care costs, follow-up care, hospitalisations, post-progression therapy, terminal care, and adverse event management costs. Medicine costs were estimated by combining the dosing regimens from the key studies included in the NMA, relative dose intensities (RDI) and mean body surface area data. Although a range of costs were included in the analysis, the only differences between the treatment arms were the medicine costs and a small difference in adverse event management costs.

A patient access scheme (PAS) was proposed by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PASs are also in place for ribociclib and palbociclib and these were included in the results used for decision-making by using an estimate of the relevant PAS prices.

The results of the cost-minimisation analysis are presented in table 3 below. The results presented do not take account of the PAS for ribociclib and palbociclib or the PAS for abemaciclib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS prices for ribociclib and palbociclib due to commercial confidentiality and competition law issues.

Table 3: Results (list prices for all medicines)

Treatment	Total cost	Incremental saving
abemaciclib plus NSAI	£130,738	-
palbociclib plus NSAI	£130,839	-£101
ribociclib plus NSAI	£130,838	-£100

NSAI=non-steroidal aromatase inhibitor

The following limitations were noted:

- The base case assumption about RDI was not initially tested in sensitivity analysis. The company subsequently provided a sensitivity analysis using the RDI from the relevant studies as this may better reflect dosing in practice. This analysis showed the conclusion of the cost-minimisation analysis was unchanged when the RDI rates from the relevant studies were used.
- There are no direct study data comparing abemaciclib with palbociclib or ribociclib. A NMA was conducted but there are some limitations with this analysis which mean the assumption of comparable efficacy is uncertain. However, despite the limitations it is reasonable to conclude abemaciclib, palbociclib and ribociclib have similar efficacy.
- Safety was not included as an outcome in the NMA, but differences in adverse events have been included in the cost-minimisation analysis resulting in a lower cost of adverse events in the abemaciclib arm. However, removing this cost-saving did not impact on the overall conclusion.

Despite the limitations outlined above, the economic case has been demonstrated.

Other data were also assessed but remain confidential.*

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups

- We received a joint patient group submission from Breast Cancer Now and Breast Cancer Care Scotland, which are both registered charities.
- Breast Cancer Care Scotland has received 0.69% pharmaceutical company funding in the past two years, with none from the submitting company. Breast Cancer Now has received 10% pharmaceutical company funding in the past two years with none from the submitting company.
- Being diagnosed with metastatic breast cancer can be extremely difficult to come to terms with for patients and their family and friends. People may feel upset and shocked or anxious which can have an impact on their mental health. As well as the emotional toll of living with metastatic breast cancer, patients often have to cope with practical concerns,

such as managing their day to day activities, including working, household responsibilities and travelling to and from hospital appointments.

- Patients with this type of untreated metastatic breast cancer will usually be offered a CDK4/6 inhibitor with an aromatase inhibitor to control their disease. This combination can extend the time that patients' are able to live without their condition progressing. Progression free survival is important to patients as it enables them to continue with their normal activities for as long as possible and spend quality time with their family and friends. It may also delay the time to chemotherapy which is an important outcome for patients because of the gruelling side effects associated with chemotherapy.
- Abemaciclib has a slightly different side effect profile to other CDK 4/6 inhibitors that are already available in Scotland. The opportunity to access abemaciclib is beneficial as it gives patients another treatment option with different side effects to consider with their clinician.

Additional information: guidelines and protocols

In August 2017 the National Institute for Health and Care Excellence 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 availability of abemaciclib.

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 or 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.⁶

Additional information: comparators

Palbociclib and ribociclib

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
abemaciclib plus letrozole	abemaciclib 150mg oral twice daily plus letrozole 2.5mg oral once daily	38,372
palbociclib plus letrozole	palbociclib 125mg oral once daily for 21 consecutive days of repeated 28 day cycle plus letrozole 2.5mg oral once daily	38,372
ribociclib plus letrozole	ribociclib 600mg oral once daily for 21 consecutive days of repeated 28 day cycle plus letrozole 2.5mg oral once daily	38,372

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online (abemaciclib cost from MIMs online) on 6 December 2018. 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 company estimated there would be 931 patients eligible for treatment each year to which confidential uptake rates were applied.

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.

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

References

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2. Sledge GW, Jr., Toi M, Neven P, Sohn J, Inoue K, Pivot X, *et al.* MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol.* 2017;35(25):2875-84. Epub 06/06.
3. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, *et al.* MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol.* 2017;35(32):3638-46. Epub 10/03.
4. European Medicines Agency. abemaciclib (Verzenios) European Public Assessment Report. Procedure No. EMEA/H/C/004302/0000. 2018 26 July 2018. Report No.
5. Eli Lilly and Company. Clinical Study Report MONARCH 3: Addendum for the Final Progression-Free Survival Analysis. February 2018.
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 and Care Excellence. Clinical Guideline 81. Advanced breast cancer: diagnosis and treatment. 2009 (Last updated August 2017) [cited 16 November 2018]; Available from: <https://www.nice.org.uk/guidance/cg81>.
8. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95 Rev.5. 2017.
9. Joint Formulary Committee. British National Formulary (online). : London: BMJ Group and Pharmaceutical Press; 03 January 2019.

This assessment is based on data submitted by the applicant company up to and including 15 February 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.