Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

# Resubmission

everolimus 2.5mg, 5mg and 10mg tablets (Afinitor®) SMC No. (872/13)
**Novartis Pharmaceuticals UK Limited**

04 March 2016

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 Scotland. The advice is summarised as follows:

**ADVICE**: following a second resubmission assessed under the end of life process:

**everolimus (Afinitor®)** is accepted for use within NHS Scotland.

**Indication under review:** For the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

The addition of everolimus to exemestane treatment significantly increased progression free survival compared with exemestane alone in postmenopausal women with disease progression following a non-steroidal aromatase inhibitor.

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

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

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

For the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

## Dosing Information

10mg everolimus orally once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. Everolimus should be taken at the same time every day, consistently either with or without food. The tablets should not be chewed or crushed but should be swallowed whole with a glass of water.

Treatment with everolimus should be initiated and supervised by a physician experienced in the use of anticancer therapies.

## Product availability date

September 2012. Everolimus meets SMC end of life criteria.

## Summary of evidence on comparative efficacy

Everolimus is a selective inhibitor of mammalian target of rapamycin (mTOR), which is a protein kinase required for oestrogen-induced breast tumour cell proliferation.[1] The mTOR pathway is thought to be an important factor in the development of endocrine resistance in breast cancer. Everolimus has been licensed for use in combination with the steroidal aromatase inhibitor (AI) exemestane on the basis that it restores sensitivity of the tumour to the effects of exemestane.[2]

The evidence for this indication is from one randomised, double-blind, placebo-controlled, phase III study (BOLERO-2).[3] This recruited 724 postmenopausal women with confirmed metastatic or locally advanced breast cancer with oestrogen receptor-positive and human epidermal growth factor receptor type 2 (HER2) negative status. Patients had recurrence or progression of disease despite previous therapy with a non-steroidal AI (letrozole or anastrozole) as either adjuvant or advanced cancer treatment. Patients had at least one measurable lesion or mainly lytic bone lesions, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Prior treatment with other anticancer endocrine drugs and a single chemotherapy regimen for advanced disease was permitted. Tamoxifen had been used by 48%, fulvestrant by 16%, and chemotherapy by 68% of patients. Letrozole or anastrozole were the most recent treatments in 74% of patients.[2,3]

All patients received open-label exemestane 25mg and were randomised in a 2:1 ratio, stratified according to the presence of visceral metastases and to previous sensitivity to endocrine therapy, to once daily oral treatment with everolimus 10mg (n=485), or placebo (n=239), until disease progression, unacceptable toxicity or death. After discontinuing study treatment, patients in both groups were allowed to receive further antineoplastic therapy; crossover was not permitted.[2,3]

The primary end point was progression-free survival (PFS), defined as time from randomisation to first documented progression or death from any cause in the full analysis set (FAS), which included all randomised patients. Objective tumour progression was determined by the local radiologist (using Response Evaluation Criteria in Solid Tumours [RECIST]) and supported by independent central radiologic assessment. A protocol specified interim analysis was conducted after accrual of 359 progression events (median follow up of 7.6 months). In the everolimus group, 42% (202/485) of patients had an investigator-assessed PFS event compared with 66% (157/239) in the placebo group, giving a median PFS of 6.9 months versus 2.8 months, respectively; hazard ratio (HR) 0.43 (95% confidence interval [CI]: 0.35 to 0.54) p<0.001. In the supportive interim analysis, with PFS events centrally assessed, 24% (114/485) of patients in the everolimus group had a PFS event compared with 44% (104/239) in the placebo group, giving a median PFS of 10.6 months versus 4.1 months, respectively; HR 0.36 (95% CI: 0.27 to 0.47) p<0.001. As the results of both the local and central assessments were significant according to the pre-specified levels, the primary outcome was deemed to be achieved.[3]

The final PFS analysis was conducted at a median follow up of 18 months when the median everolimus treatment duration was 30 weeks compared with 14 weeks for placebo, and 510 locally-assessed events had accrued. The median PFS (locally assessed) was 7.8 months for the everolimus group and 3.2 months for the placebo group; HR 0.45 (95% CI: 0.38 to 0.54), p<0.0001. Central assessment supported these findings with median PFS of 11.0 months and 4.1 months, respectively; HR 0.38 (95% CI: 0.31 to 0.48), p<0.0001. There was a consistent treatment effect favouring everolimus across the range of subgroups analysed.[4]

The major secondary endpoint was overall survival. The final analysis was conducted after 39.3 months median follow-up and on accrual of 410 events (56% of study population). Although the median overall survival was 31.0 months in the everolimus group and 26.6 months in the placebo group, there was no statistically significant survival advantage demonstrated; HR 0.89 (95% CI: 0.73 to 1.10), p=0.1426.[5]

Other secondary endpoints involved tumour response assessments, time to deterioration in ECOG performance status of one point, and health-related quality of life (HRQoL). At a median follow up of 18 months (final PFS analysis), locally-assessed objective response rate (complete response or partial response) was 13% in the everolimus group (0.6% complete responses) and 1.7% (no complete responses) in the placebo group, p<0.0001. The clinical benefit rate, defined as complete response, partial response or stable disease for ≥24 weeks, was 51% in the everolimus group and 26% in the placebo group, p<0.0001.[4] There was no difference between the treatment groups in the time to deterioration of ECOG performance status by at least one point; HR 1.05 (95% CI: 0.76 to 1.44).[2]

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire at baseline and then every six weeks until disease progression. The main analysis related to the time to definitive deterioration (TDD) in Global Health Status. The primary definition for TDD was the time to a 5% change from baseline, and a sensitivity analysis used a more stringent minimal important difference of a change of 10 points from baseline. At a median follow-up of 18 months, the cumulative proportions of patients with a definitive deterioration (5%) were 49% and 44% in the everolimus and placebo groups respectively. The median TDD was 8.3 months in the everolimus group and 5.8 months in the placebo group; HR 0.74 (95% CI: 0.58 to 0.95), p=0.0084. Definitive deterioration (10-point change) had occurred in 39% and 30% of patients in each group respectively. There was no significant advantage for patients treated with everolimus; the median TDD was 11.7 months

in the everolimus group and 8.4 months in the placebo group; HR 0.8 (95% 0.61 to 1.06), p=0.1017.[6]

## Summary of evidence on comparative safety

In BOLERO-2, at the final overall survival data cut-off, a higher proportion of patients taking everolimus experienced grade 3 or 4 adverse events (AEs) compared with placebo, 55% versus 29%, and they were considered to be treatment-related in 41% and 8.4% of patients. AEs led to treatment discontinuation in 29% of everolimus patients and in 5.0% of placebo patients.[5] Based on the analysis of data after 18 months follow up (final PFS analysis) it was found that AEs resulted in dose modification or interruption in 62% of everolimus-treated patients compared with 5.5% of patients in the placebo group.[4]

After 18 months follow-up, the most commonly reported AEs were: stomatitis (59% in the everolimus group versus 12% in the placebo group), rash (39% versus 7%), fatigue (37% versus 27%), diarrhoea (34% versus 19%), nausea (31% versus 29%) and decreased appetite (31% versus 13%). Grade 3 or 4 AE included stomatitis (8% versus <1%), fatigue (4 to 5% versus 1%), pneumonitis (3% versus 0), hyperglycaemia (5 to 6% versus <1%).[4]

Pneumonitis (non-infectious) is a potentially fatal adverse effect of this class of rapamycin-type medicine.[1] After 18 months of follow-up, pneumonitis was reported in 16% of everolimus patients compared with no patients in the placebo group. The cases of pneumonitis were rated grade 1 in 7% of patients, grade 2 in 6% and grade 3 in 3% of everolimus patients.[4]

During the study there were 26 on-treatment deaths, 17 of which were related to breast cancer progression and nine were AE-related. In the everolimus group, AE-related deaths (n=8) were due to pneumonia (n=2), and single deaths due to sepsis, Staphylococcus sepsis, tumour haemorrhage, transient ischaemic attack, suicide and renal failure. In the placebo group, the AE-related death was due to pneumonia. The risk of AE-related death was adjusted for duration of exposure; the annualised incidence rates of on-treatment death were 5.8% in the everolimus group and 3.9% for placebo.[5]

## Summary of clinical effectiveness issues

Everolimus is the first mTOR inhibitor to be licensed for this indication. Patients with advanced breast cancer have a median overall survival of two to three years, although the range is wide. Endocrine therapy is the usual treatment of choice in postmenopausal women with oestrogen receptor-positive, HER2 negative advanced breast cancer and AIs are usually considered first-line, but tumour resistance is problematic. There is no definitive treatment pathway when advanced breast cancer progresses following treatment with a non-steroidal AI. Other endocrine agents may be tried and chemotherapy is recommended if endocrine treatment is deemed to have failed or if a rapid response is required. European guidelines for the management of advanced breast cancer recommend that the decision to use everolimus should be made on an individual-case basis in order to weigh the benefits with the toxicities associated with treatment (e.g. stomatitis, hyperglycaemia and pneumonitis).[7,8] Clinical experts consulted by SMC have noted hormonal therapies such as tamoxifen, exemestane, fulvestrant and megestrol are considered at this stage in the disease. Everolimus meets SMC end of life criteria.

The primary outcome measure in BOLERO-2, PFS, was a surrogate outcome. Treatment with everolimus in combination with exemestane was associated with a significant prolongation of PFS when assessed by the local investigator and by a central-independent review, but this did not translate into a statistically significant benefit in overall survival. The addition of everolimus to exemestane was associated with a poorer safety profile, with greater incidences of grade 3 or 4 AEs, and a larger annualised incidence rate of on-treatment death. Despite this, deterioration in global health status was potentially delayed with the addition of everolimus to exemestane.[5]

An imbalance in the use of subsequent therapy could possibly have confounded the overall survival results. A lower proportion of everolimus- than placebo-treated patients subsequently received chemotherapy (53% versus 63%), or taxanes (28% and 36% respectively).[5]

Subjective treatment outcomes, specifically HRQoL may have been confounded by the recognition of everolimus-associated AEs (e.g. stomatitis and rash) compromising the blinding of the randomised treatment.

An exploratory post hoc analysis of BOLERO-2 suggests there may be a chemotherapy-delaying effect with the use of everolimus, an outcome which may be of value to patients. The median time from randomisation to first chemotherapy or death was 11.9 months in the everolimus group and 6.0 months in the placebo group.[5]

As a systemic anti-cancer treatment, patients will access everolimus in Secondary Care, whereas endocrine therapy can be accessed in Primary Care. In the pivotal study, 62% of everolimus patients required treatment dose modification or interruption to manage AEs. Introduction of everolimus may have implications in terms of oncology clinic visits.

## Summary of 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 everolimus, as an end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced breast cancer is incurable and patients have a significantly shortened life expectancy. Patients with hormone receptor positive disease experience a period of delayed disease progression and good quality of life using hormone therapies. When hormone therapies fail patients move to chemotherapy with its associated toxicity, frequent hospital visits and high adverse impact on quality of life.

- Everolimus is the only recent development for patients with HER2 negative tumours. It is a novel treatment that restores hormone sensitivity in tumours that have developed resistance thereby extending effectiveness of existing hormonal therapies.

- Everolimus offers terminal patients an extension in PFS by more than twofold and a 6-month delay in the time to chemotherapy (from 6 months to 12 months). This represents good quality extra time when they would otherwise be enduring chemotherapy and is particularly meaningful for patients and their families, allowing women to maintain their

independence for longer and to continue to work and contribute to family life.

- Importantly, quality of life is not adversely affected by the addition of everolimus. Clinicians feel that side-effects (e.g. stomatitis and rash) are manageable and patients consider them a small price to pay for the significant benefits of treatment. Furthermore, recent evidence indicates that side-effects have less impact in the 'real world' setting than the clinical trial suggests. [1]

- The PACE group gave strong support for everolimus within the licensed population on the basis that a delay in time to chemotherapy leads to a longer period of valuable high quality productive life for the patient.

## Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing everolimus in combination with exemestane with exemestane alone for the treatment of oestrogen receptor-positive, HER2 negative advanced breast cancer in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal AI.

A partitioned survival model was used consisting of three health states (stable, progressed and death) was presented over a 15-year time horizon. Patients begin in the progression free survival state and after monthly cycles either remain in that state or transition to the progressed health state if their disease has progressed, or transition to the death health state. Data for the comparison with exemestane were taken from the main clinical study described above. PFS and overall survival (OS) data from this study were extrapolated based on fitting curves. Several possible forms for these extrapolations were considered and the choice was made based on advice from a panel of clinical experts convened by the submitting company as well as goodness-of-fit statistics. In the base case for PFS and OS, the loglogistic parametric function was fitted to extrapolate the Kaplan-Meier data.

Quality of life data were collected in the main clinical study but were not used in the economic evaluation. Instead, the company selected values from the literature. For pre-progression the value was 0.791 and 0.774 for everolimus and exemestane arms respectively, and for post-progression it was 0.496. Resource use data covered NHS costs of giving drug treatment and of on-going care for breast cancer. The assumptions used in the modelling were based on clinical guidelines, as well as other sources.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of everolimus. With the PAS the cost per quality-adjusted life-year (QALY) was £24,340.

The company presented deterministic and scenario analyses. The incremental cost-effectiveness ratio (ICER) was most sensitive to the following:

- Reducing the utility values by 20% in the stable health state increases the with-PAS ICER to £39k. However, this is a conservative analysis as the utility values used in the base case analysis have been used in other submissions.
- Increasing the utility values by 20% in the progressed health states increases the with-PAS ICER to £29k.

- Reducing the time horizon to 5 years increases the with-PAS ICER to £30k.

The following weaknesses with the economic case were noted:

- The ICER based on the modelling is uncertain. For example, the approach used may have overestimated PFS for everolimus in combination with exemestane and underestimated PFS for exemestane alone. Modelling the PFS based upon the mean clinical trial data resulted in an ICER with PAS of £30k. In the main clinical study, there was no statistically significant difference between OS for everolimus in combination with exemestane versus exemestane alone. When both of these uncertainties are modelled together - PFS modelled from the clinical trial and no difference in OS - the resultant ICER is £32k.
- Furthermore, the base case analysis assumes a treatment effect for everolimus in the utility values applied. When this treatment effect is removed, coupled with PFS based on trial data and no difference in OS is modelled the ICER increases to £34k.

After considering all the available evidence and the output from the PACE process, the Committee accepted everolimus for use in NHS Scotland.

## Summary of patient and public involvement

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

- A joint submission was received from Breast Cancer Now and Breast Cancer Care, both are registered charities.

- Both Breast Cancer Now and Breast Cancer Care have received pharmaceutical company funding in the past two years, with both having received funding from the submitting company.

- Metastatic breast cancer affects people in different ways; however, all are coping with an incurable disease. As it is incurable, it is essential that treatment options which could delay progression are made available to this patient group. Delaying progression of the disease is one of the best outcomes for this patient group as this means that patients have more time to spend with their families and friends before becoming more ill.

- The current standard treatment is chemotherapy, which for most women causes side effects. These include nausea, fatigue, vomiting, diarrhoea and hair loss which can all have a significant impact on an individual's quality of life. While everolimus does cause some side effects, they may be preferable to the side effects caused by chemotherapy. Everolimus and exemestane are both administered in tablet form. This is much less disruptive to patients and their families than intravenous chemotherapy.

- Everolimus may increase the length of good quality life individuals with a terminal diagnosis have left to spend with their families. Those that tolerate it well may be able to lead a normal or near normal life, doing the things they enjoy doing such as socialising, working and caring for family.

## Additional information: guidelines and protocols

The National Institute for Health and Care Excellence published its updated guidance "Advanced breast cancer: diagnosis and treatment" July 2014.[7] In patients with oestrogen receptor-positive advanced breast cancer, endocrine therapy is the first line option unless their "disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement" in which case chemotherapy should be offered. Endocrine therapy should be offered following completion of chemotherapy. Aromatase inhibitors should be offered to postmenopausal women with oestrogen receptor-positive disease and no prior history of endocrine therapy or in those previously treated with tamoxifen. Upon disease progression, patients who have decided to be treated with chemotherapy should receive sequential systemic therapy. Combination chemotherapy is recommended for those who are likely to tolerate additional toxicity and for whom a greater chance of response is important. The guidance acknowledges that there is an absence of evidence to determine the most effective endocrine therapy for postmenopausal women with oestrogen receptor-positive disease who progress on treatment with aromatase inhibitors. It recommends that clinical studies should be designed to investigate the best sequencing of treatment for these patients.

Publication of The European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO) updated joint consensus guidelines for advanced breast cancer "ABC2" in September 2014 provided recommendations for the management of ER-positive, HER2-negative advanced breast cancer.[8] It recommends endocrine therapy first-line in preference to chemotherapy, even in the presence of visceral metastases. It recommends that chemotherapy is reserved for cases of proven endocrine resistance or in rapidly progressive disease. The type and duration of adjuvant endocrine therapy should guide the selection of which endocrine therapy to use in postmenopausal women with advanced breast cancer. Options recommended include the use of an aromatase inhibitor, tamoxifen or fulvestrant. Endocrine resistance can occur due to; alterations in the oestrogen receptor gene or upregulation of alternative pathways such as HER growth factor pathways and the mTOR pathway. The guideline noted the results of BOLERO-2 in which everolimus prolonged median PFS by five months and median survival by a non-significant 4.4 months. The decision to use everolimus should be made on an individual-case basis in order to weigh the benefits with the toxicities associated with treatment (e.g. stomatitis, hyperglycaemia and pneumonitis). "At present, no predictive biomarker exists to identify those patients who will benefit from this approach."

## Additional information: comparators

Endocrine therapies used after non-steroidal AIs include: exemestane, tamoxifen, megestrol and fulvestrant.

## Cost of relevant comparators

| Medicine | Dose Regimen | Cost per year (£) |
|---|---|---|
| **everolimus plus exemestane** | **everolimus: 10mg orally once daily exemestane: 25mg orally once daily** | **32,672** |
| fulvestrant | 500mg every month by slow intramuscular injection with an additional 500mg dose given two weeks after the initial dose | Year 1: 6,791 Subsequent years: 6,269 |
| exemestane | 25mg orally once daily | 239 |
| megestrol | 160mg orally once daily | 237 |
| tamoxifen | 20mg orally daily | 59 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 09 December 2015, except everolimus (from MIMS online on 09 December 2015). Costs do not take any patient access schemes into consideration.

## Additional information: budget impact

The company estimated the number of patients eligible for treatment with everolimus is 124 in year 1 and 144 in year 5.

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.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


1. Afinitor® tablets Summary of product characteristics. Novartis Pharmaceuticals UK Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 26 February 2015.

2. European Medicines Agency. CHMP type II variation assessment report for Afinitor. 21 June 2012. EMEA/H/C/001038/II/0020. www.ema.europa.eu

3. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012; 366: 520–9. (plus supplementary appendix and protocol)

4. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. Advances in Therapy. 2013; 30: 870-84

5. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer: overall survival results from BOLERO-2. Annals of Oncology. 2014; 25: 2357-62 (plus supplementary appendix)

6. Burris HA, Lebrun F, Rugo HS, et al. Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial. Cancer. 2013; 119: 1908-15.

7. National Institute for Health and Care Excellence. NICE Guidelines CG81 - Advanced breast cancer (update): diagnosis and treatment. July 2014 www.nice.org.uk Accessed 18 May 2015

8. Cardoso F. Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; 25: 1871-88 and The Breast 2014; 23: 489-502.


This assessment is based on data submitted by the applicant company up to and including 11 February 2016.

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.*