Application for changes to the Pharmaceutical Schedule

A guide to help people, clinicians, clinical groups and consumer groups prepare funding applications to PHARMAC

Foreword

PHARMAC is the government agency that decides, on the behalf of District Health Boards, which pharmaceuticals should be publicly fund in New Zealand. For more information on the process PHARMAC uses to make its funding decisions and how we determine if a proposal to fund a treatment would help us achieve our Statutory Objective, please visit the PHARMAC website. PHARMAC's objective is "to secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided".

Each year, PHARMAC receives a large number of applications that contain proposals either to fund new pharmaceuticals or to widen access to pharmaceuticals that we already fund. As PHARMAC must work within a fixed budget, we need to make difficult choices about which applications we should progress to a funding decision at any given time. This involves assessing large amounts of often complex information, to identify those proposals that would provide the best health outcomes.

We have written this funding application form for people, clinicians, clinical groups and consumer groups to use. We recognise that some individuals and groups won't have the same resource as pharmaceutical suppliers to prepare applications. This form is to help you provide the right information in order to progress the application.

This form is a guide – you don't have to follow it in detail, or at all, but it will make processing your application much easier and may reduce the time involved. If you don't know some information, please feel free to leave those sections blank; however the form does outline the general information that we need to assess a funding application. Having your application address these points may reduce follow-up questions to you, and could speed up how quickly we consider it.

The *Guidelines for Funding Applications to PHARMAC*, updated in 2015, set out the full information that we need to progress any funding application. We expect pharmaceutical suppliers to follow the full *Guidelines for Funding Applications to PHARMAC* when submitting a funding application. However, as an applicant, please feel free to view them should you wish to have more detailed information on submitting an application.

Send your applications to us at:

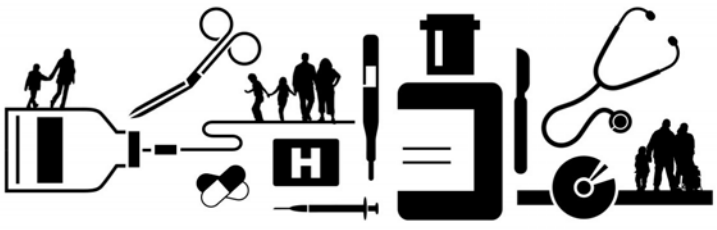
Email: **applications@pharmac.govt.nz**
Post: **PO Box 10254**
The Terrace
Wellington 6143

You may also find it beneficial to talk to the relevant Therapeutic Group Manager at PHARMAC before you make a formal funding application. Please email us as above, and we will contact you.

We will keep you informed of progress. We publish and regularly update a record of all current funding applications via the Application Tracker on our website (**www.pharmac.govt.nz**), which details the current status of applications and relevant PTAC and subcommittee minutes.

Please note:

- We need you to supply copies of referenced articles that support the application, wherever possible. Have them referenced in the relevant section of the application form, and clearly say which (if any) cited publications you cannot provide.
- We prefer funding applications related to medicines that have been registered by Medsafe. While we can consider funding applications for unregistered medicines or unregistered indications, this is determined on a case–by-case basis.
- We may decide to defer our assessment of your application until we receive a full funding application from the supplier, which they would need to prepare in accordance with the full *Guidelines*.



PHARMAC
Pharmaceutical Management Agency

New Zealand Government

Changes to the Pharmaceutical Schedule Application

Applicant

Name

Elisabeth P.J. Burgess

Department & DHB, practice or organisation

Breast Cancer Aotearoa Coalition (BCAC)

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Are you making this application on behalf of a wider group (department, society, special interest group)? If so, who?

Breast Cancer Aotearoa Coalition

Is there anyone else that we should contact if we have questions about specific parts of this application?

No

Proposed pharmaceutical

Chemical

Fulvestrant

Presentations and strengths

250mg for intramuscular injection

Brand name(s)

FASLODEX®

Suppliers (eg pharmaceutical companies, wholesalers)

Astra Zeneca

Price

The current price is unknown.

Is it registered by Medsafe?

Fulvestrant was registered in New Zealand as FASLODEX but registration has now lapsed. Note that the registration that lapsed was for a dose of 250mg monthly – whereas 500mg monthly is now the accepted dose internationally based on the CONFIRM trial (which showed superiority of the 500mg versus the 250mg dose) and subsequent studies that have used the 500mg monthly (with a loading dose after 2 weeks) as the usual dose (1, 2). Previous submissions to Pharmac were for the 250mg dose.

Describe the indication(s) that funding is being sought for.

Treatment of women with ER (oestrogen receptor) positive advanced breast cancer (ABC)

If this pharmaceutical has been registered by Medsafe, is it licenced for these indications? If not, is it licenced for these indications overseas? Please provide details.

As stated earlier, registration in New Zealand was for a lower dose and has now lapsed. Details of current overseas approvals are as follows:

European Union (EMEA)

FASLODEX was approved in the EU in 2004. In 2010, there was a change in the dose regimen from 250mg to 500mg, based on data from the CONFIRM study. In July 2017, the approved indication was extended to include the treatment of ER-positive, locally advanced or metastatic breast cancer in postmenopausal women who have not been previously treated with endocrine therapy. In November 2017, the approved indication was extended to include use in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. In pre- or peri-menopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist for FASLODEX (3-5).

USA (FDA)

The product was approved by the FDA in 2002. It is now indicated for the:

- Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously

treated with endocrine therapy.
- Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

Australia (TGA)
- FASLODEX is indicated for the treatment of postmenopausal women with HR-positive, locally advanced or metastatic breast cancer who have progressive disease following prior tamoxifen therapy.

How many people in New Zealand do you expect would receive the pharmaceutical?

The number of people who would receive the pharmaceutical annually is dependent on any restrictions (if any) that might be recommended for access to treatment. ER-positive breast cancer is the most common variant and responsible for most deaths. The likely restriction would be for advanced breast cancer in patients who have progressed on aromatase inhibitors (AIs) and/or tamoxifen.

What is the expected dosing?

FASLODEX is available as a solution for injection in prefilled syringes (250 mg). The recommended dose is 500 mg given once a month, with an additional 500-mg dose (loading dose) two weeks after the first dose. The dose is given as two injections, each given into the muscle of one buttock over one to two minutes.

What is the likely duration of treatment, if patients respond to treatment?

Treatment would probably continue until progression. The duration of therapy is dependent on the therapy line in which treatment is being administered. For example in first line in ABC, the median TTP (time to progression) in the FIRST trial in the fulvestrant group was 23.4 months (6-8) (for the whole population – not just those who respond to treatment) and in the FALCON trial (also in the first line setting in ABC) the median PFS (progression-free survival) was 16.6 months (9). In the PALOMA-3 study, in patients who had already received prior endocrine therapy for ABC, the median PFS in the combined palbociclib/fulvestrant group was 9.5 months versus 4.6 months in the fulvestrant alone group (10). In observational studies, the time to progression ranged from 6.1 months in a Japanese cohort (11) whereas the median PFS in a Spanish cohort was 10.6 months (12) and in an Italian cohort was 7 months (13).

Describe the setting that this pharmaceutical would be used in. Is the need for this this treatment limited to a hospital setting, or is it also required in the community? If in hospital, is it theatre only, on medical wards, or in outpatient clinics?

Hospital (administered in outpatient clinics) and community setting (administered in outpatient oncology setting or by GP or clinic nurse).

If this is a new pharmaceutical, are there likely to be other uses for it?

This is not a new pharmaceutical – it was available in New Zealand some years ago. It is being administered currently to patients in New Zealand (under Section 29 of the Medicines Act) provided they can afford to pay for treatment. It is currently being trialled elsewhere in conjunction with other treatments in breast cancer.

Treatment initiation

Is treatment with the pharmaceutical started empirically? If so, please describe the symptoms, signs or other features necessary to initiate therapy.

Diagnosis of advanced breast cancer with ER positivity.

Are there any specific tests needed to confirm diagnosis? If so, please name these tests, and say whether these are currently performed routinely, where they take place, and whether they are funded.

Clinical examination, Imaging and Pathology – not specific to this treatment but would be monitored for ABC patients.

Should other therapies have been used prior to starting treatment with this pharmaceutical? If so, which?

Treatment initiation

Fulvestrant will most likely be used after a patient has already received an aromatase inhibitor and/or tamoxifen in advanced breast cancer (14).
ASCO Guidelines (2016) state that sequential hormone therapy is the preferential treatment for most women with HR-positive metastatic BC. Treatment recommendations should be based on type of adjuvant treatment, disease-free interval, and organ function. For postmenopausal women, AIs are the preferred first-line endocrine therapy, with or without the cyclin-dependent kinase inhibitor palbociclib. As second-line therapy, fulvestrant should be administered at 500 mg with a loading schedule and may be administered with palbociclib (15).
NCCN Guidelines (2017) recommend that, for women with ER-positive HER2-negative ABC without visceral symptoms, three consecutive lines of endocrine therapy are recommended. AIs, SERMs (selective ER modulators), and SERDs (selective ER degraders) were recommended as first line endocrine therapies in ER-positive postmenopausal women, with modest evidence indicating a preference of AIs over tamoxifen. Palbociclib or ribociclib in combination with letrozole may be considered as a treatment option for first line therapy for postmenopausal women with ER-positive HER2-negative ABC. Palbociclib in combination with fulvestrant 500 mg may be considered for women with ER-positive HER2-negative ABC who have progressed on endocrine therapy.

Treatment continuation

How would treatment success be defined or measured?

Patients would be treated until disease progression.

What is the average length of treatment required before determining treatment response?

Treatment would be evaluated on a monthly basis.

What other interventions would be needed in the event of treatment-related adverse events?

No specific interventions.

Prescribing and dispensing

Should initiation of this therapy be limited to certain prescriber types? If so, please explain why.

Medical oncologist.

If starting this therapy was limited to certain prescriber types, would it be appropriate for ongoing prescribing to be managed by a wider group of prescribers? If so, who?

No.

Are there any other issues that PHARMAC should be aware of in relation to the administration of this pharmaceutical, such as infusion time, compounding requirements or safety issues?

Given by intramuscular injection.

Health need

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

What is the health need of people with the indication(s) for which funding is sought? Please include details of whether reduced life expectancy could be expected or details of potential loss of quality of life including the cause of this loss.

Over 3000 people are diagnosed with breast cancer each year in New Zealand and over 600 people will die from this disease. Advanced Breast Cancer (ABC) is cancer that is locally invasive (Stage III) and is not amenable to surgery or radiotherapy of curative intent or has metastasised from its primary location in the tissues of the breast to other tissues (Stage IV), most often bones, brain, lungs, or liver. ABC adversely impacts health-related quality of life (HR-QoL), both through physical symptoms and psychosocial distress. The key therapy goals for patients with ABC are focused on delaying progression and prolonging survival without compromising HR-QoL.

Is there an unmet health need in the populations that may potentially receive benefit from this treatment? If so, please explain.

Although there have been improvements in rates of survival over the past decades, New Zealand still lags behind some other countries (16). For people who have advanced breast cancer, extension of, and quality of, life are key priorities. BCAC and other patient groups such as Metavivors are concerned about poor access to treatment in New Zealand for people with advanced breast cancer. Better access to treatments that are aimed at controlling symptoms, improving or maintaining quality of life and prolonging survival is needed. ER-positive breast cancer is the most common type of breast cancer (70-80%). Limitations of current endocrine therapy are intrinsic and acquired drug resistance. The availability of an alternate agent such as fulvestrant, which has a different mechanism of action to tamoxifen and aromatase inhibitors could delay or prevent the need for chemotherapy in ABC.

Health need

Are there sub-populations within these populations that have a higher health need?

Maori and Pacific women have poorer survival and are therefore more likely to be affected by metastatic disease as well as having more co-morbidities (17-19). Late diagnosis, deprivation and differential access to and quality of cancer care services are key contributors to ethnic disparities in breast cancer survival in New Zealand (20). Patients treated in the private health care sector in New Zealand have better survival from breast cancer compared with those in public care (21). Currently people with financial means are able to access fulvestrant treatment whereas others cannot.

What are the treatments that patients with these indications currently receive, if any? Please describe the dose, duration of treatment, along with the risks and benefits associated with this treatment.

Tamoxifen and aromatase inhibitors (AIs) are the traditional endocrine therapy standard of care. The only remaining option once endocrine therapies are no longer efficacious is cytotoxic chemotherapy that impacts day to day functioning and quality of life.

Are there any issues regarding the availability or suitability of existing treatments for this indication?

Endocrine therapies target ER signalling and represent the backbone of adjuvant and first-line therapy of postmenopausal women with ER-positive HER2-negative ABC. AIs work by reducing circulating oestrogen, however the tumour cell typically develops resistance to AIs, such that the ER can still drive tumour growth even in the absence of oestrogen. Intrinsic and acquired resistance to endocrine therapy is a significant clinical problem for ABC, with all ER-positive tumours eventually becoming endocrine therapy-resistant resulting in disease progression.

Would the pharmaceutical replace or complement these existing treatments? Please explain.

Fulvestrant, as a selective ER degrader (SERD), is the only endocrine therapy that targets, binds to, blocks and degrades the ER, making it most likely a more potent inhibitor of the ER pathway than AIs and tamoxifen. Patients with ABC may have already been treated with tamoxifen or an aromatase inhibitor – fulvestrant may provide an alternative (not additive) option for such patients. Also, palbociclib is indicated in combination with fulvestrant. So fulvestrant could be used in conjunction with palbociclib – although the latter is not currently subsidised, it is approved in New Zealand for use in combination with fulvestrant.

Does this indication disproportionately affect any populations that may already be experiencing a health disparity?

Maori women have one of the highest incidences of breast cancer in the world (22). Maori and Pacific women have poorer survival and are therefore more likely to be affected by ABC as well as having more co-morbidities (17-19). Maori women are less likely to adhere to long-term adjuvant endocrine therapy (22). Patients from lower socioeconomic groups have poorer survival statistics and therefore may benefit from subsidy of a wider range of treatment alternatives (21). An intramuscular once-monthly injection may be preferred by some patients who have adherence difficulties.

Is there an unmet health need in other people due to the indication, such as in people who care for or live with those with the indication, or from spread of disease?

Families and whanau are integral to the patient's life journey at this stage of disease. ABC also poses a burden on caregivers; 69% of caregivers of women with ABC report some kind of adverse impact on their work. In addition to the impact on their day-to-day lives, caregivers report increases in depression and perceived burden as the patients' functional status declines. At the start of the terminal period of the patients' disease, 30% of caregivers reported being depressed (23).

Health benefits and risks in the indication(s) for which funding is sought

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.
Discuss the potential benefits from treatment with the pharmaceutical compared with current treatment options (if any).

See next pages
Summaries below include
Evidence for 500mg versus 250mg fulvestrant (CONFIRM and "CONFIRM" Chinese Study)
Evidence for use of fulvestrant first line in ABC (FIRST and FALCON)
Reviews – including Cochrane Review (Lee 2017) and recent review of first and second line use (Reinert 2017)
Evidence for use of fulvestrant after prior endocrine therapy failure in ABC (Observational Studies)

CONFIRM 500mg versus 250mg fulvestrant

This was a double-blind, parallel-group, multicentre, phase III randomised controlled trial (RCT) in which patients were assigned to fulvestrant 500 mg (on Days 0, 14 and 28 and every 28 days thereafter) or 250 mg every 28 days. The primary end point was progression free survival (PFS). Secondary end points included objective response rate (ORR), clinical benefit rate (CBR), duration of clinical benefit (DoCB), overall survival (OS), and Quality of Life (QOL). Results showed PFS was significantly longer for fulvestrant 500 mg than 250 mg, (Hazard ratio (HR) = 0.80; 95% CI, 0.68 to 0.94; p=0.006), corresponding to a 20% reduction in

risk of progression. ORR was similar for fulvestrant 500 mg and 250 mg (9.1% v 10.2%, respectively). CBR was 45.6% for fulvestrant 500 mg and 39.6% for fulvestrant 250 mg. DoCB and OS were 16.6 and 25.1 months, respectively, for the 500-mg group, whereas DoCB and OS were 13.9 and 22.8 months, respectively, in the 250-mg group. Fulvestrant 500 mg was well tolerated with no dose-dependent Adverse Events (AEs). QOL was similar for both arms. In summary, fulvestrant administered at a dose of 500 mg monthly was associated with a statistically significant increase in PFS and not associated with increased toxicity, corresponding to a clinically meaningful improvement in benefit versus risk compared with fulvestrant 250 mg (2). The results of this study have changed the dosing strategy of fulvestrant (1).

Chinese "CONFIRM" Study 500mg versus 250mg fulvestrant

In this randomised, double-blind study, postmenopausal Chinese women with ER-positive ABC and progression after endocrine therapy received fulvestrant 500 mg (days 0, 14, 28, and every 28 days thereafter) or fulvestrant 250 mg (every 28 days). In total, 221 patients were randomised (fulvestrant 500 mg: n = 111; fulvestrant 250 mg: n = 110). Median PFS was 8.0 months with fulvestrant 500 mg vs 4.0 months with 250 mg (HR=0.75; 95% CI 0.54-1.03; P = 0.078). PFS favoured fulvestrant 500 mg in post-antiestrogen (HR 0.86; 95%CI 0.54-1.37) and post-aromatase inhibitor (HR 0.65; 95%CI 0.42-1.03) settings. No new safety considerations were observed. These results were consistent with the international CONFIRM study, supporting the superiority of fulvestrant 500 mg in women with ABC experiencing progression following prior endocrine therapy (24).

FIRST – fulvestrant 500mg versus anastrozole in ABC -with no prior endocrine therapy

The Fulvestrant First-Line (FIRST) Study was a phase II, randomised, open-label study comparing fulvestrant 500 mg with anastrozole 1 mg as first-line endocrine therapy for postmenopausal women with HR-positive ABC. FIRST compared fulvestrant high-dose (HD) regimen (500 mg/month plus 500 mg on day 14 of month 1) versus anastrozole (1 mg/d). Included were postmenopausal women with ER-positive and/or progesterone receptor-positive locally advanced or metastatic breast cancer and no prior endocrine therapy. Key exclusion criteria were presence of life-threatening metastases and prior treatment with a non-approved drug. The primary efficacy end point was clinical benefit rate (CBR), defined as the proportion of patients experiencing an objective response (OR) or stable disease for > or = 24 weeks.

At 6 months CBR was similar for fulvestrant HD (n=102) and anastrozole (n=103), 72.5% v 67.0%, respectively (odds ratio, 1.30; 95% CI, 0.72 to 2.38; p=0.386). Objective response rate (ORR) was also similar between treatments: fulvestrant HD, 36.0%; anastrozole, 35.5%. Time to progression (TTP) was significantly longer for fulvestrant versus anastrozole (median TTP not reached for fulvestrant HD v 12.5 months for anastrozole; HR 0.63; 95% CI, 0.39 to 1.00; p=0.0496). Duration of OR and CBR numerically favoured fulvestrant HD. Both treatments were well tolerated, with no significant differences in the incidence of prespecified adverse effects. It was concluded that first-line fulvestrant HD was at least as effective as anastrozole for CBR and ORR and was associated with significantly longer TTP. Fulvestrant HD was generally well tolerated, with a safety profile similar to that of anastrozole (8).

A subsequent publication reported follow-up data for TTP for the FIRST study. Follow-up analysis was performed when 79.5 % of patients had discontinued study treatment. Median TTP was 23.4 months for fulvestrant versus 13.1 months for anastrozole; a 34 % reduction in risk of progression (HR 0.66; 95 % CI 0.47 - 0.92; p=0.01). Best overall response to subsequent therapy and CBR for subsequent endocrine therapy was similar between the treatment groups. These longer-term, follow-up results confirmed efficacy benefit for fulvestrant 500 mg versus anastrozole as first-line endocrine therapy for HR+ advanced breast cancer in terms of TTP, and, importantly, show similar best overall response rates to subsequent endocrine therapy (7).

A further publication of the FIRST study reported overall survival (OS) for fulvestrant 500 mg versus anastrozole after approximately 65% of patients had died. Treatment effect on OS across several subgroups was examined. Tolerability was evaluated by adverse event monitoring. At data cut-off, 61.8% (fulvestrant 500 mg, n = 63) and 71.8% (anastrozole, n = 74) had died. The HR (95% CI) for OS with fulvestrant 500 mg versus anastrozole was 0.70 (0.50 to 0.98; p=0.04; median OS, 54.1 months vs 48.4 months). Treatment effects were generally consistent across the subgroups analysed. No new safety issues were observed. This analysis was unplanned, but instead was added after TTP results were analysed, and not all patients participated in additional OS follow-up. However, the results suggested that fulvestrant 500 mg extends OS versus anastrozole in patients with ABC (6).

FALCON – Fulvestrant 500mg versus Anastrozole in ABC with no prior endocrine therapy

The FALCON phase 3, randomised, double-blind trial investigated whether fulvestrant could improve PFS compared with anastrozole in postmenopausal patients who had not received previous endocrine therapy. Eligible patients had histologically confirmed ER-positive or progesterone receptor-positive, or both, locally advanced or metastatic breast cancer and were recruited from 113 academic hospitals and community centres in 20 countries. Patients were endocrine therapy-naive, with WHO performance status 0-2, and at least one measurable or non-measurable lesion. Patients were randomised to fulvestrant (500 mg intramuscular (IM) on Days 0, 14, 28, then every 28 days thereafter) or anastrozole (1 mg daily). The primary endpoint was PFS, determined by RECIST v1.1, intervention by surgery or radiotherapy because of disease deterioration, or death from any cause, assessed in the intention-to-treat (ITT) population. Safety outcomes were assessed in all patients who received at least one dose of randomised treatment (including placebo). In total, 462 patients were randomised (fulvestrant=230 and anastrozole=232). PFS was significantly longer in the fulvestrant group than in the anastrozole group (HR 0.797, 95% CI 0.637-0.999, p=0.0486). Median PFS was 16.6 months (95% CI 13.83-20.99) in the fulvestrant group versus 13.8 months (11.99-16.59)

in the anastrozole group. The most common adverse effects (AEs)s were arthralgia (17% in the fulvestrant group vs 10% in the anastrozole group) and hot flushes (26 11% in the fulvestrant group vs 10% in the anastrozole group). Sixteen of 228 (7%) patients in the fulvestrant group, and 11 of 232 (5%) patients in the anastrozole group discontinued because of AEs. It was concluded that fulvestrant has superior efficacy for patients with hormone receptor-positive locally advanced or metastatic breast cancer who have not received previous endocrine therapy compared with a third-generation aromatase inhibitor, a standard of care for first-line treatment of such patients (9). OS data from this study are awaited.

PALOMA-3 – Fulvestrant and palbociclib versus fulvestrant alone – in patients who progressed on prior endocrine therapy
In this multicentre, double-blind, randomised Phase 3 study, women aged 18 years or older with HR-positive, HER2-negative metastatic breast cancer that had progressed on previous endocrine therapy were stratified by sensitivity to previous hormonal therapy, menopausal status, and presence of visceral metastasis at 144 centres in 17 countries. Eligible patients - i.e. any menopausal status, ECOG performance status 0-1, measurable disease or bone disease only, and disease relapse or progression after previous endocrine therapy for advanced disease during treatment or within 12 months of completion of adjuvant therapy - were randomly assigned (2:1) to receive oral palbociclib (125 mg daily for 3 weeks followed by a week off over 28-day cycles) plus 500 mg fulvestrant (IM injection on Days 1 and 15 of cycle 1; then every 28-days) or placebo plus fulvestrant. The primary endpoint was investigator-assessed PFS and analysis was by ITT. Endocrine therapy resistance was assessed by clinical parameters, quantitative hormone-receptor expression, and tumour PIK3CA mutational status in circulating DNA at baseline. A total of 521 patients were randomly assigned, 347 to fulvestrant plus palbociclib and 174 to fulvestrant plus placebo. By March 16, 2015, 259 PFS events had occurred (145 in the fulvestrant plus palbociclib group and 114 in the fulvestrant plus placebo group); median follow-up was 8.9 months (IQR 8.7-9.2). Median PFS was 9.5 months (95% CI 9.2-11.0) in the fulvestrant plus palbociclib group and 4.6 months (3.5-5.6) in the fulvestrant plus placebo group (HR 0.46, 95% CI 0.36-0.59, p<0.0001). Grade 3 or 4 AEs occurred in 251 (73%) of 345 patients in the fulvestrant plus palbociclib group and 38 (22%) of 172 patients in the fulvestrant plus placebo group. The most common grade 3 or 4 AEs were neutropenia (65% in the fulvestrant plus palbociclib group and 1% in the fulvestrant plus placebo group), anaemia (3% vs 2%), and leukopenia (28% vs 1%). Serious AEs (all causalities) occurred in 44 patients (13% in the fulvestrant plus palbociclib group vs 17% in the fulvestrant plus placebo group). Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response. In conclusion, fulvestrant plus palbociclib was associated with significant and consistent improvement in PFS compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, hormone-receptor expression level, and PIK3CA mutational status. The combination could be considered as a therapeutic option for patients with recurrent HR-positive, HER2-negative metastatic breast cancer that has progressed on previous endocrine therapy (10).

A further publication compared patient-reported outcomes (PROs) in PALOMA-3 using the EORTC QLQ-C30 and its breast cancer module, QLQ-BR23. This 30-item questionnaire has scales covering physical, role, emotional, cognitive and social functioning, fatigue, nausea/vomiting and pain, and dyspnea, sleep disturbance, appetite loss, constipation and diarrhea. On treatment, estimated overall global QoL scores significantly favoured the palbociclib plus fulvestrant group [66.1, 95% CI 64.5-67.7 versus 63.0, 95% CI 60.6-65.3; p=0.0313]. Significantly greater improvement from baseline in pain was also observed in this group (-3.3, 95% CI -5.1 to -1.5 versus 2.0, 95% CI -0.6 to 4.6; p=0.0011). No significant differences were observed for other QLQ-BR23 functioning domains, breast or arm symptoms. Treatment with palbociclib plus fulvestrant significantly delayed deterioration in global QoL (p<0.025) and pain (p<0.001) compared with fulvestrant alone. It was concluded that palbociclib plus fulvestrant allowed patients to maintain good QoL in the endocrine resistance setting while experiencing substantially delayed disease progression (25).

Cochrane Review (Lee et al. 2017) – including 1 clinical trial at 500mg dose
This review assessed the efficacy and safety of fulvestrant for hormone-sensitive locally advanced or metastatic breast cancer in postmenopausal women, as compared to other standard endocrine agents using searches to 7 July 2015. Included were randomised controlled trials that enrolled postmenopausal women with hormone-sensitive advanced breast cancer (TNM classifications: stages IIIA, IIIB, and IIIC) or metastatic breast cancer (TNM classification: stage IV) with an intervention group treated with fulvestrant with or without other standard anticancer therapy. Using Cochrane methods, outcome data were extracted including PFS or TTP or time to treatment failure, OS, CBR, toxicity, and quality of life.

The review included 9 studies randomising 4514 women for meta-analysis and review. Overall results for the primary endpoint of PFS indicated that women receiving fulvestrant did at least as well as the control groups (HR 0.95, 95% CI 0.89 to 1.02; p=0.18, I2= 56%, 4258 women, 9 studies, high-quality evidence). In the one high-quality study that tested fulvestrant at the currently approved and now standard dose of 500 mg against anastrozole, women treated with fulvestrant 500 mg did better than anastrozole, with a HR for TTP of 0.66 (95% CI 0.47 to 0.93; 205 women) and a HR for OS of 0.70 (95% CI 0.50 to 0.98; 205 women). There was no difference in PFS whether fulvestrant was used in combination with another endocrine therapy or in the first- or second-line setting, when compared to control treatments: for monotherapy HR 0.97 (95% CI 0.90 to 1.04) versus HR 0.87 (95% CI 0.77 to 0.99) for combination therapy when compared to control, and HR 0.93 (95% CI 0.84 to 1.03) in the first-line setting and HR 0.96 (95% CI 0.88 to 1.04) in the second-line setting. Overall, there was no difference between fulvestrant and control treatments in CBR (risk ratio (RR) 1.03, 95% CI 0.97 to 1.10; P = 0.29, I2 = 24%, 4105 women, 9 studies, high-quality evidence) or OS (HR 0.97, 95% CI 0.87 to 1.09, P = 0.62, I2 = 66%, 2480 women, 5 studies, high-quality evidence). There was no significant difference in vasomotor toxicity (RR 1.02, 95% CI 0.89 to 1.18, 3544 women, 8 studies, high-quality evidence), arthralgia (RR 0.96, 95% CI 0.86 to 1.09, 3244 women, 7 studies, high-quality evidence), and gynaecological toxicities (RR 1.22,

95% CI 0.94 to 1.57, 2848 women, 6 studies, high-quality evidence). Four studies reported QOL, none of which reported a difference between the fulvestrant and control arms, though specific data were not presented. Authors concluded that for postmenopausal women with advanced hormone-sensitive breast cancer, fulvestrant is at least as effective and safe as the comparator endocrine therapies in the included studies. However, fulvestrant may be potentially more effective than current therapies when given at 500 mg, though this higher dosage was used in only one of the nine studies included in the review. There was no observed advantage with combination therapy, and fulvestrant was equally as effective as control therapies in both the first- and second-line setting. The review demonstrates that fulvestrant is a safe and effective systemic therapy and can be considered as a valid option in the sequence of treatments for postmenopausal women with hormone-sensitive advanced breast cancer (26).

Review of First and Second Line Therapies (Reinert et al. 2017)

This review included randomised phase II/III trials comparing first- or second-line endocrine therapy as monotherapy or in combination with targeted therapies for treatment of postmenopausal patients with hormone receptor-positive advanced breast cancer. First-line was defined as treatment for endocrine therapy-naive advanced breast cancer or advanced disease treated with endocrine therapy in the adjuvant/neoadjuvant setting. Second-line was defined as endocrine therapy for advanced breast cancer following disease progression on endocrine therapy for advanced disease. Publications reporting PFS/TTP or OS for FDA-approved agents anastrozole, exemestane, fulvestrant 250 mg, fulvestrant 500 mg, letrozole (0.5 and 2.5 mg), megestrol acetate, and tamoxifen as monotherapy, or in combination with everolimus, palbociclib or ribociclib, were assessed. First-line monotherapy with anastrozole, fulvestrant 500 mg or letrozole 2.5 mg significantly improved PFS/TTP versus comparator endocrine therapy; however, only fulvestrant 500 mg improved OS. For endocrine therapy in combination with targeted therapies, palbociclib plus letrozole 2.5 mg, and ribociclib plus letrozole 2.5 mg significantly improved PFS versus letrozole 2.5 mg alone first-line. For second-line monotherapies, exemestane, fulvestrant 500 mg and letrozole 2.5 mg significantly improved PFS/TTP versus comparator endocrine therapy; only fulvestrant 500 mg and letrozole 2.5 mg improved OS. For second-line combination therapies, everolimus plus exemestane, and palbociclib plus fulvestrant 500 mg, improved PFS versus endocrine therapy alone. In both first- and second-line settings, aromatase inhibitors demonstrated PFS benefits versus comparator endocrine therapy; however, fulvestrant 500 mg was the only endocrine therapy included in the review to show both PFS and OS advantages compared with other endocrine therapies. Targeted agents in combination with endocrine therapy have demonstrated PFS improvements both first- and second-line; OS data are awaited (14).

Observational Studies (using 500mg fulvestrant) – after progression with prior antioestrogen therapy

- A Japanese cohort study included 117 postmenopausal women with metastatic breast cancer, who experienced progression after previous endocrine therapies, and who were treated with fulvestrant 500 mg. Clinical response, TTP and AEs were investigated. Ninety-nine patients had recurrent breast cancer and 18 patients had stage IV disease. Patients had received a median of two endocrine therapies and a median of two chemotherapies, prior to fulvestrant. There were 10 patients with partial response, 39 patients with long stable disease, 18 patients with stable disease, and 50 patients with progressive disease, so that the ORR was 8.5 %, with a CBR of 41.9 %. The median TTP was 6.1 months. The absence of liver metastases, a small number of previous chemotherapies, and the longer duration of first-line endocrine therapy were positively correlated with TTP in univariate analysis. In multivariate analysis, a significant association was observed between TTP and duration of first-line endocrine therapy. Serious AEs were observed in one patient with pulmonary embolism and in one patient with psychiatric symptoms. It was concluded that fulvestrant 500 mg is an effective and well-tolerated treatment for postmenopausal women with metastatic breast cancer that had progressed after prior endocrine therapies. It was concluded that patients with acquired resistance to endocrine therapies might be good candidates for fulvestrant therapy regardless of the number of prior endocrine treatments (11).
- A Spanish multicentre, retrospective, observational study included postmenopausal women with locally advanced/metastatic ER-positive breast cancer who received treatment with fulvestrant 500 mg after progression with a previous anti-oestrogen therapy. The primary endpoint was PFS and secondary endpoints were OS, CBR, duration of clinical benefit (DoCB), and safety profile. A total of 263 women were evaluated (median age, 65.8 years). At a median follow-up of 21.5 months, median PFS and OS were 10.6 and 43.2 months, respectively. PFS according to 1st, 2nd, 3rd, and >/= 4th lines were 11.5, 10.6, 9.9, and 8.5 months, respectively (p = 0.0245). PFS in patients with visceral involvement was 10 months vs 10.6 months in patients without visceral involvement (p = 0.6604), 9.6 months in patients with high Ki67 vs 10 months in patients with low Ki67 (p = 0.7224), and 10.2 months in HER2-positive patients vs 10.3 months in HER2-negative patients (p = 0.6809). The CBR was 56.5% and the DoCB was 18.4 months. The most frequently AEs were injection site pain (10.3%) and musculoskeletal disorders (7.6%). It was concluded that fulvestrant 500 mg administered in clinical practice was shown to be effective (PFS, 10.6 months; CBR, 56.5%) and well tolerated (12).
- An Italian observational prospective trial evaluated efficacy of fulvestrant 500 mg in the treatment of endocrine sensitive advanced breast cancer patients from the real world setting. The primary end point was CBR. Secondary end points were OS, progression free survival (PFS) and tolerability. One hundred sixty three patients were enrolled. At a median follow up of 20 months, the 61% of patients reached CBR, whose median duration was 10.8 months. Median PFS and OS were 7 and 35 months, respectively. Endocrine sensitive patients showed better PFS and OS. No relevant toxicity appeared when analysing safety data. In multivariate analysis, visceral involvement, endocrine sensitivity and previous endocrine therapy were prognostic factor for PFS, whereas endocrine sensitivity and metastasis at diagnosis had prognostic relevance for OS. Oestrogen receptor expression >50%, single metastatic site, and no prior endocrine therapy for advanced disease were

predictive of CBR. In summary, fulvestrant 500 mg appeared to be a safe and active treatment. A high percent expression of oestrogen receptors (above 50%) was associated with higher CBR. Treatment was very well tolerated. Endocrine sensitivity had a major impact on treatment outcome. As expected, patients who had received first-line endocrine therapy for advanced disease exhibited worse outcome and a lower CBR (13).

Discuss the potential risks from treatment with the pharmaceutical compared with current treatment options (if any).

The following AEs are associated with fulvestrant: risk of bleeding; increased exposure in patients with hepatic impairment; injection site reaction and embryo-foetal toxicity. In the FALCON study, adverse reactions leading to discontinuation for patients receiving fulvestrant 500 mg included drug hypersensitivity (0.4%), hypersensitivity (0.4%), injection site hypersensitivity (0.4%), aspartate aminotransferase increased (0.4%), and alanine aminotransferase increased (0.4%). The most common adverse reactions (≥5%) of any grade reported in patients in the fulvestrant arm (n=228) were arthralgia (16.7%), hot flush (11.4%), fatigue (11.4%), and nausea (10.5%). Grade 3 or higher adverse reactions reported in the fulvestrant arm were ALT (alanine aminotransferase) (1.3%), AST (aspartate aminotransferase) (1.3%), back pain (0.4%) and fatigue (0.4%). Vaginal bleeding has been reported infrequently (<1%), mainly in patients during the first 6 weeks after changing from existing endocrine therapy to treatment with FASLODEX. Further evaluation is required for persistent bleeding. Elevation of bilirubin, elevation of gamma glutamyl transpeptidase (GT), hepatitis, and liver failure have also been reported infrequently.

Are there sub-populations that have higher potential benefits or risks? If so, please describe.

Highest potential benefits might be expected in patients who have developed resistance to existing treatments.

Would this treatment provide any health benefits or risks to any people beyond the individual who was receiving treatment? If so, what benefits or risks would result?

Improved quality of life and extension of life in the patient will have benefits for family and whanau. Family members who are primary carers will experience less stress and worry, and dependent children of patients will have better quality/longer time with their mothers.

How would funding the pharmaceutical result in other measurable benefits or risks to the health sector, eg changes in number of surgeries, hospitalisations, nursing time, diagnostic tests?

Click here to enter text.

Suitability

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Are there any features of the treatment that may impact on its use (eg method of delivery, size, shape, taste)? If so, please explain.

The treatment is given as a 500mg intramuscular (IM) injection – administered on a weekly basis – one 250mg in each buttock. IM administration has the potential to improve compliance and is suitable for patients who have difficulty with oral therapies.

Costs and savings

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Would the funding of this treatment create any costs or savings to the health system (eg would treatment require increased monitoring, or would it free up clinician time)?

Use of this treatment may delay or prevent the need for chemotherapy – which would free up resources.

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