Application to add fulvestrant to WHO Model List of Essential Medicines

As a Medicine for Treatment of Women with Metastatic Breast Cancer

Submitted by:

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Potential conflicts of interest

All the authors declare no conflict of interest

Date: January 2021 (a new version of the original application was republished on 27th April – see Correction note).

Correction note

In the original application the absolute survival benefit associated with the use of fulvestrant was estimated using an approach that was lately recognized as suboptimal by the GRADE Working Group and Cochrane Cancer. In agreement with the Secretariat of the Expert Committee of the Selection and Use of the Essential Medicines the application authors have corrected the estimates of the absolute effect of fulvestrant using the following method:

- First identify the median of the median survival time among control groups.

- Then use the following formula to estimate the absolute difference:

MST1 = MST0 / HR; being MST1 the median survival time with intervention

MST0 the median of the median survival time in control

HR the hazard ratio obtained from the meta-analysis

Based on Skoetz et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. *J Clin Epidemiol*. 2020 Feb;118:124-131

- Repeat the process with the limits of the confidence interval of the HR to obtain the confidence interval for the absolute effect estimate.

Therefore, in the Review of benefits section - Summary of Potential Benefits table, the anticipated overall survival absolute effect with fulvestrant was corrected from 5.5 to 7 months. The correction has been reported consistently throughout the text.

General items

1. Summary statement of the proposal for inclusion, change or deletion.

This application proposes to add fulvestrant to the list of WHO Essential Medicine as treatment for Women with Metastatic Breast Cancer.

Breast cancer is the most frequent malignant disease in women. The estimated number of new cases in 2020 was 2,261,419, accounting for 25% of all the cancers in women. Although the majority of breast cancers are diagnosed at a localized stage, a substantial proportion later progress to a metastatic stage.

The use of fulvestrat in association with aromatase inhibitors, in comparison to aromatase inhibitors alone, may increase the overall survival in approximately 7 months (HR 0.85, 95% CI 0.62 - 1.15; low certainty evidence) and the progression free survival in one month (HR 0.89, 95% 0.73 - 1.08; low certainty evidence).

Despite this favorable effect, there is conflicting economic evidence regarding it cost-effectiveness. In some studies, fulvestrat showed to be cost effective while in other it was not. This has led to some agencies offering full coverage of fulvestrat, others to cover it with restrictions and some others to not list it at all. Adding fulvestrat to the WHO essential list of medications might help to boost it use, especially in low- and middle-income countries. Also, might help to promote mechanisms that may enhance its accessibility and affordability, such as pooled procurement or inclusion in the Medicines Patent Pool and Prequalification Program.

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	**Anatomical Therapeutic Chemical (ATC) code**
Fulvestrant	L02BA03

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. No specific dose adjustments are recommended for the elderly, patients with mild to moderate renal or patients with mild to moderate hepatic impairment.

The recommended administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection).

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

The association of fulvestrant plus aromatase inhibitors has been studied in women hormone receptor-positive metastatic breast cancer as a first or second line of treatment.

8. Information supporting the public health relevance.

Breast cancer is the most frequent malignant disease in women. The estimated number of new cases in 2020 was 2,261,419, accounting for 25% of all the cancers in women.[1]

Worldwide, breast cancer incidence rates are highest in Australia/New Zealand, Northern Europe (e.g. the United Kingdom, Sweden, Finland, and Denmark), Western Europe (Belgium, the Netherlands, and France), Southern Europe (Italy), and Northern America.[2] Although it is less frequent in Africa and Asia, the mortality rates are similar across multiple territories: from 9.6 per 100,000 in Eastern Asia to 27.5 per 100,000 in Melanesia (world average 13.6 per 100,000).[1]

According to the SEER database, in the USA, 63% of breast cancers are diagnosed at a localized stage, 30% with regional involvement and only 6% with metastasis.[3] However, these numbers likely underestimate the real impact of metastatic breast cancer. Many women initially diagnosed in stages I-III will progress to a metastatic stage. It has been estimated that only 25% of the women living with metastatic breast cancer are *de novo* cases, while 75% correspond to recurrences of previously localized disease.[4]

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for systematic reviews up to December 2020 on MEDLINE and EMBASE, from date of inception and without language limits (see appendix). We used the systematic reviews as a way to identify relevant studies, but conducted our own meta-analysis.

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Women with metastatic breast cancer
3. Intervention: Fulvestrant plus aromatase inhibitors
4. Comparison: Aromatase inhibitors without fulvestrant

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analysed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. Meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) or STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Results

We identified 5 systematic reviews[5-10] and 3 randomized trials.[11-13]

The first trial identified was conducted in postmenopausal women, or premenopausal women receiving a gonadotropin-releasing hormone agonist, with hormone-receptors-positive breast cancer at first relapse after primary treatment. Investigators randomized participants to fulvestrant loading dose regimen followed by monthly injection plus 1 mg of anastrozole daily or to 1 mg of anastrozole daily alone.[11]

The second trial identified included postmenopausal women with previously untreated hormone-receptors-positive metastatic breast cancer. Participants were randomized to fulvestrant (intramuscularly at a dose of 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter) plus 1 mg of anastrozole daily or to 1 mg of anastrozole daily alone.[12]

The third trial evaluated postmenopausal women with hormone-receptor-positive breast cancer who had relapsed or progressed with locally advanced or metastatic disease during treatment with aromatase inhibitors. Participants were randomized to fulvestrant (500 mg intramuscular injection on day 1, followed by 250 mg doses on days 15 and 29, and then every 28 days) plus daily oral anastrozole (1 mg); fulvestrant plus anastrozole-matched placebo; or daily oral exemestane (25 mg).[13]

Two of these these trials reported data to estimate the effect on overall survival. The meta-analysis showed that the use of fulvestrat plus aromatase inhibitors may increase the overall survival in approximately 7 months (HR 0.85, 95% CI 0.62 - 1.15; low certainty evidence) and the progression free survival in one month (HR 0.89, 95% 0.73 - 1.08; low certainty evidence). There was substantial heterogeneity on the meta-analysis, with the FACT trial suggesting no effect and the SWOG0226 trial showing a benefit of fulvestrat plus aromatase inhibitors. There were many differences between these two trials beyond the type of patients included. Without having access to the individual patient data, it was not possible to draw conclusions about the reasons for this heterogeneity.

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Fulvestrat plus AI	WITH AI only	Difference (CI 95%)	
Overall survival 2 RCTs (n=1,208)	**HR 0.85** (0.62 - 1.15)	**46** months	**39** months	**7** months more[a] (from 5 less to 24 more)	⨁⨁◯◯ **LOW** [b,c]
Progression free survival 2 RCTs (n=1,208)	**HR 0.89** (0.73 - 1.08)	**12.9** months	**12** months	**1** month more[a] (from 5 less to 24 more)	⨁⨁◯◯ **LOW** [b,c]

Abbreviations: HR: Hazard ratio; CI: Confidence interval; AI: Aromatase inhibitors

a. The anticipated absolute effect was estimated from the median survival observed in controls groups and the hazard ratio.
b. We rated down the certainty of the evidence due to imprecision. The confidence interval around the relative effect probably crosses the decisions thresholds
c. We rated down the certainty of the evidence due to inconsistency. We observed a substantial heterogeneity on the meta-analysis

10. Review of harms and toxicity: summary of evidence of safety.

The meta-analysis of the three studies identified showed that the association of fulvestrat plus aromatase inhibitors may slightly increase adverse events: 15 more per 1000 women treated (95% CI from 26 fewer to 59 more; RR 1.03, 95% CI 0.92-1.15; moderate certainty evidence).

The most common adverse events were gastrointestinal disorders (constipation, nauseas or vomiting), hot flashes, headache, arthralgia and bone pain.

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Fulvestrat plus AI	WITH AI only	Difference (CI 95%)	
Adverse Events grade 3 or more 3 RCT (n=1,264)	**RR 1.03** (0.92 - 1.15)	**385** per 1000	**370** per 1000	**15 more** (26 fewer to 59 more)	⨁⨁⨁◯ **MODERATE** [a]

Abbreviations: RR: Risk ratio; CI: Confidence interval; AI: Aromatase inhibitors.

a. We rated down the certainty of the evidence due to imprecision. The confidence interval around the absolute effect probably crosses the decisions thresholds

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to December 2020 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Center of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified 2 studies evaluating the comparison of fulvestrant plus aromatase inhibitors versus fulvestrant alone.[14,15]

The first was a cost-utility analysis from China. The authors compared fulvestrant half dose with an aromatase inhibitor (anastrozole) against fulvestrant alone and anastrozole alone as a first-line treatment for hormone receptor-positive metastatic breast cancer.[14] They found that the combination of fulvestrant and anastrozole was likely cost-effective at a wiliness to pay of US$29 383 (86.5% probability of being cost-effective).

The second study compared fulvestrant plus an aromatase inhibitor (anastrozole) against anastrozole alone in women with hormone-receptor-positive metastatic breast cancer.[15] The authors found that the combination of fulvestrant plus anastrozole was not cost-effective for either, all eligible patients or patients with no previous hormonal adjuvant therapy, at a wiliness to pay threshold of $150,000 per QALY.

Coverage recommendations regarding fulvestrant are conflicting. The Pharmaceutical Benefits Advisory Committee (PBAC, https://www.pbs.gov.au/pbs/home; Australia) recommended listing fulvestrant for the treatment of patients with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2 negatives (HER2-) unresectable advanced or metastatic breast cancer. While the Canadian Agency for Drugs and Technologies in Health (CADTH, https://www.cadth.ca; Canada), through the Pan Canadian Oncology drug review (pCODR), recommend listing fulvestrant for locally advanced or metastatic HER2-

breast cancer in postmenopausal women who have not been previously treated with endocrine therapy. However, this recommendation was conditioned to achieve a price reduction. Finally, The National Institute for Health and Care Excellence (NICE, https://www.nice.org.uk; UK), did not recommended listing fulvestrant.

Summary of Economic Evaluations

Study	Limitations	Other comments		Cost-effectiveness (ICER)	Uncertainty
Huang X. 2020[14]	potentially serious limitations [a]	Model	A three- health- state Markov model was developed as follows: progression-free, the progression of the disease (PD) and death	The ICER of F&A versus ANA was US$15,665/QALY, with an incremental cost and QALY of US$12,401.120 and 0.792, respectively, which was less than the willingness- to- pay of US$29,383/QALY.	In China, compared with FUL and ANA, the probability that F&A was cost-effective at a WTP for a QALY of US$29,383 was estimated to be 86.5%. There- fore, F&A was the most likely treatment to be cost-effective in China.
		Population	Postmenopausal women with hormone receptor-positive metastatic breast cancer		
		Time horizon	Lifetime		
		costs	The costs were estimated from the Chinese healthcare system perspective. Only direct medical costs were considered in the model, including the drug, management of treatment-related serious adverse events (SAEs)		
		Utilities	The utility values were calculated according to published utilities derived by using Visual Analogue Scale and standard gamble		
		Perspective	Chinese healthcare system perspective. Only		
		Others	Comparing half- dose fulvestrant (FUL) and anastrozole (ANA) (F&A) versus ANA monotherapy for first- line. The study compared the costs and effectiveness of F&A combination therapy with FUL and ANA monotherapy		
Study	**Limitations**	**Other comments**		**cost-effectiveness (ICER)**	**Uncertainty**
Liao W. 2020[15]	potentially serious limitations [b]	Model	Markov model. The model had three health states: stable disease, disease progression, and death	The addition of fulvestrant to anastrozole cost $194,450 per QALY gained	In probabilistic sensitivity analyses, fulvestrant plus anastrozole was cost-effective in 0% for either all eligible patients or patients with no previous hormonal adjuvant therapy at a WTP threshold of $150,000 per QALY in the US. first-line fulvestrant plus anastrozole is not a cost-effective option for HR+ metastatic breast cancer in postmenopausal women from the US payer's perspective.
		Population	Postmenopausal women; estrogen receptor-positive or progesterone receptor-positive metastatic breast cancer; with a Zubrod performance status score of 0–2; no previous chemotherapy, hormone therapy, or immunotherapy for metastatic diseases		
		Time horizon	a 15-year time horizon was		
		costs	Direct medical costs were considered, including costs associated with the acquisition of treatments, administration, management of serious adverse events and follow-up		
		Utilities	The utility scores were estimated at 0.86 in the stable state, 0.71 in the progressive state and 0 in the dead state according to previously published literature		
		Perspective	US payer's perspective		

Abbreviations Fulvestrant (FUL), hormone receptor-positive (HR+), Anastrozole (ANA)

a. The model inputs were obtained from different randomised clinical trials (RCTs). The efficacy and cost of ANA and FUL + ANA may be overestimated due to the lower of compliance. It is possible that the assumptions about the effectiveness could overestimate the final ICER results
b. Is possible that some adverse events were not considered and that could affect the cost and utilities obtained. For the used base trail there was not an available EQ-5D questionnaire applied. The effectiveness of the intervention is the most sensitive parameter on the model to different inputs.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Fulvestrant

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

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12. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med.* 2012;367(5):435-444.
13. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol.* 2013;14(10):989-998.

14. Huang X, Weng X, Lin S, et al. Half-dose fulvestrant plus anastrozole as a first-line treatment for hormone receptor-positive metastatic breast cancer: a cost-effectiveness analysis. *BMJ Open.* 2020;10(8):e036107.
15. Liao W, Huang J, Wu Q, et al. First-line fulvestrant plus anastrozole for hormone-receptor-positive metastatic breast cancer in postmenopausal women: a cost-effectiveness analysis. *Breast Cancer.* 2020;27(3):399-404.

Appendix

Appendix 1: Search strategies

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)
DATE: December 2020

1. Fulvestrant.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy]
2. exp Breast Neoplasms/
3. Carcinoma, Lobular/
4. systematic review/
5. meta-analysis/
6. (meta analy* or metanaly* or metaanaly*).ti,ab.
7. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
8. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
9. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
10. cochrane.jw.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 2 or 3
13. 1 and 11 and 12

Search strategy for economic evaluations in MEDLINE (via OVID)
DATE: December 2020

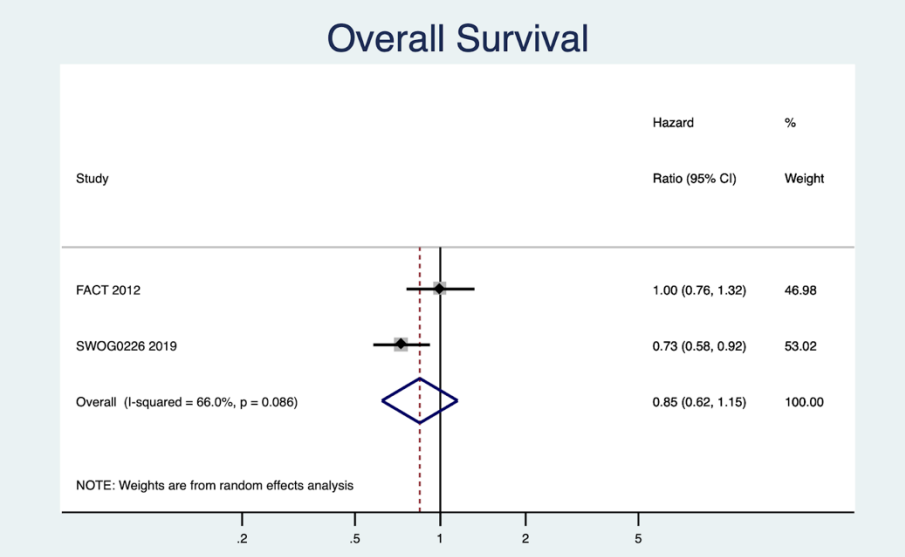
(Fulvestrant OR "fulvestrant"[MeSH Terms] OR ("aromatase inhibitors"[MeSH Terms]) Or aromatase inhibitors) AND ((((breast OR mammary) OR (carcinoma OR neoplasm OR tumor OR cancer)) OR metastatic OR advanced OR metastases OR metastasis OR breast cancer [MeSH Terms]) AND (Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab] OR “Single Technology Appraisal”OR “HTA” OR “Technology Appraisal”)

Search strategy for economic evaluations in EMBASE (via OVID)
DATE: December 2020

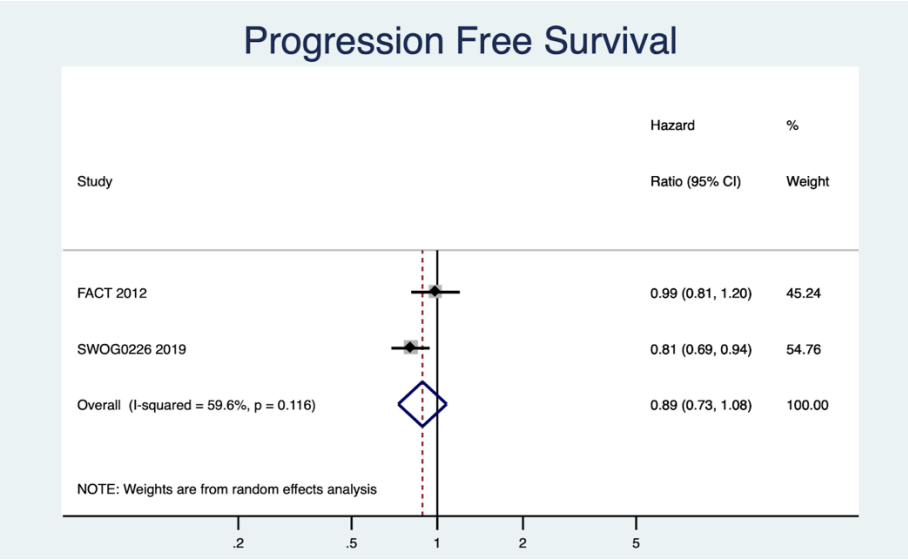
(breast cancer/ OR breast cancer.ti,ab)
AND
(Fulvestrant.ti,ab OR fulvestrant/)
AND
(Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/ or health technology assessment.mp.)

Appendix 2: Forest plots

Fulvestrant - Overall survival.



Fulvestrant - Progression free survival



Fulvestrant - Adverse events