CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Fulvestrant (Faslodex) for Metastatic Breast Cancer

February 1, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by AstraZeneca** compared fulvestrant to anastrozole for patients with non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The funding request and model population are in alignment. Fulvestrant compared with anastrozole for the hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who have not been previously treated with endocrine therapy
Type of Analysis	*CEA and CUA*
Type of Model	*Partitioned-survival*
Comparator	*Anastrozole* *A revised model was later provided addressing fulvestrant compared to palbociclib plus letrozole.*
Year of costs	*2017*
Time Horizon	*15 years*
Perspective	*Government*
Cost of fulvestrant	At the list price fulvestrant costs $582.90 per 250mg/5ml injection. At the recommended dose of 500mg on days 0, 14, 28 in cycle 1, then every 28 days thereafter, fulvestrant costs: Cycle 1: • $124.91 per day • $3497.37 per 28-day cycle Subsequent cycles: • $41.64 per day • $1165.79 per 28-day cycle
Cost of anastrozole*	At the list price anastrozole costs $1.27 per 1mg tablet. At the recommended dose of 1mg daily, anastrozole costs: • $1.27 per day • $35.64 per 28-day cycle
Cost of exemestane*	At the list price exemestane costs 1.33 per 25mg tablet. At the recommended dose of 25mg daily, exemestane costs: • $1.33 per day • $37.64 per 28-day cycle
Cost of tamoxifen*	At the list price tamoxifen costs $0.35 per 20mg tablet. At the recommended dose of 20mg daily, tamoxifen costs • $0.35 per day • $$9.8 per 28-day course
Model Structure	The model was comprised of 3 health states: Progression Free; Progressed; Death. There are two sub-states in Progression Free, complete response and partial response.
Key Data Sources	*Trial data (FALCON) + extrapolation for PFS and OS; external sources* *Utilities based on EQ-5D from trial data (FALCON)*

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on October 31, 2017*
All calculations are based on = 70kg and BSA = 1.7m^2

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel also considered that palbociclib plus letrozole is a clinically relevant comparator. In the absence of direct comparative evidence, the Submitter provided an indirect comparison addressing the comparative effectiveness and safety of these two treatment options. The CGP and EGP noted that there was insufficient data available on the trials included in this indirect comparison to do a proper critical appraisal of the methodology and results. The CGP and EGP therefore agreed that the results were uncertain and could not be used in the economic analysis to determine the cost-effectiveness of fulvestrant compared to palbociclib plus letrozole.

Relevant issues identified included:

- The CGP acknowledged the limitations in the FALCON trial as the subgroup of patients with non-visceral disease was not powered to detect a difference. Given the alignment of results with the FIRST trial and magnitude of absolute mPFS results, it is likely that a true treatment effect is present.
- Median OS has not been reached in the FALCON trial, but are unlikely to show a significant benefit given that the trial is not powered to detect a potential difference and the significant number of years needed to accumulate events. Although FIRST did suggest an overall survival advantage of fulvestrant over anastrozole, given the study's limitations, this result cannot be interpreted as conclusive.
- Health-related quality of life was not adversely affected by the use of fulvestrant, as measured by FACT-B and TOI. Toxicity was not marked different between the fulvestrant and anastrozole.
- Additional nursing visits or clinic visits will be required for the administration of fulvestrant.
- There is considerable uncertainty in the indirect results that are reported for the comparison between fulvestrant and palbociclib plus letrozole.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered.

- Fulvestrant may be regarded as an alternative to letrozole + palbociclib in patients who do not want to be treated with a CDK4/6 inhibitor. The analysis presented comparing the efficacy and safety of fulvestrant with palbociclib plus letrozole was dismissed by the EGP given the limitation in the data. Therefore the economic analysis did not address this comparison.
- Estrogen and progesterone receptor testing is the standard of care for patients with locally advanced or metastatic breast cancer.
- There is potential for expanding the use of fulvestrant as an option for second-line therapy after CDK4/6 agents. A scenario looking at the use of fulvestrant as an option after palbociclib plus letrozole was not considered in the economic analysis.

Summary of patient input relevant to the economic analysis

- The combination of palbociclib and fulvestrant was mentioned as a relevant treatment option. The availability of this combo, may affect the relative cost effectiveness of fulvestrant monotherapy vs other drugs. The current economic evaluation did not provide any information to assess this comparison.

- The diagnosis of advanced breast cancer, as well as the treatments that are used, impact both the social and physical well-being of a patient thus impacting their quality of life. The economic model incorporates quality of life data from the trial.
- Patient input indicated that disease control, symptom reduction, maintaining quality of life and ensuring longer survival were very important for the majority of patients. The economic model incorporated outcomes for PFS, OS and quality of life.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for fulvestrant which are relevant to the economic analysis:

- Nursing resources for intramuscular injection. Patients would need monthly treatment visits, which requires incremental resources over patients who receive oral endocrine therapy. This was accounted for in the economic model.
- PAG commented that the intramuscularly injected fulvestrant requires the nursing resources and monthly physician visit, which may slightly increase the total cost associated with the use of fulvestrant.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.74	0.21-1.74
Progression-free	Not reported	Not available
Post-progression	Not reported	Not available
ΔE (QALY)	1.28	0.19-1.24
Progression-free	0.64	0.64-0.63
Post-progression	0.65	-0.44-0.63
ΔC ($)	$41,405	$35,095-$52,416
ICER estimate ($/QALY)	$32,361	$33,476-$185,631

The main assumptions and limitations with the submitted economic evaluation were:

- *The key assumption in the submitted model is that fulvestrant is associated with better overall survival in the long term than anastrozole. This is based on the prediction from the chosen survival function but without the support of solid evidence. The available evidence was based on a subgroup analysis of a secondary endpoint. The considerable uncertainty regarding the observed and long term benefit in OS is not fully reflected in the chosen survival model. The CGP also indicated that there is uncertainty in the conclusions that could be drawn from this data until more mature results are available.*
- *In the absence of more mature data, the EGP used the best available evidence from the M14-032 trial which, indicated a separation of the KM curves for survival up to three years. Given the absence of data beyond 3 years, the EGP indicated there is a huge uncertainty if modelling a difference in OS beyond year 3. Other assumptions that may lead to modest increase in the ICUR include the choice of survival functions for PFS based on visual examination, and fitting a joint model to the entire group instead of an independent model for each arm.*

1.4 Detailed Highlights of the EGP Reanalysis

Bases on the best available evidence, the ICER could be substantially higher than what the submitter reported. The biggest impact on the ICER was related to the estimates for OS. When

altering the estimates for OS to reflect the data currently available from the trial, the ΔE is between 0.19 –1.24 and ΔC is $35,095 to $41,404 resulting in an ICER of between $185,631 and $33,476/QALY, an increase of $153,270 to $1,115 from the base case results.

Notably, the available evidence for OS is based on immature OS data derived from a subgroup analysis that was not powered to detect a difference in OS. In the upper estimate the OS advantage is limited to 3 years while in the lower, an OS advantage is modeled over a 15 year time horizon. Once the OS data is more mature and depending on the direction of change in the estimates for OS, the ICER may be substantially impacted.

The EGP made the following changes to the economic model:

- **FALCON trial has not reached the median overall survival for both arms**. The economic model fits the survival functions to three-year observed survival data. The long term prediction on overall survival in the base case analysis favors fulvestrant, which is uncertain but has substantial impact on the ICUR. Additionally, the results are based on a subgroup analysis of a secondary endpoint. In the absence of evidence to confirm the presence or absence of OS benefit with fulvestrant, the EGP used the best available evidence in their reanalysis which assumed that the overall survival for Fulvestrant is identical to anastrozole beyond year 3. Depending on the magnitude, or even direction, of the change in the OS data, the ICER may be substantially altered.
- **Choice of parametric function for extrapolation**: In the submitted base case results, a weibull function was chosen to fit to the PFS data but based on visual inspection. However, if AIC or BIC is used as the criterion, log-normal or log-logistic fits better to the data. In the EGP reanalysis, log logistic and log normal are used.
- **Utility estimates**: Regression models were used to calculate the health utilities based on the observed from the trial. In the EGP's reanalysis, the actual observed utilities from the FALCON participants are used.
- **Cost of comparator drug:** The cost used for anastrozole in the model is higher than the generic list price of anastrozole. Given the low cost of the comparator, the EGP do not anticipate that there will be any substantial impact on the ICER.

Following the posting of the pERC initial recommendation, the EGP provided further clarification on the following issues discussed within the pERC initial recommendation.

The submitter's analysis used data based on the subgroup of patients with non-visceral disease. Notably, the model did not have the option of exploring cost-effectiveness based on the ITT analysis. The pERC initial recommendation concluded the clinical benefit in the non-visceral subgroup is at worst similar to the efficacy outcomes seen in the overall trial results. Although the EGP did not have the ability to present results based on the ITT data, they agree that it is likely that the ICER will be higher if the ITT results were used in the economic evaluation.

Furthermore, assuming no OS benefit beyond year 3, as was done in the EGP's reanalysis exploring uncertainty in the OS data, could represent a worst case scenario. As described in the pERC initial recommendation and feedback from the submitter, the EGP agree that it is unlikely that the Kaplan-Meir curves would drop at the 3 year mark in real clinical practice. However, in the absence of updated OS analysis to provide a full picture of long term effects of the treatment (i.e. including both best or worst scenarios based on current available evidence), this was the best approach available to the EGP to demonstrate the impact of the OS uncertainty on the ICER.

Table 8. EGP Reanalysis Estimates

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Base case result	**$41,405**	**1.28**	**1.74**	**$32,362**	-----
OS is identical between Fulvestrant and Anastrazole beyond year 3	$35,095	0.19	0.21	$185,631	$153,270
independently fit Weibull function to each arm's OS data	$38,411	0.71	0.94	$53,860	$21,498
Independently fit log-logistic function to each arm's PFS data	$51,848	1.30	1.74	$39,909	$7,548
Independently fit log-normal function to each arm's PFS data	$52,416	1.30	1.74	$40,200	$7,839
Utility values from FALCON: Fulvestrant: 0.76/0.67 for PFS/PD for fulvestrant Anastrozole:0.75/0.71 for anastrozole, respectively	$41,404	1.24	1.74	$33,476	$1,115
Given that the biggest impact on the ICER is related to the estimates for OS and the uncertainty in the available evidence for OS, the EGP did not combine any of the one way analysis to provide a range of re-analysis estimates.					

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the market share taken by fulvestrant for the first year and the administration cost such as mark-up and dispensing fee, both would be increase the budgetary impact if included.

Key limitations of the BIA model include the relative low market share taken by fulvestrant in the first year underestimate the budgetary impact. These parameters were able to be modified and explored by the EGP.

1.6 Conclusions

Based on the best available evidence, the EGP's best estimate of ΔC and ΔE for fulvestrant when compared to anastrozole is:

- Between **$33,476/QALY** and **$185,631/QALY**
- It is hard to provide a best estimate from the range due to uncertainty in the long term overall survival evidence.
- The extra cost of fulvestrant is between $35,095 and $52,416. Survival function is the main factor affecting the increment costs.
- The extra clinical effect of fulvestrant is between 0.19 QALY and 1.24 QALYs (ΔE). The main factors affecting the increment QALYs include to what extent there is the long term overall survival benefit for fulvestrant and whether fitting survival model independently or jointly to the trial data.

Overall conclusions of the submitted model:

- This economic model compares the cost and QALYs between fulvestrant and anastrozole for the indicated breast cancer subpopulation. The clinical data came primarily from the FALCON trial. The results for OS, a secondary endpoint in the trial, are based on a subgroup analysis of OS in non-visceral patients. At the time of this analysis, median overall survival was not reached in the trial. Therefore, survival functions were fit to the three year observed subgroup analysis for overall survival to make a long term projection

for the model. The projected overall survival significantly favors fulvestrant for which there is no solid evidence to support. This is the largest uncertainty both on the clinical benefit and the incremental cost per QALY gained for fulvestrant. Based on the re-analyses, the submitted results could represent optimistic estimates. With more mature data, and depending on the magnitude and direction of the incremental OS benefit, the ICER could be impacted substantially.

- Letrozole plus palbociclib was identified as a relevant comparator. Upon the request from pCODR, the submitter provided an updated scenario analysis by including this combo therapy as a comparator. However, the result is based on a network meta-analysis (NMA) result for which there is not sufficient information provided to allow for a critical appraisal of the quality and validity of the NMA. Therefore the EGP did not further consider this analysis.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of fulvestrant (Faslodex) for metastatic breast cancer. A full assessment of the clinical evidence of fulvestrant (Faslodex) for metastatic breast cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

References

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