pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Eribulin (Halaven) for Metastatic Breast Cancer

August 2, 2012

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis submitted to pCODR by Eisai compared eribulin to treatment of physician's choice (TPC) which represented a combination of possible alternatives including vinorelbine, gemcitabine, capecitabine, taxanes (docetaxel, ixabepilone, paclitaxel, nab-paclitaxel), anthracyclines (doxorubicin, liposomal doxorubicin) and 'other' in patients with metastatic breast cancer who had already been treated with an anthracycline and a taxane. Eribulin would be used only after 2 to 4 other therapies had already been tried. The TPC comparator was weighted to reflect costs and prescribing patterns in Canada. Eribulin is administered intravenously, while TPC is a mix of intravenous and oral drugs.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, and reflects the fact that there is no specific standard of care and that metastatic breast cancer is most often treated with a series of treatments, rather than one single therapy or combination. There may be some minor differences in the precise mix and order of treatments between different provinces, but in general the comparator used in the main analysis appears plausible.

Patient advocacy groups considered the following factors important in the review of eribulin and relevant to the economic analysis: additional survival with treatment, and the quality-of-life while on treatment. The submitted model demonstrated that eribulin could extend survival when used as a 3rd to 5th line therapy, but the main analysis of the model did not address the issue of quality-of-life while on treatment.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for eribulin, and are relevant to the economic analysis: the evidence base, the potential for off-label use in earlier stages of metastatic breast cancer, the additional budget impact stemming from the fact that eribulin adds rather than replaces an existing treatment, and the potential for wastage if eribulin continues to only be available in a 1mg vial size. The manufacturer's submission provided details on the evidence for eribulin and accounts for wastage by rounding the average cost per dose to the next highest mg, but does not allow for off-label use.

The list price of eribulin is $540.00 per 2 mL vial (as 1mg/2mL), but the manufacturer is offering a confidential price of $ [redacted] per 2 mL vial to provincial health plans. At the recommended dose of 1.4 mg/m^2, and assuming an average body area of 1.7 m^2, the average cost per treatment cycle would be $3,427.20 at the list price. (Non- disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).At the confidential price, the cost per cycle would be $[redacted]. (Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).Treatment courses would continue every 21 days until the patient's disease progressed.

1.2 Summary of Results

The EGP's estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $114,083 and $272,275 per quality-adjusted life year (QALY) gained when eribulin is compared with treatment of physician's choice. It is likely that the ICER is at the higher end of this range (about $223,840-$272,275/QALY gained).

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's estimate of:

- the extra cost of eribulin is between $19,201 and $21,639. Cost was driven primarily by the price of eribulin and TPC. Treatments continued as long as the patient's disease did not progress, but as there was relatively little variability in progression-free survival, the number of treatment courses was not a significant cost driver.
- the extra clinical effect (ΔE) of eribulin is between 0.069 and 0.185 quality-adjusted life years (QALYs). The additional QALYs are driven primarily by the overall survival advantage associated with eribulin relative to TPC, although some of the value of this survival advantage is offset once quality-of-life during that survival time is accounted for. The model implies a survival advantage for patients treated with eribulin, even after their disease has progressed and they discontinue treatment.
- there is also uncertainty around the duration of benefit from eribulin. Based on the Kaplan-Meier curves reported by Coates et al (Lancet 2011), the overall survival curves appear to overlap over at about 18 months.

The EGP based these estimates on the model submitted by Eisai and reanalyses conducted by the EGP. The reanalysis conducted by the EGP using the submitted model showed that when:

- febrile neutropenia is included in the model as an adverse event by including hospitalization costs and quality-of-life penalties associated with febrile neutropenia, the extra cost of eribulin increases from $21,449 to $21,564 ($\Delta C_2$), with minimal impact on clinical effect, which produces an estimated incremental cost-effectiveness ratio to $114,083.
- the risk of transitioning to a progressive or terminal state with eribulin are set equal to the risks with TPC beyond the time when all deaths on the pivotal trial had occurred (about 24 months) the extra cost of eribulin falls from $21,639 to $19,270 and the clinical effect falls from 0.185 to 0.086 QALYs gained, which increases the estimated incremental cost-effectiveness ratio to $223,840.
- the risk of transitioning to a progressive or terminal state with eribulin are set equal to the risks with TPC beyond 18 months, based on the crossing of the Kaplan-Meier overall survival curves, the extra cost of eribulin falls from $19,270 to $18,898 and the clinical effect falls from 0.086 to 0.069, which increases the estimated incremental cost-effectiveness ratio to $272,275.

The EGPs estimates differed substantially from the submitted estimates.

According to the economic analysis that was submitted by Eisai, when eribulin is compared with treatment of physician's choice:

- the extra cost of eribulin is $20,0559 (ΔC). Costs considered in the analysis included costs of drug acquisition and administration for eribulin and TPC, the costs of adverse events associated chemotherapy, the costs of palliative care upon disease progression, and the mean treatment duration from the EMBRACE study.
- the extra clinical effect of eribulin is 0.2 quality-adjusted life years (QALYs) gained or 0.36 life years gained (ΔE). The clinical effect considered in the analysis was based on the overall survival advantage associated with eribulin over TPC and the mean treatment duration from the EMBRACE study based on a non-proportional hazards model.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was within the range of $100,000 to $120,000 per QALY or between $44,497 and $70,465 life years gained, depending on whether mean or median treatment duration is considered. The submitter's probabilistic sensitivity analysis (PSA) suggests that there was less than a [redacted]% probability that the cost-effectiveness ratio for eribulin would be less $100,000 per QALY. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The manufacturer's model projected that the overall survival rate at 24 months would be 24% in the eribulin arm and 17% in the TPC arm (7% survival advantage in favour of eribulin). However, based on the pivotal trial by Coates et al. (Lancet 2011), the overall survival curves appear to have converged by about 18 months. The model also implicitly assumes carry-over benefits with eribulin beyond progression. Based on the manufacture's model, almost all patients from both arms have progressed and were no longer receiving eribulin or TPC at 24 months. However, patients on the eribulin arm continued to have a lower chance of dying beyond 24 months despite progression, and this lower chance of death continues over a lifetime horizon.

By modelling a 7% overall survival benefit at 24 months in the manufacturer's model which was not supported by observed trial data, and by projecting a survival benefit beyond the end of trial, as well as assuming a benefit from eribulin beyond progression, the mean overall survival benefit of eribulin over TPC may be significantly inflated. Indeed, in the manufacturer's reference scenario, only 61 percent of the net QALYs gained with eribulin relative to TPC accrued before month 24; almost 40 percent of the incremental QALY gains modelled by the manufacturer accrued beyond the 24-month horizon of the clinical trial. As overall survival benefit with eribulin beyond 18-24 months does not appear to be supported by the results of the pivotal trial by Coates et al., the reference case must therefore be interpreted with reservation. EGP attempted to explore the above issues by testing the impact of setting the transition probabilities associated with eribulin to be the same as those for TPC in each cycle beyond 18 months (when the overall survival Kaplan-Meier survival curves appear to converge), or beyond 24 months (when all death events had already occurred on the pivotal trial according to the Kaplan-Meier overall survival curves). The model continued to have a lifetime horizon and the relative survival benefit of eribulin at 18 or 24 months was maintained, but the hazard ratio with eribulin was

effectively set to 1.0 beyond these endpoints. The ICERs in these 18- and 24-month benefit scenarios were $272,275/QALY and $223,840/QALY, respectively, and 77 and 81 percent of the QALY gains, respectively, accrued prior to setting the HR to 1.0. In the scenario that assumed a 24-month duration of benefit, the survival difference between the two survival curves was 7% at 24 months, 4% at 30 months, and 2% at 36 months, similar to what was shown on the survival curves in the exploratory analysis on Fig. 4 of the CGP report).

The manufacturer's feedback on this re-analysis suggests that it is negating the overall survival benefit of eribulin, leading to an unfavourable QALY estimate. Instead the manufacturer suggests that the re-analysis should consider the unplanned updated analysis based on extended trial follow-up. However, the EGP does not accept this approach. First, the EGP continues to support that an economic model based on the definitive planned analysis was more appropriate as this would not be subjected to the potential bias of subsequent exploratory "multiple looks" at the data, or the possibility of an arbitrary end-point that results in a more favorable cost-effectiveness ratio. Second, the manufacturer's model assumed ongoing survival benefit beyond progression, which does not appear to be clinically reasonable. EGP sought the advice of CGP on this issue, and CGP noted that it was unlikely that there would be ongoing carry-over benefit beyond progression beyond 18-24 months.

The EGP re-analysis allowed for persistent survival benefit over the lifetime horizon of the model, but limited the degree of carry-over effects beyond progression and more closely reflects the pre-planned trial analysis.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Patient advocacy group input suggested the most important factors to patients were increased survival and a reasonable quality-of-life, although patients did express a willingness to sacrifice quality for survival. The submission does demonstrate a survival advantage, but does not address quality-of-life.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

The model design and structure is adequate for the evaluation. Although the main analysis did not adjust life years gained for quality, it was possible to do so using inputs in the model. It was, however, difficult to observe the direct impact of changes to key parameters.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The model was reasonably conservative, and most of the assumptions made in the model appear justifiable. Although the decision to exclude febrile neutropenia (FN) from the model does not appear justified, the net impact of FN upon re-analysis is minimal. The implicit assumption of the model that there is significant ongoing overall survival benefit beyond trial period given the crossing over of survival curves in the trial data at about 18 months could inflate the incremental effectiveness and decrease the ICER.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

No. The survival estimates projected beyond the end of trial period, as well as the beyond with beneficial carry-over effects post-progression following eribulin may be inappropriate and could have significantly inflated the incremental effectiveness assigned to eribulin.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact is driven by the eligible population, the eribulin uptake rate and the cost of eribulin.

What are the key limitations in the submitted budget impact analysis?

The BIA is difficult to follow. The calculation of the number of eligible patients, based on a combination of overall incidence of breast cancer and proportions by stage of diagnosis, receptor status and line of therapy is not straightforward and was difficult to adjust. The BIA also showed that the gross cost of eribulin would be offset to some degree by savings elsewhere, but it was not possible to identify the calculations and assumptions behind these savings.

The BIA does not directly address the concern expressed by PAG over the potential for off-label use that may substantially increase the budget impact of eribulin. An easier way to change the proportion of metastatic patients receiving eribulin may be useful in this regard.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The ability of observe the impact of changes to key parameters in the economic and budget impact models should be improved.

Is there economic research that could be conducted in the future that would provide valuable information related to eribulin for metastatic breast cancer?

Quality-of-life data directly applicable to this patient population should be collected.

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 eribulin. A full assessment of the clinical evidence of eribulin 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.pcodr.ca).

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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

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. The Final Economic Guidance Report reflects revisions made to the Initial Economic Guidance Report following feedback from stakeholders on the Initial Recommendation.

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.pcodr.ca). 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.

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