PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Eribulin (Halaven) for Metastatic Breast

August 2, 2012

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	HALAVEN (eribulin mesylate). HALAVEN is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane administered in either the
Role in Review (Manufacturer):	Manufacturer
Organization Providing Feedback	Eisai Ltd

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees **X** agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees, agrees in part or disagrees with the initial recommendation.

The manufacturer agrees with the clinical guidance report that demonstrates the overall survival clinical benefit, tolerability and safety of the drug. The recommended positioning within the Canadian treatment algorithm is supported by the data and is in line with our label.

However, the EGR negates the overall survival benefit of eribulin demonstrated beyond 18 months and therefore calculated an unfavourable QALY for eribulin. This recalculation is based solely on data from the primary analysis published by Cortes et al, and does not incorporate the demonstrated long term survival benefit beyond 18 months in the updated analysis, presented in the same publication and referenced by the CGR (page 9/10 and Figure 4 in the CGR, page 35).

The manufacturer would encourage pERC to incorporate the long term data into the calculation of the cost per QALY as this data is included in the manufacturer's model and results in a more favourable cost per QALY range of $100,000 to $120,000.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation. Recommendation does not require reconsideration by pERC.	__X__ Do not support conversion to final recommendation. Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

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Page Number	Section Title	Paragraph, Line Number
Page 3 EGR	1.3 Summary of Economic Guidance Panel Evaluation and 2.2.1 Limitations of Model	Paragraph 1, Line 4

Comments related to Submitter or Manufacturer-Provided Information

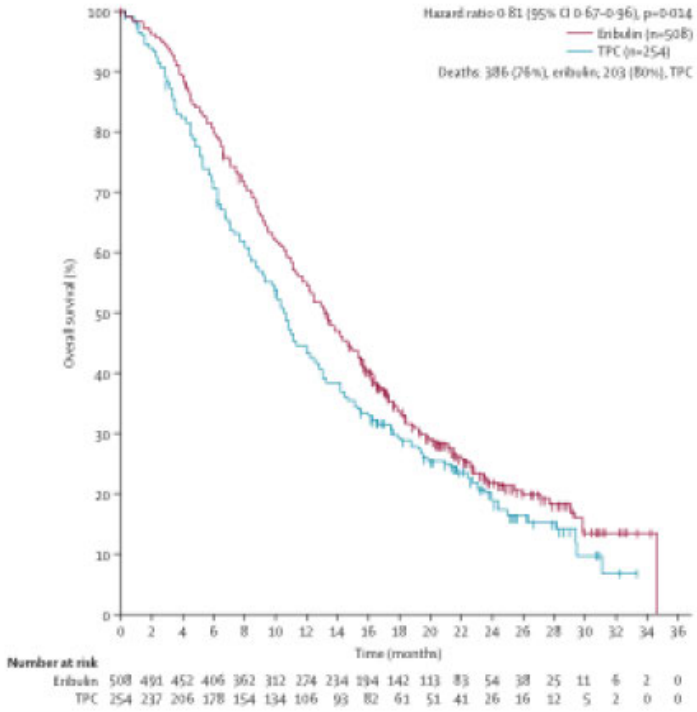
The critical difference between the manufacturer's and the EGP's analysis is the interpretation of the Overall Survival benefit based on the selection of either the Primary or Updated Analysis.

The EGP argues that because the KM curves cross at 18 months, the incremental QALY reduces from 0.189 to 0.069 increasing the ICER to $272,275. If 24 months were used as a cut-off, the 0.189 QALY reduced to 0.086 yielding a cost/ QALY of $223,840. This is substantially different from the Sponsor's claim of $114,083.

The EGP modeling is based on the primary analysis which captures only 55% of deaths available at the time, as stated in the Initial Clinical Guidance Report from pCODR, a median follow-up of 14 months (Page 33). This approach disregards the Updated Analysis which is more appropriate as it includes more mature data with 77% of deaths and a median follow-up of 24 months.

As specified on page 34-35 of the Initial Clinical Guidance Report, the survival benefit of eribulin vs TPC in this mature updated analysis yields the same hazard ration as the primary analysis with an even stronger p value and clearly separated KM survival curves out to 35 months as presented in the diagram below and is shown in Figure 4 of the CGR on page 35.

Figure 4. Kaplan-Meier survival curves for updated OS analysis of EMBRACE.[1]



Notes: CI=confidence interval; TPC=treatment of physician's choice.
Source: Cortes et al[1]

The updated analysis provides sufficient data to accurately estimate the survival benefit of eribulin following 18 and 24 months, and supports the survival benefit attributed to eribulin in the model submitted by the manufacturer. We therefore believe that the cost/QALY is closer to that presented by the

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manufacturer.		
Page 32 & 33, CGR	**6.3.2.2 Detailed Outcome Data and Summary of Outcomes**	**Pg 32: paragraph 2 Figure 2: Title**
Comments and Suggested Changes to Improve Clarity The primary analysis was mis-labeled on both page 32 and in Figure 2 as the final analysis. However the final analysis was referred to in Figure 4 (page 35) when 75% of deaths had occurred.		
Page 8 EGR	**Description of Model Inputs in Submitted Model**	**Final row – Cost of Adverse Events**
Comments and Suggested Changes to Improve Clarity The decision was made not to use OCCI data due to the inherited heterogeneity of the data (i.e. OCCI data reports on all breast cancer patients and cannot distinguish between the stages of breast cancer progression). In addition, there was uncertain association between toxicities and primary cancer indication. For these reasons the decision was made to use costing information from peer reviewed journal articles.		
Page 21, CGR	**5. Summary of PAG Input**	**Section 5.5 Paragraph 3**
Comments and Suggested Changes to Improve Clarity Access to Halaven by Canadian patients between NOC and Provincial listing is being ensured through the Expanded Access Study CUP 398 in Canada as well as through an Assistance program which explores funding alternatives for patients. In CUP 398, physicians get experience with Halaven in 8 major Cancer Centers across Canada covering 5 Provinces and have treated 42 patients. In the Assistance program, 6 patients in 3 provinces have received Halaven to date.		

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) in the submission or as additional information during the review.

Page Number	Section Title	Paragraph, Line Number	Additional Comments
NA	NA	NA	No additional comments were received.

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About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts

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and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

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