Cost Effectiveness of Eribulin (Halaven®) for the Treatment of Patients with Locally Advanced Breast Cancer or Metastatic Breast Cancer who have Progressed after at Least Two Chemotherapeutic Regimens for Advanced Disease

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1. Eribulin (Halaven®) is a first-in-class chemotherapy treatment belonging to the halichondrin class of drugs. It is licensed as monotherapy for the treatment of patients with locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane (unless patients were not suitable for these).

2. EMBRACE was a phase III open-label, multicentre randomised controlled trial (RCT) in which women with locally recurrent or MBC (who had received between two to five prior chemotherapy regimens, including an anthracycline and a taxane, unless contraindicated) were randomised to eribulin (n=508) or Treatment of Physician Choice (TPC) (n=254). TPC was defined as any single-agent chemotherapy or hormonal or biological treatment approved for the treatment of cancer and to be administered according to local practice, radiotherapy, or symptomatic treatment alone. No TPC patient received supportive care alone; 96% received chemotherapy (most often vinorelbine, gemcitabine, or capecitabine).

   The primary endpoint was overall survival (OS) in the intention-to-treat population, performed when 55% of patients had died. Median OS was 13.1 months for eribulin and 10.6 months for TPC, p=0.04 (hazard ratio (HR) 0.81; 95% CI 0.66, 0.99). In an updated analysis (performed when 77% of patients had died) median OS was 13.2 months and 10.5 months for eribulin and TPC respectively (HR 0.805; 95%CI 0.67, 0.96). Median progression free survival (PFS) was 3.7 months for eribulin vs. 2.3 months for TPC, p=0.09 (HR 0.85; 95% CI 0.70, 1.03). The objective response rate was 12% (0.4% complete response; 11.5% partial response) for eribulin and 5% (0 complete response; 5% partial response) for TPC, p=0.005.

   Grade 3/4 neutropenia occurred in 45% and 21% of eribulin and TPC patients respectively. Febrile neutropenia occurred in 4.6% vs. 1.6% of patients. The most common adverse event leading to treatment discontinuation in the eribulin group was peripheral neuropathy (4.8%) [1].

3. In September 2012, Eisai Ltd submitted a comprehensive semi-Markov state transition model (Version 10.1) to the National Centre of Pharmacoeconomics. A Q-TWiST economic model was also submitted in October 2012. Eribulin was compared with the three individual chemotherapy agents, capecitabine, vinorelbine and gemcitabine. Comparison was also made with TPC.

4. The Markov model evaluates the cost effectiveness of eribulin in a hypothetical cohort of patients with LABC/MBC. Efficacy and safety data are based directly from EMBRACE [1]. Transitions between three health states 'Treated', 'Progressive' and 'Dead' are governed by probabilities of disease progression and death derived from EMBRACE [1]. The 'Treated' health state captures both 'Stable' and 'Responder' health states. The model cycle length is 21 days. Costs and benefits (beyond Year 1) were discounted at 4.0% per annum in line with current guidelines in Ireland [2]. The review team believe that the model structure is appropriate.

   For both OS and PFS, parametric functions were fitted to the trial event rates to extrapolate beyond the EMBRACE cut-off date to a lifetime horizon. A lower OS estimate (undiscounted OS increase 2.78 months) was generated by extrapolation from the ends of the Kaplan Meier curves using an exponential curve (hybrid method). An upper OS estimate (undiscounted OS increase 4.47 months) was obtained by parameterisation of both arms of the trial.

   When it is assumed that wastage will be destroyed, the incremental cost-effectiveness ratios (ICERs) for eribulin vs. TPC are estimated to be €76,610/QALY and €39,271/LYG. There is a zero probability that eribulin will be cost effective (compared to TPC) at €45,000/QALY. The associated 10 year PEVPI (at €45,000/QALY) is about €2.24 million.

   As compared to the three individual chemotherapeutic agents the ICERs range from €28,467 (vs. oral vinorelbine) to €67,129 (vs. capecitabine). Probabilities of cost effectiveness are 0.2% (vs. capecitabine), 3.6% (vs. gemcitabine) and 41% (vs. vinorelbine) at the €40,000/QALY threshold. The model results are sensitive to a number of univariate parameter changes.

5. We believe that the true cost effectiveness of eribulin compared to the three individual comparators (as evaluated by the Markov model) is uncertain. For these analyses, the TPC efficacy data is used to inform the effectiveness of the comparator arm in the model. Further, it is assumed that wastage is not destroyed. It is assumed that the OS increase (eribulin vs. TPC) is 4.47 months (the upper estimate). This OS increase is estimated from the EMBRACE Kaplan-Meier plot which will be unreliable toward the end of the study since only small numbers of cases remain alive and uncensored toward the end. Further uncertainty is introduced through the use of literature derived utility estimates and the use of English NHS Reference Cost Data and the zero costing of a number of adverse events. The numbers of patients in EMBRACE on the three comparators were small; capecitabine (n=44), vinorelbine (n=62) and gemcitabine (n=46) [1] introducing further uncertainty surrounding the estimates of cost effectiveness.

6. The NCPE also accepted the 'Quality-adjusted, Time Without Symptoms and Toxicity' (Q-TWiST) economic evaluation model. For this model, estimates of duration of treatment and the mean duration of time with adverse events were extracted directly from EMBRACE [1] for both arms. In the Markov, adverse events were associated with utility decrements for the 21 day model cycle in which they occurred. We believe that the Q-TWiST model more accurately reflects the consequences associated with adverse events. Evidence was also presented which indicates that the OS estimates here are reasonable. This analysis assumes that wasted drug is destroyed. Costs and outcomes occurring beyond Year 1 were discounted at 4.0%. The review team consider the structure of the Q-TWiST to be appropriate.

   When eribulin was compared to each of the three individual chemotherapy agents the ICERs increased to the range of €47,706 (vs. oral vinorelbine) to €68,337 (vs. capecitabine). This model indicates that there was over a 70% probability that eribulin was cost effective as compared to each of the individual agents at €45,000/QALY. While, this model generates estimates of the ICER of eribulin which are at the higher range, it is believed that there is more certainty that these estimates are sound.

7. The Budget Impact (BI) model is informed by the Q-TWiST model. It assumes that wastage is destroyed. When it is assumed that the displaced medicines consist of vinorelbine (80%) and capecitabine (20%) the 5 year cumulative gross BI (eribulin and supportive medicine costs only) would be about €5.40 million. The 5 year cumulative net BI would be about €2.05 million.

8. At the current price, we do not believe that eribulin is cost effective for the treatment of patients with LABC or MBC who have progressed after at least two chemotherapeutic regimens for advanced disease. In view of this we recommend a price reduction to ensure value for money for the Health Service Executive.

References

1. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat L, Petrakova K. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. The Lancet 2011;377(9769):914-23.
2. Guidelines for the Economic Evaluation of Health Technologies in Ireland 2010. Health Information and Quality Authority (HIQA). Cork and Dublin, Ireland. Available at URL: http://www.hiqa.ie/healthcare/health-technology-assessment/guidelines.