Cost-effectiveness analysis of exemestane compared with megestrol in advanced breast cancer: a model for Europe and Australia

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of exemestane (EXE, 25 mg/day) for the treatment of postmenopausal women with progressive advanced breast cancer after failure with tamoxifen.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised postmenopausal women with progressive advanced breast cancer that was unresponsive to tamoxifen therapy. More detailed inclusion and exclusion criteria were reported in the original study.

Setting
The setting was a hospital. The economic studies were carried out in Australia, Belgium, France, Germany, Italy, the Netherlands, Spain and the UK.

Dates to which data relate
The effectiveness and resource use data were derived from a study published in 2000, which referred to the time period October 1995 to May 1998. The price year used for the costs was 1999.

Source of effectiveness data
The effectiveness data were derived from a single study that was published by authors different from those of the present study. Assumptions were also made and then used in the model.

Link between effectiveness and cost data
The costing was performed retrospectively on a sample of patients different from those included in the effectiveness study.

Study sample
Power calculations performed in the preliminary phase of the study showed that a sample of 750 patients was required to demonstrate an equivalence in the main outcome measure with a power of 80%. The method of sample selection was not reported. A total sample of 769 eligible women was included in the study. There were 366 patients in the EXE group with a median age of 65 years (range: 35 - 89). The women were 15 years from menopause. There were 403
patients in the MEG group with a median age of 65 years (range: 30 - 91). The women were 17 years from menopause. No patient was excluded from the initial sample.

**Study design**
This was a phase III, randomised, double-blind parallel-group trial, which was carried out in 144 centres in 19 countries. The patients were randomised to receive either EXE or MEG using a double-dummy technique and matching placebo tablets. Randomisation was performed within each country on the basis of a minimisation procedure, which balanced the treatment groups according to a number of stratification factors. The stratification factors were prior response to tamoxifen, prior chemotherapy, and sites of metastases. The median duration of follow-up was 48.9 weeks (minimum follow-up: 16 weeks). The loss to follow-up was not reported. The trial was double-blinded, but details of the blinding method were not reported.

**Analysis of effectiveness**
The basis of the clinical analysis was intention to treat. Several health outcomes were assessed in the original study. However, for the purpose of the present analysis, only survival time will be reported. The authors stated that the patients' characteristics in the two treatment groups were comparable in terms of the demographics and clinical conditions (see Other Publications of Related Interest).

**Effectiveness results**
The median survival time was significantly longer with EXE (median not reached) than with MEG (123.4 weeks), (p=0.039). The effectiveness analysis also showed that both drugs were well tolerated and, compared with the MEG group, the overall objective response rates, median duration of overall success, time to tumour progression, and time to treatment failure were significantly longer in the EXE group (see Other Publications of Related Interest).

**Clinical conclusions**
The effectiveness analysis showed that the treatment with EXE was effective in improving overall survival time more than the MEG-based therapy.

**Modelling**
An analytic model was used to extrapolate the expected costs and benefits of the two treatments on the basis of the survival data derived from the single study. It was also used to calculate the country-specific costs. Two different time horizons were considered in the model. These were the trial period (3 years) and the moment when all the patients had died. The latter frame was calculated assuming that, for the time period following the clinical trial, the cohort was reduced by 0.0003 daily. This was equal to the number of deaths observed on the final day on the clinical trial for the MEG group.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions, which were used in the decision model.

**Estimates of effectiveness and key assumptions**
The main assumption was that both treatment groups had the same rate of survival after about 3 years. It was also assumed that patients would receive the same daily dosage as reported in the clinical trial. The previous assumptions concerning drug usage and survival remained the same, regardless of which country was considered in the decision model.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the number of life-years gained (LYG) with the interventions. A
3% discount rate was used. The survival rates and survival days in the two simulation models were reported.

**Direct costs**
A 3% discount rate was used since the time horizon of the study was longer than 2 years. The unit costs were not reported separately from the quantities of resources. The health care services included in the economic evaluation were for the study drugs and treatments related to breast cancer, such as in- and out-patient visits, procedures (surgery and radiotherapy), diagnostic tests and concomitant medications. The costs of palliative therapy were also included in the analysis. The cost/resource boundary adopted was that of the third-party payer. The quantities were estimated using actual data derived from the clinical trial. The costs (other than those of the study drugs) were estimated from an unpublished retrospective observational study involving 75 patients in each country. The costs of the study drugs were mainly taken from retail prices, and assumptions were made when these prices were unavailable. The authors noted that patients in the observational study differed from those in the clinical trial in terms of their age and the proportion of bone metastases. The price year was 1999.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
Euros.

**Sensitivity analysis**
Three groups of sensitivity analyses were conducted. First, the cost-effectiveness ratio was calculated using only the costs of medications to assess the contribution of the cost of the study drugs. Second, the costs of other treatments were varied within the 95% confidence intervals. Third, the impact of different discount rates, 6% for costs and 1.5% for benefits in UK data and 4% for both in Dutch data, was used.

**Estimated benefits used in the economic analysis**
In the 1,080-day (3-year) model, the survival rate (independently from the country) was 51.40% in the EXE group and 42.13% in the MEG group. The difference was 9.27%. The mean survival was 758.5 days in the EXE group and 696.3 days in the MEG group, with a difference of 62.2 days.

In the model based on patients’ remaining lifespan, mean survival was 1,102.8 days in the EXE group and 929.3 days in the MEG group. The difference was 173.5 days.

**Cost results**
In the 1,080-day model, the total costs were:

- euro 15,850 in the EXE group and euro 13,946 in the MEG group (difference: euro 1,903) in Australia;
- euro 5,378 in the EXE group and euro 1,178 in the MEG group (difference: euro 6,911) in Belgium;
- euro 9,578 in the EXE group and euro 8,391 in the MEG group (difference: euro 1,187) in France;
- euro 11,935 in the EXE group and euro 11,705 in the MEG group (difference: euro 230) in Germany;
- euro 13,578 in the EXE group and euro 11,766 in the MEG group (difference: euro 1,812) in Italy;
euro 15,843 in the EXE group and euro 13,624 in the MEG group (difference: euro 2,219) in The Netherlands; euro 6,731 in the EXE group and euro 5,400 in the MEG group (difference: euro 1,330) in Spain; and euro 16,366 in the EXE group and euro 14,359 in the MEG group (difference: euro 2,007) in the UK.

In the model based on patients’ remaining lifespan, the total costs were:
euro 22,622 in the EXE group and euro 18,528 in the MEG group (difference: euro 4,093) in Australia; euro 9,069 in the EXE group and euro 7,079 in the MEG group (difference: euro 1,990) in Belgium, euro 13,503 in the EXE group and euro 11,047 in the MEG group (difference: euro 2,465) in France; euro 16,663 in the EXE group and euro 14,904 in the MEG group (difference: euro 1,759) in Germany; euro 19,134 in the EXE group and euro 15,524 in the MEG group (difference: euro 3,609) in Italy, euro 22,350 in the EXE group and euro 18,027 in the MEG group (difference: euro 4,321) in The Netherlands; euro 9,193 in the EXE group and euro 7,066 in the MEG group (difference: euro 2,126) in Spain; and euro 23,293 in the EXE group and euro 19,047 in the MEG group (difference: euro 4,246) in UK.

Synthesis of costs and benefits
An incremental cost-effectiveness analysis was conducted to combine the costs and benefits of the interventions.

In the 1,080-day model, the cost per LYG with EXE over MEG was euro 11,169 in Australia, euro 6,911 in Belgium, euro 6,966 in France, euro 1,353 in Germany, euro 10,638 in Italy, euro 13,016 in The Netherlands, euro 7,806 in Spain, and euro 11,733 in the UK.

The authors stated that in the model with a life-long time horizon, the cost per LYG ranged from euro 3,700 in Germany to euro 9,091 in The Netherlands.

The sensitivity analyses showed the robustness of the estimated cost-effectiveness ratios.

Authors’ conclusions
The exemestane (EXE)-based treatment for postmenopausal women with advanced breast cancer that was unresponsive to tamoxifen therapy was cost-effective in comparison with megestrol (MEG), as it presented a cost per life-year gained (LYG) ranging from euro 3,700 to euro 9,000.

CRD COMMENTARY - Selection of comparators
The authors did not explicitly justify their choice of the comparator, but, at the time of the trial, MEG was a standard second-line treatment for women with advanced breast cancer and results of a recent trial were used. You should decide whether it represents a widely used therapy in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness estimate used a phase III, randomised, double-blind controlled trial, which was appropriate for the study question. The internal validity of the analysis was enhanced by the performance of power calculations, and also by the use of the intention to treat principle as the basis for the analysis of the clinical study. The study groups were shown to be comparable at baseline and the potential impact of confounding factors was assessed. The study sample also appears to have been representative of the study population. However, extrapolation beyond the study period required...
further assumptions for survival, which were not tested in the sensitivity analysis.

**Validity of estimate of measure of benefit**
The LYG represents a widely used benefit measure for studies involving patients with cancer. It was calculated by extrapolating survival data from the clinical trial and making some assumptions. The authors discussed the difficulties in including quality of life weights in their analysis and the lack of quality-adjusted survival as a benefit measure.

**Validity of estimate of costs**
All the categories of costs relevant to the perspective adopted in the study were included in the analysis. The source of the cost data was reported and appropriate discounting was performed. The price year was given, thus facilitating reflation exercises to other settings. Also, several sensitivity analyses were performed on the cost variables and the costs were presented by country. However, the unit costs were not reported separately from the quantities of resources, thus reducing transparency. The authors discussed the implications of adopting a societal perspective and the consequent inclusion of indirect costs, as well as the potential inclusion of the costs of adverse events. Finally, data on the costs and resource use were derived from two different sources, which might not have been comparable.

**Other issues**
The authors compared their findings with those from other studies. The issue of the generalisability of the study results to other settings was addressed in that some sensitivity analyses were performed and costing by country was used. The analysis referred to postmenopausal women with advanced breast cancer and this was reflected in the conclusions of the study. The authors could have presented more of the costing data to increase transparency.

**Implications of the study**
The main implication of the study was that the EXE treatment for postmenopausal women with advanced breast cancer that was unresponsive to tamoxifen therapy proved to be a cost-effective intervention compared with MEG. Whether it is cost-effective will depend on the opportunity cost, that is, the loss of benefit (in terms of LYG or quality-adjusted life years) caused by displacing any treatment(s) in order to fund the EXE treatment.

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**Other publications of related interest**

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