CONFIDENTIAL

Gemcitabine for treatment of metastatic breast cancer

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), evidence review group (ERG) report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

Abbreviations

BPI	Brief Pain Inventory
CI	confidence interval
ERG	evidence review group
HR	hazard ratio
ITT	intention to treat
MBC	metastatic breast cancer
MS	manufacturer's submission
OS	overall survival
PFS	progression-free-survival
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
RSCL	Rotterdam Symptom Checklist
TtDPD	time to documented progression of disease

Licensed indication

Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neo-adjuvant chemotherapy. Prior chemotherapy should have included anthracyclines, unless clinically contraindicated.

Key issues for consideration

Decision problem/scope

- What is/are the most appropriate comparator/s for the gemcitabine–paclitaxel combination?

Clinical effectiveness

- Is there sufficiently robust direct and/or indirect clinical trial evidence on the effectiveness of gemcitabine in combination with paclitaxel when compared with all relevant UK comparators?

Cost effectiveness

- Is the indirect comparisons method adopted by the manufacturer to generate input data for the economic model valid?
- Are the trials from which data for the indirect comparisons and economic analysis were pooled comparable?
- What is the impact and relevance of (discounted) generic pricing of paclitaxel on the cost effectiveness of gemcitabine plus paclitaxel?
- What are the implications of uncertainties in cost-effectiveness evidence on gemcitabine plus paclitaxel versus relevant UK comparators?

1 Decision problem

1.1 Decision problem approach in the MS

Population	Patients who have relapsed and developed MBC following anthracycline-based, adjuvant or neo-adjuvant chemotherapy or non-anthracycline-based chemotherapy where anthracyclines are contraindicated. Patients should be younger and fitter, deemed suitable for taxane-based regimens and require higher efficacy than can be achieved with monotherapy.
Intervention	Gemcitabine in combination with paclitaxel. Gemcitabine in combination with docetaxel is considered in the economic analysis.
Comparators	Taxane-based chemotherapies: • docetaxel • paclitaxel • docetaxel in combination with capecitabine
Outcomes	Primary outcome: overall survival. Secondary outcomes: TtDPD, PFS, overall response rate, pain and analgesic use, quality of life, and incidence of adverse events.

1.2 ERG comments on the MS

1.2.1 **Decision problem**: decision problem appears to be a clear, concise, and accurate overview of the disease condition.

1.2.2 **Overview of current service provision**: the manufacturer provides a concise and accurate description of current treatment options for MBC: taxanes are indicated for first-line treatment of MBC in women who have been pre-treated with anthracycline-based regimens.

1.2.3 **Population**: the population defined in the MS reasonably reflects the people receiving first-line treatment for MBC in the UK. The MS states that patients in the JHQG trial do not reflect the entire population of women with metastatic breast cancer in the UK, because they are relatively younger (mean age 53.3 years), have better performance status, and have visceral-dominant metastatic disease and a more

aggressive tumour burden. However, they do represent the MBC patient group that will be deemed fit to receive combination chemotherapy following relapse from adjuvant anthracycline treatment. There is no information about whether patients in the JHQG trial were assessed for HER2-positive status.

1.2.4 **Intervention**: gemcitabine in combination with paclitaxel will be limited to first-line therapy because of its combination with a taxane-based regimen. This is the interpretation of the marketing authorisation by the manufacturer. However, single-agent gemcitabine might be used in later lines of therapy for patients who had already received a taxane-based regimen as first-line therapy or when other treatments have been unsuccessful.

1.2.5 **Comparators**: the comparator treatments considered are valid for first-line therapy. The exclusion of vinorelbine and capecitabine by the manufacturer reflects NICE guidance, but considering paragraph 1.2.4 there could be some value in comparing the gemcitabine–paclitaxel combination with second-line therapies. Exclusion of trastuzumab as a comparator for gemcitabine is justified because it is reserved for HER2-positive breast cancers.

1.2.6 **Outcomes**: the outcomes measures considered are appropriate, valid and clinically meaningful.

1.3 Clinical specialists' and patient experts' statements

1.3.1 There is no consensus among clinicians about the current best practice. Current alternative treatments to gemcitabine plus paclitaxel are taxane-based regimens (docetaxel, paclitaxel and docetaxel in combination with capecitabine). Most clinicians use docetaxel 75–100 mg/m^2 for most patients and weekly paclitaxel for patients who are unfit, elderly and frail.

1.3.2 The gemcitabine–paclitaxel combination is likely to be used for patients in whom a higher response is required, such as patients with visceral metastases and where in the absence of response, other

chemotherapies are precluded (for example, patients in whom docetaxel–capecitabine combination therapy is considered but rejected because of its toxicity).

1.3.3 Docetaxel plus capecitabine, in particular, is reserved for patients with good performance status and life-threatening disease and who are 'triple-negative' (that is, oestrogen-, progesterone- and HER-2-negative). Gemcitabine plus paclitaxel is most likely to be considered as an alternative to docetaxel plus capecitabine and limited to first-line treatment of MBC in patients with good performance status and organ function.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the MS

2.1.1 The table below shows the key features and main results of the randomised controlled trial (RCT) discussed in the MS.

Summary of results from the JHQG trial

Outcome measures	**Gemcitabine + paclitaxel**	**Paclitaxel**	**P value**
Median overall survival, months (95% CI)	18.6 (16.6 to 20.7)	15.8 (14.4 to 17.4)	P = 0.0489
Hazard ratio (95% CI)	0.817 (0.67-1.00)		P = 0.0495
Patients censored, n (%)	84 (31.6)	68 (25.9)	
Sample size, n	266	263	
Median TtDPD, months (95% CI)	5.4 (4.61-6.1)	3.5 (2.9-4.0)	P=0.0013
Hazard ratio (95% CI)	0.73(0.607-0.889)		P=0.0015
Patients censored, n (%)	60 (22.5)	45 (17.2)	
Sample size, n	267	262	

See pages 48 and 49 of the MS

2.2 ERG comments

2.2.1 **Availability of evidence**: the MS reports only one, yet to be published, RCT (JHQG) comparing gemcitabine plus paclitaxel with paclitaxel in patients pretreated with neo-adjuvant or adjuvant anthracycline-based chemotherapy, or with non-anthracycline-based chemotherapy where anthracyclines are clinically contraindicated. Systematic review of the literature was carried out, though it was not clearly reported. No meta-analysis was presented in MS.

It appears the manufacturer has applied quality assessment criteria to the JHQG trial. ERG could not confirm the assessments carried out by the manufacturer since the JHQG trial is published only in abstract form. No quality assessments were applied to other studies identified. From the ERG's own assessment, these studies were of reasonable methodological quality. The 'open label' design of the JHQG trial means some outcomes, such as tumour responses, may be biased.

2.2.2 **Effectiveness**: the MS probably contains an unbiased estimate of the effectiveness of gemcitabine plus paclitaxel when compared with paclitaxel within the stated scope of the decision problem. Trial data suggest gemcitabine plus paclitaxel provides an appreciable increase in median overall survival of 3 months compared with paclitaxel, although this is of borderline statistical significance. Overall survival of gemcitabine plus paclitaxel may have been diluted by crossovers because some patients in the paclitaxel arm received gemcitabine (regimens or single agent) as a subsequent line of therapy after the initial trial follow-up period had been completed. There was a four-fold greater use of gemcitabine in the paclitaxel arm during post-study treatment. The absolute number of patients in the paclitaxel arm who subsequently received gemcitabine has not been reported.

2.2.3 **Quality of life**: the MS states statistically significant difference between gemcitabine plus paclitaxel and paclitaxel on overall evaluation of improvement in quality of life from baseline at treatment cycles 5 and 6

using the RSCL. Using the BPI, patients who were symptomatic for pain at baseline had statistically significantly better pain alleviation in the gemcitabine plus paclitaxel arm than the paclitaxel arm at cycles 4 and 5. There were no other statistically significant differences between gemcitabine plus paclitaxel and paclitaxel on these scales.

2.2.4 **Comparisons with other licensed treatments**: there are no formal direct or indirect comparisons to estimate the relative efficacy of gemcitabine plus paclitaxel against alternative licensed treatments other than paclitaxel in the clinical effectiveness section of the MS. Indirect comparisons were only performed to inform the economic analyses.

The MS does not contain sufficiently robust evidence on the relative effectiveness of gemcitabine plus paclitaxel in comparison with docetaxel monotherapy or docetaxel plus capecitabine combination therapy. When available, a head-to-head RCT of gemcitabine plus paclitaxel versus docetaxel will provide direct evidence on clinical effectiveness relevant to the UK setting.

2.3 Clinical specialists' and patient experts' statements

2.3.1 The JHQG trial data suggest patients had less pain and reduced analgesic use when treated with gemcitabine plus paclitaxel than with paclitaxel alone. The clinical trial efficacy data accurately reflects 'real life' and UK treatment conditions, particularly on the use of anthracyclines and not taxanes in adjuvant settings.

2.3.2 The combination of gemcitabine plus paclitaxel has been shown to have efficacy similar to that of docetaxel plus capecitabine, but to have a better toxicity profile. In terms of side effects, the overall toxicity of gemcitabine plus paclitaxel compares with other chemotherapeutic agents used in clinical practice. Excess haematological toxicities associated with gemcitabine plus paclitaxel are manageable with very little additional non-haematological toxicities. A patient's response to

gemcitabine plus paclitaxel should be assessed at least every 3 treatment cycles from a baseline at the start of treatment.

2.3.3 Gemcitabine will increase treatment options for women with MBC. Single-agent gemcitabine is not available in the NHS but it is an option for privately treated patients. Gemcitabine is administered intravenously and this presents an inconvenience of use and costs for the patient (such as travelling to hospital and parking costs). Oral preparations may be more appropriate. However, most patients are willing to accept any inconveniences associated with gemcitabine use to access treatment that may benefit them.

3 Cost effectiveness evidence

3.1 Cost effectiveness in the MS

3.1.1 The table below shows the key features and main results of the economic evaluation presented in the MS.

Summary of results of economic evaluation in the MS

Analyses	Difference in mean discounted outcomes	Difference in mean discounted total costs	Incremental cost effectiveness ratios (cost per life year or QALY)
Base case – docetaxel as comparator			
Base case analysis	Life years 0.43 QALYs 0.23	£ 4,013	Life years £ 9,253 QALYs £ 17,168
Threshold analysis - overall survival with docetaxel increased			
Overall survival with docetaxel increased from 59.4 to 63 weeks	Life years 0.37 QALYs 0.20	£ 4,089	Life years £ 11,185 QALYs £ 20,073
Overall survival with docetaxel increased from 59.4 to 70 weeks	Life years 0.23 QALYs 0.14	£ 4,261	Life years £ 18,658 QALYs £ 29,742
Scenario analysis – post-patent expiration price reduction for paclitaxel			
Generic paclitaxel cost in base case analysis	Life years 0.43 QALYs 0.23	£ 1,109	Life years £ 2,556 QALYs £ 4,742
Scenario analysis – alternative reference case			
Paclitaxel as comparator	Life years 0.25 QALYs 0.15	£ 4,498	Life years £ 17,924 QALYs £ 30,096
Docetaxel/capecitabine as comparator	Life years 0.31 QALYs 0.20	£ 4,521	Life years £ 14,484 QALYs £ 23,152

See pages 134-146 of the MS

3.2 ERG comments

3.2.1 The MS contains a series of economic analyses comparing gemcitabine plus paclitaxel; gemcitabine plus docetaxel; paclitaxel; docetaxel; and docetaxel plus capecitabine against the reference comparators listed in section 1.1. The analyses are based on a Markov state transition model with an appropriate time horizon of 3 years. Inclusion of gemcitabine plus docetaxel, however, does not reflect the manufacturer's statements on relevant licensed comparators in section 1.4, page 21 of the MS. The model structure is reasonable and based on previous economic evaluations. The key assumptions adopted are the same as in previous economic studies (see pages 35–36 of the ERG report for a critical appraisal checklist for the economic evaluation in the MS).

3.2.2 Clinical effectiveness data used in the model were taken from 15 studies that included those rejected at the systematic review stage for clinical effectiveness. The studies have not been assessed for quality nor have the trial populations been assessed for comparability. The patient populations described in these studies differed in prior therapy, metastatic disease stage and lines of chemotherapy. Some trials had incomplete datasets and methodological inadequacies. In other studies, patients received treatments that were not randomly allocated. The model's input data may potentially have been affected by selection bias.

3.2.3 Validation of the economic model showed a reasonable fit with survival curves from the JHQG trial. The model, however, appears to underestimate by 30% treatment effects of gemcitabine plus paclitaxel compared with paclitaxel. Whether this affects comparisons of gemcitabine plus paclitaxel with other taxane-based regimens will depend on the observed survival curves from trials.

3.2.4 The MS adopts indirect comparisons to compute efficacy data because of the lack of direct head-to-head comparisons between gemcitabine plus paclitaxel and the other comparators. The method used in the MS pooled absolute efficacy estimates of treatments from relevant arms of different trials as if the data are from a single trial. The ERG states that this 'method of indirect comparisons may be best described as naïve' when viewed in the context of an NHS R&D HTA methodological review of indirect comparisons.

3.2.5 The 'naïve' approach adopted means a breakdown of the benefits of randomisation and fails to account for the fact that RCTs are designed to estimate relative treatment effects. In addition, there was no assessment of the heterogeneity (comparability) between trials. Results of the 'naïve' indirect comparisons that show greater survival advantage with paclitaxel than docetaxel contradict results from a head-to-head trial comparing docetaxel with paclitaxel. This in turn

biases efficacy estimates in favour of gemcitabine plus paclitaxel when compared with docetaxel.

3.2.6 The ERG carried out an adjusted indirect comparison without formal tests for heterogeneity between trials and using relative treatment effects to provide an indirect estimate of OS for docetaxel. Relative treatment effects were computed as ratios of median OS from trials reported in the MS (this computation was not reported in the ERG report). The incremental cost effectiveness ratio (ICER) for gemcitabine plus paclitaxel versus docetaxel using this estimate was £45,811 per QALY. The ERG's illustrative analysis provided estimates of the survival benefits of docetaxel over paclitaxel close to that in a head-to-head trial of docetaxel versus paclitaxel (see table 11 in the ERG report).

3.2.7 The MS uses one-way sensitivity analysis; threshold/scenario analyses and PSA to investigate the impact of uncertainty in parameters on the results of the economic model (see pages 49–60 of ERG report). One-way sensitivity analysis was carried out on a selective set of parameters, the majority of which are related to resource utilisation and costs. In contrast, the PSA mostly uses parameters related to efficacy data. In both cases, no rationale is given for the selection of parameters. Sensitivity analyses carried out in the MS are limited and selective and there maybe greater variation in cost effectiveness than presented.

3.2.8 In the entire manufacturer's economic analyses comparing gemcitabine plus paclitaxel against docetaxel deterministic ICER estimates ranged from £13,000 to £21,000 per QALY gained. The ERG carried out its own one-way sensitivity analysis and found that the costs of paclitaxel and the OS for gemcitabine plus paclitaxel were the most influential drivers of cost effectiveness (see table 9 in the ERG report). Replacing the pooled estimates for OS, TtDPD and tumour response with values observed from the JHQG trial, the ICER for gemcitabine plus paclitaxel

versus paclitaxel increases from a base case of £30,096 to £42,830 per QALY.

3.2.9 The ERG re-ran the PSA to demonstrate the impact of using direct data from the JHQG trial instead of the pooled estimates from the manufacturer's indirect comparisons. The manufacturer's pooled estimates resulted in a higher probability of gemcitabine plus paclitaxel being cost effective.

3.2.10 Since all the current taxane-based regimens (docetaxel, docetaxel plus capecitabine, paclitaxel) are licensed alternative treatments to gemcitabine plus paclitaxel, the ERG performed a frontier analysis to compare gemcitabine plus paclitaxel, docetaxel, docetaxel plus capecitabine and paclitaxel simultaneously, as an alternative to the pair-wise comparisons of the interventions against docetaxel as presented in the MS.

3.2.11 Based on the manufacturer's pooled estimates, the frontier analysis showed great uncertainty over which treatment is cost effective. Gemcitabine plus paclitaxel has the lowest probability of being cost effective below a threshold of £30,000 per QALY, but has the highest probability of being cost effective above £30,000 per QALY. None of the technologies compared had probabilities beyond 50% of being cost effective, even at higher cost effectiveness thresholds (see figure 4, pages 57–58 of ERG report).

3.2.12 The frontier analysis, however, has to be interpreted with caution given concerns about the uncertainty in efficacy data derived from the 'naïve' indirect comparisons and the fact that using the manufacturer's pooled estimates inflates the likelihood of gemcitabine plus paclitaxel being cost effective.

3.2.13 The ERG's review of the cost effectiveness evidence suggests the methodologies used to derive data for the economic analysis does not provide a robust demonstration of the cost-effectiveness of gemcitabine plus paclitaxel when compared with either docetaxel or paclitaxel.

4 Authors

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