NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Gemcitabine for the treatment of metastatic breast cancer

Response to consultee, commentator and public comments on the ACD

Consultee and Commentator response to the ACD

Consultee or Commentator	Comment	Institute Response
Eli Lilly	**1. Validity of the methods employed, and results produced from the economic evaluation in the Lilly submission** The Eli Lilly submission to NICE used phase III RCT evidence on efficacy obtained from a complete systematic review of the literature (further supported by data provided in confidence) and a review of published economic evaluations in MBC, to inform the design of its economic evaluation. The pivotal phase III RCT (JHQG) provided an unbiased estimate of the treatment effect of GT compared to paclitaxel (T), finding that GT improved overall survival, tumour response and time to documented progression of disease, when compared to T monotherapy. A multi-state transitory Markov model, based on a prior model used by NICE (Cooper et al., 2003), was developed to perform the economic evaluation of GT compared to relevant comparator therapies in the metastatic setting. This model was enhanced using systematic review of the literature and incorporated the effect of treatment on overall survival, time to disease progression and importantly, the effect of a wide range of adverse events using utility values obtained from the largest and most comprehensive study performed to date in MBC performed in accordance with the NICE reference case (Narewaska et al., 2005). The utility study has since been accepted for publication in a peer reviewed journal. This is also the first economic evaluation in MBC to incorporate the impact of adverse events into the utility estimates used. Expert clinical opinion was sought throughout the evaluation to guide the design of the model, the underlying structural assumptions and the configuration of treatment algorithms used for both the administration of chemotherapy and treatment of serious adverse events. The model reflected all relevant costs and clinically meaningful outcomes associated with the disease and its treatment. As such, it scored very highly against common check-lists for economic evaluation methods and adhered to the framework for good practice in modelling proposed by Philips et al., (2004).	Noted. The Appraisal Committee carefully considered the manufacturer's model in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See Final Appraisal Determination (FAD) paragraphs 4.4-4.9.

Consultee or Commentator	Comment	Institute Response
Eli Lilly (continued)	*1.1 Unadjusted vs. Adjusted Indirect Comparison Methods* 1.1.1 There are many areas of health care where available clinical trials have not directly compared the specific treatments or regimens of interest. The submission to NICE on the use of GT for MBC is one such example. Here, the relative effectiveness of alternative interventions is compared using results from sets of studies making different treatment comparisons. However, it is not unusual that conclusions on relative efficacy end up based on indirect evidence (Glenny et al., 2005). 1.1.2 Prior to conducting the economic evaluation on the use of GT described in our submission, we consulted the recently published Health Technology Assessment (HTA) Report entitled '*Indirect comparisons of competing interventions*' (Glenny et al., 2005) for guidance on the most appropriate methodological approaches available to deal with the problem faced by Lilly of having no single common treatment linking one phase III RCT to another. Throughout the ERGR Glenny et al (2005) is the document that is referred to. The decision to perform an unadjusted indirect comparison of gemcitabine plus paclitaxel with the relevant comparator therapies was considered appropriate and completely justifiable by Lilly. What follows is a detailed explanation as to the grounds for conducting the unadjusted indirect comparison performed. 1.1.3 In an **adjusted indirect comparison**, the comparison of the interventions of interest is adjusted by the results of their direct comparison with a common control group, partially using the strength of the RCT. Adjusted indirect comparisons can only be performed where there is a common treatment that links one clinical trial to another, such as a placebo. Glenny et al., (2005) define an **unadjusted indirect comparison** as a "naïve comparison", which is the term given to an analysis where data are pooled across treatment arms. Our submission employs this latter form of indirect comparison by using the absolute values reported for both the single trial of gemcitabine / paclitaxel treatments and the identified RCTs reporting data for the comparators, because there is no common treatment that links one RCT to another to perform an adjusted indirect comparison. *Use of* "naïve comparisons" is described as 'naïve' in the ERGR report, which is, when presented with the formal definitions used by Glenny et al., (2005), an erroneous misuse of terminology. The erroneous use of this descriptor in the ACD creates a poor impression of the economic analysis provided by Lilly and we request this statement be placed in context or removed completely.	Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See FAD 4.5 and 4.6. Noted – see FAD 4.5. The indirect comparison described by Glenny et al. (2005) as "naïve" or "unadjusted" does not only ignore between trial variance. Most importantly, it breaks down the randomised structure of clinical trial and produces inconsistent estimates of treatment effects. In the case of the analyses presented in the manufacturer submission this is reflected in inconsistencies between the indirect estimates of median overall survival for docetaxel and paclitaxel from the manufacturer's indirect analysis and the results from the head to head trial of docetaxel and paclitaxel (Jones et al., 2005). The word naïve has not been used in the FAD.

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Eli Lilly (continued)	1.1.4 An unadjusted indirect comparison treats data as if they have come from a single trial and ignores the between-trial variance. To take the simplest case with no excess heterogeneity, SE^2 (θ) for a single trial of size n is σ^2. An unadjusted indirect comparison between k arms of treatment A and k arms of treatment B is equivalent to a single trial of size kn, so that SE^2 (θ) would be estimated as σ^2/k, which is half of the variance from the adjusted indirect comparisons by the method of Bucher et al., (1997).	Comment noted and as above under 1.1.3.
	1.1.5 There is no discussion within the ERGR of circumstances where the use of unadjusted indirect comparisons is appropriate. The HTA Report by Glenny et al., (2005) makes reference to at least eight published studies where similar problems have existed (i.e. the absence of a single common treatment that links one trial to another) yet have been successfully resolved using the same unadjusted indirect comparison performed by Lilly. These are referenced as follows: drugs used to treat menorrhagia [Coulter et al., 1997], second-line drugs in rheumatoid arthritis (Felson et al., 1990), efficacy of thromboprophylaxis following total hip replacement (Imperiale & Speroff, 1994), efficacy of therapeutic agents used in the treatment of lupus nephritis using outcomes of end-stage renal disease and total mortality (Bansal & Beto, 1997), antihypertensive agents to reduce left ventricular hypertrophy (Schmieder et al., 1996), anti-*Helicobacter* pylori regimens (Unge & Berstad, 1996), a meta analysis to evaluate the speed of healing and symptom relief in grade II-IV gastroesophageal reflux disease (Chiba et al., 1997) and finally, a review comparing the antihypertensive efficacy of available drugs in the angiotensin II antagonist (AIIA) class (Conlin et al., 2000).	Noted. See below under 1.1.7.
	1.1.6 We accept that it is not appropriate or advisable to perform an unadjusted indirect comparison where the opportunity exists to link trials via a single common comparator. Given the absence of such opportunity, every effort was made to explore alternative approaches. Prior to performing the unadjusted indirect comparison, the feasibility of undertaking an adjusted indirect comparison was considered. Figure 1 illustrates the treatment options under consideration in our submission and how through a chain they inter-relate to one another.	See under 1.1.7 below.

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Eli Lilly (continued)	1.1.7 As is evident from Figure 1, there is not a single common treatment that links one trial to another, but instead 4 phase III RCTs that can be linked via a chain. Performing an adjusted indirect comparison in this way biases the results, as trials are selected solely on the basis that they provide linkages to the chain, irrespective of any formal inclusion criteria or relevant baseline characteristics. Adjusted indirect comparisons work on the premise that included RCTs are demonstrably homogeneous. According to Naylor (1989) and modified by Sutton et al., (1998), specific factors that may cause heterogeneity are: 1.1.7.1) Differences in inclusion and exclusion criteria; 1.1.7.2) Variability in control or treatment interventions (e.g. doses, timing, and brand); 1.1.7.3) Broader variability in management (e.g. pharmacological co-interventions, responses to intermediate outcomes including crossovers and different settings for patient care); 1.1.7.4) Differences in outcome measures, such as follow-up times, use of cause-specific mortality, etc; 1.1.7.5) Variation in analysis, especially in handling withdrawals, drop-outs, and crossovers; and 1.1.7.6) Other pertinent differences in baseline states of available patients despite identical selection criteria.	The Committee considered that the indirect comparison method used in the manufacturer submission ignores the randomised structure of clinical trials. By pooling absolute data from single treatment arms of different trials, the method breaks down the benefits of randomisation and produces inconsistent estimates of treatment effects. Current recommended approaches to indirect comparisons and mixed treatment comparison make use of relative treatment effects from each RCT.
Eli Lilly (continued)	1.1.8 Points 1.1.7.2 to 1.1.7.5 were not considered cause for any concern since the descriptive data extracted on each of the included trials confirms that they are sufficiently comparable. Section 2 covers the rationale for including studies of anthracycline-naïve patients so addresses point 1.1.7.1. Given the absence of individual patient data for two of the key phase III RCTs (Jones et al., 2005; O'Shaughnessy et al., 2003) that form an integral part of this chain in Figure 1 to perform an adjusted indirect comparison, it was not possible to perform a meta-regression to investigate the extent of the heterogeneity between these two trials as far as point 1.1.7.6 is concerned (i.e. selection bias). Drs. Makris and Verill in their personal statements provided to NICE both make reference to the complexity of the disease in relation to evaluations of treatment. Even if selection bias was found not to exist between the trials included in the economic evaluation, there would still be a debate surrounding whether the trial populations reflect the heterogeneous MBC patient population.	The relevant RCTs presented in the manufacturer's submission represent a connected network. This allows a mixed treatment comparison to be performed that maintains randomisation subject to an assessment for heterogeneity. See FAD 4.5.

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Eli Lilly (continued)	1.1.9 In recognition of the absence of 1) a single common treatment comparator to link the trials; 2) the problem of heterogeneity with the disease *per se* (that is also reflected in the case-mix of patients included in RCTs of any treatments for MBC); 3) trials where patients receiving clearly delineated but different lines of therapy were included but where data for each were not reported separately, and 4) the inability to statistically test for heterogeneity because of both reason 1 and no access to patient-level data to undertake regression analyses, a decision was made to perform an unadjusted indirect comparison that allowed the inclusion of data from additional phase III RCTs that otherwise would have been excluded.	Noted. See FAD 4.5.
	1.1.10 The benefits of randomisation do not hold as greatly with this approach. However, contrary to suggestions made in the ERGR, it is not appropriate to use data from observational studies in the model. Moher et al., (1996) suggest the design features of trials which affect a trial's quality and can be assessed, can be split into four areas, namely assignment, masking, patient follow-up and statistical analysis. Assignment is the single most important design feature which is why the RCT methodology is considered the most reliable method on which to assess the efficacy of treatment (Cook et al., 1992). Sutton et al., (1998) in their HTA Review entitled '*Systematic review of trials and other studies*' advise that 'it is not helpful to include evidence where the risk of bias is high, even if there is no better evidence' (page 8). Observational studies have a greater susceptibility to bias than clinical trials since treatment allocation is left to a haphazard mixture. Similarly, ascertaining that differences observed between groups of patients (in observational studies) are due to the interventions is a far harder exercise than it is in experimental studies. For this reason, we stand by our decision to use the highest quality source of evidence from randomised controlled phase III clinical trials to inform their economic evaluation.	Noted. See FAD 4.5.
	1.1.11 Under section 4.6 of the ACD, Lilly note that the AC considered that the manufacturer's indirect estimates were inconsistent with published data (Jones et al., 2005). However, this clinical trial (also named TAX311) which started in 1994 is the only phase III open label study which directly compared docetaxel to paclitaxel within their licensed doses and represents only one trial arm of docetaxel in a pooled analysis of 8 robust phase III RCTs and therefore cannot be considered representative of docetaxel effectiveness on its own. The sample size of this study was powered for its primary endpoint, overall tumour response. However the results of TAX311 trial did not demonstrate a statistical difference for overall tumour response, therefore the trial failed to meet its primary endpoint. Secondary endpoints included overall survival and time to disease progression which were reported as being statistically different.	Noted. See FAD 4.4, 4.5 and 4.6.

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Eli Lilly (continued)	*1.2. Adjustments made to account for heterogeneity relating to lines of treatment* 1.2.1 As explained in our submission (Page 56), the likely effect of RCTs not clearly delineating their results by line of treatment is that the median overall survival achieved by patients receiving first line metastatic treatment would be higher than for those patients receiving second-line metastatic treatment, yet data by line of treatment were combined in some trials. Therefore, an important distinction was made between those trials that included patients who were first-line following a prior anthracycline therapy (as in JHQG and current UK treatment) and those who received the therapy and had not been exposed to an anthracycline in an attempt to correct for this problem. These latter trials (Chan et al., 1999, Winer et al., 2004, Sledge et al., 2003, Extra et al., 2005) essentially reflected expected first-line metastatic survival for the therapy but are not reflective of patient population being addressed in this submission (i.e. anthracycline pre-treated, first-line metastatic breast cancer patients) or current UK practice (i.e. prior anthracycline used in the adjuvant setting). They were included to increase the survival estimates of docetaxel and paclitaxel as, in both of these therapies, RCT had been based upon mixed lines of therapy due to the fact that when the trials were conducted it was still standard UK clinical practice to give anthracyclines in the metastatic setting. The base case of the model included both types of patients and the effect of removing the studies where patients had not received anthracycline-based therapy was explored in the sensitivity analyses.	Noted and see above under 1.1.7.
	1.3. Concerns regarding Tumour Responses in JHQG 1.3.1 The open-label nature of the clinical trial is most unlikely to have biased the data reported on tumour response. The way in which tumour response was determined in the JHQG trial was by **independent assessment** which was defined as: *For measurable parameters e.g. CT/MRI Scans that have been assessed by same imaging test originally used to document disease and confirmed by repeat procedure not less than 4 weeks after response first seen.*	Noted.
	1.3.2 Independent assessments were made by investigators blinded to treatment and the state of the patient, making this type of assessment very robust and not subject to the level of bias that might be observed with **investigator-assessed** response rates (where response can only be estimated). Typically, independent-assessment results in lower response rates being reported because this is a more accurate method of assessment, which is the main reason why most phase III clinical trials report investigator-assessed response rates. An independent assessment of time to progressive disease, progression-free survival and overall response rate further demonstrated that there were minimal investigator biases and that the results are valid. The use of the more robust parameters in JHQG is part of the commitment of Lilly to the highest standards in clinical trials methodology.	Noted.

Consultee or Commentator	Comment	Institute Response
Eli Lilly (continued)	*1.4. Concerns regarding Comparative Safety Data on Haematological and Non-Haematological Events* 1.4.1 The ERGR raised concerns about the way in which the incidence of adverse events varied between the trials and attributed this observation to differences in baseline characteristics that they believe will have skewed the results. 1.4.2 A rapid review of the literature has retrieved no evidence to suggest that a relationship exists between the baseline characteristics of patients and the incidence of serious (grade 3 / 4) treatment-related adverse events in MBC. Although there is anecdotal evidence among clinicians that there is a link between baseline characteristics (such as performance status, organ function) and adverse events, clinical trial design will limit this risk by inclusion of patients with good organ function and good performance status. Therefore in comparing results of different clinical trials included in our submission, the extent to which baseline characteristics may have skewed the toxicity results is questionable, particularly as it was shown that these patient baseline characteristics were comparable across the clinical trials included in our submission. The lack of patient level data from key trials included in our submission also limits the ability to assess impact of baseline characteristics toxicity by line of therapy. Whilst it is difficult to compare trials in regards to toxicity, there should be no mistaking the fact that treatment with GT offers patients with MBC a much improved toxicity profile to the alternative approved treatments, and therefore represents a much needed and welcome alternative option of care. (see Appendix 1 which highlights the toxicity benefits of GT) **2. Clinical equipoise and the need for Choice for patients and physicians in Metastatic Breast Cancer** 2.1 Current best clinical practice in England and Wales is guided, in the most part, by NICE recommendation. One of the likely causes of clinical equipoise amongst clinicians in the treatment of MBC as alluded to by both Drs. Verrill and Makris, stem from the decision by NICE to approve the chemotherapy doublet, docetaxel /capecitabine (DC) for use in MBC patients, making DC the only chemotherapy doublet licensed and positively endorsed by NICE for use in patients with anthracycline pre-treated metastatic breast cancer. The Lilly economic evaluation included DC as a comparator treatment. However concerns have been raised by clinicians that the patient-felt toxicities of DC (e.g. hand/foot syndrome which leads to some patients experiencing real difficulty with walking and everyday use of their hands; lethargy/malaise; severe diarrhoea and vomiting and febrile neutropenia), limits DC use despite the high response rates and longer survival.	Noted. Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See FAD 4.2 and 4.6.

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<tr><th>Consultee or Commentator</th><th>Comment</th><th>Institute Response</th></tr>
<tr><td>Eli Lilly (continued)</td><td>
2.2 Therefore Lilly would like to draw the Committee's attention to the cost-effectiveness estimates of GT vs DC shown in table 1. As can be seen the GT option represents a cost-effective option, regardless of the post patent expiration price reduction for paclitaxel, when compared to the only other NICE endorsed chemotherapy doublet i.e. capecitabine/docetaxel (DC).
<table>
<tr><th>ICERs</th><th>GT</th><th>DC</th></tr>
<tr><td colspan="3">Without paclitaxel post patent expiration price reduction</td></tr>
<tr><td>Cost per QALY</td><td>£23,152</td><td>reference</td></tr>
<tr><td>Cost per LY</td><td>£14,484</td><td>reference</td></tr>
<tr><td colspan="3">With paclitaxel post patent expiration price reduction</td></tr>
<tr><td>Cost per QALY</td><td>£8,276</td><td>Reference</td></tr>
<tr><td>Cost per LY</td><td>£5,178</td><td>Reference</td></tr>
</table>
Table 1. Incremental Cost Effectiveness Ratios of GT vs. DC
2.3 Although there is no direct comparison from GT to DC, the advantages of the GT combination is that it offers fewer toxicities compared to other taxane-based treatments, a different toxicity profile to DC (Appendix 1), and paclitaxel is available as a generic preparation so cost of paclitaxel will typically continue to decrease. This makes GT a cost-effective combination option.
2.4 The Committee heard from the clinical specialists that 'GT would be valued as an option in a group of patients who required higher efficacy than could be achieved with a single taxane agent (for example in patients with visceral metastasis) and who were also considered fit enough to receive combination therapy' and that GT 'would probably be used as an alternative option to the combination of docetaxel plus capecitabine because it is considered to be equally effective, but with less toxicity'. For those patients, who may still be leading a relatively active life, the clinician may wish to treat using a combination treatment that has less impact on the patient in terms of toxicity.
</td><td>Noted.
See FAD 4.8 and 4.9.

See FAD 1.1.</td></tr>
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Consultee or Commentator	Comment	Institute Response
Eli Lilly (continued)	2.5 Appendix 1 provides a summary of the grade 3 and 4 adverse events (AEs) reported in the clinical trials for the comparators selected in the Lilly submission. It also provides a description of these AEs and the impact on the patient. Gemcitabine / paclitaxel offers patients an alternative treatment that produces similar efficacy benefits to docetaxel/capecitabine but with fewer toxicities and different toxicity profile, which meets the objectives of treatment for MBC, which are to delay disease progression and maintain an acceptable quality of life to patients.	Noted.
	3. Paclitaxel post patent expiration price reduction	
	3.1 In section 4.7 of the ACD, the Committee has made the following comment regarding the price of paclitaxel: *'The duration of any procurement discounts is unknown and the Committee was not persuaded that negotiated procurement discounts would be universally available within the NHS in England and Wales'*	Noted. See FAD 4.8
	3.2 Lilly provided a letter from NHS PASA (an executive agency of the Department of Health) that stated there is a procurement discount of "between 50% and 60% from the British National Formulary list price for all presentations of paclitaxel". It is surprising that NICE do not consider a DoH source to provide sufficient evidence regarding the price of generic paclitaxel. Paclitaxel at generic price was included in the model to reflect the real decision problem facing the NHS. If the NICE decision is based on branded paclitaxel price only, when the DoH agency has stated that it is available to the NHS at least 50% reduction of this price, it is questionable how useful or valid the NICE decision will be to NHS decision makers. At present NHS PASA has negotiated a new even lower price that will be available across NHS trusts in England from November 2006. Lilly would urge NICE to contact NHS PASA and Welsh Health Supplies to obtain further assurance regarding the cost of paclitaxel to the NHS.	
	3.3 In the ACD, generic paclitaxel is listed as being more expensive than branded paclitaxel (Taxol ®) i.e. The 25ml vial generic price at £561 vs the branded Taxol ® price for the same vial at £521. This is highly unlikely to reflect the reality in the NHS today as generic paclitaxel will be increasingly discounted, as stated by the NHS PASA reference letter provided in our submission.	
	4. Publication of GT registration trial (JHQG)	
	4.1 The manuscript of the GT registration trial (JHQG) will be submitted imminently to a clinical peer reviewed journal. Lilly are providing, with this response, an academic-in-confidence copy of the draft manuscript for the appraisal committee's information.	Noted. The academic-in-confidence draft manuscript was considered by the Committee in formulating the FAD.

Consultee or Commentator	Comment	Institute Response
Eli Lilly (continued)	**Conclusion** In conclusion, Lilly have set out to address the principal grounds for concern raised by the ERG on our submission, which appear to relate, in the most part, to our decision to employ an unadjusted indirect comparison of the available evidence and further concerns about the way in which tumour response was recorded in the JHQG trial and equipoise amongst clinicians surrounding current best practice. Based on this response, we have demonstrated the following: ▪ The methodological approach used to assess the available evidence on taxane-based treatments in MBC is valid and justifiable. We would be interested to hear how ERG would propose to conduct an adjusted indirect comparison given the lack of a common comparator, inability to adjust or statistically test for heterogeneity without patient level data for key trials included in our submission. ▪ Patient and physician choice are important aspects which the appraisal committee should take into account, considering the significant impact chemotherapy-associated toxicity has on a patient's life, and the lack of choice for physicians with regards to NICE-recommended combination treatments for MBC. GT is a combination option which is considered equally effective but with fewer toxicities and different toxicity profile than the only other NICE recommended doublet. ▪ Paclitaxel at generic price was incorporated to reflect the real decision problem facing the NHS. If the NICE decision is based on branded paclitaxel price only, when a DoH agency has stated that it is available to the NHS with a minimum of 50% reduction of the BNF list price, it is questionable how useful or valid the NICE decision will be to NHS decision makers. We trust that we have fully addressed all the concerns raised in the ERGR and the ACD. On this basis we believe there should be no scientific; clinical or economic grounds, for gemcitabine / paclitaxel in metastatic breast cancer, not to be approved by NICE.	Noted – comments addressed above.
Cancerbackup	Cancerbackup believes that everyone with cancer should be offered the most effective treatment, based on the available evidence and the patient's own wishes and preferences. We believe that: • Patients should have access to the most effective treatments appropriate to them as individuals; • Patients should be able to choose – in partnership with their oncologist – the treatment that is likely to suit them best in terms of relative benefits and side-effects; • The impact of treatments on patient's quality of life, as well as length of life, should be given full consideration by the Appraisal Committee. We urge the Appraisal Committee to recommend that gemcitabine should be available for the treatment of patients with locally advanced or metastatic breast cancer.	Noted.

Consultee or Commentator	Comment	Institute Response
Cancerbackup (continued)	**Gemcitabine** Gemcitabine is a chemotherapy drug that belongs to a class of drugs known as antimetabolites, used in the treatment of some types of cancer. Previously it has been used to treat non-small cell lung cancer, pancreatic and bladder tumours. More recently it has been critically evaluated and increasingly used in the treatment of breast cancer. Gemcitabine is a colourless fluid after being dissolved from a white powder. Gemcitabine may be given: as a drip (infusion) through a fine tube (cannula) inserted into a vein, over a short period of time; or through a central line, which is inserted under the skin into a vein near the collarbone, or a PICC line inserted into a vein in the crook of your arm. Gemcitabine offers an important additional treatment option for people with advanced breast cancer, offering not only greater overall survival, but also a better toxicity profile. Cancerbackup urges the Appraisal Committee to consider the following points in particular: **(1) Gemcitabine can extend overall survival for people with locally advanced or metastatic breast cancer** The JHQG trial demonstrated a three month advantage in overall survival for people given gemcitabine/paclitaxel over people given paclitaxel (18.5 months compared to 15.8 months). This represents a clinically significant difference to patients and could have an impact on the time available to patients, their families and friends **(2) Gemcitabine offers considerable improvements in quality of life for people being treated with advanced breast cancer** Side effects are an important deciding factor for many people and their families, and gemcitabine offers a better toxicity profile for patients. There is currently a need for new combinations of chemotherapy agents which can improve outcomes without toxicity impacting on quality of life, and Gemcitabine appears to be well tolerated and easy to administer. This not only offers considerable benefits to patients, but can also impact on the overall cost of treating a patient with advanced breast cancer, as they are less likely to require treatment and care for the effects of toxicity. **(3) Gemcitabine offers an additional line of treatment for people with advanced breast cancer** It is expected that gemcitabine plus paclitaxel would be used as an alternative to docetaxel plus capecitabine, as it is thought to be equally effective but less toxic. As the Appraisal Committee heard, capecitabine can be an important option in *later* lines of therapy for metastatic breast cancer, but the use of docetaxel plus capecitabine as a first-line choice would reduce the possibility of using capecitabine later on. Using gemcitabine early on would therefore offer increased options for treatment with capecitabine in later lines.	Noted. Noted. See FAD 3.2. Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See FAD 4.8.

Consultee or Commentator	Comment	Institute Response
Cancerbackup (continued)	**(4) The use of paclitaxel and gemcitabine is cost effective for the treatment of advanced breast cancer.** Gemcitabine plus paclitaxel provides effective palliation at an economic cost that is less than that associated with docetaxel based regimens. Approval of the paclitaxel-gemcitabine combination will not increase the expenditure on the management of advanced breast cancer but will offer a useful choice over existing options for patients. We urge the Appraisal Committee to consider the points above, in particular the significant impact of this technology on patients' quality of life, and to recommend gemcitabine for the treatment of metastatic breast cancer	See FAD 1.1.
British Oncology Pharmacy Association (BOPA)	**(1) Has all the relevant evidence been taken into account?** As stated in the ACD the only published phase III data available at present are the two interim analyses of the JHQG trial **(2) Are the summaries of the clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?** As stated in the ACD, whilst the comparator arm of this trial (paclitaxel) is a NICE approved therapy, in clinical practice this is not a commonly used regimen in the UK with most patients receiving docetaxel. Likewise, as stated in the ACD the analyses comparing gemcitabine plus paclitaxel with docetaxel monotherapy, paclitaxel monotherapy and docetaxel plus capecitabine were based on an indirect comparison in which weighted absolute treatment outcomes (including survival data) were pooled from single arms of different trials in published literature. No assessment of heterogeneity between the characteristics of the patients in the different study populations was performed, nor was there any adjustment for differences in the baseline characteristics. The ACD has therefore made reasonable interpretations of the evidence in the summaries of the clinical and cost effectiveness. The provisional recommendations of the Appraisal Committee to not recommend gemcitabine for the management of metastatic breast cancer as standard practice in the NHS, seems reasonable.	Noted. Noted.

Consultee or Commentator	Comment	Institute Response
BOPA (continued)	There is no information provided within the ACD about the potential resource impact and NHS implications of the guidance (presumably as it is negative at this stage). However we would like to highlight the potential impact on pharmacy and chemotherapy services ***if this guidance were to be positive in favour of paclitaxel:***	Noted. The NICE Implementation Directorate develops resource impact and implementation support materials. This information will be brought to their attention for consideration during the development of any relevant materials.
	(a) In terms of the effect on chemotherapy capacity, the use of the GT regimen would increase patient chair time. With the majority of patients currently receiving single agent docetaxel this represents a significant increase in chair time per patient (approx. 2400% increase)	
	(b) Currently most patients in the UK receive 6 cycles of Docetaxel, whilst the GT regimen is also 6 cycles it includes treatment on day 8 of each cycle. Increase in the number of cycles administered would add an additional burden on chemotherapy treatment units and patients (see also chair times above).	
	(c) Within the context of already overburdened chemotherapy treatment units and NHS pharmacy preparation services, the adoption of GT as a standard regimen for metastatic breast cancer patients would therefore have a negative impact on workload compared to current practice.	
	It would be essential that additional resources (other than funding of the drug cost) be made available to expand the infrastructure to enable this technology (and other new cancer treatments) to be delivered efficiently and safely for both this patient group and other users of the chemotherapy service.	
	Due to both the high cost of the prepared drug, treatment whilst it could be safely prepared in advance of the date of treatment there would remain a significant risk of treatment as a result of treatment delays due to myelosuppression. This would necessitate preparation of the dose only once appropriateness of treatment has been confirmed (on the day of treatment or at a pre-chemotherapy clinic) resulting in a “reactive” service for these patients where fluctuations in workload could result in an increased waiting time for patients awaiting treatment	
	(3) Are the provisional recommendations of the appraisal committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?	Noted.
	The provisional recommendations made by the appraisal committee seem sound, based on the evidence reviewed and the summary of clinical and cost effectiveness.	

Consultee or Commentator	Comment	Institute Response
The Royal College of Nursing	The Royal College of Nursing welcomes the invitation to review this consultation document and considers that the conclusion of the Appraisal Committee is reasonable. We agree that Gemcitabine could be effective for some women with secondary breast cancer. However, feel that as with all combination treatments it is necessary to consider the toxicity and the fact that other drugs may not be able to be used at a later stage. With respect to paragraph 4.7 on the issues of funding for high cost drugs and access for patients, we recognise that this is wider than this consultation process but perhaps needs to be considered in future technology appraisals and reviews. We support the proposed recommendations for further research.	Noted. The Committee does not make use of budget impact evidence in making recommendations on any technology appraisal. Noted
Royal College of Radiologists	**(i) Whether you consider that all of the relevant evidence has been taken into account** Yes. The regimen of paclitaxel plus gemcitabine considered in this STA has been submitted based on a single randomised controlled trial showing a benefit in median overall survival of 2.8 months compared with paclitaxel alone with an 'acceptable toxicity profile'. When considering the evidence for this regimen, the alternative treatment comparators should be paclitaxel alone, or docetaxel alone, or docetaxel plus capecitabine which are all in current use by UK oncologists. However, there does not appear to be any reported randomised trial of paclitaxel plus gemcitabine versus docetaxel alone or docetaxel plus capecitabine. Therefore, the only high level evidence relates to the comparison with paclitaxel. **(ii) Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.** It is noted that the Committee did conclude, on balance, that gemcitabine plus paclitaxel is likely to be more clinically effective than paclitaxel monotherapy, but was not persuaded regarding cost effectiveness. The manufacturer was unwise to attempt to compare single arms of different trials. However, there is the danger that criticism of this methodology has become the focus of this appraisal and may have distracted from analysis of the main randomised trial, and the applicability of this trial to the NHS. Based on prices in the document the drug cost of gemcitabine in 6 cycles of this regimen would be approximately £4000 for an average of 2.8 months improved survival over paclitaxel monotherapy. This equates to a cost of about £17,000 per (unadjusted) life year. Clearly, the assessments made by the evidence review group are more complex, including QoL and differential number of courses of paclitaxel received in the two arms due to differing response rates and time to progression. The ERG figure is £42,800 per QALY. The baseline cost of paclitaxel appears important in these calculations. Experience of clinicians is that cost of non-proprietary paclitaxel is falling.	Noted. No action required for FAD Noted. See FAD 4.6. Noted. See FAD 4.9.

Consultee or Commentator	Comment	Institute Response
Royal College of Radiologists (continued)	The Committee and ERG recognised that the results of the single randomised trial may represent an under-estimate of the benefit of the combination regimen, due to a higher use of 'salvage' gemcitabine use in the control arm. However, it is not clear whether any account has been taken of this in the QALY estimates. There remain concerns about the wide variations in cost effectiveness calculations that can be obtained based on different analyses and different baseline costs of drugs.	Noted. The Appraisal Committee considered these issues and accepted that whilst crossover probably influence the JHQG trial outcomes, gemcitabine plus paclitaxel was more effective than paclitaxel monotherapy.
	The committee noted that specialists would value gemcitabine plus paclitaxel as a treatment option. In the absence of this option, most UK specialists are likely to choose single agent Taxotere as the current standard for this group of patients. Taxotere is currently on average at least twice as expensive as non-proprietary paclitaxel and is likely to remain so whilst under patent. In practical terms, the cost of taxotere versus paclitaxel plus gemcitabine is similar present. The other NICE approved regimen of taxotere plus capecitabine is more expensive, more toxic, and not proven to be more effective than paclitaxel plus gemcitabine.	Noted. See FAD 4.9.
	(iii) Whether you consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance for the NHS. The recommendations of the Appraisal Committee rely heavily on the cost-effectiveness calculations by the Evidence Review Group. It is not clear whether these calculations are sound. There are variables in the analysis which could cause marked changes in the cost per QALY estimates. There are other approved treatments in this setting which are as or more expensive. Therefore, it is unclear whether failure to recommend this technology will have any effect on NHS expenditure. However, failure to recommend the treatment will reduce the choice of treatments available to patients. The recommendations should be reconsidered in view of these and other comments received.	Noted. The Appraisal Committee was aware the ERG's analysis was for illustration and therefore not a complete indirect comparison meta-analysis. See FAD 4.4.

Consultee or Commentator	Comment	Institute Response
National Cancer Research Institute	(i) I believe that all of the evidence relevant to the appraisal has been taken into account.	Noted
	(ii) I believe that the summary of the clinical effectiveness of the Gemcitabine/Paclitaxel combination under estimates the potential clinical benefit of this combination for patients with metastatic breast cancer. Although there is considerable evidence that combination chemotherapy for metastatic breast cancer improves the response rates when compared with single agent chemotherapy treatment, there are very few trials that have shown improved survival in patients with metastatic breast cancer treated with combination chemotherapy compared with single agent treatment. The JHQG trial1 which compared Gemcitabine/Paclitaxel (GT) with Paclitaxel (T) in patients with metastatic breast cancer who had received previous anthracycline based chemotherapy in the adjuvant treatment setting is only the second trial to my knowledge to show a survival benefit for combination over single agent chemotherapy in metastatic breast cancer. The only other study to have demonstrated a survival benefit for combination chemotherapy in patients with metastatic breast cancer is the study by O'Shaughnessy and colleagues2 which compared Docetaxel mono therapy with Docetaxel/Capecitabine combination therapy. The combination of Docetaxel and Capecitabine has been approved by NICE for the treatment of locally advanced or metastatic breast cancer in people for whom anthracycline containing regimens are unsuitable or have failed.	Noted. The survival benefits of the treatments were taken into account. See FAD 4.6.
National Cancer Research Institute (continued)	Balancing efficacy and safety is a key goal in delivering a positive risk benefit profile for patients with metastatic breast cancer and therefore the toxicity profile of treatment is an important factor in determining the optimum combination therapy. At present the most widely used first line chemotherapy treatment for metastatic breast cancer in patients who have previously received an anthracycline in the adjuvant treatment setting is single agent Docetaxel. In clinical practice the toxicity of combination treatment with Docetaxel and Capecitabine makes it difficult to deliver without significantly compromising patients quality of life. Docetaxel (100mg per m^2) iv mono therapy has been shown to be more active than Paclitaxel (175mg per m^2) three weekly mono therapy, but is also more toxic[3].	Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See FAD 4.2 and 4.8.
	As metastatic breast cancer is incurable and the average survival for patients with visceral metastases is less than two years, therapies that result in a survival benefit can confer a significant advantage to patients in this situation. The results of the JHQG trial demonstrate a 20% incremental increase in survival time of patients treated with the combination of Paclitaxel and Gemcitabine compared with single agent Paclitaxel. The toxicity profile of this treatment is generally favourable. Although myelosuppression is greater in the Gemcitabine/Paclitaxel group, the rates of febrile neutropenia in this group (the only clinically significant effect of myelosuppression) was only 5%, which is significantly lower than that reported for single agent Docetaxel in other trials.	Noted.

Consultee or Commentator	Comment	Institute Response
National Cancer Research Institute (continued)	The availability of a tolerable combination chemotherapy regimen that confers a survival benefit to patients with metastatic breast cancer previously exposed to an anthracycline combing regimen in the adjuvant setting would be of a significant benefit to this patient population. It would be particularly applied to patients with visceral disease who are of good performance status and have good organ function. I believe that it would be used in preference to the more toxic Docetaxel/Capecitabine regimen.	Noted. See FAD 4.2.
	As there are no randomised trials comparing Gemcitabine plus Paclitaxel with Docetaxel mono therapy or the Docetaxel/Capecitabine combination, comparisons between these treatments rely on indirect, cross trial comparisons. There is some heterogeneity between these trials in terms of the number of prior chemotherapy regimens that patients may have received. Summaries of the baseline characteristics of patients entering these studies are broadly similar with the exception that the median Karnofsky performance status of patients entered into the JHQG trial[1] was 70% whereas the median Karnofsky performance stats score for patients in the other two trials was 90%. Performance status is closely correlated with the patient's well-being, their ability to tolerate chemotherapy treatment and also their response to treatment. In this context, the results of the JHQG trial demonstrating survival benefit for the Gemcitabine/Paclitaxel combination in a group of patients with a generally poorer performance status, with very manageable toxicity, is an impressive result.	Noted.
	It would not be possible to formally assess the heterogeneity between the characteristics of the patients in the different study populations, nor to adjust for differences in baseline characteristics without access to individual patient data from each of these trials. I therefore believe that the economic analysis presented by the manufacturer linking these trials through the common comparator arm of single agent Docetaxel was appropriate and the only methodology which could be employed given the available data. I do not believe there is any way in which such a cross trial comparison can be undertaken whilst preserving the benefits of randomisation.	See above and see FAD 4.5.
	The cost effectiveness analysis for Gemcitabine/Paclitaxel combination therapy is significantly influenced by the acquisition cost of Paclitaxel. As this drug is now off patent and non proprietary formulations of Paclitaxel are available, the cost of this drug has fallen substantially. The current cost of Paclitaxel to my hospital Trust is nearly 50% of the price quoted in the ACD (paragraph 2.3). This significantly impacts on the overall drug cost of combination therapy and it is currently comparable to the cost of single agent Docetaxel. There are some additional costs involved in delivering this treatment, particularly as patients need to return for Gemcitabine on day eight and administration of Paclitaxel and Gemcitabine together on day one would take around four hours compared with one hour administration time for single agent Docetaxel. Despite this, the costs are still likely to substantially lower than those that have been used in the economic analysis that was undertaken by the ERG and I think that it is important that this is fully appreciated by the appraisal committee.	Noted. See FAD 4.9.

Consultee or Commentator	Comment	Institute Response
National Cancer Research Institute (continued)	(iii) In the light of my previous comments, I believe that the provisional recommendations of the appraisal committee should be reviewed. The availability of the Gemcitabine/Paclitaxel combination for appropriate patients with metastatic breast cancer would be of significant clinical benefit and I believe would satisfy the requirements for cost effectiveness given the current acquisition cost of a non proprietary Paclitaxel.	Noted. See FAD 1.1.
Roche	A key issue arising from this negative ACD for gemcitabine appears to us to relate to the synthesis of the available clinical effectiveness data. According to the ERG Report, the manufacturer did not adequately account for the observed heterogeneity across the numerous clinical trials utilised within the economic analysis (ACD, section 4.6). Roche would like to provide feedback on the broader issue relating to the apparent requirement and expectation of both ERG and of NICE for the manufacturer to perform more elaborate methods of indirect comparison of clinical effectiveness evidence. It is often the case that the comparators selected in clinical trials may not be optimal for the purposes of UK HTA. There are at least three reasons for this: (1) Clinical practice in the UK may, for historical reasons, be different from that in a majority of countries where clinical trials or registration studies are conducted (2) Clinical practice may have progressed to the extent that what seemed an appropriate comparator at the time of clinical study commencement might now be considered sub-optimal (3) Clinical practice in the UK may currently differ due to resource or other constraints which result in standard treatments different from those more generally acknowledged as optimal and therefore used as clinical trial comparators. Under such circumstances it may be that an intervention being reviewed by NICE has to be appraised using indirect comparisons. Although all would agree that this is less than ideal, it is incumbent upon NICE to try and make such a comparison. As section 5.2.3.3 of the Guide to Methods states: “There are always likely to be deficiencies in the evidence base available for HTA assessment…despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies”.	

Consultee or Commentator	Comment	Institute Response
Roche (continued)	The existing "Guide to the Methods of Technology Appraisal" (April 2004) does provide some guidance on evidence synthesis and on managing heterogeneity (section 5.4). However, no explicit reference or guidance is provided on the use of specific methods such as those apparently adopted by SHTAC during the course of this appraisal (which are not published in the ERG Report).	Noted. It is acknowledged that the current "Guide to the Methods of Technology Appraisal" does not give explicit guidance on indirect or mixed treatment comparisons. However, this does not mean that the Committee is to ignore the methodological robustness of the approach used in individual submissions.
	Consequently Roche wonders whether it would be useful for NICE to update the "Guide to Methods of Technology Appraisal" to provide greater detail on when methods of indirect comparison should be adopted in the preparation of HTA submissions and indeed on what methods might be preferable. This could help in the future, allay situations where manufacturers might be criticised for not adopting particular methodologies which are not outlined explicitly within the "Guide to Methods of Technology Appraisal	Noted. The "Guide to the Methods of Technology Appraisal" will be updated in due course.

Reply received but no comments:

- Guideline Development Group
- Welsh Assembly Government
- Department of Health
- Evidence Review Group
- Royal College of Physicians

Comments received from website consultation

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
Clinician/ Clinical Director	1	Breast cancer patients need to be able to have alternatives to docetaxel or docetaxel and capecitabine in combination. The side effect profile of the latter combination discourages its routine use in many patients. Paclitaxel/gemcitabine has comparable activity but is much more acceptable as an active palliative treatment. The therapeutic index is of critical importance in this non-curative setting. Anthracyclines are not usually relevant, having been used in adjuvant therapy..	Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer. See FAD 1.1.
	2	The actual cost, of course for non-proprietary paclitaxel is very much less.	Noted. See FAD 4.9.
	4	The clinical reality is that many patients are compromised by poor general health or reduced bone marrow reserve. Thus the issue of unpleasant or life-threatening complications from inappropriate therapy [for that individual] is paramount in making treatment choices for cytotoxics and cytotoxic combinations.	Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer.
	5	I don't believe further trials will provide a great deal more help.	Noted.
NHS Professional	4	The statement at the end of section 4.7 is factually incorrect. Paclitaxel is now treated as a generic medication in the NHS, and is formally contracted as such by PASA. There is a new contract coming into place in November, and the prices are less than 20% of the price listed in BNF51 for the branded product Taxol i.e. less than 200 for a 50ml vial. These contract prices are universally available throughout the NHS and all NHS hospitals will be purchasing at these prices.	Noted. See FAD 4.9.

Consultee or Commentator	Section of ACD (if specified)	Comment	Institute Response
NHS Professional	1	This is a useful and well tolerated regimen in metastatic breast cancer. It is better tolerated than Docetaxel Capecitabine and has the potential to be offered to more patients than would be suitable for the latter. The improved response rate TTP and OS therefore are achieved with little additional toxicity burden.	Noted. The Appraisal Committee considered these issues in making a recommendation on the use of gemcitabine in the treatment of metastatic breast cancer.
	2	Most of the UK uses generic paclitaxel and the cost of 6 cycles Paclitaxel Gemcitabine in our centre is 6150, compared to 6186 for Docetaxel Capecitabine, and 5916 for docetaxel alone. The latter two are subjectively (and from cross trial comparison) quite a lot more toxic than Paclitaxel Gemcitabine	Noted. See FAD 4.9.
	4	On the face of our costing, the effectiveness and the especially the side-effects paclitaxel gemcitabine would be a very useful combination to have access to in MBC	Noted.