Dear Mr Feinmann,

The following are comments on behalf of the Royal College of Radiologists on the Appraisal Consultation Document for the Single Technology Appraisal of gemcitabine for the treatment of metastatic breast cancer.

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.

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.

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.

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.

Response from the RCR
06/10/2006