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Dear Ms [redacted]

Regarding: Breast cancer (metastatic hormone-receptor) - lapatinib and trastuzumab (with aromatase inhibitor)

On behalf of NHS Portsmouth, I would like to submit our comments on the appraisal consultation document for Breast cancer (metastatic hormone-receptor) - lapatinib and trastuzumab (with aromatase inhibitor). NHS Portsmouth is in agreement with the appraisal committee's decision that this technology does not represent a cost effective use of scarce NHS resources.

- **Adding lapatinib or trastuzumab to an aromatase inhibitor improves median progression free survival (PFS), but not overall survival.** Single RCTs found that adding lapatinib to letrozole improved median PFS from 3.0 months to 8.2 months, and that adding trastuzumab to anastrozole improved median PFS from 2.9 months to 5.8 months. Indirect comparisons from the manufacturers found no differences in PFS between these two combination regimens. The RCTs found that the combination regimens did not improve overall survival compared with aromatase inhibitors alone, and indirect comparisons found no difference in overall survival between the combination regimens.

- **Adding lapatinib or trastuzumab to an aromatase inhibitor increases adverse events.** Adding lapatinib to letrozole increased adverse events compared with letrozole alone, including diarrhoea (68% vs. 8%), rash (46% vs. 8%), and nausea (27% vs. 18%; $p<0.05$ for all three events). Adding trastuzumab to anastrozole increased adverse events compared with anastrozole alone (overall adverse events: 87% vs. 65%; serious adverse events: 23% vs. 6%). The most common adverse events with trastuzumab plus anastrozole included fatigue (21% vs. 10%), diarrhoea (20% vs. 8%), and vomiting (21% vs. 5%). Lapatinib and trastuzumab have been associated with cardiotoxicity therefore both drugs require cardiac monitoring (left ventricular function) before and during

treatment. Liver function monitoring before and during treatment is also recommended with lapatinib.

- **Adding lapatinib or trastuzumab to aromatase inhibitor treatment is estimated to increase lifetime costs by around £26,000 per patient, without an extension to life.** NICE made these estimations based on acquisition drug costs alone for a mean of 55.2 weeks' treatment, and using British National Formulary 60 costs (excluding VAT).

- The Appraisal Committee concluded that the most plausible ICER for lapatinib plus letrozole compared with letrozole alone was likely to be between £74,400 and £1,000,000 per QALY gained, and for trastuzumab plus anastrozole compared with anastrozole alone was likely to be between £54,300 and £73,100 per QALY gained. NHS Portsmouth is in agreement with the appraisal committee that this far exceeds the thresholds usually accepted as a cost effective use of NHS resources.

- **The exact number of people who would be eligible to receive trastuzumab or lapatinib plus an aromatase inhibitor (if approved) in preference to alternatives is unknown**. The best estimate for an average PCT of 300,000 based on a maximum uptake is that they could expect to treat 11 women annually.

- **There were limitations to the quality of the research:** Although the RCTs were of good quality, each combination (lapatinib plus letrozole or trastuzumab plus anastrozole) was only assessed in a single RCT with about 200 women with HER2+ and hormone receptor positive metastatic breast cancer. The populations in these trials were substantially different; therefore the indirect comparisons carried out by the manufacturers should be interpreted with caution.

Yours sincerely

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