The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE:** following a second resubmission assessed under the orphan medicine process, **pertuzumab (Perjeta®)** is accepted for use within NHSScotland.

**Indication under review:** for use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.

In a phase II study conducted in women with locally advanced, inflammatory, or early HER2-positive breast cancer, in the neoadjuvant setting, the addition of pertuzumab to trastuzumab plus chemotherapy resulted in a significantly higher proportion of patients achieving pathological complete response in the breast.

This SMC advice takes account of the benefits of Patient Access Schemes (PAS) that improve the cost-effectiveness of pertuzumab and trastuzumab IV (Herceptin®). This advice is contingent upon the continuing availability of these PAS in NHSScotland or list prices that are equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman**
Scottish Medicines Consortium
**Indication**
For use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence.¹

**Dosing Information**
Pertuzumab should be administered for three to six cycles in combination with neoadjuvant trastuzumab and chemotherapy, as part of a treatment regimen for early breast cancer.

The recommended initial loading dose of pertuzumab is 840mg administered as a 60-minute intravenous infusion, followed every three weeks thereafter by a maintenance dose of 420mg administered over a period of 30 to 60 minutes.

See summary of product characteristics for additional information including doses of trastuzumab and chemotherapy.

Pertuzumab is subject to restricted medical prescription and therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents.¹

**Product availability date**
July 2015

Pertuzumab meets SMC orphan-equivalent criteria for the indication.

**Summary of evidence on comparative efficacy**
Pertuzumab is a recombinant, humanised, immunoglobulin (Ig)G1κ monoclonal antibody. It targets human epidermal growth factor receptor 2 (HER2) protein, a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Pertuzumab in combination with trastuzumab provides a more complete blockade of the HER pathway resulting in increased anti-cancer activity in patients with HER2-positive breast cancer. Pertuzumab has a marketing authorisation for use in both the metastatic and early (neoadjuvant and adjuvant) settings.¹

The current submission concerns the addition of pertuzumab to trastuzumab plus chemotherapy in the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. Risk assessment of patients with early stage breast cancer should consider the following: tumour size, grade, hormone-receptor status and lymph node metastases.²
The marketing authorisation was awarded based on efficacy data from two phase II studies, NeoSphere and TRYPhAENA; this is supported from data from the BERENICE study and GeparSepto study.\textsuperscript{2-6}

NeoSphere was a multicentre, open-label, proof of concept, randomised study conducted in adult women with locally advanced, inflammatory, or early HER2-positive breast cancer. Tumours were to be of HER2 immunohistochemistry 3+ or 2+ and positive for fluorescence or chromogenic in-situ hybridisation. Patients had an Eastern Cooperative Cancer Group (ECOG) performance status of 0 or 1, a baseline left ventricular ejection fraction (LVEF) of ≥55% and were not to have received previous cancer therapy.\textsuperscript{3}

Patients were randomised equally to one of four neoadjuvant treatment regimens given every three weeks for four cycles:

- **Group A**: trastuzumab (8mg/kg intravenously [IV] in cycle 1 then 6mg/kg IV in cycles 2 to 4) + docetaxel (75mg/m\textsuperscript{2} IV in cycle 1 then 75mg/m\textsuperscript{2} or 100mg/m\textsuperscript{2} IV [if tolerated] in cycles 2 to 4)
- **Group B**: pertuzumab (840mg IV in cycle 1 then 420mg IV in cycles 2 to 4) + trastuzumab + docetaxel (doses as before)
- **Group C**: pertuzumab + trastuzumab (doses as before)
- **Group D**: pertuzumab + docetaxel (doses as before)

Following neoadjuvant treatment, eligible patients underwent surgery and then received adjuvant treatment with three cycles of FEC (fluorouracil, epirubicin and cyclophosphamide) except patients in group C who received three cycles of docetaxel then three cycles of FEC. In addition, all patients received adjuvant trastuzumab 6mg/kg every three weeks for one year.\textsuperscript{3} Group A represents the control group and group B represents the intervention under review; therefore groups C and D are not discussed further.

The primary endpoint was pathological complete response in the breast (bpCR), defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumour at surgery. It was evaluated in the intention-to-treat (ITT) population, after patients had received four cycles of neoadjuvant treatment and surgery, or had withdrawn from the study (whichever occurred first).\textsuperscript{2,3} The proportion of patients with a bpCR was significantly higher in group B than group A. Primary and some secondary outcomes are included in table 1.
Table 1: Primary and selected secondary outcomes from NeoSphere.  

<table>
<thead>
<tr>
<th></th>
<th>Group A (trastuzumab + docetaxel) n=107</th>
<th>Group B (pertuzumab + trastuzumab + docetaxel) n=107</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bpCR</td>
<td>29% (31/107)</td>
<td>46% (49/107), p=0.014</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tpCR</td>
<td>22% (23/107)</td>
<td>39% (42/107)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>19 (18%)</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>5-yr PFS (95% CI)</td>
<td>81% (71 to 87)</td>
<td>86% (77 to 91)</td>
</tr>
<tr>
<td>Hazard ratio* (95% CI)</td>
<td>0.69 (0.34 to 1.40)</td>
<td></td>
</tr>
<tr>
<td><strong>DFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number who underwent surgery</td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td>Number of events</td>
<td>18 (18%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>5-yr DFS (95% CI)</td>
<td>81% (72 to 88)</td>
<td>84% (72 to 91)</td>
</tr>
<tr>
<td>Hazard ratio* (95% CI)</td>
<td>0.60 (0.28 to 1.27)</td>
<td></td>
</tr>
</tbody>
</table>

bpCR = pathological complete response in the breast (in situ disease might remain), tpCR = pathological complete response in the breast (in situ disease might remain) and lymph nodes, PFS = progression-free survival (the time from randomisation to the first documentation of progressive disease [excluding contralateral in situ disease], disease recurrence, or death), DFS = disease-free survival (defined as the time from the date of surgery to the first documentation of progressive disease [excluding contralateral in situ disease] or death), NR = not reached, CI = confidence interval. ± analyses conducted after median duration of follow up of approximately 5 years. *comparison group B versus group A.

TRYPHAENA was a multicentre, open-label, randomised study to assess cardiac safety of pertuzumab and trastuzumab in combination with anthracycline- or carboplatin-based neoadjuvant chemotherapy in patients with HER2-positive primary breast cancer. It had similar inclusion criteria to the NeoSphere study.  

2, 4
Patients were randomised equally to one of three neoadjuvant treatment regimens given every three weeks:

- **Group A**: pertuzumab (840mg IV in cycle 1 then 420mg IV in cycles 2 to 6) + trastuzumab (8mg/kg IV in cycle 1 then 6mg/kg IV in cycles 2 to 6) + FEC (for 3 cycles) then docetaxel (for 3 cycles, initial dose of 75mg/m² IV then 75mg/m² or 100mg/m² IV [if tolerated] for subsequent cycles)
- **Group B**: FEC (for 3 cycles) followed by pertuzumab + trastuzumab + docetaxel (doses as before for 3 cycles)
- **Group C**: pertuzumab + trastuzumab (doses as before) + docetaxel (75mg/m² IV) + carboplatin IV AUC6 (area under the plasma concentration-time curve) (all for 6 cycles)

Following neoadjuvant treatment, eligible patients underwent surgery and then received adjuvant trastuzumab 6mg/kg every three weeks for one year. The primary aim of the study was assessment of safety and tolerability. Secondary efficacy outcomes are reported in table 2.

### Table 2: Secondary outcomes from TRYPHAENA

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=73)</th>
<th>Group B (n=75)</th>
<th>Group C (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>bpCR</strong></td>
<td>62%</td>
<td>57%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>tpCR</strong></td>
<td>56%</td>
<td>55%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td>Event rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16% (35/225)</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Disease-free survival</strong></td>
<td>Event rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14% (29/208)</td>
<td>87%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>Event rate</td>
<td>9.8% (22/225)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>94%</td>
<td>94%</td>
<td>93%</td>
</tr>
</tbody>
</table>

bpCR = pathological complete response in the breast (in situ disease might remain), tpCR = pathological complete response in the breast (in situ disease might remain) and lymph nodes, PFS = progression-free survival (the time from randomisation to the first documentation of progressive disease [excluding contralateral in situ disease], disease recurrence, or death), DFS = disease-free survival (defined as the time from the date of surgery to the first documentation of progressive disease [excluding contralateral in situ disease] or death). ± analyses conducted after median duration of follow up of approximately 5 years. *estimated by Kaplan-Meier method.

The BERENICE study was an open-label, non-randomised, multicentre, phase II safety study which recruited 400 patients with previously untreated HER2-positive breast cancer that was either inflammatory, locally advanced or early-stage. Patients had ECOG performance status 0 or 1, and baseline LVEF ≥55%. Investigators chose one of two neoadjuvant regimens, each comprising
pertuzumab and trastuzumab, given for four 3-weekly cycles plus anthracycline / taxane based chemotherapy. Following surgery, adjuvant chemotherapy comprised pertuzumab, trastuzumab and taxane and was given for up to 13 cycles. The primary outcomes were related to cardiac safety; with respect to efficacy outcomes, tpCR was achieved by 61% (245/400) of patients.\(^\text{5}\)

The German Breast Group clinical study GeparSepto provides supporting evidence for use of pertuzumab in the neoadjuvant setting. Pertuzumab was used in the background regimen for all patients with HER2-positive disease; the study compared outcomes of nab-paclitaxel versus paclitaxel. The primary efficacy outcome was the pCR rate, absence of invasive tumour in breast and nodal tissue and absence of ductal carcinoma in situ; in the subgroup with HER2-positive cancer, the pCR rates were 62% (123/199) of patients given nab-paclitaxel, and 54% (106/197) of patients given paclitaxel. The tpCR rate was a secondary outcome but was not reported for the subgroup with HER2 cancer.\(^\text{6}\)

### Summary of evidence on comparative safety

In the NeoSphere study, most adverse events were grade 1/2 and included alopecia, neutropenia, diarrhoea, nausea, fatigue, rash, mucosal inflammation, myalgia, asthenia and headache. Most of these were considered to be possibly related to study treatment.\(^\text{3}\)

Adverse events, ≥grade 3 (occurring in at least 5% of patients in any group) in groups A and B included: neutropenia (57% and 45%); febrile neutropenia (7.5% and 8.4%); diarrhoea (3.7% and 5.6%). The proportion of patients with at least one serious adverse event was 17% and 10% in groups A and B respectively, and included neutropenia (0.9% and 3.7%) and febrile neutropenia (6.5% and 5.6%).\(^\text{3}\)

Mean maximum decreases in LVEF were similar across all groups (4% to 5%). Decreases in LVEF of 10% to 15% from baseline and to <50% in the neoadjuvant phase occurred in four patients (one in group A and three in group B). There were two deaths during the neoadjuvant phase, one in group B due to fulminant hepatitis (possibly related to study treatment) and the other in group D, due to lung metastases (not evident at randomisation) and progressive disease.\(^\text{3}\)

In the TRYPHAENA study, during the neoadjuvant phase, two patients (in group B) experienced symptomatic (≥grade 3) left ventricular systolic dysfunction and 11 patients had LVEF decline >10% from baseline to <50% (four patients in groups A and B and three patients in group C). No deaths were reported in the neoadjuvant phase.\(^\text{4}\)
Summary of clinical effectiveness issues

HER2-positive breast tumours are associated with higher rates of recurrence and increased mortality than HER2-negative tumours. The Scottish Intercollegiate Guidelines Network (SIGN) recommends anthracycline-taxane-based chemotherapy. A regimen of FEC followed by docetaxel plus trastuzumab is included in current protocols from some Scottish cancer networks. In patients who are not suitable for anthracycline-based chemotherapy, there are other chemotherapy regimens, mainly based on taxane therapy. For the indication under review, pertuzumab meets SMC orphan-equivalent criteria.

The pivotal comparative data are from the phase II study NeoSphere which compared pathological complete response rates, in patients allocated to a neoadjuvant chemotherapy regimen comprising trastuzumab and docetaxel, with or without pertuzumab. The primary outcome of the NeoSphere study was bpCR. Group B (pertuzumab + trastuzumab + docetaxel) was significantly superior to group A (trastuzumab + docetaxel). The European Medicines Agency (EMA) preferred definition for pathological complete response, tpCR, was assessed as a secondary outcome; tpCR was achieved in a higher proportion of patients in group B than group A (39% versus 22%), although this was not tested for statistical significance.

Pathological complete response is not a direct health outcome. Descriptive statistics for PFS and disease-free survival (DFS) with five-year follow-up data from the NeoSphere study show favourable hazard ratios (group B compared to group A) for PFS (0.69, 95% CI: 0.34 to 1.4) and DFS (0.60, 95% CI: 0.28 to 1.27). The outcome data are limited by low event rates, and in addition the study was not powered to detect a difference in long term outcomes.

No patient-reported outcomes, or outcomes concerning health-related quality of life were reported.

The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) analysis was undertaken to determine the relationship between pCR and long-term clinical benefits in neoadjuvant treatment of primary breast cancer. Whilst event-free and overall survival were improved in patients with tpCR compared to those without, the pooled analysis could not validate pCR as a surrogate endpoint for improved event-free and overall survival. The submitting company commissioned a Bayesian network meta-analysis (NMA) that sought to provide evidence of the association between pCR after neoadjuvant therapy in HER2-positive breast cancer and improved long-term clinical outcomes. The model suggested that pCR was associated with improved event-free survival and overall survival versus non-pCR but the results were limited by heterogeneity in the NMA. The authors concluded that for any new therapy, the relationship between pCR and survival may differ, and studies should adapt the relationship between pCR and survival for the treatment under review. The EMA did not consider the difference in tpCR rate between groups A and B in the NeoSphere study to be sufficiently large to translate into a significant difference with regard to DFS and overall survival. However, the EMA also noted that it is reasonably likely that neoadjuvant
treatment with pertuzumab is associated with a benefit in terms of DFS and overall survival given all the evidence, as well as significantly longer PFS and overall survival in the metastatic setting (from the CLEOPATRA study).2

The NeoSphere study used a neoadjuvant regimen of docetaxel plus trastuzumab; Scottish cancer network guidelines tend to recommend anthracycline-based regimens, or a platinum-based regimen (eg carboplatin plus docetaxel) for those not suitable for anthracyclines.13, 14 Supporting clinical data provide evidence for using pertuzumab in other neoadjuvant regimens, including anthracycline-based chemotherapy (eg TRYPHAENA, BERENICE and GeparSepto) but none of these studies included a treatment group which did not receive pertuzumab that could be used for comparison.4–6

Although there was no control group in the TRYPHAENA study, the EMA considered that the results indicated an additional benefit of combining FEC + trastuzumab with pertuzumab in the neoadjuvant setting when results are compared with similar neoadjuvant studies. Overall, bpCR and tpCR were achieved in a higher proportion of patients in the TRYPHAENA study compared to the NeoSphere study, which may be explained by the use of the anthracycline-containing chemotherapy regimen in the neoadjuvant rather than adjuvant setting.2

NeoSphere and TRYPHAENA were conducted in populations that are representative of patients who would be eligible for treatment with pertuzumab in the neoadjuvant setting and the results are considered to be clinically relevant.1 However, there are limited data on the safety and efficacy of pertuzumab in patients aged ≥65 years and no data in patients with hepatic impairment. In both studies there were too few patients with inflammatory breast cancer to draw any firm conclusions.1

Clinical experts consulted by SMC advised that the addition of pertuzumab is a therapeutic advancement due to improved pCR rates and likely benefit in longer-term outcomes.

There are likely to be some service implications in terms of length of time that the patient is in the clinic. Pertuzumab in addition to trastuzumab and chemotherapy requires sequential administration, following the 30 to 60 minute infusion of pertuzumab, an observation period of 30 to 60 minutes is recommended after each pertuzumab infusion and before commencement of any subsequent infusion of trastuzumab or docetaxel.1 Following administration of trastuzumab patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms.15 The submitting company considered that the pertuzumab containing regimen could be managed as a day case.
Patient and clinician engagement (PACE)

A Patient and Clinician Engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pertuzumab, as an orphan equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- HER-2 positive breast tumours are associated with higher rates of recurrence and an increased mortality compared to other breast cancers.
- Patients are prepared to undergo disfiguring surgery and treatment with associated significant toxicity in an attempt to cure their disease. Surgery for early breast cancer can cause scarring and be very traumatic for patients and their families.
- These patients may have potentially curative breast cancer. The addition of pertuzumab to current standard neoadjuvant chemotherapy plus trastuzumab almost doubles the pCR rate, which is expected to be a good surrogate marker of improved survival. Clinicians strongly emphasised that they believed there to be a strong correlation between pCR and survival.
- Clinicians highlighted that the outcomes they have seen in practice with pertuzumab are similar to trial outcomes. Pertuzumab is considered to be well tolerated and side effects have little impact on quality of life.
- Clinicians strongly emphasised that while they considered all patients with HER-2 positive breast cancer undergoing neoadjuvant chemotherapy to potentially benefit from pertuzumab, they suggested a multivariate prognostic approach could be used to define a higher risk subgroup in which treatment may be more cost effective.
- In NHS Scotland, the usual neoadjuvant chemotherapy regimen used is FEC-docetaxel plus trastuzumab. With this regime, only 3 pertuzumab cycles are prescribed compared to 6 cycles with other regimes.
- PACE participants considered that, although not captured in the trial data, the addition of neoadjuvant pertuzumab may allow patients to undergo less invasive breast-conserving surgery, leading to improved recovery times and less requirement for extensive reconstruction surgery or full mastectomies.

Additional Patient and Carer Involvement

We received a joint submission from Breast Cancer Care Scotland and Breast Cancer Now, which are both registered charities. Breast Cancer Care has received 0.69% pharmaceutical company funding in the past two years, including from the submitting company. Breast Cancer Now has received 10% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from Breast Cancer Care and Breast Cancer Now participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.
Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis examining the impact of adding pertuzumab to a neoadjuvant regimen consisting of trastuzumab and docetaxel in adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence. While SMC experts have indicated there may be some differences in neoadjuvant regimens currently used in Scotland, trastuzumab and docetaxel are reasonable comparators. A time horizon of 40 years was adopted.

A Markov modelling structure was used which allowed for patients to be in states such as event-free survival (EFS), locoregional recurrence (and remission there from), metastatic non-progressed and metastatic progressed. In the base case, data informing the transition from EFS to locoregional recurrence or metastatic disease were taken from the NeoSphere study. In order to model EFS rates over the longer term, tpCR rates from NeoSphere were combined with data from the CTNeoBC analysis. The tpCR rates from NeoSphere were used to weight the CTNeoBC curves on EFS associated with response / non response. EFS data were extrapolated using a gamma function. For the progressed states, the transition probabilities were the same irrespective of prior treatment and were estimated from data from the control arm of the CLEOPATRA study which looked at use of the regimen in first-line metastatic breast cancer patients. The analysis assumed that after 7 years there was no further benefit of the pertuzumab regimen. It was also assumed that patients who were still event-free at 7 years would effectively be cured and their mortality risk would revert to that of the general population.

As no HRQoL data were available from the NeoSphere study, health state utilities were estimated from published studies and the utility values were as follows: EFS first year 0.749, EFS after first year 0.847 (with the same value assumed for the remission state), locoregional after first year 0.810, metastatic not progressed 0.685 and metastatic progressed 0.5. The only disutility for adverse events included was for alopecia, estimated at -0.114 from a published standard gamble study.

Medicines costs for 4 cycles of pertuzumab in the neoadjuvant setting were included. According to SMC clinical experts, standard care in this setting consists of 3 cycles of FEC and 3 cycles of trastuzumab plus docetaxel. Hence, the base case consisted of applying the costs of this regimen with the assumption that efficacy would not differ from that estimated for the actual comparator in NeoSphere of 4 cycles of trastuzumab plus docetaxel used for the model. The company noted that biosimilar trastuzumab IV is available and explored the impact of including this in the model in a scenario analysis.

The model also included adjuvant trastuzumab treatment in both arms post-surgery. A key change in this resubmission is the assumption that the mode of administration of trastuzumab in the adjuvant setting would differ depending on a patient’s neoadjuvant treatment. Initially the
company assumed all patients in the pertuzumab arm of the model would receive trastuzumab IV (Herceptin®) in both the neoadjuvant and adjuvant phases, whereas in the trastuzumab plus docetaxel arm 84% of patients were assumed to receive trastuzumab SC and 16% trastuzumab IV (Herceptin®). SMC clinical experts confirmed this assumption is not appropriate with most patients likely to receive trastuzumab SC in the adjuvant setting regardless of their neoadjuvant treatment. Therefore, revised results were provided which assumed the same mode of administration of adjuvant trastuzumab in both arms of the model (84% of patients assumed to receive trastuzumab SC and 16% trastuzumab IV [Herceptin®]) and the results of this revised base case analysis are presented instead.

Additional costs for the administration of pertuzumab were assumed to be 20% higher than the administration costs of trastuzumab plus docetaxel. Resource use for the model health states were estimated from a range of sources including expert clinical opinion, clinical guidelines and assumptions. Costs of cardiac monitoring were included. Post progression therapies used were assumed to be trastuzumab emtansine (67%), trastuzumab SC plus capecitabine (11%), trastuzumab IV plus capecitabine (5%), lapatinib plus capecitabine (5%) or capecitabine alone (12%).

A patient access scheme (PAS) for pertuzumab was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. A PAS was also accepted for trastuzumab IV (Herceptin®) and this was included in the analysis. With the PAS, the company estimated an incremental cost-effectiveness ratio (ICER) of £11,345 based on an incremental cost of £5,115 and a quality-adjusted life-year (QALY) gain of 0.451. The incremental cost was almost entirely composed of the costs of pertuzumab in the EFS state. There were some cost offsets for lower costs in subsequent states of the model but the predominant driver was the medicine acquisition cost of pertuzumab. Benefits were driven by life years / QALY gains in the EFS state. The key sensitivity analysis results are reported in table 3 below.

Table 3: Key sensitivity analysis results (with PAS)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>ICER (cost per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing the proportion of patients with pCR assumed to have a survival benefit from 100% to 80%</td>
<td>£16,486</td>
</tr>
<tr>
<td>Varying the transition probabilities by upper and lower limits</td>
<td>£9,588 - £12,507</td>
</tr>
<tr>
<td>Varying the pCR rates by the upper and lower 95% confidence intervals</td>
<td>£7,762 - £16,486</td>
</tr>
<tr>
<td>Assuming 6 cycles of pertuzumab (upper limit in SPC)</td>
<td>£20,075</td>
</tr>
<tr>
<td>Truncating treatment effect at 5 years</td>
<td>£15,156</td>
</tr>
<tr>
<td>30-year time horizon</td>
<td>£14,804</td>
</tr>
<tr>
<td>20-year time horizon</td>
<td>£21,987</td>
</tr>
</tbody>
</table>

ICER= incremental cost-effectiveness ratio, QALY = quality-adjusted life year, pCR = pathological complete response
In this resubmission the company provided a scenario analysis which explored the impact of including biosimilar trastuzumab IV in the model. In this scenario analysis, the cost of trastuzumab IV (Herceptin®) was replaced with the cost of biosimilar trastuzumab IV. The analysis assumed biosimilar trastuzumab IV would be available in practice at a discounted price. In this analysis the ICER was estimated to be £8,462 based on an incremental cost of £3,815 and a QALY gain of 0.451. This additional analysis is provided for information only as SMC process requires companies to use list prices or accepted PAS discount prices.

The following limitations and issues were noted:

- The assumption that the surrogate outcome of pCR will result in improved survival is uncertain. The results were sensitive to reducing the proportion of patients with pCR assumed to have a survival benefit. As noted in table 3, when this was reduced to 80% the ICER increased to £16,486. Discussions at SMC and responses from SMC clinical experts concluded it was reasonable to assume patients with pCR may have improved longer term outcomes but the magnitude of this benefit was uncertain. The company provided additional sensitivity analysis to further test this aspect of the model. This showed that when the proportion of patients with pCR assumed to have a survival benefit was reduced to 50% the ICER increased to £30,431. This was considered to be a particularly conservative analysis.

- There is uncertainty relating to the method used to extrapolate EFS based on the pCR surrogate outcome. In the base case analysis only relevant data for a HER2-positive patient population were used. This was tested by the company in a scenario analysis where the whole patient population data were used instead due to this being based on much larger patient numbers in the CTNeoBC study. This increased the ICER to £19,474.

- There are concerns as to the robustness of the modelling of EFS in the base case. The approach taken was relatively complicated, relying on a surrogate relationship observed in the literature between tpCR and EFS rather than using EFS data directly from the study. An alternative method of estimating EFS using more conventional approaches of extrapolating survival data by fitting an exponential parametric function was also provided, which increased the ICER to £16,782. It should be noted that there are also limitations with using the direct study evidence given that data immaturity meant that few endpoints had occurred, and it was based on an exploratory PFS secondary endpoint with a hazard ratio CI which included 1. As a result of these limitations, this standard approach to extrapolating EFS may be less robust than the base case method used, but is useful to explore as an alternative sensitivity analysis.

The Committee also considered the benefits of pertuzumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as pertuzumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted pertuzumab for use in NHS Scotland.
The National Institute for Health and Care Excellence (NICE) updated its guideline “Early and locally advanced breast cancer: diagnosis and management” in July 2018. With respect to primary systemic therapy, the guideline made the following recommendations:

- Neoadjuvant chemotherapy should be offered to people with oestrogen receptor-negative invasive breast cancer with the aim to reduce tumour size. In patients with triple-negative cancer, a regimen that includes a platinum agent and an anthracycline should be considered.
- In people with oestrogen receptor-positive invasive breast cancer, neoadjuvant chemotherapy can be considered as a tumour-size reducing measure. In those patients without a definite indication for chemotherapy, neoadjuvant endocrine therapy is an option. The benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy are summarised in the guideline.
- In patients with HER2-positive invasive breast cancer, pertuzumab in combination with trastuzumab plus chemotherapy can be offered as a neoadjuvant treatment regimen; this is in accordance with the NICE technology appraisal (TA424) published in 2016.

The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines on Primary Breast Cancer: Guidelines for diagnosis, treatment and follow-up were published in 2015. The guidelines state that there have been improvements in the pCR rate in the neoadjuvant setting, with dual anti-HER2 blockade associated with chemotherapy (trastuzumab + lapatinib, trastuzumab + pertuzumab) when compared with chemotherapy associated with one anti-HER2 agent. However, the role of dual HER2 blockade is not yet proven; the pCR rate improvement associated with trastuzumab + lapatinib did not translate into a long-term outcome, and results from the large adjuvant therapy study of trastuzumab + pertuzumab, APHINITY, are awaited. The guidelines state that the trastuzumab + pertuzumab combination can be considered an acceptable neoadjuvant therapy in selected higher risk cases, but could not be routinely recommended.

The Scottish Intercollegiate Guidelines Network published SIGN 134: Treatment of primary breast cancer in 2013. Neoadjuvant chemotherapy should be considered for all patients with breast cancer whose disease is either:
- inoperable (locally advanced or inflammatory) but localised to the breast / locoregional lymph node groups or
- the only surgical option is mastectomy and downstaging might offer the patient the opportunity for breast conservation.
- Anthracycline-taxane-based chemotherapy combinations should be considered for all patients receiving neoadjuvant chemotherapy.
- Patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy should receive trastuzumab, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy.
Pertuzumab would be used in addition to trastuzumab plus chemotherapy (with FEC* - docetaxel being the most common chemotherapy regimen used in NHS Scotland). Other chemotherapy regimens may require up to six cycles of pertuzumab to be administered.

*FEC=fluorouracil, epirubicin, cyclophosphamide

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC then pertuzumab + trastuzumab + docetaxel</td>
<td>FEC for 3 cycles then pertuzumab 840mg IV in cycle 1, then 420mg IV in cycles 2 and 3 plus trastuzumab 8mg/kg IV in cycle 1, then 6mg/kg in cycles 2 and 3 plus docetaxel 100mg/m² IV for 3 cycles</td>
<td>16,087</td>
</tr>
<tr>
<td>FEC then trastuzumab + docetaxel</td>
<td>FEC for 3 cycles then trastuzumab 8mg/kg IV in cycle 1, then 6mg/kg in cycles 2 and 3 plus docetaxel 100mg/m² IV for 3 cycles</td>
<td>6,507</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Doses are based on a body surface area of 1.8m² or a body weight of 70kg, where relevant. Costs from BNF Legacy online on 03 September 2018. FEC=fluorouracil 500mg/m² IV, epirubicin 100mg/m² IV, cyclophosphamide 500mg/m² IV. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. IV=intravenous.

### Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 163 patients in year 1 rising to 165 patients in year 5 with an estimated uptake of 60% (98 patients) in year 1 and 90% (148 patients) in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.*
References

14. West of Scotland Cancer Network. Clinical management guideline for breast cancer, v4.0


This assessment is based on data submitted by the applicant company up to and including 12 October 2018.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.