Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

pertuzumab 420mg concentrate for solution for infusion (Perjeta®)

SMC No. (1121/16)

Roche Products Limited

04 November 2016

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 Scotland. The advice is summarised as follows:

ADVICE: following a re-submission assessed under the orphan process

pertuzumab (Perjeta®) is not recommended for use within NHS Scotland.

Indication under review: For use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with human epidermal growth factor receptor 2 (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.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

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. Following surgery, patients should be treated with adjuvant trastuzumab to complete one year of treatment.

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.

Product availability date

28 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 authorization for use in both the metastatic and neoadjuvant settings.

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.[1,2]

Evidence of efficacy comes from two phase II studies, NeoSphere and TRYPHAENA.[1-5] 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 hydridisation. 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.[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^2 IV in cycle 1 then 75mg/m^2 or 100mg/m^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.[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).[1,3] 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, below.

Table 1: primary and some secondary outcomes for the NeoSphere study[1,3,4]

	Group A	**Group B**
N randomised	N=107	N=107
Primary outcome		
bpCR, % (n/N)	29% (31/107)	46% (49/107)
P-value for group A versus B	p=0.0141	-
Secondary outcomes		
tpCR, % (n/N)	22% (23/107)	39% (42/107)
Clinical response (CR + PR), % (n/N)	80% (79/99)	88% (89/101)
Time to clinical response, weeks	6.3	6.3
Progression-free survival (PFS) and disease-free survival (DFS) at 5-year follow-up		
PFS, %	81%	86%
Hazard ratio for group A versus B	0.69; 95% CI: 0.34 to 1.4	
DFS, %	81%	84%
Hazard ratio for group A versus B	0.60; 95% CI: 0.28 to 1.27	

N=total number of patients; n=number of responders; bpCR=pathological complete response in the breast; tpCR=total pathological complete response (defined as eradication of all invasive tumour from the breast [*in situ* disease might remain] and node negative at definitive surgery); CR=complete response; PR=partial response; CI=confidence interval. Clinical response was measured using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. PFS was defined as time from randomisation to the first documentation of progressive disease (excluding contralateral *in situ* disease), disease recurrence, or death; DFS was defined as time from the date of surgery to the first documentation of progressive disease (excluding contralateral *in situ* disease) or death.

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.[1,2,5]

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/m^2 IV then 75mg/m^2 or 100mg/m^2 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/m^2 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, below.[1,5]

Table 2: secondary outcomes for the TRYPHAENA study[1,5]

	Group A	Group B	Group C
N randomised	N=73	N=75	N=77
bpCR, % (n/N)	62% (45/73)	57% (43/75)	66% (51/77)
tpCR, % (n/N)	56% (41/73)	55% (41/75)	64% (49/77)
Clinical response (CR + PR), % (n/N)	92% (67/73)	95% (71/75)	89% (69/77)
Time to clinical response, weeks	3.6	6.3	4.9

N=total number of patients; n=number of responders; bpCR=pathological complete response in the breast; tpCR=total pathological complete response; CR=complete response; PR=partial response.

An ongoing, randomised, open-label, phase III study (GeparSepto) recruited treatment-naive women with primary invasive breast cancer to compare nanoparticle-based paclitaxel (nab-paclitaxel) with solvent-based paclitaxel as part of neoadjuvant chemotherapy. The HER2-positive subgroup received treatment with neoadjuvant epirubicin 90mg/m^2 IV, cyclophosphamide 600mg/m^2 IV and pertuzumab 420mg IV (840mg initial dose) on day one of four 21-day cycles, plus trastuzumab 6mg/kg IV (8mg/kg initial dose) every three weeks and continued for one year post-surgery. This was preceded by randomly assigned paclitaxel on days 1, 8 and 15 of four 21-day cycles: nab-paclitaxel 150mg/m^2 IV (125mg/m^2 after protocol amendment) or paclitaxel 80mg/m^2 IV. Final analysis of the primary outcome, pCR (defined as no invasive or non-invasive tumour in breast and axillary lymph nodes after neoadjuvant therapy), has been reported and was achieved by 62% (123/199) and 54% (106/197) of women with HER2-positive tumours in the respective paclitaxel groups.[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.[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%).[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.[3]

In the TRYPHAENA study, during the neoadjuvant phase, two patients (in group B) experienced symptomatic (≥grade 3) left ventricular systolic dysfunction (LVSD) and 11 patients had LVEF decline >10% from baseline to <50% (four patients in groups A and B and three patents in group C). No deaths were reported in the neoadjuvant phase.[5]

Summary of clinical effectiveness issues

HER2-positive breast tumours are associated with higher rates of recurrence and increased mortality.[1] For neoadjuvant treatment, pertuzumab would be used in addition to trastuzumab plus chemotherapy, for three to six cycles followed by trastuzumab, in the adjuvant setting, to complete one year of treatment.[2] The Scottish Intercollegiate Guidelines Network (SIGN) recommends anthracycline-taxane-based chemotherapy.[7] 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.

In the NeoSphere study, the addition of pertuzumab to trastuzumab plus docetaxel resulted in a significantly higher proportion of patients achieving a bpCR.[3] However, total pathological complete response (tpCR) is the preferred definition of pathological CR for regulatory purposes, and this was also achieved in a higher proportion of patients in group B (which included pertuzumab) than group A (39% versus 22%).[1,8] Furthermore, 5-year data showed favourable (but not significant) hazard ratios for progression-free survival (PFS) and disease-free survival (DFS) for the pertuzumab containing group, although the study was not powered to detect a difference in long-term outcomes.[1]

There is uncertainty as to whether bpCR or tpCR are surrogate markers for DFS and overall survival.[1,8,9] 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.[9] 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.[10] The European Medicines Agency (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[11]). Confirmatory study data for longer term outcomes are expected from the APHINITY study (conducted in the adjuvant setting) and the BERENICE study (a post-authorisation safety study conducted in the neoadjuvant setting).[1]

There was no control group in the TRYPHAENA study. However, 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.[1]

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.[2] The phase III GeparSepto study provided supportive evidence of the activity of dual HER2 blockade as neoadjuvant therapy in early breast cancer.

Clinical experts consulted by SMC considered that pertuzumab is a therapeutic advancement due to higher response rates seen in the pivotal study, although whether this translates into prolonged survival is not clear. They considered that the place in therapy of pertuzumab is as per its licensed indication. They reported that the most common chemotherapy regimen used is three cycles of FEC then three cycles of docetaxel. Pertuzumab would be administered for three cycles when used with this chemotherapy regimen. Clinical experts considered that the introduction of pertuzumab may impact on the patient and/or service delivery in terms of some additional time in clinic as well as management of additional adverse events. The submitting company considered that the pertuzumab-containing regimen could be managed as a day case. As the pivotal studies included trastuzumab as an IV infusion, use of the subcutaneous formulation of trastuzumab is not permitted within the pertuzumab-containing regimen.[2]

Summary of patient and clinician engagement

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 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 approach could be used to define a higher risk subgroup which may be a more cost effective treatment option.
- 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 the trial data did not support it, pertuzumab treatment may lead to less invasive 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 <5% pharmaceutical company funding in the past two years, including from the submitting company. Breast Cancer Now has received 0.62% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Breast Cancer Care and Breast Cancer Now also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

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. The analysis assumed that each neoadjuvant regimen would be given for three cycles. While SMC experts have indicated there may be some differences in neoadjuvant regimens currently used in Scotland, trastuzumab and docetaxel seemed broadly reasonable as 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 loco-regional 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.

Drug costs for 3 cycles of pertuzumab in the neoadjuvant setting were included. According to SMC clinical experts, standard of care in this setting tends to consist 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. Resource use for the model health states were estimated from a range of sources including expert clinical opinion, clinical guidelines and assumptions. Additional costs for the administration of pertuzumab were assumed to be 20% higher than the administration costs of trastuzumab plus docetaxel. Costs of cardiac

monitoring were included. Post progression therapies used were assumed to be capecitabine and vinorelbine.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of pertuzumab. The company was requested to provide results for a preferred base case which included capping of all utility values to the population norm and corrected an error in adverse event costing. This resulted in an incremental cost-effectiveness ratio (ICER) with the PAS of £24,843 per quality-adjusted life-year (QALY) with incremental costs of £9,026 and incremental QALYs of 0.363.

The incremental cost was almost entirely comprised 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 event-free state. Key sensitivity analyses are reported in table 3 below.

Table 3: Key sensitivity analysis results

	ICER (cost per QALY) with PAS
Reducing proportion of EFS patients with pCR assumed to have a survival benefit to 80% (from 100%)	£32,628
Varying the transition probabilities by upper and lower limits	£22,089 - £37,165
Varying pCR rates by the upper and lower 95% confidence intervals	£13,689 - £58,638
Assuming 6 cycles of pertuzumab (upper limit in SPC)	£37,183
Truncating the treatment effect at 5 years	£30.7k

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; PAS= patient access scheme; EFS= event-free survival; pCR= pathological complete response

The following limitations and issues were noted:

- A key change in the resubmission was the correction of an error in the method used to extrapolate EFS based on the pCR surrogate such that only relevant data for a HER2-positive patient population are used in the base case. This amendment has had a favourable impact on the ICER before all other changes considered. The company was, however, asked to provide a scenario analysis in which the whole patient population data are used instead due to this being based on much larger patient numbers in the CTNeoBC study than was available for the HER2 positive sub-population. This resulted in an ICER with PAS of £34,803 per QALY using the preferred base case assumptions.
- There are uncertainties and concerns as to the robustness of the modelling of EFS in the base case, which is an important driver of cost-effectiveness. 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 estimated poorer outcomes to the base case approach. The ICER with PAS associated with this analysis was £34,741/QALY, with incremental costs of £9,482 and incremental QALYs of 0.273 (also using the alternative base case settings). Key sensitivity analysis results for this alternative analysis are summarised in table 4 below. It should be noted that there are 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.

Table 4: Key sensitivity analysis results using more conventional survival modelling

	ICER (cost per QALY) with PAS
Alternative base case	£34,741
Varying the transition probabilities by upper and lower limits	£30,326 - £39,813
Truncating the treatment effect at 5 years	£47,652
Assuming 6 cycles of pertuzumab (upper limit in SPC)	£51,022
Extrapolating data by fitting a Weibull function	£29,411

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; PAS= patient access scheme;

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 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 was unable to accept pertuzumab for use in NHS Scotland.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published SIGN 134: Treatment of primary breast cancer in 2013.[7]

Neoadjuvant therapy

- 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.

The guidelines were developed prior to approval of pertuzumab in conjunction with trastuzumab and docetaxel for the indication under review.

Adjuvant trastuzumab

- Adjuvant trastuzumab should be considered in all patients with HER2-positive breast cancer who receive adjuvant chemotherapy.
- Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane-based regimens or sequentially.
- Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab.
- Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration.

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 80: Early and locally advanced breast cancer was published in February 2009.[12] It recommends trastuzumab given at three-week intervals for one year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early breast cancer following surgery, chemotherapy, and radiotherapy when applicable. Cardiac function should be assessed before starting treatment with trastuzumab and repeated every three months. No recommendations are made with regards neoadjuvant therapy or pertuzumab. The guidelines were developed prior to approval of pertuzumab in conjunction with trastuzumab and docetaxel for the indication under review.

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.[13] 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, trastuzumab + lapatinib treatment cannot be recommended because long-term improvements did not materialise. The guidelines state that the trastuzumab + pertuzumab combination can be considered an acceptable neoadjuvant therapy in selected higher risk cases, but the results from the large adjuvant APHINITY study are required before the treatment can be routinely recommended.

The European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO) 2nd international consensus guidelines for advanced breast cancer were published in 2014.[14] The guidelines state that for those individuals with previously untreated HER2-positive breast cancer, the preferred first-line therapy is the combination of chemotherapy alongside trastuzumab and pertuzumab since it is associated with an overall survival benefit. However, outside of clinical trials, the regimen should not be given beyond the first line setting. In patients with locally advanced breast cancer which is inoperable, systemic therapy (not surgery or radiotherapy) should be the initial treatment. Following effective neoadjuvant systemic therapy with or without radiotherapy, surgery will be possible in many patients.

Additional information: comparators

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

Drug	Dose Regimen	Cost per course (£)
FEC then pertuzumab + trastuzumab + docetaxel	**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/m^2 IV for 3 cycles**	**18,266**
FEC then trastuzumab + docetaxel	FEC for 3 cycles then trastuzumab 8mg/kg IV in cycle 1, then 6mg/kg in cycles 2 and 3 plus docetaxel 100mg/m^2 IV for 3 cycles	8,686

Doses are for general comparison and do not imply therapeutic equivalence. Doses are based on a body surface area of 1.8m^2 or a body weight of 70kg, where relevant. Costs from BNF Legacy online 19/07/16. FEC=fluorouracil 500mg/m^2 IV, epirubicin 100mg/m^2 IV, cyclophosphamide 500mg/m^2 IV. IV=intravenous. NB: trastuzumab is continued in the adjuvant setting (every 3 weeks, up to week 52)

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 426 patients in year 1, rising to 435 patients in year 5. This was on the basis of 15% of early breast cancer patients who were tested being HER2-positive. The estimated uptake rate was 60% in year 1 (256 patients) and 90% in year 5 (391 patients) and, without the PAS, the impact on the medicines budget was estimated at £3.1m in year 1 and £4.7m in year 5. No medicines were displaced as pertuzumab is added to an existing regimen of neoadjuvant therapy.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. The European Medicines Agency (EMA). European public assessment report. Pertuzumab (Perjeta®). 25/6/2015. EMA/CHMP/285991/2015. www.ema.europa.eu.

2. Pertuzumab concentrate for solution for infusion (Perjeta®). Summary of product characteristics. Roche Products Limited. Last updated 18 September 2015.

3. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012; 13(1): 25-32.

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This assessment is based on data submitted by the applicant company up to and including 16 September 2016.

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.