

Resubmission

pertuzumab 30mg/mL concentrate for solution for infusion (Perjeta®)
SMC No. (897/13)

Roche Products Ltd

05 May 2017

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 second resubmission assessed under the orphan medicine process

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

Indication under review: for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Addition of pertuzumab to current first-line treatment, trastuzumab plus docetaxel, significantly increased progression-free and overall survival for women with HER2-positive metastatic breast cancer.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

This advice takes account of 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 docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Dosing Information

An initial loading dose of 840mg intravenous (iv) infusion over 60 minutes, then 420mg iv infusion over 30 to 60 minutes every three weeks. An observation period of 30 to 60 minutes is recommended after each dose of pertuzumab and before commencement of any trastuzumab or docetaxel infusions. Patients should be treated with pertuzumab and trastuzumab until disease progression or unmanageable toxicity.

(The recommended dose of concomitant trastuzumab is an initial loading dose of 8mg/kg iv infusion then 6mg/kg iv infusion every three weeks and of concomitant docetaxel is 75mg/m² every three weeks. The dose of docetaxel may be increased to 100mg/m² if the initial dose is well tolerated. The medicines should be administered sequentially. Pertuzumab and trastuzumab may be given in any order, but docetaxel should be administered after these.)

Therapy should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. It should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation service is immediately available.

Patients must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥ 2.0 by in situ hybridisation (ISH) assessed by a validated test. To ensure accurate and reproducible results, the testing must be performed by a specialised laboratory, which can ensure validation of the testing procedure.

Product availability date

March 2013.

Pertuzumab meets SMC orphan-equivalent criteria.

Summary of evidence on comparative efficacy

Pertuzumab is the first monoclonal antibody that binds to subdomain II, the dimerisation domain, of human epidermal growth factor-2 (HER2) receptor. It blocks heterodimerisation of HER2 with other HER receptors, including HER1 (epidermal growth factor receptor [EGFR]), HER3 and HER4 and it also mediates antibody-dependent cell-mediated cytotoxicity. In pre-clinical studies, it has shown a synergistic effect with trastuzumab, an anti-HER2 monoclonal antibody, which binds to the HER2 receptor at subdomain IV.¹⁻⁴

A double-blind study (CLEOPATRA) recruited 808 patients with HER2-positive, unresectable locally recurrent or metastatic breast cancer who had not received chemotherapy or biologic therapy for metastatic disease. They were randomised in a 1:1 ratio to placebo or pertuzumab 840mg intravenous (IV) infusion, then 420mg iv infusion every three weeks until disease progression or unmanageable toxicity. These were administered in combination with iv infusions

of trastuzumab 8mg/kg then 6mg/kg every three weeks and docetaxel 75mg/m² every three weeks, with the dose increased to 100mg/m² if the initial dose was well tolerated.

The primary endpoint, progression-free survival (PFS), was defined as the time from randomisation to first documented radiographic evidence of progressive disease assessed by an independent review facility using Response Evaluation Criteria in Solid Tumours (RECIST), or death from any cause within 18 weeks of the last independent assessment of tumours. PFS was analysed via a log-rank test in the intention-to-treat (ITT) population, which comprised all randomised patients.²⁻⁴

After a median follow-up of 19.3 months, the primary analysis indicated that independently-assessed PFS was significantly improved with pertuzumab compared with placebo, with median times to disease progression of 18.5 and 12.4 months in the respective groups and a hazard ratio (HR) for progression or death of 0.62 (95% confidence interval [CI]: 0.51 to 0.75). At the cut-off for this analysis, there had been 165 deaths (43% of the pre-specified number for the final analysis of overall survival). There were fewer deaths in the pertuzumab group compared to the placebo group: 69 (17%) versus 96 (24%), with a HR of 0.64 (95% CI: 0.47 to 0.88, p=0.005). This did not meet the stopping boundary. At the final analysis of overall survival, after a median follow-up of 49.5 and 50.6 months, 168 (42%) and 221 (54%) patients in the pertuzumab and placebo groups, respectively, had died. Overall survival was significantly increased in the pertuzumab group compared with placebo, with a HR 0.68 (95% CI: 0.56 to 0.84, p<0.001). Kaplan-Meier estimated median survival with pertuzumab was 56.5 months and was 40.8 months in the placebo group in analysis that did not adjust for cross over of 48 patients from the placebo group to the pertuzumab group. When data from these patients was censored at crossover, the HR was 0.63 (95% CI: 0.52 to 0.78) and median overall survival was 56.5 and 39.6 months in the respective groups.²⁻⁵

Objective response rate, defined as an independently-assessed complete or partial response as per RECIST on two consecutive occasions at least four weeks apart, was analysed in patients who had measurable disease at baseline. At the cut-off for the primary PFS analysis, the objective response rate was significantly greater with pertuzumab compared with placebo, 80% versus 69%, with a treatment difference of 11% (95% CI: 4.2% to 18%).²⁻⁴ Pre-specified analyses of the Functional Assessment of Cancer Therapy-for Breast Cancer (FACT-B) questionnaire did not indicate a difference between treatment arms in quality of life.²

Summary of evidence on comparative safety

Almost all patients in both groups of the pivotal study experienced at least one adverse event and the majority were treatment-related. Adverse events that occurred with a higher incidence (at least 5%) in the pertuzumab group compared with the placebo groups were diarrhoea (67% versus 46%), rash (34% versus 24%), mucosal inflammation (28% versus 20%), febrile neutropenia (14% versus 7.6%) and dry skin (11% versus 4.3%). These were mainly mild to moderate in severity and occurred less frequently after discontinuation of docetaxel. Serious adverse events were reported by 34% and 26% of patients in the pertuzumab and placebo groups, respectively. The most common were febrile neutropenia (11% and 5%) and infections (11% and 7.3%).²⁻⁴

Particular attention was given to potential cardiac adverse events by the study investigators. In the pertuzumab group compared with placebo, there was a lower incidence of left ventricular systolic dysfunction of any grade (4.4% versus 8.3%) and of grade 3 or above (1.2% versus 2.8%). Among patients who had left ventricular ejection fraction (LVEF) assessed post-baseline,

significant decline, defined as a reduction of at least 10% to an LVEF less than 50%, was reported by 3.8% and 6.6% in the pertuzumab and placebo groups, respectively.²⁻⁴

Summary of clinical effectiveness issues

HER2-positive metastatic breast cancer is an aggressive subtype of breast cancer despite the introduction of trastuzumab. SMC clinical experts highlighted unmet need due to the aggressive nature of the disease and also advised that it particularly affects younger patients and has a tendency to cause central nervous system metastases which are often devastating. Pertuzumab meets SMC orphan-equivalent criteria although it is not designated an orphan drug by the European Medicines Agency (EMA).

Pertuzumab is a first-in-class medicine that produces improvements of 6 months in median PFS and 16 months in overall survival, compared with current first-line treatment of HER2-positive metastatic breast cancer. An increase in overall survival of this magnitude has acknowledged clinical relevance. The data supporting these benefits derive from a well designed and conducted double-blind randomised controlled study, with an independently assessed primary outcome.²⁻⁵

In the CLEOPATRA study, the proportion of patients who had received prior (neo-) adjuvant therapy with trastuzumab was lower than expected in clinical practice: 12% (n=47) in the pertuzumab group and 10% (n=41) in the placebo group. Current adjuvant treatment of women with HER2-positive, node-positive breast cancer or women with HER2-positive node-negative tumours >1cm in size would include trastuzumab. The patients in the study who had received (neo-) adjuvant trastuzumab were mainly from North America and the EU and had demography similar to entire European and ITT study populations. Exploratory post-hoc analysis in this subgroup indicated that the treatment effects on independently-assessed PFS, HR 0.62 (95% CI: 0.35 to 1.07) and overall survival, HR 0.68 (95% CI: 0.30 to 1.55) were similar to those in the total study population. Similarly, only 14% (109/808) of patients had their docetaxel dose up-titrated to 100mg/m². However, treatment effect for PFS in the subgroup who did not have dose escalation, HR 0.62 (95% CI: 0.50 to 0.76), was similar to that in the subgroup who did, HR 0.65 (95% CI: 0.37 to 1.13).² At the time of the final analysis the HR for overall survival within the 88 women previously treated with trastuzumab was 0.80 (95% CI: 0.44 to 1.47), the interaction p-value was not reported for this subgroup analysis.^{5,6}

At the time of the final analysis the HR for overall survival in women with non-visceral disease (n=178) was 1.11 (95% CI: 0.66 to 1.85) and in women with visceral disease (n=630) was 0.59 (95% CI: 0.48 to 0.74). The interaction p-value was 0.03. The HR for investigator assessed PFS was 0.83 (95% CI: 0.58 to 1.18) in those with non-visceral disease and 0.64 (95% CI: 0.53 to 0.76) in those with visceral disease. The interaction p-value was 0.19.⁵

At the primary analysis the proportions of patients receiving subsequent treatment for breast cancer after discontinuing the study regimen were 76% (225/298) in the pertuzumab group and 77% (260/338) in the placebo group. Patients and investigators remained unaware of treatment allocation and pertuzumab was not allowed as a subsequent breast cancer treatment. After a subsequent interim analysis of overall survival at cut-off May 2012, patients in the placebo group without disease progression could cross over to receive pertuzumab and 48 patients crossed over. At the final analysis for overall survival, 77% (258/335) and 80% (291/369) of patients initially assigned to the pertuzumab and placebo groups had received treatment after discontinuing study treatment, with 73% (188/335) and 72% (208/369), respectively, having anti-HER-2 therapy. The

treatments received and the pattern of use of cytotoxic agents were generally balanced between the groups.

The study population contained only 19 patients with locally recurrent disease and 19 patients aged 75 years or more. Therefore, there are limited data in these groups.²

The addition of pertuzumab to trastuzumab and docetaxel did not appear to increase cardiac toxicity. However, it should be noted that median LVEF was 65%, and only 7.8% of the study population had LVEF of 50% to 55%. Also, only a minority of patients had been exposed to anthracyclines in the adjuvant setting.

The CLEOPATRA study demonstrated benefits relative to trastuzumab plus docetaxel. There are no direct comparative data with the other standard first-line treatment of HER2-positive metastatic breast cancer, trastuzumab plus paclitaxel. Therefore, a naïve indirect comparison of docetaxel and paclitaxel in this setting was performed using data from the pivotal studies that supported the licensed indications for trastuzumab in combination with paclitaxel (H0648g) and docetaxel (M77001) in HER2-positive metastatic breast cancer.^{7,8} This was supported by data from a direct comparison of the taxanes in the adjuvant setting.⁹ The assumption of similar clinical effectiveness for these treatment regimens derived from this is based on judgement, rather than analyses. Scottish clinical experts have advised that they tend to use 3-weekly docetaxel in patients with good performance status and weekly paclitaxel in patients who are less able to tolerate docetaxel, as the paclitaxel regimen appears to be associated with less severe adverse effects. The clinical experts' responses did not indicate any perceived differences in efficacy. However, their treatment strategy appears to indicate that they prefer docetaxel where possible.

Scottish clinical experts considered that pertuzumab, in combination with trastuzumab and docetaxel, is a therapeutic advancement given the significant increase in PFS and overall survival without an increase in cardiac side-effects.

Trastuzumab in combination with chemotherapy can be given using an IV preparation or a subcutaneous formulation and it is the subcutaneous formulation that is now routinely used in clinical practice. The summary of product characteristics for pertuzumab notes that it should be given in combination with IV trastuzumab and IV docetaxel. Clinical experts noted potential service implications associated with IV trastuzumab.

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 medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Secondary breast cancer is a severe and life-limiting condition. This HER2 positive subtype is aggressive with a poor prognosis. Commonly it affects women at a younger age. Disease progression results in increasingly difficult and debilitating symptoms which can have a significant effect on everyday activities, relationships and has a profound psychological impact.

- Pertuzumab significantly improves overall survival and the time gained is also of high quality. This longer response at first line delays the time to further chemotherapy which is highly valued as there would be fewer hospital visits and less reliance on carers and healthcare professionals as a result.
- Adverse effects of pertuzumab were reported as having little impact on patients' day to day lives.
- Patient groups advised that carers and families reported benefits of enabling the patient to enjoy a prolonged period of normality, where they are essentially well and can pursue a full life; returning to work, caring for families, resuming interests and social life, such family holidays and remaining fit and well for longer, contributing to society and the economy.
- The PACE group expressed very strong support for pertuzumab, describing it as a major advance. The normality of life observed in patients treated with this medicine has a wide ranging positive impact.
- The PACE group noted that there was an unmet need to maintain equity of care with other similar countries where pertuzumab is now part of standard treatment. It was highlighted that this presents a risk to the eligibility of Scottish oncology centres to participate in future clinical studies of other new medicines, which could potentially increase inequity of care and reduce survival for Scottish patients compared with patients in other countries.

Additional Patient and Carer Involvement

We received a joint patient group submission from Breast Cancer Care and Breast Cancer Now, both are registered charities. Breast Cancer Care has received less than 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 both charities participated in a meeting to update the original PACE statement. The key points of their joint submission have been included in the full updated PACE statement.

Summary of comparative health economic evidence

The company submitted a cost- utility analysis comparing pertuzumab in combination with trastuzumab and docetaxel to trastuzumab plus docetaxel or trastuzumab plus paclitaxel, for the treatment of adult patients with HER2 positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy. SMC clinical experts confirmed the comparators were appropriate.

A partitioned survival model was used over a 25 year time horizon which included three health states: progression-free, progressed disease and death. The model used estimated parametric survival functions for both overall survival and PFS. The source of the clinical data was the CLEOPATRA study. ⁶ In this resubmission, the model used the data from the final analysis. For the comparison with paclitaxel, the company assumed the results of the trastuzumab plus docetaxel arm would generalise to patients treated with paclitaxel. In order to extrapolate the clinical effects over time, the company used the log-logistic function to estimate PFS and the gamma function to estimate overall survival. The rationale for the selection of these parametric functions was based on goodness of fit statistics and visual inspection.

The utility values used in the model were taken from a published study.¹⁰ This study reported the results of 100 members of the public asked to value various health states and side effects associated with metastatic breast cancer using standard gamble. To estimate utility values for patients in the PFS health state, the model included a treatment-specific weighted average of the published values for stable disease and treatment response based on the response rates in the pivotal study. This resulted in PFS utility values of between 0.792 and 0.810 and a progressed disease utility value of 0.503. Within this resubmission, utility values were revised to account for the updated clinical data based on the final analysis dataset. Disutilities due to adverse events were also included.

Drug acquisition costs were included in the analysis along with administration and monitoring costs associated with each treatment. In terms of administration, the base case analysis assumed patients would receive trastuzumab IV in the intervention arm and subcutaneous trastuzumab in the comparator arms. Although the cost of subcutaneous administration is likely to be less than IV administration, the analysis assumed little difference between IV and subcutaneous administration costs. Post- progression drug costs for vinorelbine and capecitabine were also included. Health state costs for PFS and post-progression survival consisted of GP, clinical nurse specialist and community nurse contact costs. The economic model included the cost associated with grade 3 and 4 adverse events. Palliative care costs were also included.

A complex Patient Access Scheme (PAS) was proposed by the submitting company and accepted by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Without the PAS, the base case analysis for pertuzumab plus trastuzumab and docetaxel versus trastuzumab plus docetaxel resulted in an incremental cost-effectiveness ratio (ICER) of £124,629 based on an incremental cost of £116,254 and an incremental quality-adjusted life-year (QALY) gain of 0.93. When compared to trastuzumab and paclitaxel the ICER was £118,220 based on an incremental cost of £110,312 and an incremental QALY gain of 0.93.

The company provided both deterministic and probabilistic sensitivity analyses. The key results of the deterministic sensitivity analysis for the comparison with trastuzumab and docetaxel are presented in the table below;

Table: Key sensitivity analysis results versus trastuzumab plus docetaxel

Parameter	ICER (without PAS)
Duration of treatment (PFS only)	£169,680
Overall survival (estimated using Gompertz)	£162,811
Time horizon (10 years)	£157,643
Utility value for PFS state reduced in both arms (0.64 for in both arms)	£150,602

The following limitations were noted:

- There is some uncertainty surrounding the overall survival extrapolation approach used in the base case and the validity of the overall survival estimates. The company used a slightly different approach in this resubmission whereby they modelled overall survival using a gamma curve, whereas previously an exponential curve was applied to the tail of the Kaplan Meier data. The SMC statistical advisor has noted that the approach used may not be robust. The sensitivity analysis using alternative parametric functions showed that the results were not overly sensitive to most curves except using the Gompertz curve which increased the ICER to £162,811 without PAS. The company was asked to provide some means of validating overall survival estimates results but indicated that this was not possible. However, a simple comparison of median survival in the study with median survival estimated using alternative survival curves provided some support for the base case analysis where the gamma curve was used.
- Previously, the company assumed the same administration cost in both arms of the model but acknowledged that this would underestimate the cost in the pertuzumab arm as an additional 30 minutes administration time would be required. Within this resubmission the base case accounted for differences in administration costs by using trastuzumab IV costs in the intervention arm and subcutaneous trastuzumab costs in the comparator arms. Although this approach seems reasonable, within the model there was little difference in administration costs between the treatment arms. The company acknowledged this was due to an error in the model and subsequently provided corrected results which are quoted above. Additional sensitivity analysis was also provided which increased the proportion of patients receiving subcutaneous trastuzumab which resulted in a small increase in the ICER.
- Treatment-specific utility values were included in the base case analysis based on the reported objective response rate from the pivotal study. However, sensitivity analysis was provided where the same utility values were used in each arm and this did not have a major impact on the results.

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 the criterion for a substantial improvement in life expectancy was satisfied. In addition, as pertuzumab is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, 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.

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

Additional information: guidelines and protocols

In September 2013 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline 134: Treatment of primary breast cancer. This recommends adjuvant anthracycline-taxane combination chemotherapy should be considered for all patients with breast cancer where the additional benefit outweighs risk. Adjuvant trastuzumab should be considered in all patients with HER-2 positive breast cancer who receive adjuvant chemotherapy. Trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane based

regimens or sequentially. It recommends that 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 HER-2 positive breast cancer receiving neoadjuvant chemotherapy should receive trastuzumab, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy.¹¹

In 2014 the European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO) published ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). This notes that the backbone of anthracyclines and taxanes are the backbone of chemotherapy regimens. For HER-2-positive disease anthracyclines should not be administered concurrently with trastuzumab. It is recommended that anti-HER-2 therapy should be offered early to all patients with HER-2-positive metastatic breast cancer, except in the presence of contraindications to the use of such therapy. For patients with oestrogen receptor-positive / HER-2-positive metastatic breast cancer for whom endocrine therapy was chosen over chemotherapy, anti-HER-2 therapy and endocrine therapy should be considered with the initiation of endocrine therapy (provided that further anti-HER-2 therapy is available) since anti-HER-2 therapy (either trastuzumab or lapatinib) in combination with endocrine therapy has shown substantial PFS benefit compared with endocrine therapy alone. The addition of anti-HER-2 therapy in this setting has not led to a survival benefit. Patients whose tumours progress on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway. The optimal duration of anti-HER-2 therapy for metastatic breast cancer is currently unknown.¹²

In February 2009 the National Institute for Health and Care Excellence (NICE) published clinical guideline number 81, advanced breast cancer: diagnosis and treatment. This was updated in July 2014 and was assessed as requiring to be updated in November 2015. It recommends that on disease progression, systemic sequential therapy should be offered to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.¹³

Additional information: comparators

The current first-line chemotherapy regimen for metastatic or locally recurrent unresectable breast cancer in patients who have not received a taxane over the preceding year is a taxane (docetaxel or paclitaxel) plus trastuzumab. Pertuzumab is likely to be added to trastuzumab and docetaxel, to create a new regimen of pertuzumab, docetaxel and trastuzumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
Pertuzumab Docetaxel Trastuzumab	840mg, then 420mg IV every 3 weeks 75mg/m² then 100mg/m² IV every 3 weeks 8mg/kg, then 6mg/kg IV every 3 weeks	7,140 for cycle 1 then 4,489
Docetaxel Trastuzumab	100mg/m ² IV every 3 weeks 8mg/kg, then 6mg/kg IV every 3 weeks*	2,501 for cycle 1 then 2,094
Paclitaxel Trastuzumab	80mg/m ² IV every week 8mg/kg, then 6mg/kg IV every 3 weeks*	2,531 for cycle 1 then 2,214
Paclitaxel Trastuzumab	175mg/m ² IV every 3 weeks 8mg/kg, then 6mg/kg IV every 3 weeks*	2,297 for cycle 1 then 1,890

Doses are for general comparison and do not imply therapeutic equivalence. Costs from British National Formulary (BNF), November 2016 and based on 70kg body weight and 1.8m² body surface area. Costs do not take any patient access schemes into consideration. IV = intravenously. Costs calculated using full cost of ampoule or vial, assuming wastage. * Trastuzumab could also be given as 600mg subcutaneously every three weeks (no loading dose required), which has equivalent cost compared to the 6mg/kg IV dose for a 70kg patient.

Additional information: budget impact

The submitting company estimated there would be 244 patients eligible for treatment with pertuzumab in year 1 rising to 983 patients in year 5 to which confidential estimates of treatment uptake were applied.

Without the PAS, the gross impact on the medicines budget was estimated to be £4.1m in year 1 and £22.5m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £2.8m in year 1 and £16.5m in year 5.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission.

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12. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Annals of Oncology 2014; 25: 1871-88 and The Breast 2014; 23: 489-502.
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This assessment is based on data submitted by the applicant company up to and including 17 February 2017.

**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_statements/Policy_Statements

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.