Recommendation No. 134/2021
of 3 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the reimbursement of Phesgo (pertuzumab + trastuzumab) under the drug programme
"Treatment of patients with breast cancer (ICD-10 C50)"

The President of the Agency recommends the reimbursement of Phesgo (pertuzumab + trastuzumab) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)" in a new limit group and dispensing it free of charge provided that the price is reduced.

Grounds for the recommendation

The clinical analysis was based on two randomised clinical trials – FeDeriCa and PHranceSCa. The FeDeriCa study compared pertuzumab/trastuzumab for subcutaneous injection (PERT/TRAS SC) with pertuzumab and trastuzumab therapy for intravenous infusions administered as separate formulations (PERT IV+TRAS IV). The study included a period of neoadjuvant treatment, followed by surgery and 14 cycles of adjuvant anti-HER2 therapy.

The study showed no differences in the rate of complete pathological response after neoadjuvant treatment and the rate of clinical response to neoadjuvant treatment. Pharmacokinetic studies proved that the concentration of pertuzumab and trastuzumab following subcutaneous administration was not lower than the concentration obtained in the case of intravenous administration.

The PHranceSCa study compared two treatment regimens which consisted of PERT IV + TRAS IV (cycle 1-3), then PERT / TRAS SC (cycle 4-6) in group A, and in group B: PERT IV therapy + TRAS IV (cycle 1-3) followed by PERT / TRAS SC (cycle 4-6). In the study, the period of neoadjuvant treatment was analysed (6 cycles of the cross-over phase + continuation of therapy).

The results of the PHranceSCa study in relation to the assessment of the impact of treatment on health-related quality of life (HRQoL) reveal that the recorded mean changes were minimal or similar for both interventions. The assessment of the impact of the route of neoadjuvant therapy administration on the quality of life of the patients proved that in 4 out of 5 domains of the

questionnaire (satisfaction with treatment, impact on psychological functioning, impact on the performance of day-to-day activities, treatment comfort), the mean scores after the period of treatment with subcutaneous therapy were higher than after the period of treatment with intravenous therapy. However, it is not possible to determine whether the differences were also clinically significant because the questionnaire used for the assessment was not validated and minimal clinically significant differences were not determined.

According to the results of the study, the majority of patients (85%) preferred the subcutaneous route of administration. 13% of patients preferred the intravenous route of administration. Furthermore, the majority of patients (86.9%) chose the subcutaneous form of anti-HER2 adjuvant therapy for continuation of treatment when the cross-over phase was completed. The intravenous form was chosen by 13.1% of patients.

The economic analysis was performed with the use of cost-minimisation analysis from the NHF perspective. According to the estimates in the applicant's basic analysis, the use of Phesgo compared to PERT IV + TRAS SC, taking into account the proposed RSS, will be [information protected as a trade secret]in neoadjuvant therapy for early breast cancer and [information protected as a trade secret] in the treatment of advanced breast cancer. In turn, compared with the PERT IV+TRAS IV therapy, the use of Phesgo, taking into account the proposed RSS, will be [information protected as a trade secret] in neoadjuvant therapy for early breast cancer and [information protected as a trade secret] in advanced breast cancer.

The results of the basic variant of the budget impact analysis indicate that, taking into account the RSS, the payer's expenses may [information protected as a trade secret]

The main limitations of the analysis include the lack of primary studies that would fully correspond to the analysed population (no studies were found that would analyse the use of the assessed intervention in patients with advanced HER2-positive breast cancer) as well as to the established comparator (no studies were found that would directly compare the assessed intervention to the treatment with pertuzumab administered intravenously in combination with trastuzumab administered subcutaneously). Additionally, in terms of assessing the efficacy of therapy with Phesgo compared to the PERT IV+TRAS IV therapy, results related to pathological complete response and clinical response from the period of neoadjuvant treatment are the only ones available. It should also be emphasised that the RCTs included in the clinical analysis were performed without blinding.

The adopted period of therapy for advanced breast cancer constitutes a limitation of the estimates presented in the economic analysis submitted by the applicant. The length of the PERT+TRAS therapy in the basic analysis may be overestimated. However, the results of the sensitivity analysis for shorter time horizons and an average number of treatment cycles for advanced breast cancer of 21 cycles [information protected as a trade secret]

In turn, the main limitation of the estimates presented in the budget impact analysis is the forecast of the level of substitution of alternative therapies (PERT IV+TRAS SC and PERT IV+TRAS IV) used in the target population with Phesgo. [information protected as a trade secret]

In addition, the applicant assumed that the acquisition of market shares by Phesgo following its reimbursement would be at the same level for all indications in the target population (pre-surgery treatment, first-line treatment of advanced cancer). The above-mentioned assumptions of the applicant are inconsistent with the opinion of the regional consultant in the field of clinical oncology.

Two out of five agencies that assessed Phesgo were negative in terms of its reimbursement taking into account the proposed scope of indications and the proposed price conditions.

It is worth noting that the reimbursement of Phesgo may lead, in the future, to the untapped potential related to the reduction in the price of pertuzumab due to the expiry of the period of Perjeta market exclusivity in 2024 and the reimbursement of Perjeta equivalents. Given the doubts as to the actual cost of the estimates, it is reasonable to seek a reduction in the price of the drug in

question.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Phesgo, Pertuzumabum + Trastuzumabum, solution for injection, 600 mg + 600 mg, 1 vial 10 ml, EAN code: 07613326036191, for which the proposed net sales price is [information protected as a trade secret]

- Phesgo, Trastuzumabum + Pertuzumabum, solution for injection, 600 mg + 1,200 mg, 1 vial 15 ml, EAN code: 07613326036023, for which the proposed net sales price is [information protected as a trade secret]

Proposed payment and dispensing category: free of charge, the drug is to be applied under the drug programme as part of a new limit group. The applicant has submitted a proposal for a risk-sharing scheme.

Health problem

Breast (mammary) cancer is a malignant tumour that originates in the epithelium of the ducts or lobules of the mammary gland. Causes of breast cancer are still unknown (in nearly 75% of women) but there are many factors that increase the risk of developing it (including gender, age, genetic and hormonal burden, lifestyle).

According to Globocan data, breast cancer is one of the most common malignant neoplasms among women in Poland. In 2020, breast cancer accounted for approximately 24% (24,644 patients) of all new cases of malignant neoplasms and over 16% (8,805 patients) of deaths due to malignant neoplasms among women with no age limit. It should be stressed that breast cancer in men is a very rare disease (based on Globocan data, it is not possible to estimate its incidence and mortality accurately, but it is approx. 1%).

Approximately 20% of patients with breast cancer are found to have a HER2-positive biological subtype of this cancer. The status of the HER2 receptor is determined with the use of the immunohistochemical technique and it is classified as negative (0, 1+) or positive (3+). Borderline values (2+) require the assessment of the number of HER2 gene copies with the use of fluorescence in situ hybridisation method (FISH). The HER2-positive subtype of breast cancer is associated with a more aggressive course of the disease, shorter survival time until disease recurrence after radical treatment and overall survival.

Approximately 85% of relapses occur during the first 5 years after treatment. The 5-year survival rates, depending on the stage of disease advancement, are as follows: I - 95%, II - 50%, III - 25%, IV - <5% (the average 5-year survival rate in Poland is 74%).

Alternative health technology

In view of clinical guidelines and currently publicly funded technologies, combination therapy with pertuzumab (for intravenous administration) and trastuzumab (for intravenous or subcutaneous administration), further combined with chemotherapy a and identical to those specified for the proposed intervention, should be considered as comparators.

Description of the proposed intervention

Pertuzumab and trastuzumab are recombinant humanised IgG1 class monoclonal antibodies that target the human epidermal growth factor receptor type 2 (HER2). Both substances bind to specific HER2 subdomains without competing with each other and have complementary mechanisms to disrupt the HER2 signalling pathway:

- Pertuzumab targets the extracellular dimerisation domain (subdomain II) of HER2 and blocks ligand-dependent heterodimerisation of HER2 with other members of the HER family, including the epidermal growth factor receptor (EGFR), HER3 and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signalling through two major signalling pathways: mitogen-activated kinase (MAP) and phosphoinositol-3 kinase (PI3K). Inhibition of those signalling pathways can cause cell growth arrest and apoptosis.
- Trastuzumab binds to subdomain IV of the extracellular domain of the HER2 protein to inhibit ligand-independent and HER2-mediated signalling of proliferation and survival of HER2-overexpressing tumours in human cells.

According to the Summary of Product Characteristics (SmPC), Phesgo is indicated for use:

- in combination with chemotherapy:
    - neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer with a high risk of recurrence
    - adjuvant treatment of adult patients with HER2-positive early-stage breast cancer with a high risk of recurrence
- in combination with docetaxel in adult patients with HER2-positive metastatic breast cancer or unresectable local recurrence who have not been previously treated with anti-HER2 therapy or chemotherapy for a metastatic disease.

The proposed reimbursement indication is included in the registration indication.

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

The applicant based the clinical and economic analysis on two randomised, unblinded studies:

- FeDeriCa - phase III study that covered 500 patients and compared:
    - Intervention: pertuzumab/trastuzumab for subcutaneous injection - combined preparation; loading dose 1,200/600 mg, maintenance doses 600/600 mg every 3 weeks;
    - Comparator: pertuzumab + trastuzumab for intravenous infusions - different preparations; loading dose 840 mg + 8 mg / kg, maintenance doses 420 mg + 6 mg / kg.

  The follow-up period was
    - Pharmacokinetic assessment - 7 neoadjuvant treatment cycles;
    - Assessment of efficacy and safety - from the beginning of neoadjuvant treatment (8 cycles) until the end of surgical treatment;
    - Safety analysis update - additional 12 months in relation to the main analysis;
- PhranceSCa - phase II study that covered cross-over groups and included 160 persons that compared:
    - Intervention: pertuzumab/trastuzumab for subcutaneous injections - combined

preparation; loading dose 1,200/600 mg, maintenance doses 600/600 mg every 3 weeks; 3 cycles;

- Comparator: pertuzumab + trastuzumab for intravenous infusions - different preparations; loading dose 840 mg + 8 mg / kg, maintenance doses 420 mg + 6 mg / kg; 3 cycles.

The follow-up period was 6 adjuvant treatment cycles.

According to the assessment based on Cochrane Collaboration recommendations, both studies are characterised by a low risk of bias in most of the assessed domains. Due to the lack of blinding in the studies, there is a likelihood of bias in obtained results, particularly in the case of results that are affected by subjective judgement of the researcher. Moreover, it is uncertain whether the awareness of doctors and patients of the therapies affected the studies or the way the patients were looked after. With this in mind, in the Agency's assessment, the risk of bias related to failure to blind patients and personnel should be considered unclear and the risk related to failure to blind the assessment of the results should be considered high.

Efficacy

Neoadjuvant treatment

The FeDeriCa study showed no statistically significant differences between PERT/TRAS SC (Phesgo) and PERT IV + TRAS IV when it comes to:

- rate of complete pathological response after neoadjuvant treatment – 59.7% vs 59.5% respectively;
- rate of clinical response to neoadjuvant treatment – 83.1% vs 85.3% respectively.

According to the study protocol, a non-inferior serum trough concentration of pertuzumab in cycle 7 of the treatment in the PERT/TRAS SC and PERT IV + TRAS IV groups was reported if the lower limit of the 90% CI of the geometric mean ratio (GMR) for this parameter was 0.8 or higher. The geometric mean ratio of the serum trough concentration of pertuzumab in cycle 7 in the PERT/TRAS SC group compared to the PERT IV + TRAS IV group was 1.22 (90% CI: 1.14; 1.31), and the GMR of the serum trough concentration of trastuzumab in cycle 7 was 1.33 (90% CI: 1.24 ; 1.43). For both parameters, the lower limits of the 90% confidence interval for the GMR were greater than 0.8 (predefined non-inferiority margin), which is a statistical confirmation that the concentration of pertuzumab and trastuzumab following subcutaneous administration was not lower than the concentration obtained during intravenous administration.

Exposure to pertuzumab and trastuzumab, expressed by the value of the area under the curve (AUC) of the serum drug concentration on days 0-21, was similar in both groups. The mean maximum serum concentration of pertuzumab and trastuzumab in cycle 7 was lower in the subcutaneous therapy group than in the intravenous therapy group. The time necessary to reach peak concentration (Tmax) was higher in the subcutaneous group compared to the intravenous group.

Adjuvant therapy

The results of the PHranceSCa study that assessed the impact of treatment on health-related quality of life (HRQoL), expressed as mean changes in the EORTC QLQ-C30 Global Health Status score compared to the initial value after the first and second cross-over phases and until cycle 15 of adjuvant treatment or its completion, indicate that the mean changes were minimal and comparable between the assessed interventions. Thus, the study showed no difference between the groups regarding the impact of treatment on HRQoL.

The PHranceSCa study also assessed, with the use of the TASQ questionnaire, the impact of the route of neoadjuvant therapy administration on the quality of life of the patient. In 4 out of 5 domains included in the questionnaire (satisfaction with treatment, impact on psychological functioning, impact on the performance of day-to-day activities, comfort of treatment), the mean scores after the period of treatment with subcutaneous therapy were higher than after the period of treatment with

intravenous therapy. The differences in the means between the groups were IS and were MD=23.40; MD=0.80; MD=1.60; MD=33.20 respectively. Only for the domain "impact on physical functioning", the mean score after subcutaneous treatment was lower than that after intravenous treatment (MD=-5.20). It is not possible to determine whether the differences were also clinically significant because the TASQ questionnaire was not validated and minimal clinically significant differences were not determined.

Safety

In the FeDeriCa study, 2 deaths due to adverse events were reported in patients treated in the pre-surgery period, one death in each group - PERT/TRAS SC (cause of death: acute myocardial infarction that occurred before the anti-HER2 therapy was initiated) and PERT IV + TRAS IV (cause of death: urosepsis). None of the adverse events was found to have occurred due to anti-HER2 treatment. There were 2 deaths in post-surgery treatment, one in the PERT/TRAS SC group (cause of death: unknown) and one in the PERT IV + TRAS IV group (cause of death: heart failure). Death due to heart failure of the patient undergoing the intravenous treatment regimen was considered treatment-related. The differences between the groups were not statistically significant.

No fatal adverse events were reported in the PHranceSCa study.

In both studies, FeDeriCa and PHranceSCa, the proportion of patients with at least one adverse event was similar in both study groups - at least one grade 3-5 event, at least one serious adverse event.

In the FeDeriCa study, in patients undergoing adjuvant therapy, in the subcutaneous therapy group, there was a statistically significantly higher occurrence of adverse events related to anti-HER2 treatment compared with the intravenous treatment group: PERT/TRAS SC 60.1% vs PERT IV + TRAS IV 46.8%; RR=1.28 (95% CI: 1.09; 1.51), NNH = 8 (95% CI: 5; 22). There were no differences between the groups for the neoadjuvant treatment group. The proportion of patients who experienced an adverse event leading to anti-HER2 therapy discontinuation was comparable in both groups – both in pre- and post-surgery patients. In the PHranceSCa study, in the group of patients undergoing subcutaneous therapy, there was a statistically significantly higher rate of adverse events, possibly treatment-related ones, compared to that rate in the intravenous group: PERT / TRAS SC 36.3% vs PERT IV + TRAS IV 18.8%; RR = 1.93 (95% CI: 1.32, 2.83), NNH = 6 (95% CI: 4, 13).
The proportion of patients who experienced adverse events leading to the discontinuation of treatment with any drug used in the study was comparable in both groups.

The comparative analysis results for grade 1 or 2 adverse events that occurred in ≥1 of the FeDeriCa study groups, performed for patients undergoing neoadjuvant therapy, prove that the rate of adverse events was comparable in both study groups. The most common adverse events were: alopecia, nausea, diarrhoea and anaemia. In the FeDeriCa study, in the group undergoing subcutaneous therapy, the following adverse events were statistically significantly more frequent than in the intravenous group: local infusion/injection-related reactions that occurred up to 24 hours after drug administration in the group of patients undergoing adjuvant treatment. The following adverse events were less frequent in the subcutaneous therapy group than in the control group:

- neutropenia or neutropenic fever in patients undergoing adjuvant therapy - RR=0.64 (95% CI: 0.42; 0.97), NNT=15 (95% CI: 8; 181);
- grade ≥3 cardiac dysfunction throughout the study period - RR = 0.25 (95% CI: 0.07, 0.89), NNT = 29 (95% CI: 16, 169);
- injection/infusion-related reactions that occurred within 24 hours of anti-HER2 treatment - RR=0.12 (95% CI: 0.04; 0.38), NNT=11 (95% CI: 8; 20);
- grade 2 cardiac adverse events confirmed by another LVEF assessment - RR=0.20 (95% CI: 0.04; 0.92), NNT=32 (95% CI: 18; 198);
- grade 3-4 anaemia - RR=0.28 (95% CI: 0.08; 0.98), NNT=32 (95% CI: 17; 346).

The results of the comparative analysis conducted for the entire period of the PHranceSCa study

indicate that in ≥1 of the study groups, the most common adverse events of any grade were: injection site reactions - 22.5% of the patients in the study group, radiation damage to skin - 11% of the patients in the study group and diarrhoea - 8% of the patients in the study group.

In the PHranceSCa study, in the subcutaneous therapy group, there was a statistically significantly higher occurrence of adverse events related to administration in general (RR=4.22 (95% CI: 2.11; 8.44), NNT=6 (95% CI: 4; 10)) than in the intravenous treatment group; they were mainly local injection/infusion-related reactions. In turn, pulmonary adverse events were statistically significantly less frequent - RR=0.44 (95% CI: 0.22; 0.86), NNT=12 (95% CI: 7; 53).

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

- both RCTs under assessment are ongoing studies - long-term efficacy assessments are planned for both of them (including iDFS and OS) with a follow-up period of at least 3 years after the end of treatment, so the results are not yet available;
- in the presented studies, there are no data on clinically significant endpoints related to a long-term impact of the treatment on the life of patients. As regards efficacy assessment, only results from the FeDeriCa study related to complete pathological response and clinical response are available. In the studies, the other assessed endpoints concern the pharmacokinetic assessment and preferences of patients and doctors related to the form of the drug.
- no studies relating to effectiveness have been identified;
- no studies involving Phesgo being used as first-line treatment of advanced breast cancer have been found;
- no studies comparing Phesgo with PERT IV + TRAS SC have been identified.

Proposed risk-sharing scheme [information protected as a trade secret]

[information protected as a trade secret]

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

The costs of therapy are estimated in Polish currency, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times GDP per capita.

Currently, the cost-effectiveness threshold is PLN 166,758 (3 x PLN 55,586).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.

The purpose of this analysis was to assess the cost-effectiveness of Phesgo, a combination drug

containing a fixed-dose combination of pertuzumab and trastuzumab for subcutaneous (S.C.) injection:

- in combination with chemotherapy for the neoadjuvant treatment of HER2-positive early (non-metastatic) breast cancer (eBC) with a high risk of recurrence,
- in combination with docetaxel for the first-line treatment of HER2-positive generalised locally advanced (mBC) metastatic breast cancer (mBC) when local therapy is ineffective or permanently inapplicable.

The assessment was performed with the use of cost-minimisation analysis (CMA). In the economic analysis, in the indication covering the treatment of advanced HER2-positive breast cancer, a lifetime horizon was assumed [information protected as a trade secret]. In the indication covering the neoadjuvant treatment of early HER2-positive breast cancer, a horizon equal to the time period of pre-surgery treatment under the proposed drug programme (max. 6 three-week cycles) was assumed.

The NHF perspective and the joint perspective were considered. Considering the method according to which the drug is financed (i.e. the drug programme), the patient does not pay for the therapy, so the two perspectives are the same.

The following cost categories were included in the applicant's basic analysis:

- costs of the compared interventions (Phesgo [FDC of pertuzumab/trastuzumab]; PERT IV + TRAS SC; PERT IV + TRAS IV);
- chemotherapy costs;
- drug administration costs;
- diagnosis and treatment monitoring costs.

According to the applicant's estimates, the use of Phesgo, when the RSS is considered, may be less expensive than the currently reimbursed options:

- in neoadjuvant therapy for early breast cancer instead of: [information protected as a trade secret
- in the first-line treatment of advanced breast cancer instead of: [information protected as a trade secret]

Limitations

Regarding the treatment of advanced breast cancer, the applicant assumed a lifetime [information protected as a trade secret] horizon while the treatment period [information protected as a trade secret]. It is worth noting that data extrapolation always involves great uncertainty. [information protected as a trade secret] The regional consultant in clinical oncology indicated that in the first-line treatment of advanced breast cancer, patients receive an average of 21 cycles of the PERT+TRAS therapy. [information protected as a trade secret]

It is worth mentioning that changing the length of the analysis horizon for the advanced breast cancer indication [information protected as a trade secret] to 3 years in the sensitivity analysis [information protected as a trade secret]

Agency's own calculations

Using the applicant's model, an additional variant of sensitivity analysis was carried out. It considered the length of the PERT+TRAS therapy, which – for advanced breast cancer – was equal to the average number of cycles advised by the clinical expert (21 cycles). The Agency's calculations do not change the direction of conclusions regarding therapy costs.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

In the absence of randomised clinical trials proving the superiority of the proposed health technology over the comparator, the circumstances referred to in Art. 13 sec. 3 of the Reimbursement Act do arise.

According to the applicant's estimates, in the basic variant, the optional technology with the most favourable cost-effectiveness ratio (the lowest costs with the same health outcome) was: PERT IV + TRAS IV for neoadjuvant treatment and PERT IV + TRAS SC for advanced breast cancer treatment.

The official selling price of individual presentations of Phesgo, at which the cost of using the proposed technology is not higher than the cost of the optional technology with the most favourable cost-effectiveness ratio, is:

- neoadjuvant treatment of early breast cancer: [information protected as a trade secret]
- first-line treatment of advanced breast cancer: [information protected as a trade secret]

Assessment of the impact on the healthcare system, including the budget impact

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

Estimates of the expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating the health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources allocated to the treatment of the given health problem or whether it will result in savings in the payer's budget.

The budget impact assessment makes it possible to establish whether the payer has adequate resources to fund a particular technology.

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

The budget impact analysis in the case of a positive decision to reimburse Phesgo (FDC of pertuzumab/trastuzumab for subcutaneous injection) used:

- in pre-surgery (neoadjuvant) therapy of HER2-positive, early (non-metastatic) breast cancer with a high risk of recurrence, in combination with chemotherapy;
- in the first-line treatment of HER2-positive generalised or locally advanced breast cancer when local therapy is ineffective or permanently inapplicable, in combination with docetaxel;

was performed for a 4-year horizon from the public payer perspective. The following cost categories were included in the analysis:

- costs of Phesgo (FDC of pertuzumab/trastuzumab), costs of active substances used as optional technologies and costs of active substances used in chemotherapy;
- costs of diagnosis and monitoring of patients under the drug programme;
- costs of administering/prescribing the drugs. [information protected as a trade secret]

According to the applicant's estimates, if the case of the reimbursement of Phesgo (pertuzumab/trastuzumab) as proposed in the application, the expenses from the payer perspective: [information protected as a trade secret]

[information protected as a trade secret]

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

- Analysing the size of the patient population in which the applied health a technology will be used, the opinion of the regional consultant in clinical oncology was taken into account, according to which the number of new patients with HER2-positive early breast cancer eligible for neoadjuvant anti-HER2 treatment is 1,600. The applicant's estimates related to the annual number of new patients included in neoadjuvant therapy for early HER2-positive breast cancer over a 4-year horizon of the basic analysis are: [information protected as a trade secret] The results of the sensitivity analysis performed by the applicant for the range of variation (+15% from baseline estimate) in the size of the target population [information protected as trade secret]
- Based on the results of the FeDeriCa study, the cost analysis included neoadjuvant chemotherapy regimens that are most frequently used in the treatment of patients with breast cancer. [information protected as a trade secret]

Comments on the proposed risk-sharing scheme

No remarks.

Comments on the drug programme

No remarks.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on the reimbursement of the health technology covered in this recommendation.

The results of the budget impact analysis for the entity obliged to finance the benefits from public funds, presented by the applicant [information protected as a trade secret]. However, the applicant did not provide the rationalisation analysis.

Overview of recommendations in relation to the assessed technology

Clinical guidelines from 6 organisations have been identified:

- Polish Society of Clinical Oncology (PTOK) 2020;
- National Comprehensive Cancer Network (NCCN) 2021 v.8 and 2020;
- St Gallen International Consensus 2021;
- National Institute for Health and Care Excellence (NICE) 2021a and 2021b;
- European Society for Medical Oncology (ESMO) 2021, 2020a, 2020b and 2019;
- American Society of Clinical Oncology (ASCO) 2021 and 2018.

According to the most recent NCCN guidelines, a compound medicinal product containing pertuzumab, trastuzumab and hyaluronidase in the FDC form for subcutaneous administration can be used in any indication where intravenous formulations of pertuzumab and trastuzumab are administered as part of systemic therapy. In turn, according to the 2020 PTOK guidelines, in early

breast cancer, trastuzumab IV or SC and pertuzumab IV are recommended as perioperative treatment. In the case of advanced breast cancer, only trastuzumab IV and pertuzumab IV were included in first-line regimens. In other guidelines, there is no reference to the medicinal product assessed in this recommendation; also, there is no indication regarding the appropriate, recommended or preferred route of administration of anti-HER2 therapy.

Reimbursement recommendations from 5 agencies have been found:

- Scottish Medicines Consortium (SMC) 2021 - Pertuzumab/trastuzumab (Phesgo) is approved for use within NHS Scotland, subject to restrictions previously applicable to the reimbursement of pertuzumab and trastuzumab and only in accordance with the Patient Access Scheme (PAS) approved by NHS Scotland ensuring the cost-effectiveness of therapy or at the catalogue price equal to or lower for the following indications:
    - in combination with chemotherapy, for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early breast cancer at a high risk of recurrence or for the adjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early breast cancer at a high risk of recurrence;
    - in combination with docetaxel in adult patients with HER2-positive metastatic or locally advanced unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for a metastatic disease
- National Centre for PharmacoEconomics (NCPE) 2021 - full HTA assessment is not recommended. The NCPE does not recommend the reimbursement of Phesgo at the proposed price in the indication:
    - in combination with chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory or early breast cancer at a high risk of recurrence and for the adjuvant treatment of adult patients with HER2-positive early breast cancer at a high risk of recurrence;
    - in combination with docetaxel for the treatment of adult patients with HER2-positive, metastatic or locally advanced unresectable breast cancer who have not received prior anti-HER2 therapy or chemotherapy for a metastatic disease;
- Haute Autorite de Sante (HAS) 2021 - the agency gave a positive opinion on the reimbursement of Phesgo in combination with docetaxel, for the treatment of adult patients with metastatic or locally advanced unresectable HER2-positive breast cancer who have not previously received anti-HER2 therapy or chemotherapy for a metastatic disease. However, the agency gave a negative opinion on the neoadjuvant treatment of adult patients with locally advanced, inflammatory or early HER2-positive breast cancer at a high risk of recurrence. The absolute clinical benefit of neoadjuvant treatment was considered insufficient to justify reimbursement.
- Zorginstituut Nederland (ZN) 2021 - having negotiated the prices with the manufacturer, in October 2021, the agency decided to temporarily include Phesgo in the basic package of reimbursable drugs for indications:
    - in combination with chemotherapy for the preoperative treatment of adult patients with HER2-positive, locally advanced, inflammatory or early breast cancer at a high risk of recurrence; adjunctive treatment of adult patients with HER2-positive early breast cancer at a high risk of recurrence;
    - in combination with docetaxel in adults with HER2-positive metastatic breast cancer or locally recurrent, inoperable (unresectable) breast cancer who have not received prior anti-HER2 therapy or chemotherapy for a metastatic disease
- Gemeinsamer Bundesausschuss (G-BA):
    - 2021a - the agency gave a negative recommendation on the reimbursement of

Phesgo for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory or early breast cancer at a high risk of recurrence - due to the lack of any proven additional benefit;

- 2021b - the agency gave a negative recommendation on the reimbursement of Phesgo for patients with HER2-positive metastatic breast cancer or locally recurrent, inoperable breast cancer who have not previously received anti-HER2 therapy or chemotherapy for a metastatic disease - due to the lack of available data to assess an additional benefit.

Moreover, on the website of the UK HTA agency (NICE), there is information on the suspended process of assessing Phesgo as it is a new form of currently available drugs and does not constitute a significant extension of indications to justify HTA. [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 20 September 2021 (ref. no.: PLR.4500.1471.2021.19.AJA, PLR.4500.1472.2021.19.AJA) concerning the preparation of the President's recommendation on the reimbursement of Phesgo (pertuzumabum + trastuzumabum) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended), having obtained Position of the Transparency Council No. 134/2021 of 29 November 2021 on the assessment of Phesgo (pertuzumabum + trastuzumabum) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)"

References

1. Position of the Transparency Council No. 134/2021 of 29 November 2021 on the assessment of Phesgo (pertuzumabum + trastuzumabum) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)"
2. Report No. OT.4231.46.2021. Application for the reimbursement of Phesgo (pertuzumab + trastuzumab) in the indication: under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)". Verification analysis