Recommendation No. 102/2019

of 20 November 2019

issued by the President of the Agency for Health Technology Assessment and Tariff System

on the assessment of Verzenios (abemaciclib) in combination with aromatase inhibitors in the following indication: "Treatment of breast cancer (ICD-10 C50)"

The President of the Agency recommends reimbursing Verzenios (abemaciclib) in combination with aromatase inhibitors in the following indication: "Treatment of breast cancer (ICD-10 C50)" **on condition that** the risk-sharing scheme in question is enhanced.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the available scientific evidence, clinical guidelines and reimbursement recommendations, the President of the AOTMiT believes that financing of the health technology in question from public funds is justified.

In view of the clinical guidelines, opinions of the experts and technologies currently financed from public funds, palbociclib (PALB)+NSAI and ribociclib (RBC) should be considered as comparators for the abemaciclib (ABE)+non-steroidal aromatase inhibitor (NSAI) combination therapy due to their similar mechanism of action and their positioning in clinical guidelines. The following technologies should be considered as additional comparators: anastrozole (ANA), exemestane (EXE), fulvestrant (FUL), letrozole (LET).

No studies comparing directly ABE + NSAI with the basic comparators have been identified. Therefore, instead, an indirect comparison is presented, based on a randomised study comparing the efficacy and safety of ABE + NSAI therapy with a control arm receiving placebo and anastrozole or letrozole (PLC + NSAI).

Due to a lack of necessary data, it was not possible to compare the overall survival between the assessed technologies. However, the results of the indirect comparison of progression-free survival indicate that there are no statistically significant differences in the arm of patients using abemaciclib + NSAI in comparison to arms using palbociclib + NSAI or ribociclib + NSAI. In addition, in line with the indirect comparison carried out by the Agency, there are no significant differences in the assessment of the objective response to treatment in the arm of patients using abemaciclib in comparison with patients using ribociclib or palbociclib in combination with NSAI.

[information protected as a trade secret]

All the identified clinical guidelines demonstrate the possibility of using CDK 4/6 inhibitors (including abemaciclib) in combination with aromatase inhibitors in the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer.

In view of the above, *[information protected as a trade secret]*

Subject of the application

The commission of the Minister of Health concerns assessing whether the following medicinal products should be financed from public funds:

- Verzenios (abemaciclib), film-coated tablets, 50 mg, 70 pcs., EAN: 05014602500979 – the proposed net ex-factory price of PLN *[information protected as a trade secret]*;
- Verzenios (abemaciclib), film-coated tablets, 100 mg, 70 pcs., EAN: 05014602500986 – the proposed net ex-factory price of PLN *[information protected as a trade secret]*;
- Verzenios (abemaciclib), film-coated tablets, 150 mg, 70 pcs., EAN: 05014602500993 – the proposed net ex-factory price of PLN *[information protected as a trade secret]*;

The proposed payment and reimbursement availability category: a free-of-charge medicine available as part of the pharmaceutical programme, within a new joint-limit group. The applicant has proposed a risk-sharing scheme.

Health problem

Breast cancer is a malignant tumour derived from the epithelium of the ducts or lobules of the mammary gland. According to the Polish Society of Clinical Oncology (PTOK) 2018, breast cancer is the most common cancer affecting women in Poland. The latest data from the National Cancer Registry (KRN) indicate that in Poland in 2016, 18,615 women and 149 men were diagnosed with breast cancer. According to the opinion of Dr Jagielska, interviewed by the Agency, "*hormone-dependent cancer is the most common form of breast cancer which affects 70% of patients".*

In 2016, 6,493 female deaths from breast cancer were recorded, which constituted the second cause of death in women. The prognosis in breast cancer depends primarily on the early detection of the cancer, its type and stage. The majority of relapses (85%) occur during the first 5 years following treatment. The percentage of 5-year survival depending on the stage amounts to: I – 95%, II – 50%, III – 25%, IV – <5%. The average 5-year survival rate in Poland is 74%.

The condition of steroid receptors (ER and PgR) is an important predictive factor in patients with breast cancer. Patients without ER and PgR expression do not respond to hormone treatment, while their expression is associated with lower sensitivity to chemotherapy and a better prognosis.

Alternative health technologies

Taking into account the clinical guidelines, opinions of the experts and technologies currently financed from public funds, therapies with palbociclib (PALB) and ribociclib (RBC) should be considered as comparators for the intervention in question due to their similar mechanism of action and positioning in clinical guidelines. The following technologies should be considered as additional comparators: anastrozole (ANA), exemestane (EXE), fulvestrant (FUL), letrozole (LET).

The above choice of alternative technologies is in line with the technologies indicated by the applicant.

Description of the proposed intervention

Abemaciclib (ABE) is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to

suppression of tumour growth. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition with abemaciclib prevented rebound of Rb phosphorylation resulting in cell senescence and apoptosis.

In line with the SPC, Verzenios is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

In line with the draft pharmaceutical programme: B.9. "Treatment of breast cancer (ICD-10 C50)": patients with metastatic breast cancer (IV stage) or locally advanced breast cancer or locally recurrent breast cancer, if radical local treatment is impossible, with documented presence of HR receptors (ER and/or PgR) and confirmed lack of HER2 over-expression or HER2 gene amplification in tumour cells.

In view of the above, the indication in question is included in the registered indications.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

In the systematic review of the primary studies on the efficacy and safety of abemaciclib in combination with a non-steroidal aromatase inhibitor (ABE + NSAI) therapy, the applicant included one randomised study with a control arm receiving placebo and anastrozole or letrozole (PLC + NSAI):

- ABE + NSAI vs. PLC + NSAI – MONARCH 3, which included 493 patients and the median follow-up period was 26.7 months. The risk of bias assessed using the Cochrane Collaboration tool was deemed to be low for all domains.

No studies comparing ABE + NSAI directly with the selected comparators have been identified. Therefore, the results of the indirect comparison of the following 8 primary studies on active comparators have been presented:

- Studies on main comparators:
    - palbociclib + non-steroidal aromatase inhibitor (PAL + NSAI) vs. NSAI
        - PALOMA-1 – randomised trial conducted on 144 patients, with the median follow-up period:
            - in the PAL + NSAI arm: 29.6 months. (95%CI: 27.9; 36.0);
            - in the NSAI arm: 27.9 months. (95%CI: 25.5; 31.1);

            The risk of bias assessed using Cochrane Collaboration tool was deemed:

            - to be low for the domains: randomisation method, concealment of the randomisation code, incomplete data, selective reporting

- to be high for the domains: blinding of researchers and patients, blinded outcome assessment, total
- to be unknown for other factors

▪ PALOMA-2 – randomised trial conducted on 888 patients, with a 23-month median follow-up period. The risk of bias using the Cochrane Collaboration tool was assessed to be low for most domains; the risk was assessed to be unclear only for the "other factors";

- ribociclib + non-steroidal aromatase inhibitor (RBC + NSAI) vs. PLC + NSAI
  - MONALEESA-2 – a randomised trial which included 668 patients. The results were available for two direct comparisons, for which the follow-up period was 15.3 months and 26.4 months. The risk of bias using the Cochrane Collaboration tool was assessed to be low for most domains; the risk was assessed to be unclear only for the "other factors";

- studies on other comparators:
  - tamoxifen (TAM) vs. non-steroidal aromatase inhibitor
    - TAM vs. anastrozole: TARGET and North American studies;
    - TAM vs. letrozole: PO25 study.
- exemestane vs. anastrozole
  - Iwata 2013 study;
- fulvestrant vs. anastrozole
  - FALCON and FIRST studies.

The following outcomes were studied in order to demonstrate efficacy:

- CR – complete response;
- OS – overall survival;
- PR – partial response;
- ORR – objective response ratio;
- PFS – progression-free survival.

The following parameters were used to assess efficacy:

- HR – hazard ratio;
- OR – odds ratio;
- RD – risk difference.

Efficacy

<u>Abemaciclib + NSAI vs. basic comparators (palbociclib + NSAI or ribociclib + NSAI)</u>

Overall survival (OS) assessment represented the main secondary outcome in all included studies. The median overall survival rate was not achieved in MONARCH-3, MONALEESA-2 and PALOMA-2 in any of the studied arms. At the data cut-off date, the results on survival time were not mature enough to allow for a full analysis. The final results of the OS analysis were only available for PALOMA-1.

Given the above and the lack of detailed results for the estimated HR measure in terms of survival (no confidence interval value), no indirect comparison of ABE + NSAI vs. PAL + NSAI and ABE + NSAI vs. RBC + NSAI was made in MONARCH-3.

In the case of results of partial analyses in MONARCH-3 (ABE + NSAI vs. NSAI + PLC), MONALEESA-2 (RBC + NSAI vs. NSAI + PLC) and PALOMA-1 (PAL + NSAI vs. NSAI + PLC), no statistically significant differences in overall survival between the studied arms were reported. In the case of using ABE + NSAI, 63 (19%) deaths occurred during the 26.7 months of the study, while in the case of using RBC, deaths occurred during 26.4 months of the study – 50 (15%). In case of using PAL, deaths of 19 (23%) patients were reported during the 33.3 months of follow-up.

No data from partial analyses on OS were identified for PALOMA-2 (PAL + NSAI vs. PLC vs NSAI).

The results of the indirect comparison of progression-free survival indicate that there are no statistically significant differences in the arm of patients using abemaciclib + NSAI in comparison to arms using palbociclib + NSAI or ribociclib + NSAI.

Abemaciclib + NSAI vs. other comparators

Due to the lack of detailed data on OS, no indirect comparison of abemaciclib in combination with NSAI with tamoxifen (TAM), exemestane (EXE) and fulvestrant (FUL) regarding overall survival was made.

The results of MONARCH-2 demonstrate that the use of ABE + NSAI vs. PLA + NSAI is associated with statistically significant:

- risk of disease progression lower by 53% (as assessed by an independent committee HR=0.465 (95% CI: 0.339; 0.636);
- chance of an objective response to treatment higher by 68% – OR = 1.68 (95% CI: 1.15; 2.47), and RD=12.73 (95% CI: 3.59; 21.87);
- chance of partial response higher by 55% – OR= 1.55 (95% CI: 1.05; 2.27), and RD=10.59 (95% CI: 1.47; 19.70);
- chance of stable disease form lower by 35% – OR= 0.65 (95% CI: 0.44; 0.94), and RD=-10.67 (95% CI: -19.95; -1.39).

In MONARCH-3, no statistically significant differences were identified in terms of:

- a complete response (the result obtained for RD was statistically significant);
- a clinically significant response.

An indirect comparison demonstrated a statistically significantly longer progression-free survival in patients using abemaciclib in combination with NSAI as compared to exemestane (HR=0.54 (95% CI: 0.37; 0.78)) and tamoxifen (HR=0.39 (95% CI): 0.29; 0.52)). Significant results in favour of abemaciclib + NSAI in comparison with fulvestrant were obtained when calculating the result of the comparison of ABE + NSAI vs. NSAI obtained in an independent assessment (HR=0.65 (95% CI): 0.44; 0.94)).

The results of the indirect comparison demonstrate statistically significant differences in favour of the ABE + NSAI regimen in relation to patients using tamoxifen. No differences in comparison with exemestane and fulvestrant in the assessment of the occurrence of an objective response to treatment were reported.

Safety

Abemaciclib + NSAI vs. main comparators (RBC + NSAI and PALB + NSAI)

As part of the safety analysis, the applicant presented the results of an indirect comparison for abemaciclib in combination with NSAI, as well as for palbociclib and ribociclib in combination with NSAI (letrozole) on the incidence of neutropaenia, diarrhoea and any grade 3 and 4 adverse events. The

detailed safety analysis included in the applicant's analysis was limited to diarrhoea and neutropaenia as the most common adverse reactions to abemaciclib and palbociclib, respectively. In the justification, the applicant did not refer to the incidence of these outcomes in the case of using ribociclib.

In line with the above, the use of ABE + NSAI in comparison with:

- RBC + NSAI:
    - was associated with statistically significant:
        - risk of any grade 3 or 4 adverse event lower by 52% – OR=0.48 (95% CI: 0.28; 0.83), and RD=-14.84 (95% CI: -25.62; -4.06);
        - risk of diarrhoea nearly five times higher – OR=5.09 (95% CI: 2.94; 8.81), and RD=36.18 (95% CI: 25.32; 47.04);
        - lower risk of neutropaenia – RD=-29.32 (95% CI: -37.07; -21.57).
    - no differences in terms of OR for neutropaenia were demonstrated;
- PAL+NSAI:
    - was associated with statistically significant:
        - risk of any grade 3 or 4 adverse event lower by 58 % – OR=0.42 (95% CI: 0.25; 0.72), and RD=-18.23 (95% CI: -28.78; -7.68);
        - risk of diarrhoea nearly six times higher – OR=6.19 (95% CI: 3.53; 10.85), and RD=42.14 (95% CI: 31.96; 52.32);
        - lower risk of neutropaenia – RD=-32.32 (95% CI: -39.58; -25.06).
    - no differences in terms of OR for neutropaenia were demonstrated.

Abemaciclib + NSAI vs. other comparators

In line with the results of MONARCH-3, a significantly higher incidence of total adverse events, grade 3 or 4 adverse events, diarrhoea, thromboembolic events, nausea, alopecia, vomiting, anaemia, abdominal pain, infections and infestation, leukopenia, neutropenia, increased levels of ALT and ASP, rash, decreased appetite were reported in the ABE+NSAI vs. PLA+NSAI arm, .

The results of the indirect comparison indicate a statistically significant higher chance of adverse events in total, diarrhoea, alopecia, nausea and vomiting in patients using abemaciclib in combination with NSAI as compared to patients using tamoxifen.

As compared to exemestane, during the use of abemaciclib, grade 3 and 4 adverse events were statistically significantly more frequent. In the case of serious adverse events, the results for OS and RD parameters are ambiguous as to the statistical significance of the difference.

No statistically significant differences were reported between abemaciclib and fulvestrant in terms of the incidence of adverse events and adverse reactions.

Additional safety and efficacy data

Since the applicant has carried out an indirect comparison of abemaciclib with ribociclib and palbociclib for two outcomes, i.e. overall survival and progression-free survival, the Agency decided to carry out an additional analysis for the outcome of the objective response rate (ORR).

The results of the indirect comparison indicate that there are no significant differences in the assessment of the ORR in the arm of patients using abemaciclib in comparison with patients using ribociclib or palbociclib in combination with NSAI.

In line with the SPC for Verzenios, the most common adverse reactions include diarrhoea, infections, neutropaenia, anaemia, fatigue, nausea, vomiting and decreased appetite.

Limitations

The main limitation of the reliability of the presented results is the fact that there are no studies that directly compare the intervention in question with ribociclib and palbociclib used in combination with NSAI. Analysing efficacy and safety results based solely on the results of indirect comparisons may be associated with uncertainty. The aromatase inhibitor used in the control arm in PALOMA and MONALEESA was letrozole (LET). It was assumed that the comparison with LET is representative for the comparison with all aromatase inhibitors.

The following factors impact the uncertainty of the presented results:

- The assessment of the efficacy of abemaciclib was based on just one RCT, i.e. MONARCH-3. Lack of pragmatic studies and long-term results on efficacy and safety for the intervention in question which could confirm the efficacy of abemaciclib treatment under clinical practice conditions.
- The results of the overall survival analysis are not available for either the study on the intervention in question (MONARCH-3) or its primary comparators, i.e. ribociclib (MONALEESA-2) and palbociclib(PALOMA-2). At the time of the data cut-off, the results on survival time were not mature enough to allow for performing a full analysis of survival time. The final results of the OS analysis were available only for PALOMA-1. At the same time, statistical power to assess significant differences in overall survival was not achieved in PALOMA-1 (too few patients included). However, it should be borne in mind that MONARCH-3, MONALEESA-2, PALOMA-2 have been designed to demonstrate differences for the primary outcome, that is progression-free survival. According to AOTMiT's guidelines, outcomes relating to mortality, course/severity of the disease and health-related quality of life may be considered as clinically significant outcomes. The EUnetHTA 2015 guidelines on the use of surrogate (substitute) outcomes in the assessment of the relative efficacy of technologies indicate that in cancer treatment, in adjuvant therapy, progression-free survival (PFS) seems acceptable as an outcome, while PFS is insufficient in metastatic disease. This parameter may be considered if it is combined with data on the quality of life and overall survival, the maturity of which should be assessed on a case-by-case basis.
- A relatively high number of patients with deviations from the study protocol was reported in MONARCH-3; 84% in the ABE arm vs. 77.6% in the comparator arm.

Proposals of risk-sharing schemes

As part of the proposed risk-sharing scheme (RSS), the applicant *[information protected as a trade secret]*

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

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

The comparison of values concerning the costs and effects related to the implementation of a new therapy and comparing them to the costs and effects of already reimbursed therapies allow to answer the question whether the health effect achieved as a result of a new therapy is associated with higher costs in comparison to already reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select a therapy associated with the potentially best use of the currently available resources.

The following analyses were conducted as part of the cost-effectiveness analysis:

- cost-minimisation analysis (CMA) as part of the comparison with palbociclib and ribociclib in a one-year time horizon
- cost-utility ratio (CUR) analysis as part of the comparison of abemaciclib with other comparators (anastrozole (ANA), letrozole (LET), exemestane (EXE) and fulvestrant (FUL)) in a lifetime (35 years) time horizon.

The analysis was carried out from the common perspective (payer+patient). Due to the low costs incurred by patients, it was decided against presenting the results of the analysis from the common perspective.

However, a decision was made to present detailed results of the analysis comparing the intervention in question with the basic comparators (palbociclib and ribociclib) due to the same positioning in the latest clinical guidelines and the same mechanism of action.

Only on the cost of medicines were taken into account in the cost estimates. Costs which, in the applicant's opinion, had little influence on the results of the analysis, such as the costs of treatment of adverse events, were disregarded. In addition, the costs of treatment with hormone therapy, i.e. anastrozole or letrozole in the case of abemaciclib and the costs of treatment with letrozole in the case of ribociclib and palbociclib, were not considered to have a significant impact on the costs of combination therapy; therefore the costs of these medicines were not included in the analysis.

[information protected as a trade secret]

Limitations

The basic limitation of the applicant's calculations consists in the failure to include actual prices of PAL and RBC available in public procurement tenders.

Furthermore, the uncertainty of the presented results was impacted by the following aspects:

- The applicant has chosen the cost-minimisation analysis as the analytical method of comparing ABE +NSAI vs. PAL + NSAI and RBC + NSAI. As part of the clinical analysis, indirect comparisons of ABE + NSAI vs. PAL + NSAI and ABE + NSAI vs. RBC + NSAI were conducted, which demonstrated the lack of statistically significant differences between these interventions in terms of efficacy. Statistically significant differences between ABE +NSAI vs. PAL + NSAI and RBC + NSAI were identified in terms of safety – the use of ABE + NSAI was associated with a higher risk of diarrhoea and a lower risk of neutropaenia and any grade 3 and 4 adverse event in relation to PAL + NSAI and RBC + NSAI. As indicated by the applicant, the SPC for Verzenios specifies that the treatment of diarrhoea consists of the administration of anti-diarrhoeal medicines such as loperamide (as verified by the Agency's analysts, it is also possible to modify the dosing or discontinue the treatment), while the SPC for Ibrance and the SPC for Kisqali provide for dosing modification or treatment discontinuation in the case of neutropaenia. On the basis of the applicant's clinical analysis, it is not possible to determine whether the differences observed in the safety of the compared technologies are clinically insignificant, which, in line with the HTA Guidelines, constitutes a prerequisite for conducting a cost-

minimisation analysis. However, it should be emphasised that the vast majority of diarrhoea cases reported in MONARCH-3 in the arm using ABE + NSAI (71.8%) were grade <3 events and no grade 4 diarrhoea cases were reported, while the results of PALOMA-1 indicate that grade 3 or 4 neutropaenia was experienced by 54% of patients using PAL and in PALOMA-2 by approx. 67% of patients; in the case of MONALEESA-2, in which ribociclib was used, grade 3 or 4 neutropaenia was experienced by approx. 59% of patients. It can therefore be concluded that failure to take the effects affecting safety of the therapy into account in the economic analysis is an expression of a conservative approach.

- Threshold prices for Verzenios were estimated incorrectly in the analysis due to the fact that the daily dose of the medicine was indicated as 1 tablet, which is inconsistent with the SPC for Verzenios, which indicates 2 tablets as a daily dosing of the medicine.
- The applicant's model assumes that in the one-year horizon PAL and RBC are used for 39 weeks, which is based on the assumption that the year includes 52 weeks. This assumption should correspond to the assumption that the year has 364 days. At the same time, the estimation of ABE costs is based on a 365-day horizon. This inconsistency is conservative in nature, since it generates a longer period of use of the intervention in question in relation to its comparator, which influences the costs of the intervention. A similar type of inaccuracy applies to the estimates of the price of Verzenios, where the difference between the cost of using ABE and the cost of using PAL and RBC equals zero. In this case, the annual cost of PAL and RBC estimated as indicated above and the number of doses of PAL and RBC determined on the assumption that the year has 365 days were presented. This way, the net ex-factory price of ABE is slightly lower than while maintaining consistency in terms of the duration of use of the compared medicines (the difference is less than 0.3%).
- The applicant did not make any reference to the differences in the diagnostic tests to be performed as part of qualification of patients for the programme and treatment monitoring of the current pharmaceutical programme for PAL and RBC as well as the proposed programme for ABE. However, these differences are minor and should not generate significant differences in the costs associated with the implementation of pharmaceutical programmes, which is why the omission of the associated costs in the proposed model should be regarded as acceptable.

AOTMiT's own calculations

Due to the fact that data from public procurement tenders announced by healthcare providers concerning the price of palbociclib and ribociclib have been identified, own calculations were performed, as part of which the following were implemented into the applicant's model:

- price of Ibrance (palbociclib) was adopted on the basis of data from public procurement tenders conducted by the University Hospital of Lord's Transfiguration and the State Hospital in Koszalin – PLN 5,748.17.
- price of Kisqali (ribociclib) was adopted on the basis of data from the public procurement tender conducted by the State Hospital in Koszalin – PLN 5,298.05.

According to the Agency's estimates, the costs of using the medicine in question in a one-year horizon in comparison with:

- palbociclib:

[information protected as a trade secret]

- ribociclib:

[information protected as a trade secret]

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of medicines, foodstuffs for particular nutritional uses and medical devices apply (Journal of Laws of with 2019 item 784 as amended);

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the medicine over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the medicine which must be calculated in such a way that the cost of using the medicine applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

The circumstances referred to in Article 13 (3) of the Act on reimbursement apply in the present case because a randomised trial has not been presented to prove the superiority of the technology in question over the reimbursed comparator.

[information protected as a trade secret]

Due to the fact that an incorrect dosing regimen had been adopted, the Agency carried out its own calculations, which corrected the daily dosing of abemaciclib from 1 tablet to 2, as specified in the SPC for Verzenios. The other assumptions of the analysis were adopted in line with the applicant's proposal.

[information protected as a trade secret]

As information on the actual prices of palbociclib and ribociclib from hospital tenders is available, the Agency has carried out its own calculations, in which the dosing of abemaciclib was adjusted and comparator prices were included on the basis of information from hospital tenders. The other assumptions of the analysis were adopted in line with the applicant's proposal.

[information protected as a trade secret]

Analysis of the effects on the healthcare system, including budget impact analysis (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

Results of the budget impact analysis carried out by the applicant were presented in a two-year horizon. The analysis was carried out from the payer's perspective. According to the applicant's estimates, the number of patients who will be newly enrolled in the pharmaceutical programme in question will amount to:

[information protected as a trade secret]

Direct medical costs were considered in the budget impact analysis, i.e.

- costs of medicines;
- costs of medicines administration ;

- costs of treatment monitoring.

In line with the above assumptions, the financing of the intervention in question will involve:

- without taking the RSS into account, an increase in the payer's expenditure by:

[information protected as a trade secret]

- with taking the RSS into account, a decrease in the payer's expenditure by:

[information protected as a trade secret]

Limitations

The basic limitation of the presented estimates is the fact that the prices of the comparators in the variant of analysis including a RSS adopted by the applicant were taken from the Minister of Health's announcement. It should be noted that the information on public procurement tenders for palbociclib and ribociclib available in the public domain indicates that these medicines are bought by hospitals at a significantly lower price than the price indicated in the announcement and adopted by the applicant. Therefore, the applicant's estimates in the variant including the RSS are significantly overestimated in favour of the intervention in question, which makes drawing any reliable conclusions on the basis of the applicant's analysis impossible.

The following factors impact the uncertainty of the presented results:

[information protected as a trade secret]

AOTMiT's own calculations

Given the Agency's objections to the cost of comparators from the Minister of Health's announcement adopted by the applicant in its basic cost analysis, the analysts performed their own estimations for the variant including the RSS, taking into account the price of comparators on the basis of available cost data from hospital tenders:

- Gross wholesale price of palbociclib: PLN 5,748.17;
- Gross wholesale price of ribociclib: PLN 5,298.05.

The Agency's own estimates indicate that the adoption of comparator prices from hospital tenders and not from the Minister of Health's announcement *[information protected as a trade secret]*

Remarks on the proposed risk-sharing scheme

In line with the analysis carried out by the applicant, *[information protected as a trade secret]*

Remarks on the pharmaceutical programme

The inclusion criteria for the pharmaceutical programme in question differ from those currently in force for the B.9 pharmaceutical programme for ribociclib and palbociclib in combination with aromatase inhibitors *[information protected as a trade secret]*.

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

As part of the rationalisation analysis, the applicant proposed a solution allowing for generating savings for the public payer to cover additional expenditure associated with the reimbursement of Verzenios

in the indication in question. The proposed mechanism consists in the reimbursement of the equivalent of MabThera. It should be noted the first equivalent containing rituximab became reimbursed upon the publication of the Minister of Health's announcement of 30 August 2019. The Minister of Health's announcement of 23.10.2019 included another equivalent of MabThera which obtained reimbursement coverage. In consequence, the time horizon within which savings will be generated in relation to the solution proposed by the applicant will not correspond to the time horizon of the budget impact analysis. Therefore, the savings may be redirected to other NHF expenditures until Verzenios is reimbursed.

Review of recommendations issued in other countries in relation to the technology in question

Four clinical recommendations have been identified for breast cancer treatment:

- Polish Society of Clinical Oncology (Polskie Towarzystwo Onkologii Klinicznej, PTOK) 2018;
- National Comprehensive Cancer Network (NCCN) 2019;
- National Institute for Health and Care Excellence (NICE) 2019;
- European School of Oncology (ESO) – European Society for Medical Oncology (ESMO) 2019.

All the identified clinical guidelines demonstrate the possibility of using CDK 4/6 inhibitors in combination with aromatase inhibitors in the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer.

In line with the latest 2019 NCCN guidelines, abemaciclib in combination with aromatase inhibitors may be considered as a possible therapy for post-menopausal or pre-menopausal women (with ovarian ablation using an LHRH antagonist or ovarian suppression) with HR-positive, HER2-negative recurrent or metastatic breast cancer. No specific line of treatment was indicated in the guidelines, but it was emphasised that this therapy could be considered as an option in first-line treatment. Furthermore, the NCCN guidelines indicate that abemaciclib may also be used following progression in previous hormone therapy or chemotherapy in the metastatic stage.

Abemaciclib in combination with an inhibitor is listed in the NICE 2019 guidelines as another option for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer.

The ESO-ESMO 2018 guidelines refer to the entire group of CDK 4/6 inhibitors and recommend the use of medicines from this group in combination with aromatase inhibitors in patients following previous hormone therapy or patients not subjected to such treatment because of their proven efficacy in improving the patients' PFS median (by approx. 10 months) and acceptable toxicity profile. The guidelines describe this therapy as one of the preferred treatment options for premenopausal and perimenopausal women after ovarian suppression/ablation, for postmenopausal women and for men (with LHRH antagonists).

Polish PTOK 2018 guidelines place the combined therapy with letrozole and CDK 4/6 inhibitor in the first-line treatment of advanced ER+/HER2- breast cancer together with tamoxifen, high-dose of fulvestrant and aromatase inhibitors.

Six reimbursement recommendations on the funding of the intervention in question have been identified:

- Two were positive:
    - Scottish Medicines Consortium (SMC) 2019;
    - NICE 2019;
- Two were conditionally positive:

  - Canadian Agency for Drugs and Technologies in Health (CADTH);
  - Zorgnisinstituut Nederlad (ZIN) 2019;
- in two, the population of patients who can use abemaciclib in combination with aromatase inhibitors was limited:
  - Gemeinsamer Bundesausschuss (G-BA) 2019;
  - Haute Autorité de Santé (HAS).

The NICE 2019, SMC 2019, CADTH 2019 guidelines list the extension of the progression-free survival (PFS) in case of using abemaciclib in combination with aromatase inhibitors as one of the main arguments for a positive reimbursement recommendation.

CADTH 2019 and Zorgnisinstituut Nederlad 2019 mention the need to reduce the cost of abemaciclib as a condition for issuing a positive recommendation. Also, in SMC 2019, attention was drawn to the need of improving cost-effectiveness in the recommendation justification. In the CADTH 2019 recommendation, a positive decision was made conditional on lowering the cost of therapy with abemaciclib to that of other available CDK 4/6 inhibitors.

G-BA 2019 and HAS 2018 guidelines limit the population of patients who may be treated with the medicine to postmenopausal patients. However, it should be emphasised that the SPC for Verzenios indicates that in pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

NICE 2019, CADTH 2019 and HAS 2018 documents highlight the lack of data on patients' overall survival.

In line with the information provided by the applicant, Verzenios is reimbursed in 12 EU and EFTA Member States: *[information protected as a trade secret]*In line with the information provided by the applicant, the risk-sharing scheme has been introduced*[information protected as a trade secret]* .

Legal basis for the recommendation

The recommendation was prepared on the basis of a commission of the Minister of Health of 30/08/2019 (reference numbers: PLR.4600.711.2019; PLR.4600.712.2019; PLR.4600.714.2019), with regard to preparation of the recommendation of the President of AOTMiT on Verzenios (abemaciclib) in combination with aromatase inhibitors in the following indication: “Treatment of breast cancer (ICD-10 C50)” under Article 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of medicines, foodstuffs for particular nutritional uses and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 104/2019 of 18 November 2019 on the evaluation of Verzenios (abemaciclib) under the following pharmaceutical programme: B.9. “Treatment of breast cancer (ICD-10 C50)”, where the medicine is to be used in combination with aromatase inhibitors.

References

1. The Position of the Transparency Council No. 104/2019 of 18 November 2019 on the evaluation of Verzenios (abemaciclib) under the following pharmaceutical programme: B.9. “Treatment of breast cancer (ICD-10 C50)”, where the medicine is to be used in combination with aromatase inhibitors
2. Report No. OT.4331.49.2019. Reimbursement application for Verzenios (abemaciclib) in combination with aromatase inhibitors in the following indication: “Treatment of breast cancer (ICD-10 C50)”. Verification analysis