Recommendation No. 101/2019

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 fulvestrant in the following indication: "Treatment of breast cancer (ICD-10 C50)"

The President of the Agency recommends reimbursing Verzenios (abemaciclib) in combination with fulvestrant 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 AOTMiT believes that financing of the health technology in question from public funds is justified.

Taking into account the clinical guidelines, opinions of the experts and technologies currently financed from public funds, palbociclib (PALB)+FUL should be considered as the comparator for the abemaciclib (ABE)+fulvestrant (FUL) combination therapy due to the medicine's 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).

No studies comparing directly ABE + FUL with the basic comparator have been identified. Therefore, instead, an indirect comparison is presented, based on a randomised study comparing the efficacy and safety of ABE + FUL therapy with a control arm receiving placebo and FUL (MONARCH-2 study).

In line with the results of the indirect analysis, no statistically significant differences were identified for the Abemaciclib + fulvestrant vs. palbociclib + fulvestrant comparison in terms of: overall survival, progression-free survival, quality of life (for domains: overall quality of life assessment, pain).

However, in line with the results of MONARCH-2, the use of the therapy in question vs. placebo was associated with a statistically significant increase in overall survival by 9.4 months (46.7 vs. 37.3) and an increase in progression-free survival by 7.6 months (16.9 vs. 9.3).

[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 FUL 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 medicine 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 suffered from 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 are not susceptible 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, palbociclib (PALB)+FUL should be considered as the comparator for intervention in question due to its 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 outline of the proposed medicine programme for the therapy of abemaciclib in combination with fulvestrant: "Treatment of breast cancer (ICD-10 C50)", covering female patients with HR-positive, HER2-negative locally advanced breast cancer or metastatic breast cancer (stage IV) following prior first-line treatment for advanced breast cancer or *[information protected as a trade secret]* regardless of the menopausal status.

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.

As a result of the conducted search, the applicant included one study on abemaciclib in combination with fulvestrant – MONARCH-2 (12 publications) and 13 studies for the comparators (40 publications).

The following publications have been included in the applicant's clinical analysis:

1. Study on abemaciclib:
    - abemaciclib + fulvestrant vs. placebo (PLA) + fulvestrant
        - MONARCH-2 – double-blind phase III randomised study. The median follow-up period was 19.5 months. 669 patients were included in the study. The risk of bias using the Cochrane Collaboration tool was assessed to be low for the majority of domains except for the "incomplete data" domain;
2. Studies on palbociclib (main comparator):
    - Study on palbociclib (palbociclib + fulvestrant vs. placebo + fulvestrant)
        - PALOMA-3 – phase III randomised study, double-blind, multi-centre. The median follow-up period was:
            - PALB + FUL arm – 14.0 months;
            - FUL + PLA arm – 14.6 months;

The risk of bias using the Cochrane Collaboration tool was assessed to be low;

3. studies on other comparators:
    - studies on fulvestrant

  - CONFIRM – fulvestrant 500 mg vs. fulvestrant 250 mg + placebo (Dileo 2010a, Dileo 2010b, Dileo 2011, Dileo 2012, Dileo 2014, Migliaccio 2014);
  - FINDER I – fulvestrant 500 mg vs. fulvestrant 250 mg + placebo (Ohno 2010);
  - FINDER II – fulvestrant 500 mg vs. fulvestrant 250 mg (Pitchard 2009 (conference abstract), Pitchard 2010);
  - Zgang 2016 – fulvestrant 500 mg vs. fulvestrant 250 mg + placebo – (Jiang 2015 (conference abstract), Zgang 2016);
- studies on exemestane
  - EFECT – exemestane + placebo vs. fulvestrant + placebo – (Chia 2008a, Chia 2008b, Chia 2007 (poster), Mauriac 2008, Ranganathan 2007 (conference abstract);
  - SoFEA – exemestane vs. fulvestrant – (No authors listed 2013 (conference abstract), Johnston 2012 (conference abstract), Johnston 2013);
- studies on anastrozole
  - Trial 0020 – anastrozole vs. fulvestrant (Howell 2000 (conference abstract), Howell 2002, Vergote 2003 (conference abstract));
  - Trial 0021 – anastrozole vs. fulvestrant (Osborne 2000 (conference abstract), Osborne 2002);
  - XU 2010 – anastrozole vs. fulvestrant – (both arms in combination with placebo) (Xu 2010);
  - Buzdar 1997 – anastrozole vs. megestrol acetate – (Buzdar 1997);
- studies on letrozole
  - Buzdar 2001 – letrozole vs. megestrol acetate – (Buzdar 2001);
  - Rose 2003 – letrozole vs. anastrozole – (Rose 2003);

The analysis of heterogeneity of PALOMA-3 vs. MONARCH-2 demonstrated differences between the studies in terms of patient baseline data. In PALOMA-3, 34% of patients have had previous chemotherapy in the treatment of metastatic disease, which may indicate a poorer health status of the patients included in the study and may significantly affect the obtained results. In addition, differences have been identified in the percentage of patients with positive hormone receptor status, or in the percentage of patients who received chemotherapy as part of (neo)adjuvant treatment in these studies.

The analysis of the heterogeneity of studies on the other comparators demonstrates that clinical differences in terms of the study size have been identified, due to the different numbers of patients included in particular studies and the different number of centres conducting the study. The differences were also identified in terms of patients input data, i.e. different percentage of patients with a positive hormone receptor status. In addition, there were differences in the manner of reporting information on previous treatment and HER2 receptor status (or there was no information on this subject). Furthermore, with regard to the outcomes which have been included in the indirect comparisons, no differences in definitions were identified. It should also be mentioned that the duration of follow-up of the studies included in the analysis differed (e.g. the follow-up period in Buzdar 2001 was 60 months, in Rose 2003 – 30 months, whereas in CONFIRM, no information on the length of the follow-up period was given). It is also important to note that three of the studies included in the applicant's analysis were conducted on Asian populations (FINDER I, Xu 2010, Zhang 2016).

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

Abemaciclib + fulvestrant vs. palbociclib + fulvestrant (indirect comparison through placebo + fulvestrant arm)

Based on the results of the indirect analysis, no statistically significant differences were identified for the Abemaciclib + fulvestrant vs. palbociclib + fulvestrant comparison in terms of:

- Overall survival
- Progression-free survival

Abemaciclib + fulvestrant vs. other comparators

In line with results of MONARCH-2, the use of ABE + FUL vs. PL + FUL resulted in statistically significant:

- Increase in overall survival by 9.4 months – 46.7 vs. 37.3, and HR=0.757 (95% CI: 0.606; 0.945)
- Increase in progression-free survival by 7.6 months – 16.9 vs. 9.3, and HR=0.536 (95% CI: 0445; 0.645).

No indirect comparison of abemaciclib + fulvestrant with other comparators (exemestane, letrozole, anastrozole) for clinically significant outcomes i.e. overall survival and quality of life has been conducted.

An indirect comparison demonstrated that the use of ABE+FUL was associated with a statistically significantly lower risk (ranging from 56% to 67%) of disease progression in comparison with EXE, ANA, LET.

In addition, the results demonstrate a statistically significant over 3 times greater chance of obtaining an objective response in patients using abemaciclib in combination with fulvestrant in comparison with patients using anastrozole (OR=3.30 (95% CI): 1.73; 6.29). The odds ratio for other comparisons were not statistically significant. The results of the risk difference demonstrate a statistically significantly higher percentage of patients receiving an objective response to treatment in the arm receiving abemaciclib in combination with a fulvestrant than in the comparator arm.

Safety

Abemaciclib + fulvestrant vs. palbociclib + fulvestrant (indirect comparison through placebo + fulvestrant arm)

In line with the results of the indirect analysis, the use of abemaciclib + fulvestrant vs. palbociclib + fulvestrant was associated with the following results:

- To the detriment of the intervention in question:

- Nearly twelve times higher risk of diarrhoea – OR=11.90 (95% CI: 6.53; 21.67), and RD=52.37 (95% CI: 42.24; 62.50);

- In favour of the intervention in question:
  - 49% lower risk of occurrence of any grade 3 or 4 adverse event – OR=0.51 (95% CI: 0.29; 0.91); and RD=-12.17 (-22.66; -1.68);
  - 84% lower risk of neutropaenia – OR=0.16 (95% CI: 0.05; 0.49), and RD=-34.95 (95% CI: -42.09; -27.81),

Abemaciclib + fulvestrant vs. other comparators

The results of the comparison in terms of safety demonstrate the following results (unless otherwise indicated, the inference applied to both OR and RD):

- For the direct ABE + FUL vs. PLA + FUL comparison:
  - For a statistically significantly higher chance of: adverse events in total, serious adverse event, serious adverse reaction, nausea,
  - No statistically significant differences were identified in terms of: death due to adverse events, headache, constipation, joint pain, hot flushes, back pain;
- For the indirect ABE + FUL vs. ANA comparison:
  - For a statistically significantly higher chance of: adverse events in total (no statistically significant differences with regard to the risk difference), serious adverse reactions, nausea;
  - No statistically significant differences were identified in terms of: serious adverse events (a statistically significant difference in RD was demonstrated), death due to adverse events, headache, constipation, joint pain, hot flushes, back pain;

Additional safety and efficacy data

Since the applicant has carried out an indirect comparison of abemaciclib and palbociclib used in combination with fulvestrant with regard to two outcomes, i.e. overall survival and progression-free survival, a decision was made to carry out an indirect comparison for two outcomes: quality of life and objective response rate.

The quality of life in both MONARCH-2 and PALOMA-3 was assessed using the EORTC QLQ-C30 questionnaire. The indirect comparison was carried out using the Bucher method for two domains: global health and pain. The results of the indirect comparison demonstrate that in both domains there are no statistically significant differences in the assessment of quality of life between abemaciclib and palbociclib, both used in combination with fulvestrant.

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 palbociclib and exemestane, anastrozole and letrozole. Analysing efficacy and safety results based solely on the results of an indirect comparison may not reflect the payer's reality.

The following factors impact the uncertainty of the presented results:

- differences in patient baseline data have been identified. In PALOMA-3 , 34% of patients received chemotherapy in the treatment of metastatic disease, and in MONARCH-2, patients who received chemotherapy in metastatic disease were not eligible for the study. Such a high

percentage of patients after chemotherapy in the treatment of metastatic disease may significantly affect the therapy effect and, consequently, the reliability of the indirect comparison results

- lack of analysis on the heterogeneity of the studies used in the indirect abemaciclib vs. palbociclib comparison and lack of assessment of the appropriateness of conducting an indirect comparison;
- the indirect comparison of abemaciclib and palbociclib has been limited to two outcomes in terms of efficacy, i.e. PFS and OS, and the assessment of the occurrence of: grade 3 and 4 adverse events, diarrhoea and neutropaenia, as part of the safety analysis. At the same time, no justification has been provided for the adopted approach;
- The results of additional secondary studies identified as a result of the review update have not been taken into account in the analysis. It was limited to providing only a brief description of the above studies, without assessing their methodological quality and presenting their results;
- limiting the search of studies on palbociclib to a single database (Pubmed), which is inconsistent with HTA guidelines.
- the assessment of the efficacy of abemaciclib in combination with fulvestrant was based on just one RCT, i.e. MONARCH-2. 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 in combination with fulvestrant under clinical practice conditions;
- only two outcomes were included in the efficacy assessment in the indirect abemaciclib vs. palbociclib comparison. No reference was made to other clinically relevant outcomes such as quality of life.

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.
- cost-utility analysis as part of the comparison of abemaciclib + FUL with the other comparators: anastrozole (ANA), letrozole (LET), exemestane (EXE) and fulvestrant (FUL).

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

The CMA was carried out from the payer's perspective and the common perspective (payer + patient) in a one-year time horizon. Due to the low costs incurred by patients, it was decided against presenting the results of the analysis from the common perspective.

Only the costs of the compared medicines, i.e. ABE and PAL, were taken into account in the analysis. In the case of ABE, the variant adopting the proposed risk-sharing scheme and without an RSS was considered, while the cost of palbociclib was adopted on the basis of the Minister of Health's announcement. The costs of fulvestrant used in combination with the above-mentioned technologies were considered to be non-differentiating – the dosing of fulvestrant was considered to be the same, regardless of the combination with ABE or PAL. It was decided not to include the cost of treating adverse reactions because the cost of diarrhoea treatment which, according to clinical analysis, is more frequent in patients taking ABE, was considered negligible, whereas only dosing reduction or treatment discontinuation are recommended as a course of action to resolve neutropaenia, which is more frequent in patients treated with PAL.

In line with the applicant's estimations *[information protected as a trade secret]*, the use of the intervention in question is *[information protected as a trade secret]* in relation to the palbociclib therapy. *[information protected as a trade secret]*It should be noted that the applicant's calculations do not provide for a possible RSS in the case of PAL.

The price at which the difference between the cost of the intervention in question and the cost of using an optional technology equals zero amounts to *[information protected as a trade secret]*

In line with the applicant's analysis, the ABE+FUL combination in comparison with medicines used in hormone therapy is a technology *[information protected as a trade secret]* of the cost-effectiveness threshold which currently amounts to PLN 147,024/QALY *[information protected as a trade secret]*

Limitations

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

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

- The applicant has chosen cost-minimisation analysis as the analytical method of comparing ABE and PAL. As part of the clinical analysis, an indirect comparison of ABE and PAL was conducted; it demonstrated the lack of statistically significant differences between these interventions in terms of efficacy. Statistically significant differences between ABE and PAL were identified in terms of safety – the use of ABE was associated with a higher risk of diarrhoea and a lower risk of neutropaenia and any grade 3 or 4 adverse event as compared with PAL. According to the applicant, the SPC for Verzenios indicates that the treatment of diarrhoea consists in the administration of anti-diarrhoeal drugs such as loperamide (according to the verification of the Agency's analysts, it is also possible to modify the dosing or discontinue the treatment), while the SPC for Ibrance provides for dosing modification or discontinuation of treatment in the case of haematological toxicity, such as 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, the vast majority of diarrhoea cases reported in MONARCH-2 in the ABE arm (84.5%) was of grade <3 and no grade 4 diarrhoea cases were reported, and the results of PALOMA-3 indicate that 70% of patients receiving PAL experienced grade 3 or 4 neutropaenia. It can therefore be concluded that failure to take the safety effects of the therapy into account in the economic analysis is an expression of a conservative approach. However, it is important to bear in mind the limitations of the conducted indirect comparison, which are reflected in the uncertainty as to whether cost-minimisation analysis was the right type of analysis to have been chosen.

- *[information protected as a trade secret]*

AOTMiT's own calculations

Due to the fact that data from public procurement tenders announced by healthcare providers concerning the price of palbociclib have been identified, own calculations were performed, as part of which the price of one package of Ibrance (palbociclib) in the amount of PLN 5748.17 was implemented into the applicant's model. In addition, the time horizon for the cost estimates of both drugs was aligned (it was assumed that the year has 364 days).

According to the Agency's estimates, within a one-year horizon, the use of the medicine in question is *[information protected as a trade secret]* of palbociclib the therapy*[information protected as a trade secret]*

The net ex-factory price at which the difference between the cost of the intervention in question and the cost of using an optional technology equals zero amounts to *[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 of the Act on reimbursement does not apply in the present case because a randomised trial has been presented to prove the superiority of the technology in question over the reimbursed comparator.

Analysis of the effects on the healthcare system, including budget impact analyses (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 medicine programme in question will amount to:

[information protected as a trade secret]

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

- cost of the medicine in question,
- cost of alternative technologies,
- cost of medicine administration,
- cost of treatment monitoring,
- costs of medicines used after the progression.

In line with the above assumptions, the financing of the intervention in question will involve *[information protected as a trade secret]*

- without taking the proposed RSS into account:

[information protected as a trade secret]

- taking the proposed RSS into account:

[information protected as a trade secret]

Limitations

The following factors impact the uncertainty of the presented results:

- no reliable data are available on the number of patients currently treated with CDK 4/6 inhibitor (since 01.09.2019, palbociclib is reimbursed in the treatment of the population in question), due to the fact that the reimbursement decision became effective relatively recently. *[information protected as a trade secret].* At the same time, the fact that the applicant's calculations are based on the number of newly diagnosed cancer cases, which is of significant importance in the case of patients with advanced cancer recurrence, raises doubts. Taking into account only the newly diagnosed within this group of patients results in the disregarding of a group of patients who were diagnosed in the past and who do not progress – the number of these patients accumulates over the years. The size of the difference between the prevalence and incidence is demonstrated by the comparison of the number of patients with the C50 diagnosis in 2016 according to the NHF data – 194,621 and the number of new breast cancer cases defined using the ICD-10 C50 code according to National Cancer Registry data – 18,615. *[information protected as a trade secret]* the size of the target population and the population in which Verzenios will be used if reimbursed, indicates that *[information protected as a trade secret]*the number of patients who would use the intervention in question as reported by the clinical expert surveyed by the Agency (600 patients vs. *[information protected as a trade secret]*). It should also be noted that the applicant has not justified the exclusion of the possibility of *[information protected as a trade secret]*
- In the applicant's BIA, the treatment regimen for patients using abemaciclib and palbociclib is the same (same percentage of progression-free patients, same treatment following progression). The indirect comparison of the efficacy of the abemaciclib in combination with

fulvestrant regimen vs. the palbociclib in combination with fulvestrant regimen did not demonstrate statistically significant differences in terms of efficacy, therefore the applicant's assumption seems to be correct. However, it is important to bear in mind the limitations of the conducted indirect comparison, which are reflected in the uncertainty of the above assumptions.

- The applicant did not include the cost of treating adverse reactions despite significant differences obtained in the applicant's clinical analysis between abemaciclib in combination with fulvestrant and palbociclib in combination with fulvestrant. In the arm treated with abemaciclib in combination with fulvestrant, diarrhoea was statistically significantly more frequent and neutropaenia was statistically significantly less frequent in the arm treated with palbociclib in combination with fulvestrant. Any grade 3 and 4 adverse events were statistically significantly more common in patients treated with palbociclib in combination with fulvestrant than in patients treated with abemaciclib in combination with fulvestrant; therefore the applicant's approach may be considered conservative.
- The cost of medicines: anastrozole, letrozole and exemestane, adopted in the applicant's BIA has changed due to the publication of the Minister of Health's announcement of 23.10.2019 on the list of reimbursed medicines, foodstuffs for particular nutritional uses and medical devices as at 1 November 2019. However, due to the fact that differences are insignificant, these changes will have only a slight impact on the analysis results,
- *[information protected as a trade secret]*

AOTMiT's own calculations

Due to the identified mistakes in the formulas used in the applicant's model, as well as identification of data from public procurement tenders announced by healthcare providers concerning the price of palbociclib, the Agency's own calculations have been performed. In the first variant, only the relevant formulas were corrected using the cost data implemented in the applicant's model, while in the second variant, the price of palbociclib was also changed.

In line with the first variant, the financing of the intervention in question will involve *[information protected as a trade secret]*

- without taking the proposed RSS into account:

[information protected as a trade secret]

- taking the proposed RSS into account:

[information protected as a trade secret]

In line with the second variant, the financing of the intervention in question will involve *[information protected as a trade secret]*

- without taking the proposed RSS into account:

[information protected as a trade secret]

- taking the proposed RSS into account:

[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 medicine programme

[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 that with the publication of the Minister of Health's announcement of 30 August 2019, the first equivalent containing rituximab became reimbursed. In the Minister of Health announcement of 23.10.2019, another equivalent of MabThera 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 Society for Medical Oncology (ESO-ESMO) 2018.

In line with the latest 2019 NCCN guidelines, abemaciclib in combination with fulvestrant may be considered as a possible therapy for post-menopausal or pre-menopausal women (with ovarian ablation with 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 fulvestrant is recommended by NICE as an option for the treatment of HR-positive, HER2-negative, locally advanced or metastatic breast cancer in patients who have received previous hormone therapy, where exemestane in combination with everolimus would be the most suitable alternative to this therapy.

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 fulvestrant in patients following previous hormone therapy because of their proven efficacy in improving the patients' PFS median (by 6-7 months)and quality of life. The above therapy is one of the preferred treatment options if CDK4/6 inhibitors have not been used before.

The Polish PTOK 2018 guidelines refer jointly to the group of CDK 4/6 inhibitors. Combination therapy with CDK 4/6 inhibitor and fulvestrant is indicated as one of the treatment options in patients with progression during aromatase inhibitor treatment or less than 12 months after its completion in adjuvant therapy.

6 reimbursement recommendations have been identified:

- Positive on condition that cost-effectiveness is improved:
    - Canadian Agency for Drugs and Technologies in Health (CADTH) 2019;
    - Zorgnisinstituut Nederlad 2019;
- Conditional positive
    - Gemeinsame Bundesausschuss (G-BA) 2019 – in line with the recommendation, the use of Verzenios should be limited to the following patient groups:
        - women after menopause with HR+, HER2- locally advanced or metastatic breast cancer who have not received hormone therapy before,
        - women after menopause with HR+, HER2- locally advanced or metastatic breast cancer who have previously received hormone therapy,
        - women of pre- or perimenopausal age with HR+, HER2- locally advanced or metastatic breast cancer who have previously received hormone therapy.
    - Haute Autorité de Santé (HAS) 2018 – recommended in postmenopausal women suffering from breast cancer with HR+, HER2- in the locally advanced stage or with metastases, without parenchymal crisis in combination with fulvestrant in the first-line of metastatic disease treatment in the case of early relapse after adjuvant hormone therapy or in the second-line treatment after hormone therapy used in the first-line.
    - National Institute for Health and Care Excellence (NICE) 2019 – in line with the recommendation, abemaciclib in combination with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for the treatment of HR+ HER2 - locally advanced or metastatic breast cancer in patients previously treated with hormone therapy only if:
        - exemestane in combination with everolimus would be the most optimal alternative therapy;
        - the terms of the agreement on access to therapy with abemaciclib and fulvestrant will be respected.
    - Scottish Medicines Consortium (SMC) 2019 – in line with the recommendation, the SMC restricts the use of Verzenios to the treatment of women with progression during or after (neo)adjuvant hormone therapy or with progression during first-line hormone therapy in advanced breast cancer.

In addition, the All Wales Medicines Strategy Group (AWMSG) 2018 document was identified; it states that the product meets the exclusion criteria due to the NICE assessment.

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.4600.710.2019; PLR.4600.713.2019; PLR.4600.715.2019), with regard to preparation of the recommendation of the President of AOTMiT on Verzenios (abemaciclib) in combination with fulvestrant 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. 103/2019 of 18 November 2019 on the evaluation of Verzenios (abemaciclib) under the following medicine programme: B.9. “Treatment of breast cancer (ICD-10 C50)”, where the medicine is to be used in combination with fulvestrant

References

1. The Position of the Transparency Council No. 103/2019 of 18 November 2019 on the evaluation of Verzenios (abemaciclib) under the following medicine programme: B.9. “Treatment of breast cancer (ICD-10 C50)”, where the medicine is to be used in combination with fulvestrant
2. Report No. OT.4331.48.2019. Reimbursement application for Verzenios (abemaciclib) in combination with fulvestrant in the following indication: “Treatment of breast cancer (ICD-10 C50)”. Verification analysis