Recommendation No. 132/2021
of 3 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the reimbursement of
Piqray (alpelisib), coated tablets, 150 mg, 56 tablets, GTIN code: 07613421024826 and 200 mg, 28 tablets, GTIN code: 07613421024840 and 50 mg + 200 mg, 56 tablets, GTIN code: 07613421024833, in the indication to use in combination with fulvestrant in patients with progressive or recurrent breast cancer during or after completion of hormonal treatment with an aromatase inhibitor, under the B.9. drug programme "Treatment of patients with breast cancer (ICD-10 C50)"

The President of the Agency does not recommend the reimbursement of Piqray (alpelisib), coated tablets, 150 mg, 56 tablets, GTIN code: 07613421024826 and 200 mg, 28 tablets, GTIN code: 07613421024840 and 50 mg + 200 mg, 56 tablets, GTIN code: 07613421024833
in the indication to use in combination with fulvestrant in patients with progressive or recurrent breast cancer during or after completion of hormonal treatment with an aromatase inhibitor, under the B.9. drug programme "Treatment of patients with breast cancer (ICD-10 C50)", as proposed in the application.

Grounds for the recommendation

First of all, the results of the clinical analysis were taken into account, which presented the SOLAR-1 randomised controlled trial (RCT) comparing the efficacy and safety of alpelisib in combination with fulvestrant (ALP + FLV) versus placebo in combination with fulvestrant (PLC + FLV). According to the presented data, the assessed technology does not extend overall survival. Moreover, the technology does not affect the quality of life.

An extension of progression-free survival (PFS) in the ALP + FLV group versus the PLC + FLV group was observed. With regards to the safety assessment, there was a significant increase in the risk of grade 3 hyperglycemia in the ALP+FLV group compared to the PLC+FLV group - the risk ratio was RR 47.50 (95%CI: 11.82; 190.87), and the result was statistically significant. Overall hyperglycaemia, that is regardless of grade, occurred in 184 patients out of 284 (65%) in the ALP+FLV group and in 27 patients out of 287 (9%) in the PLC+FLV group (RR 6.89; 95%CI: 4.76; 9.96). The following adverse events (AEs) occurred statistically significantly more frequently in the ALP + FLV group: diarrhoea,

nausea, rash, weight loss, including grade 3 weight loss.

According to the applicant's estimates, the use of the ALP+FLV regimen instead of FLV monotherapy is [information protected as a trade secret]. The estimated ICUR for the comparison of ALP+FLV vs. FLV was [information protected as a trade secret] According to the probabilistic analysis, the likelihood of the cost-effectiveness of the proposed technology is [information protected as a trade secret]

According to the results of budget impact analysis, a positive decision on financing Piqray from public funds will result in [information protected as a trade secret] of the public payer expenditure by approximately [information protected as a trade secret] in the first year and approximately [information protected as a trade secret] in the second year of the reimbursed period.

According to clinical recommendations, it is possible to use alpelisib in combination with fulvestrant as one treatment option in patients with a confirmed PIK3CA mutation at adequate HbA1c levels. The IQWIG 2021 reimbursement recommendation indicates a small additional benefit compared to the comparators.

Piqray has been included in the list of drug health technologies of high clinical value. At that time, attention was paid to, for example, the mechanism of action (other mutation) and the different clinical outcome (PFS difference, no OS difference), which would require further monitoring in clinical practice in accordance with the requirements specified in the Medical Fund Act (in the medical registry, in accordance with the scope of the assessment provided for in the Act, with funding time restrictions). Financing technologies in the mode provided for highly innovative technologies makes this possible.

Keeping in mind [information protected as a trade secret] with no effect on overall survival and quality of life, the reimbursement of Piqray (alpelisib) as proposed in the application is baseless.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of financing the following medicinal products from public funds:

- Piqray (alpelisib), coated tablets, 150 mg, 56 tablets, GTIN code: 07613421024826, proposed net sales price [information protected as a trade secret];
- Piqray (alpelisib), coated tablets, 200 mg, 28 tablets, GTIN code: 07613421024840, proposed net sales price [information protected as a trade secret];
- Piqray (alpelisib), coated tablets, 50 mg + 200 mg, 56 tablets, GTIN code: 07613421024833, proposed net sales price [information protected as a trade secret];

Proposed payment and dispensing category: patient payment - free of charge, product available under the B.9 drug programme "Treatment of patients with breast cancer (ICD-10 C50)," financed under a new limit group. [information protected as a trade secret]

Health problem

Breast (mammary) cancer (ICD-10 C50) is a malignant tumour that originates in the epithelium of the ducts or lobules of the mammary gland. The disease is divided into categories (pre-invasive and invasive) and stages (early, locally advanced, metastatic and advanced).

The growth of some tumours is stimulated by hormones: estrogen and progesterone. The presence of estrogen receptor (ER), progesterone receptor (PgR), or HER2 stimulates the growth of cancer cells. Tumours can be classified into subtypes based on the status of the hormone receptor and HER2. The dominant subgroup of breast cancer is HR-positive and HER2-negative.

Taking into account new cases of breast cancer diagnosed worldwide, approxima1tely 60-65% are HR-positive, 20-25% are HER2-positive, and 15-18% are triple-negative. PIK3CA mutations are reported in 36% of all cases of breast cancer and in 45% of HR-positive and HER2-negative ones.

According to Globocan 2020 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 emphasised that breast cancer in men is a very rare disease, and according to GLOBOCAN 2020 data, the incidence and mortality of men due to breast cancer is approx. 1%.

Prognosis primarily depends on early detection of the cancer, its type and stage. Approximately 85% of relapses occur during the first 5 years after treatment. 5-year survival rates according to disease stages are: I - 95%, II - 50%, III - 25%, IV - <5%. The average 5-year survival rate in Poland is 74%.

Prognostic and predictive factors of breast cancer include a hormone receptor and HER2 expression. Although hormone-sensitive tumours have a better prognosis than other subtypes, they still account for the majority of breast cancer-related deaths due to their high incidence, which is 60-65% of all breast cancers. The median OS (overall survival) is approximately 42 months in the above-mentioned population of patients. According to the assessment of nearly 2,000 patients with advanced breast cancer, the presence of the PIK3CA mutation was considered an independent negative prognostic factor.

Alternative health technology

The proposed indication includes patients with advanced HR+/HER2- breast cancer with the PIK3CA mutation after disease progression or recurrence, during or after hormonal treatment with an aromatase inhibitor (AI).

The applicant indicates fulvestrant monotherapy (FLV) as an alternative technology to Piqray in combination with fulvestrant. The choice of the comparator is justified but not sufficient.

According to the latest ESMO 2021 guidelines, CDK4/6 inhibitors in combination with hormonal treatment is standard treatment in the first line of advanced HR+/HER2- breast cancer treatment and this option is currently financed from public funds in Poland. Apart from FLV, CDK4/6 inhibitors in combination with hormonal treatment is an optional technology and it should also be taken into account by the applicant (e.g. palbocyclib, ribociclib).

Description of the proposed intervention

Alpelisib is a specific α inhibitor of class I phosphatidylinositol-3 kinase.

Piqray in combination with fulvestrant is recommended for the treatment of postmenopausal women and men with locally advanced or disseminated hormone receptor-positive (HR-positive) and non-expressing human epidermal growth factor receptor type 2 (HER2-negative) breast cancer and PIK3CA mutation if disease progression is observed during or after hormonal treatment used in monotherapy.

The proposed indication (first or second line of systemic treatment) 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.

As part of the clinical analysis, the SOLAR-1 randomised controlled trial (RCT) was presented, the purpose of which was to compare the efficacy and safety of alpelisib in combination with fulvestrant (ALP + FLV) versus placebo in combination with fulvestrant (PLC + FLV) in postmenopausal women and men with hormone-sensitive (HR+), HER2 negative (HER2-), locally advanced or metastatic breast cancer and with PIK3CA mutation. There were 341 patients in the PIK3CA mutation group, with 169 patients being in the ALP + FLV arm and 172 patients being in the PLC + FLV arm. The assessed endpoints were: overall survival (OS), progression-free survival (PFS) and endpoints related to quality of life and safety. The median follow-up period was 42.4 months.

Efficacy

Overall survival (OS)

In the SOLAR-1 study, 181 deaths were reported by the cut-off date: 87 in the APL + FLV group and 94 in the PLC + FLV group. The median *follow-up* for OS (defined as the period from randomisation to death or censoring) was 30.1 months (range: 0.4-53.4). In the group of patients with PIK3CA mutation, the median OS in the ALP+FLV group was 39.9 months (95%CI: 34.1; 44.9) compared with 31.4 months (95%CI: 26.8; 41.3) in the PLC+FLV group (HR 0.86; 95%CI: 0.64; 1.15), with the difference not being statistically significant.

Progression-free survival (PFS)

In the SOLAR-1 study, the median follow-up period from randomisation to the cut-off date for the PFS analysis in the group of patients with PIK3CA mutation was 20 months (range: 10.7; 33.3). In the researcher's opinion, in the group of patients with PIK3CA mutation, the median PFS was 11.0 months (95% CI: 7.5, 14.5) for the ALP + FLV arm versus 5.7 months (95% CI: 3,7; 7.4) for the PLC + FLV arm (HR 0.65; 95% CI: 0.50; 0.85), the difference between the arms was statistically significant. According to the blinded assessment of the Independent Response Review Committee, in the group of patients with PIK3CA mutation, the median PFS was 11.1 months (95% CI: 7.3, 16.8) for 85 patients in the ALP + FLV arm
versus 3.7 months (95%CI: 2.1; 5.6) in the case of 88 patients in the PLC+FLV arm (HR 0.48; 95%CI: 0.32; 0.71), with the difference being statistically significant.

Quality of life according to EORTC-QLQ-C30 questionnaire

In the SOLAR-1 study, the mean change in the questionnaire results related to the assessment of overall quality of life compared to the initial value on the Global Health Status/QoL scale was -3.50 in the ALP + FLV group (95% CI: -8.02, 1.02) and 0.27 in the PLC + FLV group (95% CI: −4.48, 5.02), with the negative change indicating a deterioration in quality of life. There was no statistically significant difference between the groups.

Pain severity assessment (BPI-SF)

In the SOLAR-1 study, no statistically significant differences were reported between the ALP + FLV and PLC + FLV groups in terms of changes in BPI-SF scores, both in terms of the most severe pain and pain scale.

Safety

In the SOLAR-1 study, adverse events (AEs) were reported in 282 out of 284 patients (99%) in the ALP+FLV group and 267 out of 287 patients (93%) patients in the PLC+FLV group. The risk ratio was RR 1.07 (95% CI: 1.03, 1.10) and the result was statistically significant to the disadvantage of ALP+FLV. Also, statistically significant results to the disadvantage of ALP+FLV versus PLC+FLV were reported for the occurrence of grade 3 AEs (187/284, 66% vs 90/287, 31%;
RR 2.10 95%CI: 1.74; 2.54), grade 4 AEs (35/284, 12% vs 17/287, 6%; RR 2.08 95%CI 1.19; 3.63)
and AEs leading to therapy discontinuation (75/284, 26% vs 16/287, 6%; RR 4.74 95%CI 2.83; 7.92). Due to the occurrence of AEs, some patients had to be excluded from further participation in the study - 75 patients (26.4%) in the ALP+FLV group and 16 patients (5.6%) in the PLC+FLV group.

In the SOLAR-1 study, the most common AE in the ALP + FLV group compared to the PLC + FLV group was hyperglycaemia. Overall hyperglycaemia, that is regardless of grade, was reported in 184 out of

284 patients (65%) in the ALP+FLV group and 27 out of 287 patients (9%) in the PLC+FLV group (RR 6.89; 95%CI: 4.76; 9.96). In turn, grade 3 hyperglycaemia was reported in 94 out of 284 patients (33%) in the ALP + FLV group and in 2 out of 287 patients (1%) in the PLC + FLV group. The risk ratio was RR 47.50 (95%CI: 11.82; 190.87), and the result was statistically significant.

Other AEs that were statistically significantly more frequent in the ALP + FLV group compared to the PLV + FLV group were:
diarrhoea (169/284, 60% vs 47/287, 16%; RR 3.63 95%CI: 2.75; 4.80), grade 3 diarrhoea (20/284, 7% vs 2/287, 1%; RR 10.11 95% CI: 2.38; 42.83), nausea (133/284, 47% vs 65/287, 23%; RR 2.07 95% CI: 1.62; 2.65), grade 3 nausea (8/284, 3% vs 1/287, <1%; RR 8.08 95% CI: 1.02; 64.22), rash (103/284, 36% vs 20/287, 7%; RR 5.20 95% CI: 3.32; 8.16), grade 3 rash (28/284, 10% vs 1/287, <1%; RR 28.30 95%CI: 3.88; 206.56), weight loss (79/284, 28% vs 7/287, 2%; RR 11.40 95% CI: 5.36; 24.27) and grade 3 weight loss (15/284, 5% vs 0/287, 0%; RR 31.33 95%CI: 1.88; 521.05). In the SOLAR-1 study, the most common grade 4 AEs included hyperglycaemia (11/284, 4% vs 1/287, <1%; RR 11.12 95%CI: 1.44; 85.54) and diarrhoea (153/284, 54% vs 26/287, 9%; RR 5.95 95%CI: 4.06; 8.71).

Additional efficacy and safety information

The EMA website includes a *risk management plan* (RMP) for Piqray. According to the document, important identified risks associated with Piqray administration include hyperglycaemia, pneumonitis, severe skin reactions and jaw bone necrosis.

In June 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) provided information about the increased risk of hyperglycaemia and jaw bone necrosis that must be taken into account when using alpelisib.

An update to the Piqray patient information leaflet was identified on the FDA website: in the section on special warnings and precautions for use, information on an increased risk of severe skin reactions (toxic epidermal necrolysis and drug reaction with eosinophilia and systemic manifestations; DRESS syndrome), as well as an increased risk of hyperglycaemic hyperosmolar nonketotic syndrome (HHNKS) was added. The update of the Piqray patient information leaflet includes recommendations for more frequent fasting glucose monitoring for the first few weeks of treatment in patients with risk factors for hyperglycaemia such as obesity, elevated FPG, HbA1c at or above the upper limit, concomitant corticosteroid use or age ≥75.

No alerts or safety communications concerning the use of alpelisib were identified on the website of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products.

Limitations

A limitation in assessing therapy efficacy may include the difficulty of blinding patient adherence to the study arm due to the effects of PI3K inhibitors on serum glucose levels and skin.

There was 1 male participant in the SOLAR-1 study (<1%), so the results obtained should be interpreted as concerning women.

No comparison with CDK4/6 inhibitors in combination with hormonal treatment was presented in the clinical analysis.

Other limitations are presented in the Agency Verification Analysis.

Proposed risk-sharing scheme
[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.

As part of the economic analysis, cost-utility analysis was performed in which the use of Piqray (alpelisib; ALP) in combination with fulvestrant (ALP+FLV) was compared to fulvestrant monotherapy (FLV) in this indication. The analysis was conducted over a lifetime horizon, which was assumed to be 40 years. The cycle length in the model is 28 days and a mid-cycle correction is included. The results were presented from the public payer perspective (NHF) and from the joint perspective (NHF + patient). The costs of: PIK3CA mutation testing, drugs and their administration, therapy monitoring, subsequent lines of treatment after progression, terminal care and treatment of adverse events were considered. The efficacy and incidence of adverse events for the ALP+FLV regimen were based on data from the SOLAR-1 study.

According to the applicant's estimates, the use of the ALP+FLV regimen instead of FLV monotherapy is [information protected as a trade secret] The estimated ICUR for the comparison of ALP+FLV and FLV was [information protected as a trade secret] The estimated ICUR values [information protected as a trade secret] the cost-effectiveness threshold referred to in the Act on Reimbursement (PLN 166,758/QALY), [information protected as a trade secret]

The threshold net sales price of the drug at which the cost of an additional quality-adjusted life year is equal to the threshold referred to in Art. 12 point 13 and Art. 19 sec. 2 point 7 of the Act is [information protected as a trade secret]

The deterministic sensitivity analysis tested alternative values or assumptions for the following parameters: time horizon length, distributions for PFS, OS and TTD curves, utility values, discount rate values and treatment costs after progression. The [information protected as a trade secret] the biggest change in ICUR (i.e. maximum and minimum value) was observed after taking into account [information protected as a trade secret]

Limitations

The limitations of the clinical analysis are also the limitations of the economic analysis.

Other comments are presented in the Agency Verification Analysis.

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 view of the presentation of the randomised clinical trial proving the superiority of the proposed technology over the adopted comparator, the circumstances of Art. 13 of the Act on Reimbursement do not arise.

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.

A budget impact assessment determines whether a payer has adequate resources to reimburse 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 was performed for a two-year time horizon. The analysis was carried out from the public payer perspective (NHF) and the joint perspective (NHF and patient). The analysis considered two scenarios - the existing and the new ones. In the existing scenario, it was assumed that [information protected as a trade secret] In the new scenario, it was assumed that [information protected as a trade secret] within a separate limit group for Piqray.

The target population size in 2021 was estimated by the applicant to be [information protected as a trade secret] . In the first year of the analysis, the number of patients with the indication specified in the application in the new scenario, i.e. [information protected as a trade secret] was estimated at [information protected as a trade secret]] In the second year of the analysis, the number of patients was estimated at [information protected as a trade secret] The number of patients who will start the proposed therapy in the new scenario was estimated at [information protected as a trade secret] in the first year of the analysis [information protected as a trade secret] and in the second year of the analysis.

A positive decision on public funding for alpelisib (Piqray) in the treatment of patients from the target population will result in [information protected as a trade secret]. The incremental results of the analysis, [information protected as a trade secret]

The results of the sensitivity analysis indicate that [information protected as a trade secret]

In contrast, the largest decrease in estimated incremental expenditure, [information protected as a trade secret]

Agency's own calculations

In view of the uncertainty regarding the calculation of the cost of PIK3CA mutation diagnosis in the applicant's model, the Agency performed calculations taking into account the cost of the test taken from the applicant's economic analysis and leaving the remaining parameters of the basic analysis unchanged. Considering the adjusted cost of mutation diagnosis resulted in [information protected as a trade secret]

Limitations

The main limitation of the budget impact analysis is the lack of data on the efficacy of some treatment

regimens included in it.

Considerable uncertainty in estimating the size of the target population constitutes a significant limitation. It was based on a compilation of data from sources with diverse characteristics. [information protected as a trade secret]

Other limitations are presented in the Agency Verification Analysis.

Comments on the proposed risk-sharing scheme [information protected as a trade secret]

Comments on the drug programme

Given the significant effect on the progression of hyperglycaemia demonstrated in the SOLAR-1 study, it would be reasonable to include provisions for monitoring the occurrence of this adverse event in the drug programme inclusion criteria and in treatment monitoring.

Other drug programme comments are presented in the Agency Verification Analysis.

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 rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding indicates an increase in reimbursement costs.

Solutions that generate savings aim to reduce the actual prices of reimbursed drugs in inpatient treatment by 10% when issuing subsequent administrative decisions. The applicant focused on drugs for which the reimbursement decision expires by the end of 2021, i.e. on [information protected as a trade secret]. NHF savings resulting from a reduction in the actual price were estimated at 10% of the NHF reimbursement amount from the last 12 months for which sales data of the Department of Drug Administration are available, i.e. from August 2020 to July 2021. The applicant obtained the sales data from IKAR Pro.

The savings for the National Health Fund estimated by the applicant will amount to [information protected as a trade secret]

[information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

In the clinical guidelines found, alpelisib – the evaluated active substance – is recommended by the European ESO/ESMO 2020 guidelines in advanced hormone-dependent HER2-negative breast cancer, emphasising that alpelisib is only applicable to tumours with a PIK3CA mutation. Alpelisib is among the drugs recommended for use in second-line treatment in combination with fulvestrant. It is recommended for patients previously treated with AIs such as exemestane, anastrozole and letrozole, taking into account pre-existing diabetes and baseline HbA1c levels, as well as the toxicity of the drug itself. Therapy with alpelisib in combination with fulvestrant is recommended for pre- and perimenopausal women with OFS/OFA, men and postmenopausal women. The ESO-ESMO guidelines emphasise that patients should take non-sedating antihistamines at the start of treatment to prevent rash, which may occur mainly in the first 2 weeks of treatment. Other options available for first- and second-line treatment include: AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus, AI, tamoxifen, fulvestrant. The 2021 ESMO guidelines maintain the recommendation for

the use of aplelisib in combination with fulvestrant in patients with a PIK3CA mutation, prior exposure to an aromatase inhibitor and adequate HbA1c levels.

Among second-line therapy in patients with HR+ HER2- recurrent or stage IV (i.e. advanced cancer with the presence of distant metastases) breast cancer with a PIK3CA mutation, the NCCN 2021 guidelines point to FDA-approved combination therapy alpelisib + fulvestrant, but it is considered beneficial to add alpelisib to fulvestrant if the tumour has a PIK3CA mutation. Other options for second-line treatment include fulvestrant + CDK 4/6 inhibitors, everolimus with AI, tamoxifen or fulvestrant monotherapy, steroidal (exemestane) and non-steroidal (anastrozole, letrozole) AI or SERM. In the male population with advanced breast cancer, it was also considered appropriate to recommend PIK3CA inhibitors (alpelisib) due to comparable efficacy and safety in both populations.

The Polish PTOK 2020 guidelines recommend the use of alpelisib in combination with fulvestrant in patients with a PIK3CA mutation with progression during postoperative aromatase inhibitor treatment or within 12 months after its completion. The guidelines list substances to be used when disease progression is observed during or after hormone treatment used in monotherapy. In case of progression during tamoxifen treatment, recommended agents include high-dose fulvestrant or AI, whereas in case of progression during AI treatment, recommended agents are tamoxifen (also as adjunctive therapy in men), high-dose fulvestrant with a CDK4/6 inhibitor (including abemaciclib, palbociclib and ribociclib) or exemestane in combination with everolimus. In subsequent lines of treatment, steroidal or non-steroidal AIs (exemestane, anastrozole, letrozole), tamoxifen or fulvestrant, and, in selected cases, megestrol acetate, medroxyprogesterone acetate or estrogens are recommended.

Reimbursement recommendations

One reimbursement recommendation was found – IQWIG 2021. The recommendation identifies a possible minor additional benefit in the population of postmenopausal women with locally advanced or disseminated hormone receptor-expressing (HR+) and non-expressing human epidermal growth factor type 2 (HER2-) breast cancer and with a PIK3CA mutation present compared to the comparators (ribociclib in combination with a non-steroidal aromatase inhibitor, ribociclib combined with fulvestrant, anastrazole, letrozole, fulvestrant or tamoxifen when aromatase inhibitors are not suitable). No additional benefits were demonstrated in the male population with locally advanced or disseminated breast cancer expressing hormone receptor (HR+) and not expressing human epidermal growth factor type 2 (HER2-) and with a PIK3CA mutation.

According to the information provided by the applicant, Piqray (alpelisib) is funded in [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared under the order of the Minister of Health of 16 September 2021 (ref. no. PLR.4500.1463.2021.19.AJA, PLR.4500.1464.2021.19.AJA, PLR.4500.1465.2021.19.AJA) on the preparation of the President's recommendation on the assessment of Piqray, Alpelisib, Coated tablets, 150 mg, 56, tablets, GTIN code: 07613421024826; Piqray, Alpelisib, Coated tablets, 200 mg, 28, tablets, GTIN code: 07613421024840; Piqray, Alpelisib, Coated tablets, 50 mg + 200 mg, 56, tables, GTIN code: 07613421024833, in the indication under the B.9. 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 intended 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. 132/2021 of 29 November 2021 on the assessment of Piqray (alpelisib) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)".

References

1. Position of the Transparency Council No. 132/2021 of 29 November 2021 on the assessment of Piqray (alpelisib) under the drug programme "Treatment of patients with breast cancer (ICD-10 C50)"
2. Report No. OT.4231.44.2021 "Application for the reimbursement of Piqray (alpelisib) under the B.9. drug programme »Treatment of patients with breast cancer (ICD-10 C50)« Verification Analysis" of 19 November 2021