Recommendation No. 6/2020

of 30 January 2020

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

on the evaluation of Kisqali (ribociclib) under the following drug programme: B.9. "Treatment of breast cancer (ICD-10 C50)"

The President of the AOTMiT recommends reimbursing Kisqali (ribociclib) under the following drug programme: B.9. "Treatment of breast cancer (ICD-10 C50)".

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 public funding of the health technology in question is justified.

As part of the efficacy assessment, 6 randomised trials were included, including: MONALEESA-3 (comparing the ribociclib + fulvestrant regimen with fulvestrant monotherapy in a population of postmenopausal patients), MONALEESA-7 (comparing the ribociclib + hormone therapy with hormone therapy in a population of pre- and postmenopausal patients). Additionally, 4 randomised clinical trials were included to carry out an indirect comparison with other comparators.

In line with the presented studies, a statistically significant advantage in favour of the ribociclib (RBC) + fulvestrant (FLV) regimen over FLV was observed in terms of: increase in progression-free survival regardless of the treatment line as assessed both by the researcher and by an independent committee, increase in progression-free survival in first-line therapy, second-line therapy and early relapse therapy, increase in overall survival, general response to treatment as assessed both by the researcher and by an independent committee. However, no differences between the study arms were observed with regard to the quality of life.

The head-to-head study also showed a statistically significant advantage of the RBC + aromatase inhibitor (AI) regime over AI in relation to: increase in progression-free survival as assessed both by the researcher and by an independent committee, increase in overall survival, general response to treatment as assessed by the researcher. A statistically significant advantage of the RBC + AI therapy over AI was also demonstrated with regard to the increase in the time to deterioration in the quality of life. The median time to total deterioration in overall health by at least 10% from baseline was longer in the RBC + AI arm than in the AI arm.

Indirect comparisons between the following regimens were carried out: RBC + FLV v. palbociclib (PALB) + FLV and RBC + AI v. PALB + AI. In line with their results, no statistically significant differences were demonstrated in relation to: prolonging progression-free survival as assessed by both the researcher and an independent committee, increase in overall survival, general response to treatment as assessed by the researcher.

An indirect comparison between RBC + AI and tamoxifen (TMX) was also carried out, the results of which indicate the superiority of the technology in question in terms of: increase in progression-free survival in the general population regardless of the HR and HER2 status and of the AI used, increase in progression-free survival in the population of patients with HR-positive breast cancer regardless of the AI used, increase in overall survival regardless of the HR and HER2 status, general response to treatment in the general population, regardless of the HR and HER2 status and of the AI used, as assessed by the researcher, general response to treatment in the population of patients with HR-positive breast cancer as assessed by the researcher.

When interpreting the above results, one needs to bear in mind that, due to the lack of head-to-head studies comparing the technology in question with all the comparators, an indirect comparison had to be conducted. Additionally, it should be borne in mind that [*information protected as a trade secret*]

In line with the conducted economic analysis, the technology in question, in comparison with monotherapies, [*information protected as a trade secret*]. In the case of the comparison [*information protected as a trade secret*]. However, one should bear in mind that all limitations on the clinical analysis also impact the economic analysis. [*information protected as a trade secret*]. The decision to use different utility standards, where the patient-reported utilities were converted to EQ-5D-3L utilities using British utility standards or were converted to EQ-5D-5L utilities using Canadian utility standards, was also unclear. The use of Polish utility standards was not considered either.

[*information protected as a trade secret*]. The most significant limitation of these estimations is the lack of historical data on the prevalence of RBC and other therapies used in the treatment of patients from the target population. Considering the costs of alternative breast cancer therapies in Poland, the results of the budget impact analysis depend primarily on the prevalence of RBC and PALB therapies.

Based on the latest guidelines, it can be pointed out that the regimens based on CDK 4/6 (including ribociclib) are the preferred treatment options in the population of patients, which is in line with the submitted reimbursed application. This is reflected in reimbursement recommendations where the majority takes a positive view on the public funding of the intervention in question.

Subject of the application

The order of the Minister for Health concerns assessing whether the following medicinal product should be financed from public funds: Kisqali (ribociclib), film-coated tablets, 200 mg, 63 tablets, EAN: 05909991336769, the ex-factory price for which amounted to[*information protected as a trade secret*].

The proposed payment and reimbursement availability category: a free-of-charge drug available as part of the drug programme, within the 1195.0 Ribociclib joint-limit group. The applicant has proposed a risk-sharing scheme.

Health problem

Malignant breast cancer (ICD-10: C50). Breast cancer is a malignant tumour derived from the epithelium of the ducts or lobules of the mammary gland. In 2013, 17,286 new cases (including 144 in men; incidence rate 44.9/100,000) and 5,881 deaths due to breast cancer were recorded (mortality rate 15.3/100,000) were registered in Poland.

Poland is one of the Central and Eastern European countries characterised by an average incidence of breast cancer, however since the early 1980s a systematic increase in the number of new cases in all age groups of women has been observed. Breast cancer is the most common malignant cancer in women in Poland. In 2014, the standardised breast cancer incidence rate in Poland amounted to 51.6/100,000, which constituted 22% of all registered cancers in women.

As the incidence rate increases, the mortality rate in the 20-49 age group decreases and stabilises in the next age group (50-69 years of age). High mortality due to breast cancer is still observed in older women (> 70 years of age). The lower mortality rate is associated with a change in the structure of the advancement of the detected and registered breast cancers – cancer is more frequently detected at an early stage.

The prognosis depends primarily on the early detection of the cancer, its type and stage. About 85% of recurrences occur during the first 5 years after treatment. 5-year survival rates depending on the stage: I-95%, II-50%, III- 25%, IV-<5%. The average 5-year survival rate in Poland is 74%.

Alternative health technologies

Taking into account the clinical guidelines and currently publicly funded technologies, the following technologies should be considered as comparators for the drug in question:

- Intervention: ribociclib (RBC) + fulvestrant (FLV) +/ LHRH (luteinizing-hormone-releasing hormone) agonist
    - FLV monotherapy +/- LHRH agonist
    - palbociclib (PALB) + FLV +/- LHRH agonist
- Intervention: RBC + aromatase inhibitors (AIs) +/- LHRH agonist:
    - AI/tamoxyfen (TMX) +/- LHRH agonist
    - PALB + AI +/- LHRH agonist.

Description of the proposed service

Ribociclib is a selective cyclin-dependent kinase (CDK) 4/6 inhibitor. These kinases are activated upon binding to D-cyclins and play a key role in signaling pathways leading to cell cycle progression and cell proliferation. The cyclin D-Cdk4/6 complex regulates the progress of the cell cycle by pRb (retinoblastoma protein) phosphorylation.

In accordance with the Summary of Product Characteristics (SPC) Kisqali is indicated for the treatment of women with locally advanced or metastatic breast cancer with hormone-receptive positive (HR+), without overexpression of the human epidermal growth factor receptor 2 (HER2) in combination with an aromatase inhibitor or fulvestrant as first-line hormone treatment or in women who have previously received hormone treatment. In premenopausal or perimenopausal women, hormone treatment should be combined with LHRH agonists.

The indication included in the application is included in the above list.

The proposed drug programme constitutes an extension of the currently funded B.9 drug programme. “Treatment of breast cancer (ICD-10 C50)" by adding the possibility of treating patients suffering from advanced breast cancer with ribociclib, including:

- [*information protected as a trade secret*]

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 part of the efficacy assessment, 6 randomised clinical trials (RCTs) were included, including:

- 1 RCT comparing RBC + FLV and FLV in a population of postmenopausal patients:
    - MONALEESA-3 – the median observation period for the trial was 20.4 months, 726 patients were included in the trial:
        - RBC + FLV: 484
        - PLC + FLV: 242
- 1 RCT comparing RBC + HTH (AI/TMX) and HTH (AI/TMX) in a population of pre- and postmenopausal patients:
    - MONALEESA-7 (where stratification of the HTH type used was present and 74% of patients used AI, while 26% used TMX) – the median observation period was:
        - first indirect analysis – 19.2 months
        - second indirect analysis – 34.6 months

      672 patients were included in the trial:
        - RBC + HTH: 335
        - PLC + HTH: 337
- 2 RCTs comparing AI (LTR/TMX) and TMX (PO25: comparison between letrozole (LTR) and TMX, Bonneterre 2001: comparison between anastrozole (ANS) and TMX) allowing for an indirect comparison between RBC + AI and TMX through a common AI reference group,
- 2 RCTs comparing PALB + AI and AI, as well as PALB + FLV and FLV (PALOMA2, PALOMA3) allowing for an indirect comparison between RBC + AI and RBC + FLV and PALB + FLV.

Due to the large number of comparisons, only the most important results were presented.

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

- For MONALEESA-3 – low for most domains. The risk was found to be unclear only for a selective presentation of results.
- For MONALEESA-7 – low for all domains

In order to demonstrate efficacy, the following endpoints were studied:

- CR – complete response,
- ORR – objective response ratio,

- OS – overall survival,
- PFS – progression-free survival,
- TTD – time to treatment discontinuation,
- CBR – clinical benefit rate – percentage of patients with the best response to treatment lasting ≥24 weeks

Efficacy

RBC + FLV v. FLV (MONALEESA-3)

The use of the RBC + FLV regimen in comparison with FLV contributed to the following statistically significant results (results for the longest available observation period were presented):

- prolonging progression-free survival:
    - as assessed by an independent committee with the median observation period equal to 20.4 months, the median was not reached in the RBC + FLV arm, and amounted to 10.9 months in the FLV arm – HR = 0.492 (95% CI: 0.345; 0.703);
    - as assessed by the researcher, regardless of the treatment line and observation period, the result was statistically significant in favour of RBC + FLV compared to FLV, among others:
        - for median observation period equal to 39.4 months in the general population – by approx. 7.8 months (20.6 months v. 12.8 months) and HR=0.587 (95% CI: 0.488; 0.705);
        - for median observation period equal to 39.4 months in the first-line therapy – by approx. 14.4 months (33.6 months v. 19.2 months) and HR=0.546 (95% CI: 0.415; 0.718);
- prolonging overall survival in the general population – with the median observation period equal to 39.4 months, the median was not reached in the RBC + FLV arm, and amounted to 10.9 months in the FLV arm – HR=0.724 (95% CI: 0.0568; 0.924);
- higher likelihood of overall response to treatment:
    - as assessed by an independent committee in the general population – by 78% - RR=1.78 (95% CI: 1.06; 2.98), and NNT=9 (95% CI: 5; 42)
    - as assessed by the researcher in the general population – by 51% - RR=1.51 (95% CI: 1.15; 1.98), and NNT=10 (95% CI: 6; 24)
    - as assessed by the researcher in the population of patients with measurable disease at the beginning of the trial – by 42% - RR=1.42 (95% CI: 1.10; 1.85), and NNT=9 (95% CI: 5; 26)
- higher probability of obtaining a clinical benefit:
    - as assessed by an independent committee in the general population – by 44% - RR=1.44 (95% CI: 1.15; 1.81), and NNT=5 (95% CI: 3; 11)
    - as assessed by the researcher in the population of patients with a measurable disease at the beginning of the trial – by 16% - RR=1.16 (95% CI: 1.01; 1.33), and NNT=11 (95% CI: 6; 84).

No statistically significant differences were found, among others, in the following scopes:

- overall survival for: first line, second line or early relapse;
- clinical benefit as assessed by the researcher in the general population;
- complete response;
- quality of life.

RBC + AI/HTH v. AI/HTH (MONALEESA-7)

The use of the RBC + AI regimen contributed to a statistically significant result in comparison with AI (results for the longest observation period were presented):

- prolonging progression-free survival:
    - [*information protected as a trade secret*]
    - as assessed by the researcher with the median observation period equal to 19.2 months – by approx. 13.7 months (27.5 months v. 13.8 months– HR =0.57 (95% CI: 0.44; 0.74);
- prolonging overall survival – with the median observation period equal to 34.6 months, the median was not reached in the RBC + AI arm, and amounted to 40.7 months in the AI arm – HR=0.70 (95% CI: 0.50; 0.98);
- a 34% increase in the likelihood of obtaining a general response to treatment – RR= 1.34 (95% CI: 1.05; 1.72), and NNT=11 (95% CI: 6; 61)
- an over 19% increase in the probability of obtaining a clinical benefit - RR= 1.19 (95% CI: 1.07; 1.33), and NNT=8 (95% CI: 5; 19);
- with the median observation period equal to 34.6 months – increase in the median time to total deterioration in the quality life by 10.9 months (34.2 months v. 23.3 months) – HR=0.69 (95% CI: 0.52; 0.91).

No statistically significant differences were found for the RBC + AI and AI comparison, among others in terms of the overall response.

The use of the RBC + HTH regimen contributed to a statistically significant result in comparison with HTH (results for the longest observation period were presented):

- prolonging overall survival – with the median observation period equal to 34.6 months, the median was not reached in the RBC + HTH arm, and amounted to 40.9 months in the HTH arm – HR=0.49 (95% CI: 0.35; 0.70).

RBC + FLV v. PALB + FLV (MONALEESA-3 v. PALOMA-3)

As part of the indirect comparison, no statistically significant differences were found between the RBC + FLV therapy and PALB + FLV in relation to:

- increase in progression-free survival assessed by both the researcher and an independent committee;
- increase in overall survival;
- overall response to treatment as assessed by the researcher; comparing the overall response to treatment was not possible according to an independent committee, because no such results were reported for the comparison between PALB + FLV and FLV.

RBC + AI v. TMX (MONALEESA-7 v. PO25/Bonneterre 2001)

In line with the indirect comparison, the use of the RBC + AI regimen in comparison with TMC contributed to the following statistically significant results (results for the longest observation period were presented):

- prolonging progression-free survival in the general population regardless of the HR and HER2 status and of the AI used (HR = 0.41 [0.30; 0.55]),
- prolonging progression-free survival in the population of HR-positive breast cancer patients regardless of the AI used (HR = 0.43 [0.32; 0.57]),
- prolonging overall survival in the general population regardless of the HR and HER2 status (HR = 0.68 [0.47; 0.99]),
- a 69% increase in the likelihood of obtaining an overall response to treatment as assessed by the researcher (comparing the overall response to treatment was not possible according to an independent committee, because no such results were reported for the comparison between RBC + AI and AI, as well as AI and TMX) in the general population regardless of the HR and HER2 status and of the AI used – HR = 1.69 (95% CI: 1.12; 2.54),
- double increase in the likelihood of obtaining a general response to treatment in the population of HR-positive breast cancer patients as assessed by the researcher – RR = 2.03 (95% CI: (1.40; 2.95).

Ribociclib + AI v. PALB + AI (MONALEESA-7 v. PALOMA-2)

As part of the indirect comparison, no statistically significant differences were found between the RBC + AI therapy and PALB + AI in relation to:

- prolonging progression-free survival assessed both by the researcher and an independent committee,
- prolonging overall survival, with the results for the PALB + AI arm derived from PALOMA-1,
- overall response to treatment as assessed by the researcher; comparing the overall response to treatment was not possible according to an independent committee, because no such results were reported for the comparison between RBC +AI and AI, as well as PALB + AI v. AI.

Safety

Direct comparison: RBC + FLV v. FLV

The addition of RBC to FLV therapy significantly increased the risk of overall adverse events, including grade 3 and 4 events, as well as serious overall adverse events, including grade 3, and those associated with the treatment regimen/suspected to be associated with the treatment. The percentage of patients discontinuing treatment regardless of the cause and due to disease progression was lower in the RBC + FLV arm, while the risk of treatment discontinuation due to adverse events was higher.

Direct comparison: RBC + AI v. AI

The risk of overall adverse events, as well as grade 3 and 4 adverse events, was higher in the RBC + AI arm in comparison to the AI arm. The percentage of patients discontinuing treatment due to disease progression was statistically significantly lower in the RBC + AI arm compared to the control arm.

Indirect comparison: RBC + FLV v. PALB + FLV

The risk of overall serious adverse events and grade 3 serious adverse events was statistically significantly higher in the RBC + FLV arm. No statistically significant differences between the arms were found regarding the risk of treatment discontinuation regardless of the cause and due to adverse events.

Indirect comparison: RBC + AI v. TMX

The risk of overall adverse events was higher in the RBC + AI arm in comparison to the TMX arm. The percentage of patients discontinuing treatment regardless of the reason was statistically significantly lower in the RBC + AI arm than in patients receiving TMX.

Indirect comparison: RBC + AI v. PALB + AI

No statistically significant differences were found between RBC + AI and PALB + AI therapies regarding the risk of adverse events, serious adverse events and overall death, as well as treatment discontinuation regardless of the cause and due to adverse events.

Additional safety information

In line with the Summary of Product Characteristics, the most common adverse events and grade 3 and 4 adverse events (reported with a frequency of ≥20% and ≥2%, respectively) in the pooled dataset, the frequency for which was higher in the Kisqali arm for every combination therapy, were as follows: infections, neutropaenia, leukopaenia, headache, cough, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash, as well as infections, neutropaenia, leukopaenia, anaemia, abnormal results in liver function tests, lymphopaenia, hypophosphataemia and vomiting.

The US Food and Drug Administration (FDA) warns that Ibrance (palbociclib), Kisqali (ribociclib) and Verzenio (abemaciclib), used to treat selected patients with advanced breast cancer, may cause rare but severe pneumonia. New risk warnings have been approved in the prescription drug information and package leaflets for the entire class of these cyclin-dependent kinases 4/6 (CDK 4/6). The overall benefit of CDK 4/6 inhibitors is still greater than the risk, when used as directed.

CDK 4/6 inhibitors are a class of prescription drugs which are used in combination with hormone therapies in the treatment of adults with positive hormone receptor (HR), human epidermal growth factor receptor 2 (HER2), advanced or metastatic breast cancer which has spread to other body parts. CDK 4/6 inhibitors block some molecules involved in promoting the growth of cancer cells. The FDA approved Ibrance in 2015, Kisqali and Verzenio in 2017. CDK 4/6 inhibitors have been shown to improve progression-free survival rates.

Limitations

The main limitation of the reliability of the presented results is the lack of head-to-head clinical trials comparing the technology in question and all the comparators.

The following factors impact the uncertainty of the presented results:

- *[information protected as a trade secret]*
- MONALEESA-7 includes the use of one of the AIs (LTR or ANS) or TMX as part of HTH. The intervention assessed as part of this analysis was the RBC + AI combination, which was administered to the majority of patients included in the trial (74%). Moreover, the type of the HTH assigned, i.e. AI or TMX was one of the factors in relation to which the trial was stratified, and the vast majority of MONALEESA-7 results covering the efficacy and safety of the therapy is available for the RBC + AI intervention in question (OS, PFS, response to treatment, therapy toxicity, overall quality of life of patients).
- Lack of a direct comparison with some of the comparators (RBC + AI v. TMX, RBC + FLV v. PALB + FLV and RBC + AI v. PALB + AI) resulted in the need to draw indirect conclusions adjusted using the Bücher method:
    - Differences were found between the studies included in the indirect comparison between RBC + AI and TMX, the most important of which concerned the patient populations (menopausal status, HR and HER2), endpoint definitions, median observation period and disease progression criteria. However, the analyses carried out

in subgroups regarding HR and HER demonstrated that the study outcome is consistent both in the general TMX populations and in the population of HR-positive breast cancer patients or patients with normal levels of HER2/neu.

- Differences between studies included in the indirect comparison between RBC + FLV and PALB + FLV were found. The differences could appear due to discrepancies related to patient populations included in the studies (menopausal status, age, prior treatment) and the available observation periods. It is worth noting, however, that MONALEESA-3 and PALOMA-3 are the best available data sources for RBC and PALB used in combination with FLV. A similar approach (indirect comparison based on PALOMA-3 and MONALEESA-3) was adopted in other published systematic reviews.

- *[information protected as a trade secret]*
- No long-term studies on the safety of using ribociclib in the female population were available [*information protected as a trade secret*].
- No data on effectiveness was presented.

Proposals of risk-sharing schemes

[*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 use of a new therapy and comparing them to the costs and effects of currently reimbursed therapies allow for obtaining an answer to the question on whether the health effect achieved as a result of the new therapy is associated with higher costs in comparison to the currently 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.

As part of the cost-effectiveness analysis, the following analyses were conducted:

- cost-utility analysis (CUA) – comparing RBC + FLV vs FLV and RBC + IA vs IA/TMX;
- [*information protected as a trade secret*]

The analysis was conducted in a lifelong time horizon (40 years) from the perspective of the public payer – an entity obliged to finance services from public funds, i.e. the National Health Fund (NHF) and a common perspective, i.e. the NHF and the patient. Results for the RBC + FLV comparison with comparators from the common perspective are similar to the results for the comparison conducted from the NHF perspective, therefore it was decided not to present them.

The analysis took into account the following types of direct medical costs:

- costs of drugs ;
- costs of drug administration;
- cost of treatment monitoring;
- costs of subsequent treatment lines following disease progression;
- costs of palliative care;
- costs of treating adverse events.

[information protected as a trade secret]

Taking the above values for ICUR into account, the threshold ex-factory price, taking into account the current cost-effectiveness threshold amounts to:

- [*information protected as a trade secret*] – for the RBC + FLV vs FLV comparison:
- [*information protected as a trade secret*] – for the RBC + IA vs IA comparison:
- [*information protected as a trade secret*] – for the RBC + IA vs TMX comparison.

In line with the results of the one-way sensitivity analysis [*information protected as a trade secret*]

Limitations

As in the case of the clinical analysis, the key limitation is lack of head-to head clinical trials comparing the technology in question with its comparators. Additionally one should bear in mind the differences between the population covered by the reimbursement application and the population of the study subjects and the heterogeneity of the studies in terms of compared populations RBC+FLV vs PALB+FLV and RBC+IA vs PALB +IA.

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

- [*information protected as a trade secret*]
- PFS, PPS (post-progression survival), OS and TTD parameters for the compared interventions were determined on the basis of data from clinical trials. For modelling in a lifelong horizon to be possible, extrapolation of those data was necessary.
- For the RBC + IA vs TMX comparison, clinical data implemented into the original model was used. For the RBC vs PALB treatment regimens comparison, based on findings from the conducted clinical analysis, the same efficacy for the intervention and comparator was adopted. All limitations of the clinical analysis in this regard also constitute limitations of this analysis.
- The analysis took into account the prevalence of hormone therapy and chemotherapy used in subsequent treatment lines after failure of the intervention/comparator. Due to the large number of possible treatment options and their similarity to the options included in the calculations, the prevalence of subsequent lines was not determined. Due to the model construction, taking into account the therapy following disease progression impacts solely the costs incurred (drugs, administration, monitoring), however it does not impact parameters regarding efficacy and therefore does not affect LY and QALY results. To determine the costs of treatment following disease progression, data from i.a. an analysis on everolimus assessed by the AOTMiT, which applied to the population of patients with advanced breast cancer with oestrogen receptor expression, no HER2 over-expression or amplification, post-menopausal, no symptomatic involvement of parenchymal organs whose recurrence after treatment with a nonsteroidal aromatase inhibitor used as part of adjuvant therapy was considered.

- Utilities for health conditions included in the model were determined on the basis of data from MONALEESA-3 and MONALEESA-7 clinical trials, differentiating utilities depending on the adopted treatment. That way, reduction of the quality of life related to the occurrence of adverse events was taken into account. For PALB, utility values at the same level as RBC values were adopted, the therapies were indirectly considered equal also in terms of utility reduction due to the occurrence of adverse events. Similar limitations apply to TMX, for which AI utility values were adopted.
- To determine the effective price of ribociclib and palbociclib, it was necessary to use results of the conducted budget impact analysis. Thus, any limitations applicable to the budget impact analysis which impact the calculated effective price translate into limitations of this analysis.
- In the analysis, costs after disease progression were calculated from the moment of progression onset until end of life, in line with the original model. Costs included after disease progression onset have an insignificant impact on results, as demonstrated in the one-way sensitivity analysis.
- *[information protected as a trade secret]*
- Patient-reported utilities were converted to EQ-5D-3L utilities using British utility standards or were converted to EQ-5D-5L utilities using Canadian utility standards. The reason for using different utility norms has not been provided. The use of Polish utility standards was not considered either.

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of Laws No. 2019, item. 784, as amended) occur;

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug 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.

Due to the fact that the clinical analysis did not present any RCTs which would demonstrate the advantage of:

- RBC + FLV compared to PALB + FLV;
- RBC + IA compared to PALB + IA;
- RBC + IA compared to TMX

the circumstances referred to in Article 13 of the Act on reimbursement apply.

[*information protected as a trade secret*]

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 analyses have been carried out from the perspective of the public payer and a common perspective. Kisqali is currently reimbursed under the B.9. drug programme, i.e.:

- histologically confirmed advanced breast cancer,
    - metastatic breast cancer or
    - locally advanced breast cancer if radical local treatment (surgery, radiation therapy) was ineffective or permanently inapplicable;

- postmenopausal women (age ≥55 years old and at least one year since the last menstrual period or age <55 years old and <20 pg/ml estradiol concentration or condition after bilateral oophorectomy);
- documented presence of oestrogen (ER +) and/or progesterone (PR +) receptors;
- documented lack of HER2 overexpression in cancer cells (IHC /0 or 1+/ score) or lack of HER2 gene amplification (/-/ in-situ hybridisation (ISH) score);
- no prior systemic treatment for advanced breast cancer;
- general health condition - 0-1 in the WHO scale;

In the case of a positive reimbursement decision, RBC will be financed in the target population under a drug programme in the population of breast cancer patients in which the drug is currently not reimbursed, i.e.

- [*information protected as a trade secret*]

In view of the above, the applicant assumed that in the case of a positive decision on RBC reimbursement, it will generally be financed in:

- [*information protected as a trade secret*]

The budget impact analysis was conducted taking into account the following direct medical costs differentiating the assessed health technologies:

- costs of drugs,
- costs of chemotherapy,
- costs of drug administration,
- costs of patient qualification and treatment monitoring,
- costs of treating adverse effects,
- costs of treatment following disease progression,
- costs of palliative care.

[*information protected as a trade secret*]

Limitations

Considering the costs of alternative breast cancer therapies in Poland, the main limitation of the presented results of the budget impact analysis depends primarily on the prevalence of RBC and PALB therapies. Due to the lack of historical data, the prevalence of RBC and other therapies used in the treatment of patients in the target population was determined based on the results of a survey.

The following factors impact the uncertainty of the presented results:

- The size of the target population was estimated by compiling data from various sources; KRN [National Cancer Registry] and Health Needs Maps, reports, observational studies and surveys were used. The included data is subject to certain limitations which may affect the analysis results. At the same time, a conservative approach, consisting in overestimation of the target population size, was adopted. A sensitivity analysis was also performed in this regard.
- The prevalence of RBC and other therapies used in the treatment of patients in the target population was determined based on the survey results. A sensitivity analysis was performed in this regard.
- The percentages of AI and TMX drugs were estimated based on sales data referring to a population wider than the population specified in this analysis. Due to the low cost of monthly therapy using these drugs, this assumption has no significant impact on the results of the analysis.
- In patients receiving RBC, the dosage may be reduced in the course of treatment. The decision is made individually depending on the patient's health condition. The calculations included data from the clinical trial regarding the percentage of patients receiving individual doses in subsequent treatment cycles. The actual consumption in the target population may be different from that included in the analysis.
- In patients receiving PALB who showed symptoms of intolerability to treatment, reduction of the dosage may be necessary. The analysis did not include calculations in this regard due to the fact that reducing PALB dosage makes it necessary to purchase a new packaging of Ibrance (with a smaller unit dose), and the cost of the unused part of the packaging, which was previously used by the patient, is borne by the payer. The adopted assumption is therefore conservative, while its impact on the results of the analysis is insignificant.
- It has been assumed that CTH, which constitutes an alternative to the assessed technology used in the target population, includes the same regimens as CTH used after disease progression determined based on the assumptions of the economic analysis. In light of the lack of alternative data concerning therapies used as part of CTH in the treatment of advanced cancer in Poland, the data used is characterised by the maximum possible level of reliability.
- The analysis equated the efficacy of NSAI-based regimens (RBC + NSAI + GOS, NSAI + GOS) determined based on the clinical trial results with the efficacy of relevant AI-based regimens (RBC + AI + GOS, AI + GOS), which resulted from the conclusions of the clinical analysis indicating that no differences in efficacy were found between individual AI drugs (LTR, ANS, exemestane).
- The results of the economic analysis for the placebo + AI + GOS and placebo + FLV regimens were adopted in the BIA analysis for the AI + GOS regimen and FLV monotherapy.
- Due to the lack of distinction between the efficacy of therapies used in the first and second lines of advanced breast cancer treatment in the economic model, the BIA assigned the same percentages of patients in specific health conditions, in line with the results of the economic analysis for a given regimen, regardless of the treatment line.

- Due to the lack of data on the percentage of patients in specific health conditions for the FLV + GOS therapy in the population of pre- and post-menopausal patients, as well as the AI and TMX therapies in the population of post-menopausal patients, they were assigned the same values as the FLV regimen in the population of post-menopausal patients and the AI + GOS and TMX + GOS regimens in the population of pre- or perimenopausal patients.
- Due to using the results of the economic analysis in the BIA analysis, the limitations of the economic analysis constitute also limitations of the BIA analysis.
- The analysis assumes that a year is made up of 13 28-day cycles, which has no significant impact on the analysis results.

Remarks on the proposed risk-sharing instrument

No remarks.

Remarks on the drug programme

No remarks.

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.

The objective of the analysis is to indicate savings allowing for coverage of expenses associated with the reimbursement of Kisqali (RBC, ribociclib) in combination with fulvestrant (FLV) or aromatase inhibitors (AIs) used in women with human epidermal growth factor receptor 2-negative, hormone-sensitive, generalised (metastatic) or locally advanced breast cancer."

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The potential, generated savings should exceed the public payer's expenses related to reimbursement of Kisqali (ribociclib) under the B.9. "Treatment of breast cancer (ICD-10 C50)" drug programme, as estimated in the budget impact analysis.

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

On the basis of the latest guidelines:

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

it can be indicated that treatment regimens based on CDK 4/6 inhibitors (ribociclib included) are the preferred treatment options in the population of patients indicated in the submitted reimbursement application. Previously issued recommendations (American Society of Clinical Oncology 2016) did not include ribociclib, however they recommend the use of palbociclib – a drug in the CDK 4/6 inhibitor group. It should be underlined that Kisqali (ribociclib) first received marketing authorisation from the EMA on 22 August 2017. ESO-ESMO 2018 guidelines were published on 19 July 2018, i.e. before the marketing authorisation indications were broadened by the EMA (17 December 2018).

Furthermore, all identified guidelines recommend ovarian ablation or suppression in pre-menopausal women and the same therapy as for post-menopausal women, which is a population for which the largest number of clinical trials has been conducted.

Reimbursement recommendations issued by 6 organisations have been identified:

- All Wales Medicines Strategy Group (AWMSG) 2019;
- Haute Autorité de santé (HAS) 2019;
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) 2019
- The National Institute for Health and Care Excellence (NICE) 2019
- Scottish Medicines Consortium (SMC) 2019
- National Centre for Pharmacoeconomics (NCPE) 2018

In the defined indications, positive recommendations for Kisqali were issued by the French organisation (HAS), English organisation (NICE) and the Scottish organisation (SMC). IQWIG 2019 documents indicate that no additional benefit was proven for most of the analysed indications. Following a quick review, NCPE does not recommend reimbursement of ribociclib for the currently proposed price. Furthermore, the AWMSG website stated that Kisqali met the exclusion criteria following a NICE appraisal.

In line with information presented by the Applicant, Kisqali (ribociclib) 200 mg is financed in 8 EU and EFTA states (of the 31 indicated states): Cyprus, Czech Republic, Spain, the Netherlands, Iceland, Latvia, Germany, United Kingdom. Usually the drug is reimbursed from public funds in 100%. The drug is reimbursed in one country with the *per capita* GDP similar to Poland's – i.e. Latvia.

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 28/11/2019 (reference number: PLR.4600.1279.2019.29.MO), with regard to preparation of the recommendation of the President of the AOTMiT on Kisqali (ribociclib) under the following drug programme: B.9. "Treatment of breast cancer (ICD-10 C50)" pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 6/2020 of 27 January 2020 on the evaluation of Kisqali (ribociclib) under the following drug programme: "Treatment of breast cancer (ICD-10 C50)".

References

1. The Position of the Transparency Council No. 6/2020 of 27 January 2020 on the evaluation of Kisqali (ribociclib) under the following drug programme: "Treatment of breast cancer (ICD-10 C50)".
2. Report No.OT.4331.67.2019. Reimbursement application for Kisqali (ribociclib) to be available under the following drug programme: B.9. "Treatment of breast cancer (ICD-10 C50)". Verification analysis