Recommendation No 17/2021

of 17 February 2021

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

on the evaluation of Lenvima (lenvatinib) in the framework of the drug programme

"Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)"

President of the Agency recommends the reimbursement of the medicinal product Lenvima (lenvatinib) under the drug programme "Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)", **provided that** the risk-sharing scheme is deepened.

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, considers the public financing of the technology named in the application to be justified **provided that** the risk-sharing scheme is deepened.

Considering the results of the clinical analysis, it can be concluded that the use of lenvatinib in patients with differentiated thyroid cancer is more effective in terms of progression-free survival compared to placebo (HR= 0.21 [99% CI: 0.14-0.31]) and compared to sorafenib (trade secret). However, it should be noted that the inference of superior efficacy of lenvatinib versus sorafenib involves a high degree of uncertainty as it is based on an indirect comparison (no studies directly comparing the assessed interventions are available). At the same time, both therapies are recommended in clinical recommendations related to the analysed indication.

(trade secret)

The results of the budget impact analysis showed in turn (trade secret)

A significant limitation of the analysis is the uncertainty in the assumed size of the patient population using the technology named in the application in the new scenario, which in practice may be several times higher than the submitted estimates. Consequently, deepening the risk-sharing scheme is all the more justified.

It was also recognised that currently the only therapeutic option for patients from the analysed population, i.e. with advanced radioiodine-refractory thyroid cancer, is the treatment based on emergency access to drug health technologies.

Taking into account the above arguments, including (trade secret), it seems reasonable to finance Lenvima (lenvatinib) on the condition that the risk-sharing scheme is deepened or extended to include a mechanism limiting the total payer's budget expenditure on the financing of the technology named in the application.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public financing of a medicinal product:

- Lenvima (lenvatinib), hard capsules, 4 mg, 30 capsules, EAN code: 05036519003763, net sales price (trade secret)
- Lenvima (lenvatinib), hard capsules, 10 mg, 30 capsules, EAN code: 05036519003770, net sales price (trade secret).

Proposed payment and dispensing category: free of charge under a drug programme as part of a new limit group.

(trade secret)

Health problem

Thyroid cancer is a malignant neoplasm that originates:

- from thyroid follicular cells:
    - differentiated carcinomas (DTC, differentiated thyroid cancer):
        - papillary carcinoma (PTC, papillary thyroid cancer),
        - follicular cell carcinoma (FTC follicular thyroid cancer)
        - Hürthle cell (oxyphilic) carcinoma (HCC),
    - undifferentiated carcinoma (anaplastic - 2-5%),
        - from C cells (parafollicular cells) that produce calcitonin,
    - medullary carcinoma (5%).

Another rare thyroid malignancy is lymphoma, usually of the marginal zone of the MALT (B-cell) system, which is a variant of malignant non-Hodgkin's lymphoma.

Thyroid cancer is the most common malignant tumour of the endocrine glands. The incidence is approx. 7.4 in women and 1.7/ 100,000/year in men. The disease can occur at any age, with a peak between 40 and 50 years of age The number of thyroid cancer cases according to the data of the Polish National Cancer Registry (KRN) for 2015 was 3,529, of which about 605 were men and 2,924 women. The incidence of the disease has increased significantly over the past two decades. The incidence of thyroid cancer is increasing in developed countries, and due to the good prognosis of thyroid cancer, the population of patients requiring treatment and post-treatment monitoring is relatively high, probably amounting to >20,000 in Poland.

The natural history of thyroid cancer has a positive prognosis when treatment is instituted early (95-98% of patients survive at least 5 years). While differentiated thyroid cancer is curable in most cases, locally advanced or metastatic cancer refractory to radioactive iodine (RAI) therapy is more resistant and is associated with shorter patient survival of up to 2.5 to 3.5 years. Approximately 5-15% of patients become refractory to RAI therapy.

The growth of thyroid cancers is slow, which can lead to a false belief that the nodule is benign. In ca. 5% of patients, the diagnosis is reached late, at the stage of generalised dissemination, when the

prognosis is already worse and, despite treatment, approx. 50% of patients survive 10 years. The development of distant iodine-refractory metastases is particularly unfavourable.

In iodine-sensitive metastases in the lungs, complete remission can be achieved. In bone metastases, even iodine-sensitive, the prognosis is much worse. Lymph node metastasis is associated with a worse prognosis.

Untreated differentiated thyroid cancer inevitably, although often very slowly, leads to death, most often from upper airway obstruction or respiratory failure due to lung metastasis.

Alternative health technology

Taking into account clinical guidelines and technologies currently financed from public funds, sorafenib was indicated as a comparator for the technology named in the application.

In Poland, sorafenib is used in the analysed indication under emergency access.

Description of the benefit named in the application

The medicinal product Lenvima is a drug containing lenvatinib, which is a tyrosine kinase inhibitor that selectively inhibits kinase activity in vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), as well as the activity of other tyrosine kinases involved in proangiogenic and oncogenic pathways, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, or platelet-derived growth factor (PDGF) receptors PDGFRα, KIT, and RET. In addition, lenvatinib demonstrated selective direct antiproliferative effects in hepatic cell lines dependent on the activation of FGFR signalling, which is associated with the inhibition of FGFR signalling by lenvatinib.

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

- as monotherapy and in the treatment of adult patients with progressive locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) radioiodine-refractory thyroid cancer;
- as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy.

The indication applied for is included in the registration indication.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the assessment of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

Patients with progressive locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) radioiodine-refractory thyroid cancer are the target population for the present study.

No studies were found to directly compare the use of lenvatinib with sorafenib in the study population.

The following studies were included in the clinical analysis:

- SELECT - a multicentre double-blind randomised trial comparing oral lenvatinib at 24 mg/day (LEN) with placebo (PLC) in 392 patients with differentiated thyroid cancer (papillary, follicular thyroid cancer);
- DECISION - A multicentre, double-blind randomised trial comparing sorafenib at 400 mg/twice a day (SOR) with placebo (PLC) in 417 patients with differentiated localised or metastatic (papillary, follicular, and Hürthle cell) thyroid cancer.

An indirect comparison was performed using two methods:

- indirect comparison using Bucher's method;

(trade secret)

In addition, results from 3 secondary research studies meeting the inclusion criteria are presented: Kawalec 2016, Yu 2019, Fleeman 2019/2020.

For the analysis of the effectiveness of lenvatinib, the applicant included 32 papers describing 29 studies on treatment using lenvatinib in patients with advanced radioiodine-resistant differentiated thyroid cancer.

The following endpoints were assessed in the primary studies:

- Primary endpoints:
    - progression-free survival (PFS);
- Other (selected):
    - overall survival (OS);
    - complete response (CR);
    - partial response (PR);
    - stable disease (SD);
    - duration of stable disease (DSD ≥ 23 weeks);
    - progressive disease (PD);
    - disease control rate (DCR);
    - clinical benefit rate (CBR):
    - safety of treatment.

The reliability of SELECT and DECISION studies was assessed using the Cochrane descriptive scale criteria, whereas systematic reviews were assessed using the AMSTAR 2 scale.

The general quality of randomised control trials (SELECT and DECISION) was assessed as high (low risk of bias for most domains except for a high risk for the data completeness domain). In contrast, the quality of the included systematic reviews is critically low (Yu 2019, Kawalec 2016) and low (Fleeman 2019).

Efficacy

SELECT LEN vs PLC

Significantly higher benefits of lenvatinib compared to placebo were demonstrated in:

- progression-free survival: HR= 0.21 (99% CI: 0.14-0.31), p<0.0001;
- (trade secret)
- partial response: OR = 110.86 (95% CI: 26.82; 458.23), p <0.0001;

- progressive disease: RD =-32.80 (95% CI: 41.72; -23.87), p<0.0001
- disease control rate (DCR): OR = 5.69 (95% CI: 3.43; 9.43), p<0.0001
- clinical benefit rate (CBR): OR = 8.82 (95% CI: 5.47; 14.23), p<0.0001

It should be noted that the study showed results that were statistically significantly in favour of placebo over lenvatinib in terms of stable disease (SD) and duration of stable disease (DSD ≥ 23 weeks).

Indirect comparison of LEN vs SOR

(trade secret)

Results in favour of LEV were further obtained for partial response and disease control rate (for OR).

Kawalec 2016

The review concluded that based on currently available clinical data, lenvatinib is more effective than sorafenib in the treatment of RR-DTC. The safety profile of the drugs was acceptable and comparable.

Yu 2019

The incidence of adverse events was different for the two drugs. Patients in the sorafenib group had a significantly higher incidence of hand-foot syndrome, hypocalcemia, rash, elevated alanine aminotransferase (ALT), and elevated aspartate aminotransferase (AST). Voice change, hypertension, nausea and vomiting were more common in the lenvatinib group.

Fleeman 2019

Both LEN and SOR were confirmed to improve median PFS compared to placebo: 18.3 months (LEN) vs 3.6 months (PLC) and 10.8 months (SOR) vs 5.8 months (PLC).

Using crossover-adjusted OS data, the study authors found a statistically significant improvement in OS in patients treated with LEN compared with patients receiving placebo (SELECT); no such findings were presented for SOR versus placebo (DECISION).

Lenvatinib and sorafenib were associated with a higher incidence of adverse events (AEs) and dose reduction was needed in more than 60% of patients.

Effectiveness

Analysis of the 29 practice effectiveness studies identified by the applicant demonstrates that lenvatinib has significant effectiveness in clinical practice among RR-DTC patients, with results comparable to those obtained in the SELECT trial.

Safety

SELECT trial

Treatment-related adverse events (TRAE) of any grade that occurred in more than 40% of patients in the lenvatinib group were hypertension (67.8%), diarrhoea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), weight loss (46.4%), and nausea (41.0%).

Discontinuation due to adverse events occurred in 37 patients receiving lenvatinib (14.2%) and 3 patients receiving placebo (2.3%).

In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered treatment-related.

EMA

The most common adverse events associated with the use of Lenvima (which may occur in more than 3 out of 10 people) are hypertension, diarrhoea, decreased appetite and weight, fatigue, nausea, proteinuria, oral mucositis, vomiting, dysphonia, headache, and palmar-plantar erythrodysesthesia.

Major serious adverse events included: renal failure and dysfunction, heart failure, clots in the arteries leading to stroke or heart attack, bleeding in the brain, "posterior reversible encephalopathy syndrome" characterised by headache, confusion, convulsions, and loss of vision, liver failure, hepatic encephalopathy (brain damage due to hepatic insufficiency), stroke, and myocardial infarction.

FDA

The most common adverse events observed in lenvatinib-treated patients with HCC (≥20%) were: hypertension, fatigue, diarrhoea, decreased appetite, arthralgia, myalgia, weight loss, abdominal pain, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, bleeding events, hypothyroidism and nausea.

Limitations

A major limitation of the analysis presented here is that no studies were found that would directly compare lenvatinib with sorafenib, so the inference is based on the results of the indirect comparison.

In addition, the uncertainty of the presented results of the clinical analysis is affected by the following limitations, among others:

- different criteria for including patients in the SELECT and DECISION trials (e.g. in the SELECT trial it was allowed to include patients who had previously received anti-VEGF therapy);
- High heterogeneity of included studies in terms of population characteristics, duration of active therapy;
- The SELECT study aimed to evaluate the efficacy of lenvatinib in a population of patients with metastatic and locally advanced differentiated thyroid cancer (metastatic disease was reported in 99% of patients, so the population in the study does not fully reflect the population named in the application);
- In the included studies, patients with progressive disease were allowed to receive other anticancer treatments;
- The SELECT and DECISION study protocol allowed for continued use of the drugs, even after disease progression. (trade secret);

Proposed risk-sharing scheme

(trade secret)

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

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

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (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 the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

The cost effectiveness evaluation included a cost utility analysis (CUA) over a lifetime horizon (37 years), from the perspective of the public payer - the entity required to fund the benefits with public funds, i.e. National Health Fund (NHF) and from the shared perspective of the payer and the beneficiary (the results from the shared perspective are similar to the results from the perspective of the NHF, which is why they have not been presented).

The following medical costs were included in the analysis:

- the cost of the drugs lenvatinib and sorafenib;
- costs of treatment monitoring, costs of visits to specialists, and costs of hospital stay, so-called medical costs;
- costs of treatment after disease progression: BSC, including (trade secret)
- terminal care;
- treatment of adverse events.

Data on the efficacy and safety of LEN and SOR therapy were obtained from studies included in AKL.

Given these assumptions, the incremental cost utility ratio (ICUR) from the perspective of the NHF was:

(trade secret)

Considering the above ICUR values, the threshold net sales price at the current break-even point is: (trade secret)

Limitations

The uncertainty of the presented results was mainly due to the lack of studies directly comparing the analysed technology with the comparator, which translates into the limited reliability of model inputs.

Agency's own calculations

No additional own calculations were performed.

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended) apply;

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

Not applicable.

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

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

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

A budget impact assessment determines whether a payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The results of the applicant's budget impact analysis are presented over a two-year horizon. The analysis was conducted from a public payer (NHF) and a shared payer perspective. The results of the analysis from both perspectives were similar.

The analysis considered costs determined based on an economic model and (trade secret)

The applicant estimated the number of patients using the technology named in the application in the new scenario to be:

(trade secret)

The results of the primary analysis from the perspective of the NHF indicate that the inclusion of the medicinal product Lenvima (lenvatinib) in the reimbursement scheme will entail (trade secret)

Limitations

The main limitations of the budget impact analysis stem from the uncertainty of target population estimates and the evolution of the market share of the analysed drugs (trade secret). Alternative population size values tested in the analysis of extreme variants and the Agency's own estimates had a significant impact on the evolution of future public payer expenditure.

It should also be noted that not only sorafenib but also lenvatinib is a therapeutic option currently reimbursed under the principles of emergency access to drug health technologies. However, the analysis assumes that there are no patients for whom the technology indicated in the application is currently used.

Agency's own calculations

(trade secret)

Comments on the proposed risk-sharing scheme

(trade secret)

Comments on the drug programme

(trade secret)

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction 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 reimbursement of the health technology named in the application.

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

As part of the submitted rationalisation analysis, the applicant proposed a solution based on the assumption that there will be a decrease in the funding limit, which will result from the introduction on the market of cheaper equivalents of the currently used active substance - dasatinib.

The analysis conservatively assumed a minimum of 25% savings resulting from a reduction in the total amount of reimbursement allocated to the original drug. A two-year time horizon was adopted.

(trade secret)

Discussion of recommendations issued in other countries in relation to the assessed technology

Seven clinical recommendations were presented relating to the indication applied for, from:

- Polish Scientific Societies (Jarząb 2018);
- European Society for Medical Oncology (ESMO 2019);
- European Thyroid Association (ETA 2019);
- National Comprehensive Cancer Network (NCCN 2020);
- National Cancer Institute (NCI 2018);
- Italian Scientific Societies (SIE 2018);
- American Thyroid Association (ATA 2015).

All guidelines identify lenvatinib as a recommended or possible therapy for the treatment of patients with progressive, locally advanced and/or metastatic radioiodine-refractory thyroid cancer.

As a first-line tyrosine kinase inhibitor, sorafenib is listed alongside lenvatinib, with the former registered for this indication in the European Union (central procedure). The latest U.S. NCCN 2020 guidelines identify lenvatinib as a therapy preferred over sorafenib.

Reimbursement recommendations

The search found 6 reimbursement recommendations related to the use of lenvatinib for treating advanced radioiodine-refractory thyroid cancer.

Positive recommendations (NICE 2018, SMC 2016, AWMSG 2017, HAS 2015) indicate that lenvatinib and sorafenib are the only treatment options for patients with progressive, locally advanced or metastatic differentiated radioiodine-refractory thyroid cancer. The superiority of lenvatinib over placebo was also indicated.

A conditionally positive Canadian recommendation (pCORD 2016) noted that it is justifiable to recommend reimbursement for lenvatinib, but there is a need to improve cost-effectiveness to an acceptable level.

In addition, the 2015 Irish NCPE recommendation reported that a full HTA is recommended to determine the cost-effectiveness of lenvatinib.

According to the information provided by the applicant, the medicinal product Lenvima (lenvatinib) is funded in (trade secret) EU and EFTA countries (out of 31 indicated).

PRESIDENT

dr n. med. Roman Topór-Mądry

/document signed electronically/

Basis for the recommendation

The recommendation was prepared under an order dated 23/11/2020 issued by the Minister of Health (letter reference: PLR.4500.763.2020.17.KK, PLR.4500.762.2020.17.KK), regarding the preparation of the President's recommendation on the evaluation of the drug Lenvima (lenvatinib) within the drug program: "Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)" 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 (Journal of Laws 2020, item 357 as amended), having received the Position of the Transparency Council No. 17/2021 of 15 February 2021 on the evaluation of the drug Lenvima (lenvatinib) within the framework of the drug program "Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)"

References

1. Position of the Transparency Council No. 17/2021 of 15 February 2021 on the evaluation of Lenvima (lenvatinib) within the framework of the drug programme "Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)"
2. Report no. OT.4331.48.2020 Application for reimbursement of the medicinal product Lenvima (lenvatinib) within the framework of the drug program "Treatment of advanced radioiodine-refractory thyroid cancer (ICD-10: C73)"