Recommendation No. 129/2021
of 26 November 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the assessment of Vitrakvi (larotrectinib)
under the drug programme:
"Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene"

The President of the Agency recommends the reimbursement of Vitrakvi (larotrectinib) in the indication of papillary thyroid cancer with the presence of the TPR-NTRK1 fusion gene after the exhaustion of available treatment options under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene" **provided that [information protected as a trade secret]**

The President of the Agency does not recommend the reimbursement of Vitrakvi (larotrectinib) in other indications under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene" **as proposed in the application.**

Grounds for the recommendation

The proposed health technology is a drug that targets a molecular agent – a rare fusion of the NTRK gene and is indicated for the treatment of various types of solid tumours, i.e. regardless of tumour location.

The efficacy and safety of larotrectinib were evaluated in three single-arm studies (no control group), while the results presented in the clinical analysis [information protected as a trade secret]

In the assessment of the papillary thyroid cancer indication, information on the effects of therapy in a clinical practice setting in Poland provided by experts was considered.

The conclusions of the 2020 NICE analysis were taken into account. They suggest that there is insufficient scientific evidence to confirm that people with solid tumours showing the NTRK fusion have a worse prognosis than those with tumours without genetic changes. Available data are based on a

small population. Prognosis may depend not only on the presence of a fusion in the NTRK gene, but also on the ECOG status, tumour type and NTRK gene fusion type. This also indirectly points to the need to observe the effects of therapy in a clinical practice setting.

Consideration was also given to estimates of [information protected as a trade secret] The reimbursement decision regarding the proposed technology should also include access to diagnostic tests for the detection of the NTRK gene fusion and the cost connected to their performance.

Considering the above arguments, including the uncertainty of drawing conclusions from the clinical analysis, the likely [information protected as a trade secret] and the unpredictability of costs associated with NTRK diagnostics, the funding of Vitrakvi (larotrectinib) in the papillary thyroid cancer indication is justified only if the above-mentioned conditions are met. There is also a need to continue to monitor data on the efficacy of the evaluated health technology and the impact of the NTRK gene fusion on prognosis in cancer patients.

It cannot be excluded that larotrectinib therapy may bring clinical benefits to patients in Poland in the other indications, but due to clinical uncertainties and uncertainty of economic estimates, reimbursement in this group of indications is justified provided that [information protected as a trade secret]

Observation should include monitoring the impact of the NTRK gene fusion on prognosis and survival in individual indications.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Vitrakvi (larotrectinib) hard capsules, 25 mg, 56 capsules, EAN code: 04057598011792, net sales price: [information protected as a trade secret]
- Vitrakvi (larotrectinib) hard capsules, 100 mg, 56 capsules, EAN code: 04057598011815, net sales price: [information protected as a trade secret]
- Vitrakvi (larotrectinib) oral solution, 20 mg/ml, 1 bottle 100 ml, EAN code: 04057598011808, net sales price: [information protected as a trade secret]

Proposed price and dispensing category: free of charge under the drug programme, in a new limit group. [information protected as a trade secret]

Health problem

The indication covers various types of solid tumours showing fusion of the neurotrophin receptor tyrosine kinase (NTRK) gene. The fusion of the above-mentioned gene is identified as a major oncogenic agent and the primary cause of many different types of solid tumours (regardless of location and tissue type) in people of all ages.

NTRK fusions are rare in adult cancers, e.g. < 1% in non-small-cell lung carcinoma and 1-2% in colorectal cancer, and are more commonly observed in some rare cancers, e.g. 90-100% in mammary analogue secretory carcinoma (MASC), a rare form of salivary gland cancer, and secretory breast cancer. The overall incidence of the NTRK fusion is estimated to be 0.25-0.31% in adult cancer patients and 0.34-0.49% in paediatric cancer patients (approx. 0.3% according to the EPAR).

As pointed out in the 2020 NICE analysis, there is insufficient scientific evidence that people with solid tumours showing NTRK fusion have a worse prognosis than those with tumours without genetic changes. Available data are based on a small population. Prognosis may depend not only on the presence of a fusion in the NTRK gene, but also on the ECOG status, tumour type and NTRK gene fusion type.

Alternative health technology [information protected as a trade secret]

In the Agency's opinion, taking into account clinical guidelines, currently publicly funded technologies, expert opinions and [information protected as a trade secret] best supportive care (BSC) can be considered as an optional technology for Vitrakvi.

Description of the proposed intervention

Vitrakvi contains larotrectinib as an active substance, which is an adenosine triphosphate (ATP)-competitive and selective inhibitor of tropomyosin receptor kinase (TRK), designed to prevent binding to a non-target kinase. Larotrectinib targets the TRK family of proteins, including TRKA, TRKB and TRKC, which are encoded by the NTRK1, NTRK2 and NTRK3 genes respectively.

According to the Summary of Product Characteristics (SmPC), Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion:

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options.

Accordingly, the registration indication includes the indication in question.

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. [information protected as a trade secret]

The clinical analysis included:

- Primary studies for larotrectinib (LAR)
    - LOXO-TRK-14001 – single-arm study, involving adult patients with advanced solid tumours with the NTRK gene fusion;
    - NAVIGATE (LOXO-TRK-15002) – single-arm study conducted using the affinity method in children over 12 years of age and in adults with advanced solid tumours with the NTRK gene fusion;
    - SCOUT (LOXO-TRK-15003) – single-arm study involving children over 1 month and adults up to 21 years of age with advanced cancer or primary CNS tumours. [information protected as a trade secret]

  In addition, data from two conference abstracts were included: Brose 2021 and Laetsch 2021 (results with cut-off date of 20 July 2020).
- Trials for the comparator in:
    - lung cancer: 23 trials;
    - salivary gland cancer: 2 trials;
    - melanoma: 5 trials;

- colorectal and appendiceal cancer: 3 trials;
- soft tissue sarcoma (GIST): 1 trial;
- soft tissue sarcoma (other than GIST): 5 trials;
- soft tissue sarcoma in children and IFS: 1 trial;
- breast cancer: 7 trials;
- biliary tract cancer: 2 trials;
- CNS tumours/gliomas: 5 trials;
- pancreatic cancer: 2 trials;
- thyroid cancer: 5 trials.

- Secondary studies
  - Pollack 2021 – systematic review to investigate the efficacy of larotrectinib compared to historical data on the treatment of selected solid tumours with the NTRK gene fusion at advanced/metastatic stage (non-small-cell lung carcinoma, colorectal cancer, thyroid cancer, glioma, soft tissue sarcoma, salivary gland cancer and infantile fibrosarcoma). Past interventions were included in the indirect comparison (e.g. chemotherapy, immunotherapy, VEGF inhibitor) that were used in a specific tumour type and also tailored to the line of therapy in which larotrectinib would be used, which amounts to further lines of treatment (no satisfactory alternative treatments) for adult and paediatric patients with metastatic solid tumours with the NTRK gene fusion;
  - Chu 2020 – systematic review with meta-analysis on clinical, quality of life and economic data for NTRK inhibitors in patients with solid tumours with the NTRK gene fusion. A total of 55 patients were included in the LAR studies (NCT02122913, SCOUT, NCT02637687, NAVIGATE, NCT02576431).

The studies mainly evaluated overall survival (OS), progression-free survival (PFS), treatment response (ORR, DCR, CR, PR, SD and PD) and safety profile.

Reliability assessment of the LOXO-TRK-14001, SCOUT and NAVIGATE studies was performed using the NICE tool. The studies are highly reliable, with each study scoring 8 out of 8 possible points.

Secondary studies were assessed using the AMSTAR II scale. The reviews that were included have a very low reliability. The points were deducted for missing information on the previously developed review methodology, the lack of an appropriate method for assessing the risk of bias individually for each of the included study, the lack of assessment of publication bias and the lack of analysis of the impact of the above-mentioned factors on the results of the studies, and because of the lack of assessment of possible heterogeneity of results (this applies to the Pollack 2021 review), the lack of a list of excluded studies with exclusion reasons, the lack of detailed characteristics of the studies included in the review, or the lack of information on the source of funding.

Efficacy

Results for larotrectinib were presented [information protected as a trade secret]

[information protected as a trade secret]

[information protected as a trade secret]

Pollack 2021

The results of the comparison are not conclusive. The ORRs achieved in the larotrectinib group are significantly higher especially in further lines of treatment compared to the results achieved in the past

intervention group applied in cases such as lung cancer, salivary gland cancer or soft tissue sarcomas (non-GIST) (70-80% vs. approx. 20-30%). However, for some cancers, the response rates achieved are comparable to those achieved for larotrectinib: colorectal cancer, thyroid cancer or IFS. In contrast, for gliomas, lower ORRs were reported in the larotrectinib group compared with patients in the past intervention group (11% vs 63-95%).

The results of the review suggest that the clinical outcome of larotrectinib may vary according to tumour type.

Chu 2020

According to the results of the review, the use of LAR was associated with ORRs of 75-80%. The one-year survival rate was 71%.

Adverse events were generally grade 1/2, and the most common grade 3 or 4 adverse events included increased ALT or ASPAT levels, dizziness and nausea. Adverse events leading to dose reduction occurred in 15% of patients. There was no reported case of treatment termination due to non-response.

Safety [information protected as a trade secret]

Limitations [information protected as a trade secret]

The uncertainty of the presented results of the clinical analysis is affected by the lack of studies directly comparing larotrectinib with the comparator. There was also failure to present [information protected as a trade secret]

[information protected as a trade secret]

The reliability of the conclusion is also reduced by the fact that [information protected as a trade secret]

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 / QALY (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 on that basis, among other things, choosing the therapy related to potentially best outcome.

Cost-utility analysis (CUA) was performed taking into account a lifetime horizon (80 years), from the public payer perspective – the entity obliged to finance the services from public funds, i.e. the National Health Fund (NHF) and from the joint perspective of the payer and the patient. The results of the analysis from both perspectives were similar.

The following medical costs were included in the analysis:

- drugs (administered in the first and subsequent lines of treatment);
- prescription and administration of drugs;
- diagnostics, monitoring and assessment of the efficacy of treatment;
- palliative treatment;
- treatment of adverse events.

In the analysis, Vitrakvi was compared with [information protected as a trade secret]

Taking into account the above ICUR value, the threshold net sales price of Vitrakvi (larotrectinib), at the current cost-effectiveness threshold (PLN 166,758/QALY) is [information protected as a trade secret]

Limitations

The reliability of the results of the analysis is limited and there are doubts as to the correctness of the selection of the analytical technique (CUA) [information protected as a trade secret] Furthermore, there was no consistency in the choice of comparators in the economic and clinical analysis.

Agency's own calculations

The estimates were updated in relation to the level of the cost-effectiveness threshold (the results of the threshold analysis were included above).

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 in a particular indication, the official selling price of the drug must be calculated so that the cost of use of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio

In the considered case, the circumstances referred to in Art. 13 sec. 3 of the Reimbursement Act 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 results of the applicant's budget impact analysis were presented in a three-year time horizon from the public payer perspective (NHF) and the joint perspective (NHF and patient). The results of the analysis from both perspectives were similar.

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

[information protected as a trade secret]

The results of the basic analysis from the NHF perspective indicate that the reimbursement of Vitrakvi (larotrectinibum) will involve

[information protected as a trade secret]

Limitations

The budget impact analysis is characterised by a number of limitations, concerning mainly the uncertainty in estimating the target population, [information protected as a trade secret]

Agency's own calculations

No additional calculations were performed.

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

Comments on the drug programme [information protected as a trade secret]

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. [information protected as a trade secret]

[information protected as a trade secret]

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

The guidelines found, published before 2021, do not indicate the possibility of larotrectinib application.

The NCCN guidelines identify larotrectinib as:

- the preferred first-line treatment for advanced or metastatic non-small-cell lung carcinoma with the NTRK1/2/3 gene mutation, and if a mutation is identified during first-line treatment, the guidelines recommend completing or discontinuing maintenance therapy and initiating larotrectinib treatment;

- a useful treatment option for recurrent, unresectable or metastatic salivary gland cancer with the NTRK gene fusion;
- useful for second and the next line of treatment of metastatic or unresectable melanoma with the presence of NTRK gene fusions;
- an option in subsequent lines of systemic treatment for patients with advanced or metastatic colorectal cancer with the presence of the NTRK gene fusion keeping in mind that these drugs will not be suitable for the majority of patients and considering the rarity of NTRK gene fusions in the colorectal cancer patient population;
- a useful option in patients with metastatic, unresectable and recurrent GIST soft tissue sarcoma after registered treatment options (limited data available). The ESMO 2021 guidelines reveal that larotrectinib may be used in patients with advanced or metastatic GIST with the NTRK gene mutation in the absence of sensitivity to imatinib;
- a useful option for first-line treatment of advanced/metastatic soft tissue sarcoma other than GIST when the NTRK mutation is present. The ESMO 2021 guidelines indicate NTRK inhibitors – larotrectinib and entrectinib (III, A) – as standard treatment in patients with locally advanced or metastatic disease with the NTRK gene fusion in initial lines of treatment;
- a useful treatment option in recurrent/inoperable, local or regional, stage IV (M1) breast cancer with the presence of the NTRK gene fusion (patients without a known acquired resistance mutation) for whom there are no satisfactory alternative treatment options or who have experienced disease progression after treatment (level of evidence: 2A);
- a useful option for first- and subsequent-line treatment of unresectable and metastatic biliary tract cancer with NTRK gene fusions;
- a useful option in the treatment of recurrent or progressive low-grade glioma (WHO 1 or 2) in adults, in the treatment of recurrent anaplastic gliomas, recurrent glioblastoma multiforme - in tumours with the NTRK gene fusion;
- a useful option in first-line therapy for metastatic pancreatic cancer patients in poor performance status and in next-line therapy for patients with recurrent locally advanced or metastatic pancreatic cancer in good and poor performance status – in patients with the NTRK gene fusion;
- one of systemic treatment options for locally advanced, recurrent, unresectable and/or metastatic papillary/ follicular/ oxyphilic Hürthle cell thyroid cancer with the NTRK gene fusion unresponsive to radioactive iodine treatment and the preferred systemic treatment option in anaplastic metastatic thyroid cancer (not recommended in medullary cancer).

Reimbursement recommendations

The search identified recommendations from 5 organisations: 3 conditionally positive – CADTH 2021 (reassessment), Zorginstituut Nederland 2021 and NICE 2020, 1 positive G-BA 2020 (indicating that the drug is recommended while listing numerous limitations to drawing conclusions) and 1 conditionally positive for only part of the proposed indications (HAS 2020).

The CADTH 2021 recommendation identifies significant uncertainty in assessing the magnitude of observed response and long-term efficacy of therapy, but emphasises the rare nature of the indications in question. The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) assessed available evidence from a tumour-agnostic perspective, concluding that the benefit shown in some cancer types outweighed the lack of benefit or lack of conclusive evidence of benefit in other cancer types. At the same time, the Committee assessed that larotrectinib at the current cost-effectiveness threshold was not cost-effective, and that if the public payer was to bear the cost of identifying patients eligible for treatment, larotrectinib would not be cost-effective regardless of its price.

The NICE 2020 recommendation pointed to the lack of evidence for the efficacy of larotrectinib in all types of cancers with the NTRK gene fusion and the uncertainty of cost-effectiveness estimates.

The G-BA 2020 recommendation indicates that larotrectinib may be a suitable treatment option in some cases, but no additional benefit over the comparator – BSC – was demonstrated. It was pointed out that the separate consideration of the results by cancer unit is justified. As in the recommendation of CADTH 2021 and Zorginstituut Nederland 2021, attention was drawn to the uncertainty of population estimates.

The French HAS recommendation of 2020 was only conditionally positive for the treatment of children with recurrent and refractory, locally advanced or metastatic infantile fibrosarcoma or other soft tissue sarcoma with the NTRK gene fusion. The document points out mainly the low reliability of the data and the unlikely public health impact of Vitrakvi used in the above-mentioned population. The Committee stated that the clinical benefit of Vitrakvi was insufficient in adults with the registration indication to justify its public funding.

According to the information submitted by the applicant, Vitrakvi (larotrectinib) [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 6 September 2021 (ref. no.: PLR.4500.1331.2021.14.KKL, PLR.4500.1332.2021.13.KKL, PLR.4500.1333.2021.15.KKL) regarding
the preparation of the President's recommendation on the assessment of Vitrakvi (larotrectinibum) under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene" 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. 129/2021 of 22 November 2021 on the assessment of Vitrakvi (larotrectinib) under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene"

References

1. Position of the Transparency Council No. 129/2021 of 22 November 2021 on the assessment of Vitrakvi (larotrectinib) under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene"
2. Report No. OT.4231.42.2021 Application for the reimbursement of Vitrakvi (larotrectinib) under the drug programme: "Treatment of solid tumours that show the fusion of the neurotrophin tyrosine receptor kinase (NTRK) gene"