Recommendation No. 12/2021

of 12 February 2021

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

on the inclusion of Venclyxto (venetoclax)

in the reimbursement under the drug programme "Treatment of patients with chronic lymphocytic leukaemia with venetoclax in combination with rituximab (ICD-10 C91.1)"

The President of the Agency recommends the reimbursement of Venclyxto (venetoclax) within the framework of the drug programme "Treatment of patients with chronic lymphocytic leukaemia with venetoclax in combination with rituximab (ICD-10 C91.1)" provided that the applicant proposes an additional risk-sharing instrument based on the resources used.

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines, considers public funding of the applied technology to be justified.

The results of a clinical analysis based on 3 secondary trials and 2 randomised clinical trials were considered. The basis for the comparison of VEN+RTX with BEND+RTX was the MURANO trial. It showed that (trade secret)

A qualitative comparison with IBR was carried out on the basis of the results from RESONATE and MURANO trials. (trade secret)
In interpreting these results, it should be borne in mind that the MURANO and RESONATE trials were not blind trials, furthermore the progression outcomes were not assessed at each cut-off point by an independent committee of radiologists, in MURANO it is explicitly stated that only the first sub-analysis after two years was performed by an external committee, in RESONATE this is vaguely defined, the publication cites the iwCLL 2008 criteria and therefore the risk of bias is unclear.

Furthermore, the results of the economic analysis indicate that (trade secret) (despite the availability of indirect comparisons).

The results of the budget impact analysis indicate (trade secret) One limitation of the presented results is the size of the target population, which, based on the 2013 NFZ data, was extrapolated to 2022-2023. This makes the consideration of data from 9 years ago subject to uncertainty. An additional limitation affecting the uncertainty of the presented estimates was that the prevalence of regimens used in third and subsequent lines of treatment was taken from a single presentation.

In this evaluation, all recent clinical guidelines unanimously recommend the use of venetoclax in combination with rituximab in second- and subsequent-line treatment. Similarly, reimbursement recommendations also positively refer to the public financing of the requested intervention. In one of the reimbursement recommendations, funding of venetoclax was indicated as justified under the condition that the cost-effectiveness of the therapy improves.

Taking into account the above, the President of the Agency considers funding of the technology in question to be justified; however, given the uncertainty regarding the superiority of venetoclax to ibrutinib therapy, the estimates of the economic analysis and the impact on the payer's budget, it is appropriate to deepen or propose an additional risk-sharing instrument, which in part will bring costs closer to those of ibrutinib therapy.

Subject of the application

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

- Venclyxto, Venetoclaxum, coated tablets, 50 mg, 7, tabs, EAN code: 08054083013718 - for which the proposed net sales price amounts to (trade secret);
- Venclyxto, Venetoclaxum, coated tablets, 10 mg, 14, tabs, EAN code: 08054083013688 - for which the proposed net sales price amounts to (trade secret);
- Venclyxto, Venetoclaxum, coated tablets, 100 mg, 7, tabs, EAN code: 08054083013695 - for which the proposed net sales price amounts to (trade secret);
- Venclyxto, Venetoclaxum, coated tablets, 100 mg, 14, tabs, EAN code: 08054083013701 - for which the proposed net sales price amounts to (trade secret);
- Venclyxto, Venetoclaxum, film-coated tablets, 100 mg, 112, tabs, EAN code: 08054083013916 - for which the proposed net sales price amounts to (trade secret).

Proposed payment and reimbursement availability category: free of charge, as part of the drug programme, within the existing limit group - 1186.0 Venetoclax. (trade secret)

Health problem

Chronic lymphocytic leukaemia (CLL) is a malignant disease of morphologically mature lymphocytes found in the blood, bone marrow, lymphoid tissue and other organs.

The most common form of leukaemia in Europe and North America. The annual incidence is ~5/100,000 and increases with age - > at 60 years it is ~20/100,000.

The natural course of CLL varies widely. In most cases, after a mild phase, the disease ends with a period of severe complications and death (after 5-10 years). A benign course, with survival times of up to 10-20 years, in which deaths are usually associated with CLL progression or infection, occurs in < 30% of patients. In some patients the disease is aggressive from the start and leads to death over a period of 2-3 years.

The most common cause of death in CLL is infection (~50% of patients), usually pneumonia and sepsis; other causes include haemorrhage and cachexia. CLL patients have a 2-7 times higher risk of developing another malignancy than the general population.

Alternative health technology

Currently, the treatment of chronic lymphocytic leukaemia in Poland is financed from public funds within the framework of drug programmes B.103, B.92, and within the framework of the chemotherapy catalogue. Medicinal products containing rituximab (Blitzima, MabThera and Riximyo), fludarabine: (Fludara Oral), bendamustine (Bendamustine Glenmark, Bendamustine Accord, Bendamustine STADA and Bendamustine Zentiva), cyclophosphamide (Endoxan) and venetoclax (Venclyxto) are reimbursed.

Considering the clinical practice of PBL treatment, ibrutinib monotherapy and bendamustine therapy in combination with rituximab should be considered as the primary comparator for venetoclax therapy in combination with rituximab. Furthermore, bendamustine therapy in combination with rituximab is considered

most effective in patients without del17p and/or mTP53 previously treated with the FCR regimen (among chemoimmunotherapies). There is scientific evidence directly comparing this therapy with the proposed therapy.

Description of the benefit named in the application

Venetoclax is a selective inhibitor of the anti-apoptotic protein Bcl-2 (*B-cell lymphoma 2*). Overexpression of Bcl-2 has been shown in PBL cells, where it mediates tumour cell survival, which has been linked to resistance to chemotherapeutics.

Venclyxto is indicated for treatment in combination:

- with rituximab in *chronic lymphocytic leukaemia* (PBL, CLL) in adult patients who have received at least one prior therapy;
- with obinutuzumab in adult patients with previously untreated chronic lymphocytic leukaemia (PBL, CLL).

Whereas in monotherapy, the requested drug is indicated for the treatment of PBL:

- in adult patients with a 17p deletion or TP53 mutation in whom treatment with an inhibitor of the B-cell receptor signalling pathway is inappropriate or has failed, or
- in adult patients without deletion in the 17p region or a TP53 mutation who have failed both immunochemotherapy and treatment with an inhibitor of the B cell receptor signalling pathway.

The requested indication concerns the treatment of chronic lymphocytic leukaemia with venetoclax in combination with rituximab (ICD-10 C91.1). It is consistent with the registration.

In the proposed drug programme, the provisions on the criteria for defining the target population are in line with those currently in place, with the exception that the proposed drug programme is an extension to remove the criteria for relapsed or refractory forms of the disease and to differentiate treatment availability based on the presence of the 17p deletion and/or mTP53 mutation status.

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.

The effectiveness of the proposed intervention was based on:

- 2 secondary studies:
  - (trade secret)
  - Chen 2019 - A network meta-analysis assessing the relative efficacy of targeted drugs in the treatment of relapsed or refractory chronic lymphocytic leukaemia. The systematic literature search ultimately consisted of seven randomised, controlled-group clinical trials that were eligible and included in a network meta-analysis, with a total of 2,512 patients being treated with nine therapeutic regimens:
    - VEN + RTX;
    - IDE + OFA;
    - IBR in monotherapy;
    - IDE + BEND + RTX;
    - OFA in monotherapy;
    - DUV in monotherapy;

- RTX in monotherapy;
- BEND + RTX;
- IBR + BEND + RTXc;

- 2 primary randomised trials, including a comparative trial:
  - VEN+RTX with BEND+RTX (MURANO) - a randomised, unblinded trial that included 391 patients, with a follow-up period of:
    - Analysis I: 23.8 (0.0-37.4) months. (cut-off: 8 May 2017)

      VEN + RTX: 24.8 months, BEND + RTX: 22.1 months.
    - Analysis II: 36.0 (n.d.) (cut-off: 8 May 2018);
    - Analysis III: 47,9 (0,0; 60,1) months (cut-off: 8 May 2019)

      VEN + RTX: 48.1 months; BEND+RTX: 47.7 months;
  - IBR with OFA (RESONATE) - a randomised unblinded trial in which 391 patients were included, with a follow-up period of:
    - Analysis I: 9.4 (0.1-16.6) months. (cut-off: 06 November 2013)

      IBR: 9.6 (0.33-16.62), OFA: 9.2 (0.07-16.49)
    - Analysis II: 16.0 (n.d.) months.

      IBR:16.4 (n.d.-24.0) months, OFA 11.9 (n.d.-24.0)
    - Analysis III: 19 (n.d.-26) months
    - Analysis IV: 48 (n.d.) months

      IBR: 44 (n.d.-53) months
    - Analysis V: 74 months

      IBR: 65.3 (0.3-71.6) months

      OFA: 65.6 (0.1-73.9) months

In both studies, due to the lack of blinding of patients and staff, the risk of bias in this area was assessed as high. In addition, in the MURANO trial the safety outcomes were assessed by one of the investigators, therefore the risk of bias in terms of blinding the assessment of safety outcomes was also considered high. No other types of errors that could reduce data quality were identified.

The following parameters were used to evaluate efficacy:

- HR – *Hazard ratio*;
- MD – *Mean diffence*
- OR – *Odds ratio*.

The following endpoints were assessed in this study:

- *Overall survival* (OS), the time from randomisation to death from any cause;
- *Progression free survival* (PFS), the time from randomisation to the first observation of disease progression or death from any cause;
- *Overall response ratio* (ORR), percentage of patients with *complete response* (CR), complete unconfirmed response (CRu) and *partial response* (PR).

Clinical efficacy

(trade secret)

Chen 2019

The publication presents the results of a meta-analysis for progression-free survival, overall survival and progression-free survival in a patient population without a 17p deletion. The results of the comparisons suggest that both ibrutinib monotherapy and the use of the combination of venetoclax and rituximab have a high probability of being the most effective treatment for relapsed or refractory chronic lymphocytic leukaemia for both the PFS parameter assessment - SUCRA: 0.90 and OS - SUCRA: 0.85.

(trade secret)

Quality of life in the MURANO trial was assessed for a horizon of 24 weeks of follow-up indicating that there were no statistically significant differences between the compared groups in terms of quality of life assessment.

(trade secret)

In the RESONATE trial, quality of life in the analysis covering the broadest time horizon was assessed using the FACIT-F questionnaire consisting of two and the EQ-5D-5L. For qualitative comparison, results from patients at week 24 of treatment in both the MURANO and RESONATE trials were used; these were the only data available for comparison.

For both VEN + RTX as well as IBR, there were no statistically significant changes in quality of life as measured by the EORTC-QLQ-C30 questionnaire compared with baseline values after treatment.

Safety

There were no statistically significant differences between VEN + RTX and BEND + RTX in the rate of reporting adverse events, including treatment-related adverse events; also the risk of discontinuation of therapy and dose reduction due to adverse events was comparable. A statistically significantly higher proportion of patients experiencing grade 3 and 4 adverse events was observed in the VEN + RTX group than in the BEND + RTX group; nevertheless, the risk of serious adverse events, including treatment-related adverse events, was comparable. The use of VEN + RTX compared with BEND + RTX was associated with a statistically significantly lower overall risk of death.

Additional efficacy and safety information

A summary of the overall safety profile of Venclyxto is based on clinical trial data from 758 patients with PBL treated with venetoclax in combination with obinutuzumab or rituximab or as monotherapy. The safety analysis included patients from two phase III trials (CLL14 and MURANO), two phase II trials (M13-982 and M14-032) and one phase I trial (M12-175). The CLL14 trial was a randomised controlled trial in which 212 patients with previously untreated PBL and comorbidities received venetoclax in combination with obinutuzumab. MURANO was a randomised controlled trial in which 194 previously treated PBL patients received venetoclax in combination with rituximab. The phase II and phase I trials involved 352 previously treated PBL patients, including 212 patients with the presence of a deletion in the 17p region and 146 patients who had not been successfully treated with an inhibitor of the B cell receptor signalling pathway. Patients were treated with venetoclax in monotherapy.

The most common adverse reactions (≥20%) of any grade in patients receiving venetoclax in combination treatment trials with obinutuzumab or rituximab were neutropenia, diarrhoea and upper respiratory tract infection. In monotherapy trials, the most common adverse reactions were neutropenia/neutrophil count reduction, diarrhoea, nausea, anaemia, fatigue and upper respiratory tract infection.

The most commonly reported serious adverse reactions (≥2%) in patients receiving venetoclax in combination with obinutuzumab or rituximab were pneumonia, sepsis, neutropenic fever and TLS. In trials using monotherapy, the most commonly reported serious adverse reactions (≥2%) were pneumonia and neutropenic fever.

Limitations

The main limitation of the reliability of the presented results is the fact that there are no randomised head to head studies comparing the proposed intervention with ibrutinib monotherapy.

The uncertainty of the presented results is affected by the following aspects:

- the MURANO and RESONATE trials, which form the core of the analyses, were not blinded; moreover, the progression outcomes were not assessed by an independent committee of radiologists at each cut-off point; the MURANO trial explicitly states that only the first sub-analysis after two years was

performed by an external committee; in the RESONATE trial this is unclear, and the publication cites the International Workshop CLL (iwCLL) 2008 criteria, so there is a risk of bias;

- the type of research hypotheses adopted in the trials does not affect internal validity, the most plausible ones were used for a given type of trial, the research hypotheses were consistent - superiority;
- the population included in the trials is not entirely consistent with the population in which the intervention will be applied, i.e. patients with chronic lymphocytic leukaemia undergoing at least one line of treatment irrespective of genetic mutation status, irrespective of ECOG performance status, irrespective of the type of prior therapy, in the MURANO trial, the combination of venetoclax and rituximab was most commonly used as a second-line treatment after prior alkylating agents, whereas in the RESONATE trial the median prior therapy was 3, which may suggest that these were more over-treated patients and generally in worse shape, although the definition of treatment line may vary between trials, whether in full-text publications, supplementary material or clinical trials registry https://clinicaltrials.gov, no subgroup analyses due to the therapeutic plan were included;
- the MURANO trial, which qualified for clinical analysis, is a multicentre randomised clinical trial for which the pooled results were derived from consecutive subanalyses. The trial has not formally been completed yet. All included patients have now completed the period of planned treatment and are currently undergoing further follow-up. The results for most of the assessed endpoints are from the most recent sub-analyses (e.g. PFS, ORR, MRD(-)).
- The Huang 2017 trial, included in the analysis, was conducted mainly in a population of people of Asian origin, with results consistent with those of a trial conducted mostly on Caucasians (RESONATE);
- discrepancies were encountered during data extraction between data presented in individual source documents and also within the same source documents, in each case data from the main publications, textual descriptions, or a conservative approach to data presentation was used to resolve the situation.
- for some endpoints, data were read from graphs, which may imply uncertainty regarding the precision of results.
- the applicant has correctly and fully indicated the methodological limitations of the carried out clinical analysis, although attention is drawn to the fact that in the main part of the clinical analysis, the applicant has not presented the results from the indirect comparisons, explaining that it is not possible to make such a comparison.
- the applicant also refers to minimising bias in the included studies by assessing the results of the key endpoints by an independent IRC radiology committee, but it is worth noting that in the MURANO trial, which is the main evidence of the efficacy of the VEN+RTX combination, such an assessment was performed only after the first sub-analysis. In the publications describing the results for the subsequent cut-off points, after three and four years respectively, there is no information about the planned external verification of the results. Analysing the direction of the discrepancy, the reported survival results according to the IRC for the comparator (BEND+RTX) show higher medians than the researchers' assessments. The discrepancies for reported treatment responses are more apparent, with overall response rates being similar, but investigator ratings were far more likely to report a complete response than IRC ratings (27% vs 8% in the VEN+RTX group and 8% vs 4% in the BEND+RTX group), which led to statistically significant results in the analysis of investigator ratings and non-significance in the analysis of IRC results.

Proposed risk-sharing instruments

(trade secret)

Economic evaluation, including a cost-effectiveness assessment

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, its use to choose the therapy associated with the potential best use of the currently available resources.

The aim of the economic analysis was to determine the cost-effectiveness of including Venclyxto (venetoclax) in combination with rituximab (VEN+RTX) in public funding in Poland compared with alternative treatments for adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy. For this purpose, a cost-utility analysis over a lifetime horizon (30 years) was performed from the perspective of the public payer (the same as the joint perspective, i.e. the National Health Fund and the patient). The analysis included a comparison of:

- venetoclax + rituximab (VEN + RTX) vs. bendamustine + rituximab (BEND + RTX) - in patient population without 17p deletion and/or TP53 mutation
- venetoclax + rituximab (VEN + RTX) vs. ibrutinib (IBR) - in the patient population with a 17p deletion or TP53 mutation.

The following cost categories were included in the analysis:

- the cost of drugs and their administration;
- the cost of monitoring;
- the cost of treatment after progression (subsequent lines of treatment);
- the cost of treating adverse reactions;
- the cost of terminal care.

(trade secret)

According to the one-way sensitivity analysis, for the comparison of VEN + RTX vs. BEND + RTX, the change in inference occurred in scenarios with a 4-year analysis horizon (ICUR higher than the threshold), minimum cost after progression (ICUR higher than the threshold), maximum cost after progression (only variant with RSS, VEN + RTX dominant) and for utility per Ferguson 2008 (only variant without RSS, ICUR higher than the threshold). The results of the applicant's probabilistic analysis indicate that the probability of cost-utility of VEN + RTX is approximately 50% without RSS and 90% with RSS.

For the VEN + RTX vs. BEND + RTX comparison, there was no change in inference in any of the RSS scenarios - VEN + RTX is always cheaper and more effective. In a scenario with a 4-year analysis horizon and without RSS, it is more efficient but more expensive.

Limitations

The uncertainty of the presented results is affected by the following aspects:

- In the applicant's opinion, an indirect comparison cannot be made for the comparison of VEN + RTX vs IBR. The applicant's estimates are based on a combination of arms from two RCTs, i.e. MURANO for VEN + RTX and RESONATE for IBR. The applicant has not provided an exhaustive justification for such action. It should be noted that the applicant found three publications, two of which are detailed (Chen 2019 and (trade secret)). The aforementioned analyses present the results of indirect comparisons for VEN + RTX vs. IBR, (trade secret). However, for the 2019 refund application, the same applicant based its analysis on the previously mentioned (trade secret). The analysis based on indirect comparisons should at least be tested in a sensitivity analysis. In addition, it should be noted that the comparison of arms from two RCT trials cannot be described as an indirect comparison.

- the applicant assumed "different costs for rituximab depending on whether it will be used in combination with VEN (as part of a drug programme) or in combination with bendamustine (as part of chemotherapy)". The cost estimation was based on the DGL reports of the National Health Fund on the costs of rituximab used in the drug programme and chemotherapy, respectively. However, rituximab, taken as an active substance, used in combination with venetoclax and bendamustine is always funded under the chemotherapy services contract, so the differences will concern the cost of administration. Drug programmes in which rituximab is reimbursed include B.33. "Treatment of aggressive rheumatoid arthritis and juvenile idiopathic arthritis" and B.75. "Treatment of active granulomatosis with vasculitis (GPA) or microscopic vasculitis (MPA)".

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 (Dz. U. /Journal of Laws/ of 2019, item 784 as amended)

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.

The applicant's clinical analysis includes a randomised clinical trial proving the superiority of the drug over BEND vs RTX, while there are no randomised trials proving superiority over ibrutinib (in a patient population with a 17p deletion or TP53 mutation).

(trade secret)

In addition, calculations were carried out over a one-year time horizon. Costs for venetoclax, ibritinib, monitoring and administration as in the applicant's analysis. In the case of rituximab, the decision was made to use the applicant's quoted costs for the active substance applied in chemotherapy. (trade secret)

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 budget impact analysis in the event of a reimbursement decision for Venclyxto (venetoclax) in combination with rituximab for the treatment of refractory or relapsed chronic lymphocytic leukaemia in adults who have received at least one prior therapy was conducted over a 2-year time horizon. The analysis was conducted from the perspective of the payer The applicant assumed that in the following years the following will be included in the programme respectively:

- (trade secret)

The following cost categories were included in the analysis:

- the cost of drugs and their administration;
- the cost of optional technologies;
- the cost of monitoring and diagnostics;

- the cost of treatment after progression (subsequent lines of treatment);
- the cost of treating adverse reactions;
- the cost of terminal care.

If the decision is made to reimburse Venclyxto in the requested drug programme, public payer's expenses to be incurred in the target population (trade secret):

- including RSS:
    - (trade secret)
- not including RSS:
    - (Trade secret) *Limitations*

The uncertainty of the presented estimates is affected by the following aspects:

- the analysis assumed that after disease progression some patients would receive another line of active treatment, while the remaining patients would receive palliative treatment. The percentage of patients who will receive the next line of active treatment is taken from the economic analysis; in reality, under Polish conditions, this percentage may be different;
- the applicant assumed "different costs for rituximab depending on whether it will be used in combination with VEN (as part of a drug programme) or in combination with bendamustine (as part of chemotherapy)". The cost estimation was based on the DGL reports of the National Health Fund on the costs of rituximab used in the drug programme and chemotherapy, respectively. However, rituximab used in combination with venetoclax and bendamustine is only funded within the chemotherapy services contract, although the cost of administration, when used with venetoclax, would be that of administration of the drug under the drug programme and when used with bendamustine the cost of administration of the chemotherapy.
- The size of the target population was based on 2013 NFZ data, estimating the population for 2022-2023 involves uncertainty;
- the applicant estimated the prevalence of regimens used in the third and subsequent lines of treatment from a presentation by Prof. I. Hus dated July 2020. This represents a limitation of the analysis and implies an uncertainty of the estimates.

Comments on the proposed risk-sharing instrument

(trade secret) Therefore, it appears reasonable for the applicant to propose a consumption-based instrument.

Comments on the drug programme

The following issues were highlighted during the analysis:

- attention is drawn to the definition of patients eligible for treatment with the combination of venetoclax and rituximab, who are explicitly defined as having a diagnosis of chronic lymphocytic leukaemia. In comparison with the current drug programme, it is noticeable that a change has been introduced to remove the definition of a refractory patient or a patient with relapse of the underlying disease, which may result in certain abuses and earlier progression to the requested therapy. The remark was presented to the applicant in a letter informing about non-compliance of the analyses with the minimum requirements set in the regulation, the applicant presented the opinion of a clinical expert, according to whom such a situation may occur in casuistic cases
- the maximum duration of treatment is set in the programme at a limit of 24 months according to the provision in the SmPC, the content of such a provision could be considered in terms of a possible extension of the duration of treatment until the disease progresses or the patient no longer tolerates it
- the provisions concerning the eligibility of patients between drug programmes, the programme with ibrutinib and the existing use of the provision: patients with a diagnosis of refractory or relapsed chronic lymphocytic leukaemia (PBL) would require clarification; such clarification of the proposed programme would organise the reimbursement matters.

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.

(trade secret)

Discussion of recommendations in relation to the evaluated technology

Six clinical recommendations for the treatment of chronic lymphocytic leukaemia were found:

- Alberta Health Services (AHS) 2019;
- European Society for Medical Oncology (ESMO) 2020;
- British Society for Haematology (BSH) 2018;
- National Comprehensive Cancer Network (NCCN) 2020;
- British Society for Haematology (BSCH) 2012;
- Polskie Towarzystwo Onkologii Klinicznej (Polish Society of Clinical Oncology) (PTOK) 2020.

All but one of the clinical guidelines mentioned above unanimously recommend the use of venetoclax with rituximab in second and subsequent lines of treatment. The BCSH guidelines do not mention this possibility due to the fact that they were written in 2012, before venetoclax was introduced to the market.

The NCCN clinical practice guidelines differentiate their recommendations in PBL according to the patient's overall condition and del17p and/or mTP53. According to the most current guidelines, the preferred regimens for 2nd line treatment of PBL in the patient population, regardless of the presence of del17p/mTP53, are acalabrutinib, ibrutinib, venetoclax + rituximab, duvelisib, idelalisib + rituximab, venetoclax.

The Polish Society of Clinical Oncology recommends the use of BCR inhibitors, regimens with drugs not previously used (e.g. BR), corticosteroids with rituximab or venetoclax therapy, noting the fact that the venetoclax + rituximab regimen was registered by the EMA in September 2018.

A search found 6 reimbursement recommendations:

- 5 favourable ones:
    - National Institute for Health and Care Excellence (NICE) 2019;
    - Scottish Medicines Consortium (SMC) 2020;
    - Haute Autorité de Santé (HAS) 2019;
    - Canadian Agency for Drugs and Technologies in Health (CADTH) 2020;
    - Pharmaceutical Benefits Advisory Committee (PBAC) 2018;
- 1 favourable one with limitations:
    - National Centre for Pharmacoeconomics (NCPE) 2019 - the condition was to improve the cost-effectiveness of the therapy.

The positive recommendations mainly highlight the possibility of using venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia who have already undergone at least one therapy. The possibility of using venetoclax therapy in combination with rituximab is also highlighted

According to the information provided by the applicant, Venclyxto is financed in (trade secret)

Basis for the recommendation

The recommendation was prepared under an order dated 23/11/2020 of the Minister of Health (reference numbers: PLR.4500.702.2020.11.AP, PLR.4500.703.2020.11.AP, PLR.4500.704.2020.11.AP, PLR.4500.705.2020.12.AP, PLR.4500.706.2020.11.AP) regarding the preparation of the President's recommendation on coverage of the drug Venclyxto (venetoclax) within the framework of the drug programme "Treatment of patients with chronic lymphocytic leukaemia with

venetoclax in combination with rituximab (ICD-10 C91.1)", 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 of 2020, item 357, as amended), upon receipt of the Position of the Transparency Board No. 12/2021 of 8 February 2021 on the evaluation of the drug Venclyxto (venetoclaxum) within the framework of the drug programme "Treatment of patients with chronic lymphocytic leukaemia with venetoclaxum in combination with rituximab (ICD-10 C91.1)"

PRESIDENT

dr n. med. Roman Topór-Mądry

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References

1. Position of the Transparency Board No. 12/2021 of 8 February 2021 on the evaluation of the drug Venclyxto (venetoclaxum) within the framework of the drug programme "Treatment of patients with chronic lymphocytic leukaemia with venetoclaxum in combination with rituximab (ICD-10 C91.1)"
2. Report No. OT.4331.49.2020. Application for reimbursement of Venclyxto (venetoclax) under the medicinal programme: treatment of patients with chronic lymphocytic leukaemia with venetoclax in combination with rituximab (ICD-10 C91.1). Verification analysis.