Recommendation No. 140/2021 of 20 December 2021 of the President of the Agency for Health Technology Assessment and Tariff System on the assessment of Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with lymphoma CD30+ (ICD-10 C81; C84.5)"

The President of the Agency recommends reimbursing Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with lymphoma CD30+ (ICD-10 C81; C84.5)" **provided that** the RSS includes a refund to the National Health Fund (NHF) of 100% of the total reimbursement amount incurred by the NHF if the specified value of expenditure on the assessed drug is exceeded and [information protected as a trade secret]

Grounds for the recommendation

Based on the results of the clinical analysis, it was reported that in previously untreated patients with systemic anaplastic large cell lymphoma (sALCL), the combination of brentuximab vedotin (BV) and chemotherapy in the CHP (BV + CHP) regimen reduces disease progression or death by 41% compared to the CHOP chemotherapy regimen (PFS, HR=0.59, p=0.0031). At the same time, attention is paid to uncertainty regarding overall survival (OS) due to the failure to achieve median OS in both study arms.

[information protected as a trade secret] The latest NCCN 2021 guidelines recommend using BV in combination with CHP in sALCL patients with ALK+ and ALK- subtypes as first-line treatment.

Moreover, the results of the economic analysis were considered, which revealed that the use of BV+CHP is [information protected as a trade secret] The reimbursement of the proposed technology should be assessed to be [information protected as a trade secret]

The assessment also stated that for the treatment of sALCL patients, Adcetris is reimbursed [information protected as a trade secret] with a GDP similar to Poland.

Moreover, foreign HTA agencies issued positive recommendations on the reimbursement of Adcetris in the case of previously untreated patients with systemic anaplastic large cell lymphoma (two institutions, CADTH and HAS, excluded a subpopulation of ALK+ patients with an IPI score of <2).

Taking into account the above-mentioned arguments, including the uncertainty of the results of the clinical analysis (due to the lack of OS results and the possibility of using the drug in a population wider than assumed) and the risk of doubling the impact on the payer's budget, it is reasonable to propose a risk-sharing scheme involving a refund to the NHF of 100% of the total reimbursement amount incurred by the Fund in case of exceeding a certain value of expenditure on the assessed drug (e.g. the value indicated in the BIA) and [information protected as a trade secret]

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:

- Adcetris (brentuximab vedotin), powder for concentrate for solution for infusion, 50 mg, 1 vial of powder, EAN code: 05909991004545; net sales price: [information protected as a trade secret]

Proposed price and dispensing category: free of charge under the drug programme in the existing limit group 1142.0 Brentuximab vedotin. [information protected as a trade secret]

Health problem

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive non-Hodgkin's lymphoma based on peripheral T lymphocytes. It belongs to the group of CD30-positive lymphoproliferative disorders involving lymph nodes and areas outside the nodes.

A characteristic feature of ALCL cells, although not a specific one, is the presence of CD30 antigen (Ki-1) on their surface. In most cases, the cells are also characterised by the presence of other T-cell activation markers, including CD25, CD71 and CD45.

In ALCL, the involvement of peripheral, mediastinal or abdominal lymph nodes occurs. It manifests itself in the development of painless and enlarged lymph nodes, especially in the cervical and axillary regions. General symptoms include loss of appetite, fatigue and fever, weight loss and night sweats. Mediastinal involvement is manifested by coughing, dyspnoea and/or oedema. ALCL can also cover extra-nodal areas such as bones, bone marrow, subcutaneous tissue, lungs, spleen and liver.

Contrary to primary cutaneous anaplastic large cell lymphoma, which occurs mainly in older people, the ALK+ form of ALCL occurs in young (median - 30 years old, mostly men) or middle-aged people (ALCL ALK-). ALCL accounts for approximately 3% of non-Hodgkin's lymphoma in adults and 10% to 20% of lymphoma in children.

The incidence of non-Hodgkin's lymphoma (NHL) depends on the geographical area (the highest incidence in Europe and the USA) and it is 2-18/100,000 men and 1-11/100,000 women. In Poland, there are approximately a dozen new cases per 100,000 inhabitants per year. The first peak of incidence is recorded in the second and third decade of life and the second peak - in the sixth and seventh decade of life. Most NHL are hyperplasia of B lymphocytes (86% of cases), less often T lymphocytes (12% of cases) and natural cytotoxic cells (2% of cases).

Patients with the ALK + subtype (approximately 60% of anaplastic large cell lymphoma) have a better prognosis (five-year survival of 70-80%) than patients with the ALK– subtype (five-year survival of 33-49%). Disease relapse also indicates a worse prognosis.

Alternative health technology

Taking into account clinical guidelines and currently publicly-funded technologies, two chemotherapy regimens are considered to be the comparator for the proposed technology:

- CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone;
- CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone.

Description of the proposed intervention

Brentuximab vedotin is an antibody-drug conjugate (ADC) containing a monoclonal antibody directed against CD30 (recombinant chimeric antibody G1).

It is a cancer drug used to treat adults with a certain type of lymphoma (Hodgkin's lymphoma, systemic anaplastic large cell lymphoma, cutaneous T-cell lymphoma). It is administered when the CD30 protein (CD30 + cells) is present on the surface of cancer cells.

The indication in question is included in the registration indication of the assessed drug. [information protected as a trade secret]

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.

The efficacy and safety of Adcetris (brentuximab vedotin, BV) in combination with a CHP chemotherapy regimen (i.e. cyclophosphamide, doxorubicin, prednisone) were assessed.

The target population was a group of previously untreated patients with systemic anaplastic large cell lymphoma (sALCL).

The following study was included in the assessment of the clinical analysis:

- ECHELON-2 - multicentre, double-blind, randomised phase III study comparing the efficacy and safety of brentuximab vedotin (BV) + CHP regimen (cyclophosphamide, doxorubicin, prednisone) vs CHOP (CHP + vincristine) in the group of 452 patients with CD30 + peripheral lymphoma (including 316 patients with sALCL); (full-text publication Horwitz 2019, EMA 2020 report, applicant's details, Iyer 2021 conference abstract).

The reliability of the ECHELON-2 study was assessed with the use of Cochrane descriptive scale criteria. In each of the analysed domains, the risk of bias was assessed as low.

In the subpopulation consistent with the one in the application, i.e. patients with systemic anaplastic lymphoma, the following endpoints were assessed:

- disease progression or death (PFS);
- overall survival (OS).

Efficacy

<u>Results in the sALCL subgroup of the ECHELON-2 study</u>

PFS

The BV+CHP vs CHOP comparison showed statistically significant differences in favour of the assessed intervention in terms of reduced risk of disease progression or death (PFS):

- HR = 0.59 (95% CI: 0.42; 0.84), p=0.0031 (PFS following BICR assessment); [information protected as a trade secret]

The likelihood of 36-month PFS was 65.5% (95% CI: 57.1, 72.7) in the BV+CHP group and 50.2% (95%

CI: 41.6, 58.1) in the CHOP group.

Median PFS in the BV+CHP group following BICR assessment was 55.66 months (95% CI: 48.20, NO[1]) and [information protected as a trade secret] and [information protected as a trade secret] 54.18 months (95% CI: 13.44, NO) [information protected as a trade secret] in the CHOP group.

OS

Median overall survival (OS) was not achieved in the control and study groups. [information protected as a trade secret]

Additional information

Results in the sALCL subgroup - Iyer 2021 conference abstract (median in the follow-up period of 47.6 months).

The comparison of BV+CHP vs CHOP showed statistically significant differences in favour of the assessed intervention in terms of reduced risk of disease progression or death (PFS):

- HR = 0.55 (95% CI: 0.39; 0.79), (PFS as assessed by the researcher).

The estimated likelihood of 5-year PFS was 60.6% (95% CI: 49.5; 69.9) in the BV+CHP group and 48.4% (95% CI: 39.6; 56.7) in the CHOP group.

SmPC for Adcetris (updated 12 October 2021)

According to the data presented in the updated SmPC for Adcetris, in the sALCL population, the reduction in the risk of death in the BV+CHP group was not statistically significant compared to the CHOP group (HR = 0.66 [95% CI (0.43, 1.01)]).

Safety

ECHELON-2 study

In the safety analysis, there were fewer deaths in the BV+CHP group than in the CHOP group in the population assessed (cut-off date 15 August 2019) (22.4% vs 32.3%, statistically significant difference). In terms of the incidence of adverse events (AEs), however, a similar safety profile was reported for the control and study groups.

The most common serious AEs reported during treatment in both arms were nausea, peripheral sensory neuropathy, diarrhoea, neutropenia, constipation, alopecia, fever and vomiting, occurring in more than 25% of patients. The incidence and intensity of adverse events related to peripheral neuropathy were similar in both groups (52.5% of patients in the BV+CHP group and 54.9% of patients in the CHOP group - no statistically significant difference between the groups).

The safety profile in the sALCL population was found to be consistent with the safety profile for the general population. In the study group, the most frequently reported adverse events of any severity were: neutropenia (33.8%), infections and infestations (14.4%) and febrile neutropenia (12.5%).

A statistically significant difference in the sALCL population in favour of the study group was noted for events of any severity such as: overall benign, malignant and unspecified neoplasms (including cysts and polyps), diarrhoea (also grade ≥ 3 diarrhoea). Statistically significant differences to the disadvantage of the study group were noted for events of any severity such as vomiting, diarrhoea, as well as abnormal results of overall diagnostic tests.

[1] Not achieved

Limitations

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

- the OS results in the main study in the ITT population are immature (no median OS was reached in either group);
- the lack of presentation of efficacy and safety data for the population of patients with ALK+ sALCL and an IPI score of <2 results in uncertainty regarding generalisation of the results for the above subpopulation;
- the CHOEP comparator determined based on clinical guidelines (in the case of patients younger than 60 years old with ALCL ALK+, CHOEP may be an alternative chemotherapy regimen, which brings some benefit in terms of adverse event-free survival but no OS benefits) was not included in the results of the clinical analysis due to the lack of studies comparing the proposed technology with the CHOEP scheme. No studies were found that met the inclusion criteria for indirect comparison either.

Moreover, no studies conducted in actual clinical practice were found, which limits the possibility of drawing conclusions regarding the effectiveness of the assessed treatment.

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 (45 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 – the National Health Fund (NHF) and the beneficiary (patient).

The assessed intervention, which covers therapy with Adcetris (brentuximab vedotin, BV) in combination with cyclophosphamide, doxorubicin and prednisone (CHP) under the agreed drug programme, was compared with the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen.

The following categories of medical costs were included in the analysis:

- costs of drugs and their administration,

- costs of qualifying for the programme, diagnosis and monitoring of treatment,
- costs of adverse event treatment,

From the National Health Fund (NHF) perspective, the incremental cost-utility ratio (ICUR) was: [information protected as a trade secret]

Limitations

The uncertainty of the presented results is mainly due to the lack of long-term data for the assessed technology and the reliance on immature OS data, which translates into the need to extrapolate the data in the model. Moreover, not all data used in the analysis [information protected as a trade secret]

Agency's own calculations

No additional own calculations were performed.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise;

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

In connection with the presentation of the randomised clinical trial proving the superiority of the BV+CHP scheme over the health technology currently reimbursed in the indication (CHOP scheme), in the case under consideration, 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 assessment of the impact on the applicant's budget were presented for a four-year horizon from the public payer (NHF) perspective and from the joint perspective.

The analysis included the costs of drugs and their administration, qualification for the programme, diagnosis, monitoring of treatment and adverse events.

The applicant estimated the number of patients using the technology proposed in the application in the new scenario: [information protected as a trade secret]

Limitations

The main limitations of the budget impact analysis stem from the uncertainty of estimations related to the target population. According to the NHF data, the number of patients diagnosed with ICD-10 C84.5 treated with the combination therapy: doxorubicin, vincristine, without etoposide (assumed to correspond to the CHOP regimen) was 87 in 2020, while the number of patients diagnosed with ICD-10 C84.5 treated with the combination therapy: doxorubicin, vincristine, etoposide (corresponding to the CHOEP regimen) was 29. The maximum variant adopted in the applicant's analysis [information protected as a trade secret]

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]

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

Three clinical recommendations were presented relating to the indication covered in the application:

- Polish Society of Clinical Oncology (PTOK 2020);
- National Comprehensive Cancer Network (NCCN 2021);
- European Society for Medical Oncology (ESMO 2015).

All available guidelines indicate the possibility of using the CHOP chemotherapy regimen - cyclophosphamide, doxorubicin, vincristine, prednisone - and CHOEP - cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone - as one of therapeutic options in first-line treatment (the PTOK 2020 and ESMO 2015 guidelines specify that the CHOEP regimen can be used in the case of patients under 65 years of age and 60 years of age respectively) The guidelines indicate the possibility of additional treatment with radiotherapy in the involved area, in selected patients.

The application of BV in combination with CHP in sALCL patients with ALK+ and ALK- subtypes is recommended as first-line treatment, according to the latest NCCN 2021 guidelines.

The Polish PTOK 2020 guidelines point to an ongoing, randomised phase III clinical study assessing the efficacy and toxicity of the combination of BV with CHP vs CHOP in previously untreated patients with mature CD30 + T cells (ECHELON-2, NCT01777152).

It should be noted that ESMO 2015 guidelines were published prior to the registration of Adcetris in the indication under assessment, while the PTOK 2020 recommendations were published 14 days after the registration of Adcetris in the indication under assessment.

Reimbursement recommendations

Five HTA recommendations (PBAC 2021, CADTH 2020, HAS 2020, NICE 2020, SMC 2020) related to the use of Adcetris in combination with cyclophosphamide, doxorubicin and prednisone (CHP) in the case of previously untreated patients with systemic anaplastic large cell lymphoma (sALCL) were

identified.

The recommendations highlight benefits of treatment with BV+CHP compared to CHOP chemotherapy in terms of PFS and OS (but emphasise the uncertainty of OS outcomes).

At the same time, positive recommendations, CADTH 2020 and HAS 2020, relate to: patients with ALK- sALCL and patients with ALK+ sALCL and the International Prognostic Index (IPI) score of ≥ 2. According to the HAS recommendation, ALK+ patients with an IPI score of < 2 were excluded from the study, so there are no clinical data on the use of brentuximab vedotin as first-line therapy in this population.

According to the information submitted by the applicant, Adcertis (brentuximab vedotin) is financed [information protected as a trade secret] with a similar GDP per capita to Poland.

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 29 September 2021 (ref. no.: PLR.4500.1139.2021.23.PRU) regarding the preparation of the President's recommendation on the assessment of Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with CD30+ lymphomas (ICD-10 C81; C84.5)" 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. 140/2021 of 20 December 2021 on the assessment of Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with CD30+ lymphoma (ICD-10 C81; C84.5)".

References

1. Position of the Transparency Council No. 140/2021 of 20 December 2021 on the assessment of Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with CD30+ lymphoma (ICD-10 C81; C84.5)".
2. Report No. OT.4231.48.2021 Application for the reimbursement of Adcetris (brentuximab vedotin) under the drug programme: "Treatment of patients with CD30+ lymphoma (ICD-10 C81; C84.5)".