Recommendation No. 14/2020

of 11 February 2020

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

on the evaluation of Blincyto (blinatumomab)

under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia"

The President of the AOTMiT recommends reimbursing Blincyto (blinatumomab) under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia" **on condition** that a performance-based risk-sharing scheme is proposed.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the available scientific evidence, clinical guidelines and reimbursement recommendations, the President of the AOTMiT believes that public funding of the health technology in question is justified.

The clinical analysis was based on BLAST, a single-arm phase II study assessing the efficacy and safety of blinatumomab (BLIN) in adult patients with acute precursor B-lymphoblastic leukaemia, in first or subsequent remission with minimal residual disease (MRD) greater than or equal to 0.1%. According to the presented study, the median overall survival in the population (110 persons) was 36.5 months. The 18-month overall survival rate was 67%, as estimated on the basis of Kaplan-Meier curves. In contrast, the median disease-free survival was 18.9 months. 78% of patients reported complete MRD response after 1 cycle of BLIN treatment. Two subsequent patients achieved complete MRD response after the 2nd treatment cycle, the following cycles of BLIN treatment (cycles 3 and 4) did not result in additional cases of complete MRD response.

Results of Study 148 for standard of care (SoC) were used to make the indirect comparison. The observation period in the study was 22.5 months. In line with results of Study 148, the median overall survival was 32.5 months, and the probability of a 3-year overall survival was 48%. The median relapse-free survival time was 12.4 months. The three-year relapse-free survival rate was 33%.

Due to the lack of randomised trials regarding the technology in question, to compare blinatumomab with the selected comparator, results *[information protected as a trade secret]* were presented.

[information protected as a trade secret].

[information protected as a trade secret]. However, as in the case of the clinical analysis, the key limitation consisting in lack of head-to head clinical trials comparing the technology in question with its comparators should be taken into consideration. The only available clinical trial is a single-arm study. It is not possible to reliably determine the relative efficacy of BLIN in comparison with the SoC on that basis, and the conducted indirect comparison is associated with certain limitations.

According to results of the budget impact analysis, the introduction of reimbursement for Blincyto under the drug programme will result in *[information protected as a trade secret]* in the first year of reimbursement and *[information protected as a trade secret]* in the second year of reimbursement. However, it should be borne in mind that the presented model implements the efficacy presented in the BLAST study, therefore the uncertainty of the presented results is also impacted by the limitations accompanying the clinical analysis. In line with the applicant's assumptions, the use of blinatumomab is associated with prolonged relapse-free survival (RFS) and with increased frequency of performing allo-HSCTs and, therefore, a decrease in the risk of relapse. In accordance with the presented estimates, this procedure *[information protected as a trade secret]*.

Subject of the application

The order of the Minister of Health concerns assessing whether the following medicinal product should be financed from public funds: Blincyto (blinatumomab), powder for concentrate for solution for infusion, 38.5 mcg, 1, 1 vial of powder + 1 vial of solution (stabiliser) 10 ml, EAN: 05909991256371, the ex-factory price for which amounted to *[information protected as a trade secret]*.

The proposed payment and reimbursement availability category: a free-of-charge drug available as part of the drug programme, within the existing 1188.0 Blinatumomab joint-limit group. The applicant has proposed a risk-sharing scheme.

Health problem

Acute leukaemia/lymphoblastic lymphoma are neoplasms derived from B- or T-lymphocyte line, found in:

- mainly in bone marrow and blood:
    - B-cell acute B lymphoblastic leukaemia
    - T-cell acute B lymphoblastic leukaemia
    - main lymph nodes and non-nodular tissues
        - *B-cell lymphoblastic lymphoma;*
        - *T-cell lymphoblastic lymphoma.*

They account for approx. 75% of acute leukaemia cases in children and approx. 20% of cases in adults.

The 2016 WHO classification distinguishes between genetically and molecularly defined forms of B-ALL/LBL, while others are referred to as "B-ALL/LBL, unspecified".

The immunophenotypic classification is of fundamental practical importance:

- B-ALL ($CD19^+$, $CD22^+$, $CD79a^+$) – pro-B (pre-pre-B), *common* ($CD10^+$, most common), pre-B
- T-ALL ($cyCD3^+$, $CD7^+$) – pro-T and pre-T ($CD4^-$, $CD8^-$), cortical (thymocyte; $CD1a^+$, $CD4^+$, $CD8^+$, relatively better prognosis), from mature T cells ($sCD3^+$, $CD4^+$ or $CD8^+$).

Overall, the incidence of acute lymphoblastic leukaemia / lymphoblastic lymphoma in Europe is estimated at 1.28 per 100,000 inhabitants per year. A significant relation between age and the incidence rate is observed (0.53 per 100,000 inhabitants in the age group between 45 and 54 years, approximately 1 in 100,000 inhabitants in the age group between 55 and 74 years and 1.45 per 100,000 inhabitants in the age group between 75 and 99 years).

According to data from the acute leukaemia registry in Poland in the years 2004-2010, an average of 105 diagnoses of acute lymphoblastic leukaemia were reported to the registry every year. These leukaemias accounted for less than 20% of all reported cases of acute leukaemia, an average of 16% per year. The vast majority (68-83% of patients) were diagnosed with acute B-cell lymphoblastic leukaemia. In each reported year most patients (i.e. 70-80%) with acute lymphoblastic leukaemia were patients under 60 years of age.

The treatment effects depend on the patient's age and the intensity of treatment. Most ALL Ph– forms respond to polychemotherapy and the response depends on the drug dose. Therefore, the prognosis largely depends on the initial tumour mass and the possibility of adequate escalation of drug doses, which in turn is limited by the performance status and age.

In adults, complete remission in ALL is achieved in >70% of cases, while in young patients – >90%. The overall 5-year survival rate for adults aged 35-55 is 54%. Introducing TKI to the ALL Ph+ treatment significantly increased the CR rate (>90%), CR duration and the long-term survival rate (>50%).

Unfavourable prognostic indicators based on response to treatment is of greatest practical importance:

- low sensitivity to glucocorticosteroids (peripheral blood blasts >1000/µl after pre-treatment phase);
- bone marrow blasts after 8-15 days of treatment >5%;
- achieving CR after >1 induction cycle;
- persistence of minimal residual disease (MRD) >10–3 after induction treatment or >10–4 after consolidation.

The MRD status monitored as part of an immunophenotypic or molecular study at particular treatment stages is, like cytogenetic changes (as indicated above), the most important factor impacting the prognosis, determining the stratification of patients to standard and high-risk groups.

Alternative health technologies

Taking into account the clinical context for the population in question, given the absence of alternative technologies, patients with MRD continue their basic anti-leukaemia treatment, as do patients without MRD in line with the given treatment protocol, however, none of them is dedicated directly to the treatment of minimal residual disease. Therefore, the standard of care (SoC), understood as a continuation of the initiated anti-leukaemia treatment was selected as the comparator. All active substances included in the treatment of leukaemia are currently financed by the public payer as part of the chemotherapy catalogue.

Therefore, taking into account the recommendations of clinical guidelines, clinical experts and the availability of health technologies financed from public funds in the Republic of Poland, the selection of the comparator is justifiable.

Description of the proposed intervention

Blinatumomab (BLIN) is a bispecific antibody which engages T lymphocytes, which specifically binds to the CD19 molecule, expressed on the surface of B cells and to the CD3 molecule expressed on the surface of T lymphocytes. Blinatumomab activates endogenous T cells by connecting the CD3 molecule in the T-cell receptor (TCR) with the CD19 molecule on the surface of normal and malignant B lymphocytes. The antineoplastic effect of blinatumomab immunotherapy is not dependent on T lymphocytes with a specific TCR or on peptide antigens presented by cancer cells, while it maintains polycyclonal characteristics and is independent of human leukocyte antigens (HLA) present on target cells. Blinatumomab is involved in the formation of a cyclotic synapse between the T cell and the tumour cell, within which proteolytic enzymes are released, which destroy both proliferating and resting cells. Blinatumomab is associated with a transient increase in cellular adhesion molecule expression, cytolytic protein production, proinflammatory cytokine release and T cell proliferation, which consequently eliminates CD19+ cells.

In line with the Summary of Product Characteristics, Blincyto is indicated:

- as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).
- as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- as monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation.

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

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

As part of the analysis, the following documents were presented:

- for blinatumomab – BLAST, a prospective uncontrolled phase II clinical trial assessing the efficacy and safety of blinatumomab in adult patients with acute precursor B-lymphoblastic leukaemia, in first or subsequent remission with minimal residual disease (MRD) greater than or equal to 0.1% (*Goekbuget 2018, Goekbuget 2018a*). The observation period was 30 months (the longest observation period was 53.1 months). The number of patients in the trial was: 116
    - – full-analysis set (FAS) – all patients who received at least one dose of BLIN,

- 113 – primary endpoint full-analysis set (EP-FAS) – patients from the FAS, who did not receive confirmation from the central laboratory regarding MRD or the test sensitivity did not reach 10^{-4}. The population taken into account for the assessment of the primary endpoint,
- 103 – primary endpoint full-analysis set (EP-FAS) – all patients from the EP-FAS population with complete haematological response and MRD> 10^{-3}. The population taken into account for the assessment of MDR responses,
- 110 – key secondary endpoint full-analysis set – all patients from the FAS without the Philadelphia chromosome and with complete haematological response. the population taken into account for the assessment of, among others, relapse-free survival.

- for the standard of care comparator – retrospective, non-interventional Study 148 presenting the health effects obtained as a result of using the standard of care in patients with acute precursor B-lymphoblastic leukaemia, without the BCR-ABL gene and/or the Philadelphia chromosome in first or second complete remission with minimal residual disease greater than or equal to 0.1% (*Goekbuget 2019*). The observation period was 22.5 months

  (interquartile range: 9.6-40.6). 272 patients were included in the trial:

In addition, the applicant provided one published systematic review, Bassan 2019, regarding the assessment of the effect of residual disease on long-term treatment outcomes in adult patients with acute lymphocytic leukaemia.

To compare blinatumomab with the selected comparator, the following results have been presented *[information protected as a trade secret]*.

The NICE tool was used to assess uncontrolled trials included in the applicant's systematic review. BLAST and MT 103-202 obtained maximum possible number of points (8 points). Study 148 obtained 6 out of 8 possible points. The loss of points was due to the lack of a statement confirming consecutive recruitment of patients and from the fact that the study was not prospective.

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

- OS – overall survival;
- RFS – progression-free survival;
- DOR – duration of remission;

The following parameters were used to describe the efficacy:

- HR – hazard ratio;
- OR – odds ratio;

Efficacy

Blinatumomab

According to the results of the BLAST study, 48 deaths occurred during BLIN treatment. The median overall survival in the total population (110 patients) was 36.5 months (95% CI: 19.8; NR). The 8-month overall survival rate estimated on the basis of the Kaplan-Meier curves is 67% (95% CI: 58; 75).

The overall survival results in subgroups indicate that in patients who achieved MRD response after 1 cycle of BLIN treatment, the median overall survival was statistically significantly longer by 26.4 months. The median overall survival in the MRD responders arm was 38.9 months, while in the MRD

non-responders arm – 12.5 months, with the HR=2.63 (95% CI: 1.40; 4.96). The cumulative 18-month likelihood of overall survival calculated by the authors of the study was 70% in MRD responders (95% CI: 59; 79) and 34% in MRD non-responders (95% CI: 15; 54).

Subgroup analysis regarding the relapse status indicated that patients in the first complete remission (CR1) experienced longer overall survival in comparison with the overall survival in the population of patients in subsequent complete remission (CR2/3).

The results of the longest available clinical observation (median follow-up of 53.1 months) in overall survival are consistent with the results of the primary analysis. The median overall survival was: 36.5 months (95% CI: 22.0; NR) in the general population;

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- The median overall survival was not reached in the population of MRD responders; 12.5 months (95% CI: 3.2; 39.7) in the population of MRD non-responders.
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The median overall survival was not achieved in the population of MRD responders in first complete remission (CR1), undergoing BLIN therapy or the subpopulation of patients in continuous complete remission after receiving BLIN treatment and HSCT.

In total, the median relapse-free survival time for all patients undergoing BLIN therapy was 18.9 months (95% CI: 12.3-35.2). The likelihood of 18-month relapse-free survival is 54% [95% CI: 33; 70], as estimated on the basis of Kaplan-Meier curves. The median relapse-free survival in MRD responders was 23.6 months (95% CI: 17.4; NR) and was significantly longer compared to MRD non-responders – 5.7 months [95% CI: 1.6-13.6]. The 18-month relapse-free survival rate in this arm of patients was 58% (95% CI: 46; 68) and 20% (95% CI: 5; 42), respectively.

The results of the subgroup analysis indicate that the median relapse-free survival was 13.6 months longer in the population of patients in first remission (CR1) compared to the survival rate observed in the subgroup of patients in subsequent remission (CR2+). The medians were 24.6 months vs 11 months, respectively, with the HR=2.09 (95% CI: 1.26; 3.48).

In total, out of 110 patients, 48 patients remained in complete remission (of which 36 had received HSCT), 38 had relapses, while 24 died during complete remission. The authors of the BLAST study reported that the median remission time for the total population was not reached.

Similarly, in the subgroups of MRD responders and MRD non-responders, this median was not reached. The likelihood indicator of 18-month remission was statistically significantly higher by 22% in MRD responders vs MRD non-responders (77% vs 53%).

The results of the next subgroup analysis regarding the relapse status indicate that, in patients with first remission, the median remission time was not reached. The median complete remission time was determined only for patients in second or subsequent remission and lasted 19.1 months.

78% of patients reported complete MRD response after 1 cycle of BLIN treatment (88 out of 113 patients). Two subsequent patients achieved complete MRD response after the 2nd treatment cycle, the following cycles of BLIN treatment (cycles 3 and 4) did not result in additional cases of complete MRD response.

The subgroup analysis carried out by the authors of the publications in terms of selected clinical evidence (i.a. age, sex, MRD level and relapse status at the beginning of the study) indicated that none of the evidence had significant impact on the total MRD response.

In total, out of 110 patients, 74 (67%) patients underwent bone marrow transplantation. 36 out of these 74 patients (49%) remain in remission. 9 out of 36 patients (25%) who did not undergo HSCT or chemotherapy after BLIN therapy were still in complete remission.

No significant differences were found between patients who underwent bone marrow transplantation and patients who did not undergo transplantation in the population of patients in first complete remission (CR1). In the subgroup of patients in second or subsequent complete remission, failure to perform HSCT was associated with a 69% lower chance of survival compared to the arm of patients who underwent transplantation 14.5% vs 45.0%, OR=0.31 (95%CI: 0.12; 0.83). Similarly, the overall mortality was lower (42.1%) in transplant patients than in patients who did not undergo transplantation (52.5%).

BLIN treatment was associated with added value in some elements of the EQ-5D questionnaire. Compared to the baseline at the end of the study (last assessment), an improvement in the quality of life was reported in terms of normal daily activities, as well as negative experiences/sensations, including pain, discomfort, anxiety and depression.

Standard of Care

According to the results of Study 148:

- the median overall survival was 32.5 months, and the overall likelihood of 3-year survival was 48% (95%CI: 41%; 54%);
- The median relapse-free survival time was 12.4 months. The three-year relapse-free survival rate was 33% (95% CI: 27%; 39%);
- the median complete remission time is 18.5 months. The three-year survival rate for complete remission is 38% [95% CI: 32%; 45%].

Blinatumomab vs Standard of Care

Due to the lack of randomised trials on the technology in question, the results were presented to compare blinatumomab with the selected comparator *[information protected as a trade secret]*.

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Safety

As part of BLAST, a total of 2 fatal adverse events were reported during BLIN treatment (both events occurred during the first BLIN treatment cycle). The first patient died as a result of complications following atypical pneumonia with influenza A virus subtype H1N1, this event was deemed to be related to the therapy. The second patient died of subdural haemorrhage; this event was deemed to be unrelated to the therapy.

After the completion of BLIN treatment, the authors of the study reported a total of 4 deaths. Two deaths, one resulting from a multifocal change in the central nervous system (124 days after BLIN treatment), the second one from a disease (136 days after BLIN treatment), occurred in patients who had undergone the HSCT procedure. The other two deaths, resulting from disease progression (154 days after BLIN treatment) and organ failure (359 days after BLIN treatment) after the next relapse in non-transplant patients.

According to the BLAST study, all patients experienced at least one adverse event after the first BLIN treatment cycle. The percentage of patients who experienced at least one adverse event after the

second, third and fourth cycle of BLIN treatment was 85%, 79% and 75%, respectively. In total, up to 33% and 27% of patients experienced grade 3 or 4 adverse events. Respectively, in 29% and 22% of patients, these events were assessed as treatment-related adverse events.

The results of BLAST indicate that the most common adverse events which occurred in patients undergoing BLIN therapy were:

- overall: fever (88.8%), headache (37.9%), spasms (30.2%), chills (25.9%), fatigue (24.1%), nausea (23.3%), vomiting (22.4%), diarrhoea (19.8%), hypokalaemia (15.5%), neutropenia (15.5%), insomnia (14.7%), aphasia (12.9%), joint pain (12.9%), cough (12.9%), lower blood pressure (12.1%) and constipation (11.2%);
- grade 3: fever (7.8%), spasms (5.2%), leukopenia (4.3%), headache (3.4%), neutropenia (3.4%), anaemia (2.6%), encephalopathy (2.6%), increased C-reactive protein (2.6%), increased lactate dehydrogenase activity (2.6%), Streptococcus aureus sp. infections (2.6%) and injection site reactions (2.6%);
- grade 4: neutropenia (13.8%), increased alanine aminotransferase activity (3.4%), thrombocytopenia (2.6%), increased aspartate aminotransferase activity (2.6%), encephalopathy (1.7%), leukopenia (1.7%), anaemia (0.9%) and lower blood pressure (0.9%).

Additional safety information

In line with the SPC for Blincyto, very common adverse reactions (≥1/10) include:

- infections and infestations: bacterial infections, fungal infections, viral infections, infections – pathogen unspecified;
- blood and lymphatic system disorders: febrile neutropenia, anaemia, neutropenia, thrombocytopenia, leukopenia;
- immune system disorders: cytokine release syndrome;
- psychiatric disorders: insomnia;
- nervous system disorders: headache, tremor;
- cardiac disorders: tachycardia;
- vascular disorders: hypotension;
- respiratory, thoracic and mediastinal disorders: cough;
- gastrointestinal disorders: nausea, diarrhoea, vomiting, constipation, abdominal pain;
- skin and subcutaneous tissue disorders: rash;
- musculoskeletal and connective tissue disorders: back pain, pain in extremity;
- general disorders and administration site conditions: pyrexia, chills, oedema;
- investigations: hepatic enzyme increased, decreased immunoglobulins;
- injury, poisoning and procedural complications: infusion-related reactions

Limitations

The main limitation of the reliability of the presented results is the lack of head-to-head clinical trials comparing blinatumomab and the selected comparator in the population in question, or any randomised trial proving the efficacy of the technology in question.

The following factors impact the uncertainty of the presented results:

- *[information protected as a trade secret].* In contrast, the BLAST clinical trial included patients regardless of the presence of the BCR-ABL gene and/or the Philadelphia chromosome, however, only patients without changes in the karyotype were included in the result analysis;
- The BLAST study included patients in first and second (according to the drug programme for Blincyto), as well as third complete remission (CR3); however, in total, the percentage of patients in third remission was marginal, i.e. only 2%;
- Study 148 originally included a wider population than that defined by the BLAST criteria, therefore, it was necessary to make adjustments to enable an indirect analysis;
- Study 148 included a marginal percentage of patients in second complete remission, so there is no comparative analysis between BLIN and SoC in the population of patients in second complete remission (CR2).

Proposals of risk-sharing schemes

Under the proposed risk-sharing scheme, the MAH *[information protected as a trade secret]*.

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

The costs of the therapy are estimated in the Polish currency and the health effects are usually expressed using the life years gained (LYG) or the quality-adjusted life year (QALY) as a result of the therapy.

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

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select a therapy associated with the potentially best use of the currently available resources.

As part of the cost-effectiveness analysis in a life-long time horizon *[information protected as a trade secret]* from the perspective of the public payer (NHF). Due to minimal differences between the common perspective and the public payer's perspective, it was decided against additionally presenting the results of the analysis from the common perspective, as it was considered to be identical with the NHF's perspective.

The model includes the following direct medical costs:

- cost of blinatumomab;
- hospitalisation costs associated with the administration of blinatumomab;
- costs of monitoring blinatumomab treatment under the drug programme;

- costs associated with assessing the patient's health condition; costs related to allogenic haemopoietic stem cell transplantation (allo-HSCT); costs of post-relapse treatment.

From the NHF's perspective, the incremental cost utility ratio (ICUR) was estimated at:

- *[information protected as a trade secret]* PLN/QALY taking into account the risk sharing scheme (RSS) and
- PLN 85,329/QALY without taking the RSS into account.

Taking into account the above ICUR values, the threshold price is:

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[information protected as a trade secret].

The results of the deterministic sensitivity analysis indicated the stability of the conclusions from the basic analysis – the cost of obtaining an additional year corrected for quality did not exceed the profitability threshold (PLN 147,024/QALY) in any of the scenarios considered in the deterministic sensitivity analysis. The highest results [*information protected as a trade secret*] without the RSS and [*information protected as a trade secret*] with RSS – was achieved with the time horizon of 20 years.

Limitations

As in the case of the clinical analysis, the key limitation is lack of head-to head clinical trials comparing the technology in question with its comparators. The only available clinical trial is a single-arm study. It is not possible to reliably determine the relative efficacy of BLIN in comparison with the SoC on this basis, and the indirect comparison carried out is associated with some limitations.

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

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

In the absence of a reimbursed comparator in the indication in question (including treatment of minimal residual disease), the circumstances specified in Article 13 of the Act on reimbursement do not occur.

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

Results of the budget impact analysis carried out by the applicant were presented in a two-year horizon. The analysis was carried out from the payer's perspective, due to minimal differences between the common perspective and the public payer's perspective, it was decided against additionally presenting the results of the analysis from the common perspective, as it was considered to be identical with the NHF's perspective.

[information protected as a trade secret]. This means that the annual population of patients covered by the technology in question will include [*information protected as a trade secret*].

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

- cost of the technology in question (Blincyto)
- hospitalisation costs associated with the administration of blinatumomab;
- costs of monitoring blinatumomab treatment under the drug programme;
- costs associated with assessing the patient's health condition;
- costs related to allogenic haemopoietic stem cell transplantation (allo-HSCT);
- costs of post-relapse treatment.

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Limitations

The efficacy presented in the BLAST study has been implemented within the presented model, therefore the limitations accompanying the clinical analysis impact also the uncertainty of the presented results. In line with the applicant's assumptions, the use of blinatumomab is associated with prolonged relapse-free survival (RFS) and with increased frequency of performing allo-HSCTs and, therefore, a decrease in the risk of relapse. In accordance with the presented estimates, this procedure *[information protected as a trade secret]*.

Remarks on the proposed risk-sharing instrument

[information protected as a trade secret]. However, as in the case of the clinical analysis, the key limitation consisting in lack of head-to head clinical trials comparing the technology in question with its comparators should be taken into consideration. The only available clinical trial is a single-arm study. It is not possible to reliably determine the relative efficacy of BLIN in comparison with the SoC on that basis, and the conducted indirect comparison is associated with certain limitations. Considering the above, it seems reasonable for the applicant to propose a performance-based risk-sharing scheme.

Remarks on the drug programme

No remarks.

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

As part of expenditure rationalisation, the applicant proposes to generate savings through more frequent use of drugs with a retail price below the limit.

In the rationalisation analysis, the simulation of the effects of the proposed savings solution concerns the limit group (1035.0) used as an example. The effects of the intervention based on the dissemination of knowledge about the existence of cheaper counterparts, only in this arm, will allow the payer to save PLN 56.26 million per year. This amount exceeds the highest incremental expenditure of the public payer related to the financing of Blincyto (blinatumomab) presented in the BIA – *[information protected as a trade secret]*, therefore it is sufficient to offset the expenditure resulting from a positive reimbursement decision.

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

Four clinical recommendations regarding the analysed indication have been identified:

- National Comprehensive Cancer Network (NCCN) 2019;
- Polish Adult Leukaemia Group (PALG) 2018;
- Polish Society of Clinical Oncology (Polskie Towarzystwo Onkologii Klinicznej, PTOK) 2013;
- European Society for Medical Oncology (ESMO) 2016.

The 2019 American NCCN guidelines indicated that, in patients in complete remission after induction therapy and with minimal residual disease in the consolidation phase, blinatumomab should be used (in precursor B-lymphoblastic leukaemia) and allogenic haemopoietic stem cell transplantation should be performed.

The 2018 Polish PALG guidelines describe the following: a protocol for managing adult patients (under 55 years old) with acute precursor B-lymphoblastic leukaemia, without the BCR-ABL gene and a protocol for managing patients over 55 years old with acute lymphoblastic leukaemia without the Philadelphia chromosome:

- for the first protocol, it was indicated that the first induction is performed in patients with acute lymphoblastic leukaemia if the patient has not achieved complete remission or if he/she achieved it, but the MRD is ≥0.1%, a second induction is carried out. If, after the second induction, the patient achieved complete remission, he/she goes into the consolidation or transplantation phase (the guidelines do not refer to MRD values at this stage). If the patient has undergone only one induction phase (achieved complete remission and MRD <0.1%), two consolidation cycles are carried out. Each of them is followed by an assessment of remission and MRD. Patients with MRD results other than MRD <0.1% after induction and <0.01% after the first and second consolidation are treated as high-risk and should be treated with alloHSCT

(no additional therapy prior to allogeneic haematopoietic stem cell transplantation was mentioned),

- for the second protocol, it was indicated that all patients undergo the same treatment programme including pre-treatment, induction, 2 or 3 consolidations and maintenance therapy or allogenic haemopoietic stem cell transplantation (checking MRD levels after 3 treatment cycles prior to allogenic haemopoietic stem cell transplantation was not mentioned).

According to the 2016 ESMO guidelines, the recommendations did not refer to the management of minimal residual disease in patients with haematological remission of acute lymphoblastic leukaemia. The document only indicated that the use of blinatumomab is efficacious i.a. in patients with minimal residual disease.

As part of 2013 PTOK guidelines, the now non-binding PALG ALL6 recommendations were referred to.

The search results found 4 reimbursement recommendations:

- The National Institute for Health and Care Excellence (NICE) 2019 – this recommendation positively referred to the financing of the technology in question, focusing mainly on the efficacy of blinatumomab in first complete remission and the fact that ICER falls within the range normally recognised by NICE as cost effective.
- Pharmaceutical Benefits Scheme (PBS) 2018 and 2019 – in the first assessment in 2018, the recommendation was negative due to the difficulty in determining the benefit-risk balance of blinatumomab versus standard anti-leukaemia chemotherapy (SoC), as well as high and uncertain ICER. However, in 2019, PBAC withholding the decision to reimburse blinatumomab in the assessed indication indicated that the following steps should be made:
    - reducing the price of the drug, to take into account the uncertainty of clinical data and the economic model,
    - undertaking further work in the field of RSS;
- National Centre for Pharmacoeconomics (NCPE) 2019 – the recommendation was negative; it highlighted:
    - the uncertainty of clinical data (immature results of the BLAST study) and the economic model;
    - the drug's excessive price.

In addition, 1 document (All Wales Medicines Strategy Group 2019) which contained information on the lack of recommendation due to the previously issued NICE recommendation was found.

[information protected as a trade secret].

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 06/11/2019 (reference number: PLR.4600.1194.2019.14.AP), with regard to preparation of the recommendation of the President of the AOTMiT on Blincyto (blinatumomab) under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia" pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 14/2020 of 10 February 2020 on the evaluation of Blincyto (blinatumomab) under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia"

References

1. The Position of the Transparency Council No. 14/2020 of 10 February 2020 on the evaluation of Blincyto (blinatumomab) under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia"
2. Report No. OT.4331.62.2019. Reimbursement application for Blincyto (blinatumomab) to be available under the following drug programme: "Blinatumomab treatment in adults with minimal residual disease in acute lymphoblastic leukaemia" Verification analysis