Recommendation No. 110/2019

of 17 December 2019

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

on whether Afstyla, Lonoctocog alfa, should be reimbursed in the following indication: under the following drug programme: "Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)"

The President of the Agency does not recommend reimbursing the following medicinal product:

- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 250 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326098;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326104;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326111;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326128;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326135;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326142;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 3000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326159,

in the following indication: under the following drug programme: "Prevention of bleeding in children with haemophilia A and B (ICD-10 D 66, D 67)".

Statement of reasons for the recommendation

The President of the AOTMiT, taking into account the position of the Transparency Council and the available scientific evidence, as well as the results of pharmacoeconomic analyses and

clinical guidelines, has concluded that financing of the health technology in question from public funds is not justified.

The assessment of efficacy and safety of Afstyla (lonoctocog alfa) in the indication in question was mainly conducted on the basis of one single-arm study – Stasyshyn 2017.

It should be emphasised that the main limitation of the clinical analysis is the fact that there are no studies allowing for a direct or indirect comparison of the assessed technology with selected comparators, i.e. all recombinant coagulation factor VIII concentrates financed in Polish conditions, conducted on the same population of patients eligible for prophylactic treatment (Advate, Kogenate Bayer – octocog alfa, Nuwiq – simoctocog alfa, NovoEight – turoctocog alfa and Elocta – efmoroctocog alfa).

In Stasyshyn 2017, the median annualised bleeding rate (ABR) in the entire population treated prophylactically amounted to 3.69 (IQR: 0.00; 7.20) and the median annualised spontaneous bleeding rate (AsBR) occurring without a visible external cause amounted to 0.00 (IQR): 0.00; 2.20). In case of joint bleeds, the median ABR amounted to 1.62 (IQR: 0.0; 4.87).

In Stasyshyn 2017, a total of 347 bleeding episodes were treated, of which 132 (38.04%) occurred in patients in the rescue treatment arm and 215 (61.96%) in 80 patients in the prophylactic treatment arm. Haemostatic efficacy of lonoctocog alfa was assessed to be very good in the vast majority of bleeding episodes (85.3%). Good haemostatic efficacy was observed in 11.0% of cases. In Stasyshyn 2017, one haemostatic response was assessed as weak (or non-existent). The vast majority of bleeding episodes (> 80%) were stopped following the administration of a single drug dose (85.9%), and two infusions of the drug were necessary to stop approx. 10% of bleeds (9.8%). In order to stop 2.0% of bleeding episodes, more than 3 infusions had to be administered.

In line with the results of Stasyshyn 2017 concerning the safety profile, adverse events were reported in 76% of patients (183 events), most of which were mild (75%) or moderate (23%).

In line with the results of Klamroth 2016 concerning the pharmacokinetics of Lonoctocog alfa (Afstyla) v. octocog alfa (Advate), no statistically significant differences between the two drugs were demonstrated for the incremental recovery (IR) of the coagulation factor.

The results of the applicant's economic analysis, conducted using the cost-minimisation method, indicate that using Afstyla is more expensive than using any of the comparators (by between approx. PLN *[information protected as a trade secret]* and approx. PLN *[information protected as a trade secret]*) in the RSS variant.

The assumptions concerning body weight and drug consumption have the greatest impact on the results of the economic analysis.

In the event a positive decision on reimbursing Afstyla under the drug programme in question is taken, without the RSS, the public payer's expenditure will decrease in relation to the existing scenario by*[information protected as a trade secret]* between 2019 and 2020, respectively.

However, in the RSS variant, the public payer's expenditure will increase in relation to the existing scenario by*[information protected as a trade secret],* respectively.

It should be underlined that the purchase of the coagulation factors is carried out through public procurement tenders. The supply of a given product is determined by the price which

allows for winning the tender. Therefore, forecasting of how often specific products will be chosen is subject to uncertainty.

Subject of the application

The order of the Minister of Health concerns assessing whether the following medicinal product should be reimbursed:

- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 250 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326098 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326104 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326111 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326128 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326135 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326142 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 3000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326159 with the net ex-factory price of PLN *[information protected as a trade secret]*

in the following indication: under the following drug programme: “Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)”.

Proposed reimbursement availability category – drug available as part of the following drug programme: “Prevention of bleeding in children with haemophilia A and B (ICD-10 D 66, D 67)”. Proposed patient co-payment level – free-of-charge. The drug is to be financed as part of an existing limit group – “1090.1, Factor VIII coagulationis humanus recombinate”. A risk-sharing scheme was proposed.

Health problem

Haemophilia A is a congenital haemorrhagic disorder caused by a decrease of the coagulation factor VIII (FVIII) activity in serum. Haemophilia can be severe, moderate and mild.

Severe haemophilia usually manifests itself at the turn of 1 and 2 years of age in the form of subcutaneous and intramuscular haemorrhages and prolonged bleeding following tongue or lip injuries. Characteristic symptoms of this disease form include:

- joint bleeds (usually occurring at the age of 2-3 years, most often in the knee, elbow and ankle joints), occurring as a result of minor injuries or spontaneously, leading to progressive degeneration (haemophilic arthropathy);

- muscle bleeds, spontaneous or following and injury (usually in the shins, thighs, buttocks, forearms or the hip-lumbar muscle); the resulting haematoma often puts pressure on blood vessels and nerves;
- haematomas in the back wall of the throat and the floor of the oral cavity which can press on the airways;
- haematuria which can lead to anaemia;
- upper gastrointestinal bleeding, as well as bleeding following the removal of a permanent tooth or tonsils and from surgical wounds (in the absence of appropriate haemostatic treatment).

Moreover, approx. 5% of patients experience intracranial bleeding which is the main cause of death in patients with severe haemophilia.

In moderate haemophilia, joint haemorrhages are less frequent than in severe haemophilia and rarely lead to degeneration, muscle bleeding is rare, however, internal and external bleeds following trauma are as dangerous as in severe haemophilia.

There are hardly any joint or muscle bleeds in the mild form, and the disorder can become apparent only during surgery or an injury.

Haemophilia A concerns mainly men, while the carriers of the disease are women. The prevalence in Poland amounts to 7/100,000. 1 in 5,000 male infants is diagnosed with haemophilia A. The mutation is spontaneous and there is no family history of the disease in approx. 30-50% of patients.

According to the data of the Institute of Haematology and Transfusion Medicine in Warsaw, 4,623 patients, including 2,263 patients with haemophilia A, were included in the register of persons diagnosed with a haemorrhagic disorder by July 2013. The severe form of the disease accounts for 53.7% of all haemophilia A cases.

The prognosis associated with haemophilia A and B is favourable, provided that appropriate replacement therapy is used. Currently, life expectancy of haemophilia patients is approaching the average value for the general population. In most developed countries, haemophilic arthropathy has been largely eliminated thanks to the widespread use of primary prevention. In Poland, almost 100% of adult patients with severe haemophilia have a motor system disability.

According to the NHF data, the number of patients aged ≤18 years (unique, non-repeating patient identifiers) treated under the B.15 and B.94 drug programme diagnosed with ICD-10: D66 in the years 2016-2018 amounted to a total of:

- 294 in 2016, with plasma-derived factors – 215, with recombined factors – 93,
- 316 in 2017, with plasma-derived factors – 198, with recombined factors – 111,
- 319 in 2018, with plasma-derived factors – 181, with recombined factors – 129.

Alternative health technologies

According to the identified guidelines for the treatment of haemophilia A, the use of factor VIII concentrates is recommended, and most guidelines promote the use of recombinant factors VIII over plasma-derived factors.

Pursuant to the announcement of the Minister of Health of 23 October 2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices, as of 1 November 2019, the following coagulation factors VIII are currently financed from public funds in Poland under the following drug programmes: B.15 “Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)” and B.94 “Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)”:

- recombinant coagulation factor VIII concentrates (Advate Kogenate Bayer – octocog alfa, Nuwiq – simoctocog alfa, NovoEight – turoctocog alfa, Elocta – efmoroctocog alfa);
- plasma-derived coagulation factor VIII concentrates (Immunate, Octanate – human coagulation factor VIII/ von Willebrand factor).

Furthermore, patients with haemophilia A have access to coagulation factor VIII concentrates under the following health policy programme: "National Programme for Haemophilia and Related Haemorrhagic Disorders for 2019-2023".

Specific factor VIII products available under drug and health policy programmes are selected through public procurement tenders conducted by the Public Procurement Department at the Ministry of Health.

In view of the above, all recombinant coagulation factor VIII concentrates financed in Poland which apply to the same population of patients eligible for prophylactic treatment (Advate, Kogenate Bayer, Nuwiq, Novo Eight and Elocta) should be treated as comparators for the assessed intervention, as taken into account in the applicant's analysis.

Description of the proposed intervention

Afstyla (lonoctocog alfa) is a recombinant human protein which replaces the missing coagulation factor VIII needed for effective haemostasis. Afstyla is a single polypeptide chain with a truncated B-domain that allows for a covalent bridge to link the factor VIII heavy and light chains. Afstyla has demonstrated a higher VWF affinity relative to full-length rFVIII. VWF stabilises factor VIII and protects it from degradation. Activated Afstyla has an amino acid sequence identical to endogenous FVIIIa.

In line with the summary of product characteristics (SPC), Afstyla's registered indication include treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The assessed application regards possible reimbursement of Afstyla (lonoctocog alfa) in a narrower indication than indicated in the marketing authorisation. The narrower population results from the inclusion and exclusion criteria of the proposed drug programme.

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.

The applicant's systematic review included a total of 24 publications describing 19 studies:

- 2 studies on lonoctocog alfa (Afstyla products): Stasyshyn 2017 (number of patients n=84, observation period: Exposure Days (EDs) in total: 5239, median 5.6 months), Mahlangu 2016 2017 (number of patients n=174, including 14 children, observation period: 14306 EDs); 1 publication describing the first stage of Mahlangu 2016 – comparison of lonoctocog alfa (Afstyla) vs. octocog alfa (Advate) in pharmacokinetics: Klamroth 2016;

- 4 studies for octocog alfa (3rd generation products – Advate): Auerswald 2012, EPIC (Auerswald 2015), Blanchette 2008, Tarantino 2004 and Fischer 2011 (to Blanchette 2008 and Tarantino 2004);
- 6 studies on octocog alfa (2nd generation products – Kogenate Bayer): Barnes 2006, Giangrande 2002, Kreuz 2005, ReCARE (Li 2017), JOS (Manco-Johnson 2007), PAC (Zhao 2017);
- 3 studies on simoctocog alfa (4th generation products – Nuwiq): GENA-03 (Klukowska 2016), GENA-13 (Klukowska 2018), NuProtect (Liesner 2018);
- 3 studies on turoctocog alfa (2nd generation products – NovoEight): guardian™3 (Kulkarni 2013), guardian™1 (Lentz 2013), guardian™2 (Ozelo 2015 I Lentz 2016);
- 3 studies on efmoroctocog alfa (sustained-release 4th generation products – Elocta): ASPIRE (Nolan 2016), Wang 2018, Kids A-LONG (Young 2015).

It should be emphasised that all of the analysed studies were prospective studies which did not include randomisation or a control arm (no different coagulation factors VIII were compared). Only ReCARE and Wang 2018 were retrospective studies. In turn, JOS was a randomised trial in which Kogenate Bayer or Kogenate FS were used in prophylaxis and emergency use schemes.

The conducted search failed to identify studies directly comparing the efficacy of lonoctocog (Afstyla products) with the chosen comparators. Due to the high heterogeneity of the identified single-arm studies and analysed populations, as well as different presentation of data and assessed parameters, carrying out a comparative statistical analysis of the included studies for lonoctocog (Afstyla) and other coagulation factors VIII other than a descriptive list of results, was not possible. Therefore, this analysis does not include a detailed description of the results of the above-mentioned studies. The annualised bleeding rate (ABR) for particular drugs was as follows:

- Afstyla (lonoctocog alfa) – median: 3.69;
- Advate (octocog alfa) – median: from 3.1 to 4.83;
- Kogenate Bayer (octocog alfa) – median: from 0.0 to 1.15;
- Nuwiq (simoctocog alfa) – median: from 0.00 to 3.63;
- NovoEight (turoctocog alfa) – median: from 1.4 to 3.98;
- Elocta (efmoroctocog alfa) – median: from 0.00 to 2.01.

Of the studies included in the analysis, two studies (Stasyshyn 2017, Mahlangu 2016) evaluating the pharmacokinetics, efficacy and safety of lonoctocog alfa (rFVIII-SC, Afstyla products) in the population of patients with severe HA, FVIII activity < 1% of standard) were identified. Both studies were multi-centre prospective single-arm experimental unblinded trials.

Stasyshyn 2017 was conducted exclusively in a paediatric population, whereas Mahlangu 2016 included adults and adolescents, aged 12 to 65 years old. Stasyshyn 2017 and Mahlangu 2016 were conducted on previously treated patients (PTPs) which had received treatment using coagulation factor VIII, recombinant (rFVIII) or plasma-derived (pdFVIII) products. As part of the assessed therapy, patients underwent prophylactic or on-demand treatment, and in Mahlangu 2016, additional periprocedural treatment was applied. The dosing was determined by physicians based on the treatment regimen applied prior to inclusion in the study, pharmacokinetic data, the patient's clinical condition and type of surgery performed in the arm treated perioperatively. In the case of on-demand treatment, dosing and frequency of administration were in line with the World Federation of Hemophilia (WFH) guidelines determined by the bleed location and its intensity.

The efficacy assessment was conducted on the basis of the assessment of the annualised bleeding rate (ABR), in particular of the annualised spontaneous bleeding rate (AsBR) of bleeding episodes occurring without a visible external cause.

As part of the safety analysis, both studies have been designed to evaluate the risk of factor VIII inhibitor, as well as IgG and/or IgM anti-drug-antibodies (ADAs) to rFVIII and antibodies to Chinese hamster ovary cell proteins during lonoctocog alfa treatment. Moreover, the tolerance of infusions (as assessed by patients and doctors) and the occurrence of adverse events (AEs) were evaluated.

The quality of the studies was estimated at 7/8 points on the NICE scale.

Efficacy

The analysis presents the results of studies on the efficacy of Afstyla (lonoctocog alfa) with respect to endpoints related to primary and secondary prevention.

Bleeding episodes – primary prevention

Stasyshyn 2017 provides information on the annualised bleeding rate (ABR). The results for total ABR (including all types of bleeding episodes) and ABR for joint bleeds and AsBR for spontaneous bleeds (without a visible external cause) were presented. The obtained results were presented for sub-groups distinguished by the dose frequency in the prophylactic treatment scheme.

In Stasyshyn 2017, the median ABR amounted to 3.69 (Interquartile Range IQR: 0.00; 7.20) and the median AsBR amounted to 0.00 (IQR: 0.00; 2.20). In case of joint bleeds, the median ABR amounted to 1.62 (IQR: 0.0; 4.87).

In the sub-arm of 40 patients in whom the dose did not need to be changed the ABR amounted to 2.73. In 5 children, spontaneous bleeding within the period of 14 days occurred ≥ 2 times, however no dosing adjustment was made – the median ABR in these children amounted to 6.94. In comparison, the ABR amounted to 2.58 in 44 patients in whom dosing was not adjusted in the course of the study and in whom ≥2 spontaneous bleeding episodes within the period of 14 days did not occur. The ABR in patients with ≥ 1 dosing adjustment amounted to 2.48 following the adjustment, compared to ABR = 7.83 before the dosing adjustment. The individual adjustment of the drug dosing can help reduce the frequency of bleeding episodes.

An additional analysis in Stasyshyn 2017 was carried out in sub-groups of patients distinguished by age (< 6 years and ≥ 6 to < 12 years). The annualised bleeding rate (ABR) was over twice as high in older children (median 5.11, IQR: 2.52; 10.50) as compared to the arm of < 6-year-old children (median 2.12, IQR): 0.00; 4.54). Similar differences were observed in the median joint bleed ABR, whereas the results relating to AsBR were similar in both age groups.

Haemostatic response and treatment success

In Stasyshyn 2017, a total of 347 bleeding episodes were treated, of which 132 (38.04%) occurred in patients in the on-demand treatment arm and 215 (61.96%) in 80 patients in the prophylactic treatment arm. Haemostatic efficacy of lonoctocog alfa was assessed as very good in the vast majority of bleeding episodes (85.3%). Good haemostatic efficacy was observed in 11.0% of cases. In Stasyshyn 2017, one haemostatic response was assessed as weak (or non-existent).

The vast majority of bleeding episodes (> 80%) were stopped after the administration of a single drug dose (85.9%), and two infusions of the drug were needed to stop approx. 10% of bleeds (9.8%). In order to stop 2.0% of bleeding episodes, more than 3 infusions had to be administered.

Lonoctocog alfa (Afstyla) vs. octocog alfa (Advate) – Pharmacokinetics comparison based on Klamroth 2016

In the case of incremental recovery (IR) of the coagulation factor, no statistically significant differences were demonstrated between the two drugs, either in the analysis including the correction for initial

values or in the analysis without adjustment. Obtaining similar values for both medicinal products means that these drugs may be characterised by similar efficacy following administration of a similar dose. Moreover, the maximum drug activity (Cmax) did not demonstrate significant differences between the drugs (in either analysis).

Afstyla was characterised by a longer half-life than Advate, lower clearance, longer average half-life and greater area under the FVIII activity-time curve.

Safety

In Stasyshyn 2017 and Mahlangu 2016, the safety analysis was carried out in all patients who received at least one dose of lonoctocog alfa. As part of the assessment, adverse events, immunogenicity of the evaluated drug and infusion tolerance were reported. The safety analysis in Mahlangu 2016 was carried out for the entire population, with no possibility of distinguishing the results in the sub-group of patients under 18 years of age.

Adverse events in Stasyshyn 2017 were reported in 76% of patients (183 events); most of them were mild (75%) or moderate (23). In Mahlangu 2016, TEAEs occurred in a smaller percentage of patients – 65% (292 events), of which 54% were mild and 25% moderate. Severe adverse events represented less than 3% of all TEAEs in both studies.

In Stasyshyn 2017, only one patient (1.2%) experienced a treatment-related adverse event (TRAE) which consisted in a mild hypersensitivity not requiring a change in dosing. In Mahlangu 2016, TRAEs occurred in 7.5% of patients (19 events in 13 patients).

Adverse events (AEs) leading to treatment discontinuation occurred only in Stasyshyn 2017 – it was a single case of mild hip joint pain, unrelated to the administered treatment.

Severe adverse events (SAEs) occurred in approx. 10% of patients in Stasyshyn 2017 and 4.6% of patients in Mahlangu 2016. Only one event was considered to be treatment-related (in Mahlangu 2016).

The studies reported no thromboembolic events.

The immunogenicity of the administered drug – lonoctocog alfa (Afstyla) was evaluated in both studies and neither of them identified the development of lonoctocog alfa inhibitors.

<u>Additional safety information</u>

No alerts on the safety of use of Afstyla have been identified on the websites of organisations monitoring safety of care (i.a. the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), the European Medicines Agency (EMA), the Food and Drug Administration (FDA); the Medicines and Healthcare products Regulatory Agency (MHRA).

In line with the SPC for Afstyla, the adverse reactions include:

- Blood and lymphatic disorders: FVIII inhibition, uncommon in previously treated patients and very common in naive patients;
- Immune system disorders: hypersensitivity (common);
- Nervous system disorders: dizziness, paraesthesia (common);
- Skin and subcutaneous tissue disorders: rash (often), erythema, pruritus (uncommon);
- General disorders and administration site conditions: fever (common), injection site pain, chills, feeling hot (uncommon).

Limitations of the analysis

The following aspects impact the reliability of the clinical analysis:

- the main limitation of the analysis is the lack of RCTs concerning both the technology in question and its comparators. Only single-arm studies were identified in the course of the conducted systematic review. Therefore, the analysis was carried out on the basis of single-arm studies, which makes it impossible to draw conclusions in terms of direct and indirect comparison of the drug in question with the selected comparators.
- Stasyshyn 2017 which was included in the clinical analysis, was conducted on previously treated patients. However, the drug programme also provides for the inclusion of newly diagnosed patients.

Furthermore, the studies included in the analysis are characterised by:

- high heterogeneity of the identified single-arm studies and analysed populations, as well as different presentation of data and assessed parameters, which makes it impossible to carry out a comparative statistical analysis of the included studies for lonoctocog (Afstyla) and other coagulation factors VIII, other than a descriptive list of results;
- in one of the two main studies concerning the intervention in question, it is impossible to single out data for the paediatric population (Mahlangu 2016), which is the target population in line with the application;
- some of the studies also include patients with moderate haemophilia A, which is an exclusion criterion for the proposed drug programme.

Furthermore, no studies concerning the effectiveness of the technology in question are available.

Proposals of risk-sharing schemes

The following has been proposed as part of the risk-sharing scheme: *[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.

The applicant carried out an economic analysis using the cost-minimisation analysis (CMA), comparing the use of lonoctocog alfa under the "Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)" drug programme, in children up to 18 years of age with severe haemophilia

A as part of primary and secondary bleeding prevention and in patients in whom central venous access is necessary, compared with other available coagulation factors VIII. Advate (octocog alfa) which, similarly to Afstyla, belongs to the third generation of coagulation factors and is also the most frequently ordered product for the treatment of haemophilia A, was selected as the main comparator. In addition, the following (at least second-generation) coagulation factors have also been included as comparators: Kogenate Bayer (octocog alfa), Nuwiq (simoctocog alfa), NovoEight (turoctocog alfa) and the long-acting Elocta (efmoroctocog alfa).

The estimates include the perspective of the public payer (the National Health Fund, NHF); due to the lack of patient co-payment, the common perspective (the NHF and the patient) was assumed to be the same. The analysis was conducted in a one-year time horizon.

Direct medical costs, i.e. costs of recombinant coagulation factor VIII concentrates, were included in the analysis. Moreover, the costs of diagnostics, drug administration, treatment monitoring and periprocedural treatment have been taken into account, although these costs do not differentiate between the compared regimens. The costs of immune tolerance induction in patients with the inhibitor were not been taken into account – these costs are fully covered by the marketing authorisation holder. The costs of adverse events were also not taken into account, as it was assumed they do not differentiate between the compared regimens.

According to the applicant's estimates, in the variant assuming no RSS, lonoctocog alfa (Afstyla) is cheaper than the comparators, respectively fort:

- Octocog alfa by PLN *[information protected as a trade secret];*
- Turoctocog alfa by PLN *[information protected as a trade secret];*
- Efmoroctocog alfa by PLN *[information protected as a trade secret]*;
- Simoctocog alfa by PLN *[information protected as a trade secret]*.

However, it should be mentioned that, in practice, this variant is not applicable, since the purchase of coagulation factors VIII is made through a public procurement tender.

In the RSS variant, the use of Afstyla is more expensive than each of the comparators, respectively for:

- Octocog alfa by PLN *[information protected as a trade secret];*
- Turoctocog alfa by PLN *[information protected as a trade secret];*
- Efmoroctocog alfa by PLN *[information protected as a trade secret];*
- Simoctocog alfa by PLN *[information protected as a trade secret].*

The net ex-factory price of the technology in question, where the difference in costs between the use of the technology in question and the cost of using the optional technology amounts to zero in the RSS variant (as more illustrative):

- *[information protected as a trade secret]*/IU for the comparison with octocog alfa;
- *[information protected as a trade secret]*/IU for the comparison with turoctocog alfa;
- *[information protected as a trade secret]*/IU for the comparison with efmoroctocog alfa;
- *[information protected as a trade secret]*/IU for the comparison with simoctocog alfa.

According to the results of the deterministic sensitivity analysis, body weight and drug consumption have the greatest impact on CMA results. In the RSS variant, the largest increase in the cost difference takes place assuming the drug consumption level as specified in the drug programme – up to PLN *[information protected as a trade secret]*, and then the price which would ensure Afstyla's price to equal that of its comparators drops to PLN *[information protected as a trade secret]* IU. A similar,

although slightly smaller, increase occurs assuming the drug consumption level as specified in the summary of product characteristics.

If an alternative body weight, determined on the basis of data from the Polish Central Statistical Office (GUS), is adopted by adjusting the body weight to the age of patients calculated on the basis of the age determined according to NHF data from AWA Nuwiq 2015, the cost difference increases to PLN *[information protected as a trade secret]* in comparison with simoctocog alfa and to *[information protected as a trade secret]* in comparison with efmoroctocog alfa. The net ex-factory price at which the cost of Afstyla equals the cost of comparators ranges between PLN *[information protected as a trade secret]* /IU and PLN *[information protected as a trade secret]* /IU depending on the comparison.

The results of the sensitivity analysis indicate that the identified limitations of the input data have a significant impact on the results.

Limitations of the analysis

All limitations regarding the reliability and uncertainty of estimates concerning the efficacy and safety of the technology in question apply also to the economic assessment of the technology in question.

Furthermore, the uncertainty of economic analysis estimates is affected by the following limitations:

- annual consumption of particular drugs – in the applicant's basic analysis, drug consumption was estimated on the basis of the studies (all characterised by a very high degree of heterogeneity) presented in the clinical analysis. Very large differences in annual drug consumption can be identified between different studies carried out for the same product. In addition, a significant difference of drug consumption estimates is also visible in the use of alternative sources on which estimates are made, such as SPC, NHF data and the drug programme.
- patients' body weight – the NHF data used by the applicant to estimate the mean body weight in the basic analysis regarded the mean body weight of patients using recombinant coagulation factors VIII under the drug programme in the years 2010-2014. Thus, the population using plasma-derived factors (which constituted most of the market share at that time) was disregarded, which may significantly result in the lower mean age and, consequently, lower body weight of patients. The average age of patients using recombinant factors according to the same NHF data amounted to 1.5 years in 2011 and 4 years in 2014; if a linear trend prognosis is applied, it would amount to 9.085 in 2019 and 12.35 in 2023. The entry of recombinant factors into the market resulted in gradual exclusion of plasma-derived factors, however, second-generation recombinant factors could be used only in newly-diagnosed patients, previously untreated with plasma-derived factors. This resulted in recombinant factors being used in the youngest children (the restrictions in this respect were not abolished until November 2019). For this reason, estimating a patient's body weight based on data collected from patients using ≥ second generation recombinant factors may result in underestimations.

  According to the data presented by the MAH for Advate for the purpose of the proceedings conducted at the Agency, the average patient's body weight using bleeding prevention in Poland amounts to *[information protected as a trade secret]*. (Advate is the most commonly ordered product in haemophilia A treatment). It differs significantly from the applicant's basic estimates. *[information protected as a trade secret]*
- target population – the applicant's analyses correspond to the company's original application and not to the agreed upon drug programme. In its assessment, the Agency is bound by the agreed upon programme. The population specified in the agreed upon drug programme is broader than in the original application. The change of the proposed drug programme at the

stage of it being agreed upon had a significant impact on the scope of the analysis, *[information protected as a trade secret]*

- dosing – the dosing of the intervention in the established drug programme is based on different assumptions than those adopted in the analysis.
- comparators – *[information protected as a trade secret]* However, it should be expected that, due to clinical recommendations, plasma-derived and recombinant factors will continue to have a lesser share on the market and, in the public procurement tenders, the choice will be made de facto between recombinant ≥ second-generation products (although a significant number of patients who have started a therapy with plasma-derived factors continues such a therapy).

AOTMiT's own calculations

In accordance with the information from the opening of public procurement tenders carried out by the Ministry of Health, a better price offer per one unit of Advate is available, i.e. PLN 0.56. Therefore, the Agency's own calculations were carried out taking into account such a price in the RSS variant. The results of the calculations indicate that the use of Afstyla is more expensive than the use of Advate by PLN *[information protected as a trade secret]* per year.

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. 2016, item. 1536, 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.

Given the fact that the advantage of the intervention in question over its comparators has not been demonstrated, circumstances referred to in Article 13 paragraph 3 of the Act on reimbursement occur.

In line with the applicant's estimations, the statutory ex-factory price set out in accordance with Article 13 of the Act on reimbursement amounts to *[information protected as a trade secret]* /IU.

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.

The analysis of the effects on the healthcare system, in the event that Afstyla (lonoctocog alfa), used for the treatment and prevention of bleeding episodes in children with haemophilia A (congenital

factor VIII deficiency) is reimbursed under the drug programme in question "Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)", was carried out from the public payer's perspective (the National Health Fund, NHF) and from the common perspective (identical to the NHF's perspective). A one-year impact on the payer's budget for the horizon of two calendar years 2019-2020 is estimated in the analysis, assuming that the likely date of introducing reimbursement of the technology in question is January 2019. The costs were included in a similar way as in the economic analysis. The number of patients eligible for the technology in question was estimated to be *[information protected as a trade secret].*

Analysis without risk-sharing scheme

In line with the applicant's estimations, the expected expenditure of the public payer in the target population in question for the period from 2019 to 2020 will amount to *[information protected as a trade secret]*, respectively in the variant without the RSS.

In the event it is decided that Afstyla is reimbursed under the proposed drug programme, the public payer's expenditure will decrease in relation to the existing scenario by *[information protected as a trade secret],* between 2019 and 2020, respectively.

The cost component, representing the amount of the reimbursement of Afstyla, amounts to – in the first two years of the time horizon in the analysis – *[information protected as a trade secret]* in the new scenario and to PLN 0.00 per year in the existing scenario, respectively.

Analysis with the risk-sharing scheme

In line with the results of the analysis, the expected expenditure of the public payer in the target population in question for the period from 2019 to 2020 (new scenario) will amount to *[information protected as a trade secret]* in the variant without RSS, respectively.

In the event that it is decided that Afstyla is reimbursed under the proposed drug programme, the public payer's expenditure will decrease in relation to the existing scenario by *[information protected as a trade secret]* between 2019 and 2020, respectively.

The cost component, representing the amount of the reimbursement of Afstyla, amounts to – in the first two years of the time horizon in the analysis, – *[information protected as a trade secret]* in a new scenario and to PLN 0.00 per year in the existing scenario, respectively.

Furthermore, a one-way sensitivity analysis was carried out.

In line with the results of the analysis, the maximum incremental expenditure in the variant not taking the RSS into account from the public payer's perspective was observed in the variant where the comparators' price was adopted at the level of NovoEight's price applicable in 2016-2018, estimated on the basis of the data of the NHF's Department of Pharmaceutical Management. Therefore, the unit price of comparators is lower than the proposed unit price of Afstyla without the RSS. In this variant, in the event that it is decided that Afstyla is reimbursed, additional expenditure of the public payer will respectively amount to *[information protected as a trade secret]* (2019) and *[information protected as a trade secret]* (2019). However, the expenditure related solely to Afstyla will be equal to *[information protected as a trade secret]* in the period between 2019 and 2020, respectively.

The highest incremental savings, from the public payer's perspective, were observed in the variant where equal proportions of comparators in the existing scenario were assumed. In this variant, in the event that it is decided that Afstyla is reimbursed, the savings of the entity obliged to finance services from public funds will amount to *[information protected as a trade secret]* (2019) and *[information protected as a trade secret]* (2019), respectively. However, the expenditure related solely to Afstyla

will be equal *[information protected as a trade secret]* in the period between 2019 and 2020, respectively.

However, in the variant taking RSS into account from the public payer's perspective, the maximum incremental expenditure was reported in the variant where the drug consumption was based on the dosing from the currently applicable drug programme. In this variant, in the event that it is decided that Afstyla is reimbursed, additional expenditure of the entity obliged to finance services from public funds will amount to *[information protected as a trade secret]* (2019) and *[information protected as a trade secret]* (2019), respectively. However, the expenditure related solely to Afstyla will be equal to *[information protected as a trade secret]* and *[information protected as a trade secret]* in the period between 2019 and 2020, respectively.

The highest incremental savings, from the public payer's perspective, were observed in the variant where it was assumed that the price of comparators will be at the level of the highest price from the public procurement tenders (data obtained from the Public Procurement Department -223/17). Therefore, the unit price of the comparators is significantly higher than the proposed unit price of Afstyla (with the RSS). In this variant, in the event that it is decided that Afstyla is reimbursed, the savings of the entity obliged to finance services from public funds will amount to *[information protected as a trade secret]* (2019) and *[information protected as a trade secret]* (2019), respectively. However, the expenditure related solely to Afstyla will be equal to *[information protected as a trade secret]* in the period between 2019 and 2020, respectively.

Limitations of the analysis

The uncertainty of drawing conclusions based on the budget impact analysis depends i.a. on the following aspects:

- The applicant estimated the population of patients treated with rFVIII at *[information protected as a trade secret]* According to the NHF data, in 2018, the number of patients treated under the B.15 and B.94 drug programme amounted to 181 and 129, for prevention with pdFVIII and rFVIII, respectively.

  The proposed changes to the agreed upon B.15 drug programme assume the increased use of recombinant factors in the target population. The number of patients using rFVIII will continue to increase. Both newly-diagnosed patients and patients currently using pdFVIII will be able to use rFVIII.

  [information protected as a trade secret]

  It should be expected that, due to clinical recommendations, the crowding out of first generation plasma-derived and recombinant factors will progress and, in the public procurement tenders, the de facto choice will be made between recombinant ≥ second-generation products (although a significant number of patients who have started a therapy with plasma-derived factors will continue such treatment).

- Coagulation factors are bought through public procurement tenders. The supply of a given product is determined by the price that allows to win the tender. Therefore, forecasting the consumption of specific products is subject to high uncertainty.

AOTMiT's own calculations

In line with the provisions of the drug programme, the new scenario should assume that there are no new (newly-diagnosed) patients who start bleeding prevention with pdFVIII in the time horizon of the analysis. The proposed changes to the B.15 drug programme will result in the increased use of recombinant factors in the target population. The number of patients using rFVIII will continue to increase. Both newly-diagnosed patients and patients currently using pdFVIII will be able to use rFVIII.

According to data from the NHF database, the total number of patients treated in the B.15 and B.94 drug programmes in 2016, 2017, 2018 amounted to 308, 309 and 310, respectively. Taking into account the above data and the increase of the target population by 1 patient per year, it was determined that the estimated number of patients will amount to 311 in 2019, 312 in 2020 and will increase to 313 in 2021.

As part of the AOTMiT's own calculations, the above data concerning the target population and data concerning the best price for 1 IU of (minimum second generation) recombinant coagulation factor VIII (taken from the public procurement tender ZZP-198/19) of PLN 0.56 (Advate) were taken into account, assuming that all patients start using rFVIII.

In conclusion, in the event that it is decided that Afstyla is reimbursed under the drug programme in question, the public payer's expenditure will increase in relation to the existing scenario by *[information protected as a trade secret]* between 2019 and 2021 in the RSS variant, respectively.

However, in the variant without the RSS, the public payer's expenditure will increase in relation to the existing scenario by *[information protected as a trade secret]* in the period between 2019 and 2021, respectively.

Remarks on the proposed risk-sharing scheme

In line with the Council's suggestion, the increased costs of the programme for the public payer indicate the need to enhance the risk-sharing scheme.

Remarks on the drug programme records

It is worth drawing attention to a number of issues concerning the drug programme in question.

[information protected as a trade secret]

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 the rationalisation analysis, the applicant proposed a solution allowing for generating savings for the public payer to cover additional expenditure associated with the reimbursement of Afstyla in the indication in question, consisting of *[information protected as a trade secret]*

The implementation of the proposed rationalisation solutions will allow for the release of public funds exceeding the payer's estimated expenditure in the analysed period resulting from the implementation of the programme for the prevention of bleeding episodes in children with haemophilia A using Afstyla by *[information protected as a trade secret]* in 2019 and by *[information protected as a trade secret]* in 2020.

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

The search resulted in the identification of 11 clinical guidelines regarding treatment of haemophilia, including Polish guidelines:

- Polish Society of Haematologists and Transfusionologists (PTHiT) 2016 (Polish)
- World Federation of Haemophilia (WFH) 2012, 2014, 2017 (global);
- Medical and Scientific Advisory Council (MASAC) 2017, 2018 (American);
- European Association for Haemophilia and Allied Disorders (EAHAD) 2008 (European);
- Nordic Hemophilia Council (NHC) 2017 (Nordic countries);
- Australian Haemophilia Centre Directors' Organisation (AHCDO) 2016 (Australian);
- UK Haemophilia Centres Director's Organisation (UKHCDO) 2008, 2010 (British).

All of the above guidelines recommend using factor VIII concentrates in the treatment of haemophilia A, most of which prefer using recombinant factor VIII over plasma-derived factor (Polish PTHiT 2016, American MASAC 2017/2018, Australian AHCDO 2016, Nordic NHC 2017). The WFH 2012 global guidelines leave the choice between recombinant and plasma-derived factors to local recommendations.

The guidelines do not indicate specific products to be used. Some guidelines only list available products which contain factor VIII, including lonoctocog alfa (Afstyla in American guidelines MASAC/NHF 2017 and MASAC 2018). None of the guidelines make any reference to the existence or lack of differences in terms of efficacy or safety between available products containing recombinant factor VIII.

Pursuant to the WFH 2012 global guidelines, the WFH does not support any specific medicinal products or manufacturers. Dosing and treatment regimens are constantly reviewed, and new adverse effects are identified.

The WFH 2012 and PTHiT 2016 guidelines indicate that treatment must be individualised, adjusted to the patient's needs and available treatment methods. According to PTHiT 2016 guidelines, while preparing a long-term prevention plan for a specific patient, such factors as the following should be taken into account:

1. individual pharmacokinetic parameters, of which T ½ of the deficient coagulation factor is the most important for long-term prevention;
2. haemorrhagic phenotype (severe v. mild);
3. age of patients when prevention treatment is initiated (any delays should be avoided);
4. patient's physical activity (high level of physical activity in young patients v. usually lower level in older people);
5. adherence to the requirements of the long-term prevention regime, in particular requirements expressed by the systematic use of injections of the deficient coagulation factor (without omitting planned injections).

In the case of using rFVIII and rFIX concentrates with an extended half-life, less spectacular results for rFVIII-Fc were indicated in PTHiT 2016 guidelines, which is explained by linking the injected FVIII to the von Willebrand factor which determines the FVIII clearance rate (both endogenous and exogenous). The half-life of rFVIII-Fc amounts to 19.0 h, which means that it is about 1.5 times longer compared to standard rFVIII. In practice, the interval between injections in a patient with severe haemophilia A receiving long-term bleeding prevention can be prolonged by about 3-5 days, and in selected patients with very favourable pharmacokinetic parameters, even up to 7 days. The WFH 2012 guidelines indicate that products with an extended half-life offer the theoretical benefits resulting from less frequent infusions and/or achieving higher minimum coagulation factor levels through a preventive

treatment regimen with infusion frequencies comparable to those of conventional products. Whereas, according to the NHC 2017 guidelines, molecules with an extended half-life should be carefully assessed for their economic value as regards health.

In the majority of the guidelines, the recommendations for treatment of haemophilia A are presented without distinguishing between primary and secondary bleeding prevention. Primary bleeding prevention is defined in the WFH 2012 global guidelines and this definition is quoted in the Polish PTHITH 2016 and Nordic NHC 2017 guidelines.

Two reimbursement recommendations for the use of Afstyla in the treatment of haemophilia A have been identified:

- Haute Autorité de Santé (HAS 2017) France;
- Institut für Qualität und Wirtschaftlich-keit im Gesund-heitswesen (IQWiG 2017) Germany;

A positive reimbursement decision for the use of Afstyla was issued in HAS 2017, however, it was noted there that there was no evidence of additional benefits resulting from the use of Afstyla compared to currently applicable treatment regimens.

IQWiG 2017 also analysed the potential benefits of lonoctocog alfa in the treatment and prevention of bleeding episodes in children and adults with haemophilia A. No additional therapeutic benefit resulting from its use compared to standard therapy has been identified on the basis of the collected evidence.

According to the information provided by the applicant, the majority of Afstyla products are reimbursed in 14 EU and EFTA states (of 31 indicated states). Afstyla products are not reimbursed in any country with per capita GDP similar to Poland's. No risk-sharing schemes are in place in countries where Afstyla products are financed.

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 09/09/2019 (reference number: PLR.4600.3440.2018; PLR.4600.3439.2018; PLR.4600.3438.2018; PLR.4600.3437.2018; PLR.4600.3436.2018; PLR.4600.3435.2018; PLR.4600.3433.2018), with regard to preparation of the recommendation of the President of the AOTMiT on whether to reimburse Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 250 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326098; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326104; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326111; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 1500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326128; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326135; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 2500 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326142; Afstyla, Lonoctocog alfa, powder and solvent for solution for injection, 3000 IU, 1 vial of powder + 1 vial of solvent + administration set, EAN: 5909991326159, in the indication: under the following drug programme: "Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)" (combination of B.15 and B.94) 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. 113/2019 of 16 December 2019 on the evaluation of Afstyla (lonoctocog alfa) under the following drug programme: "Treatment in children with haemophilia A and B (ICD-10 D 66, D 67)".

References

1. The Position of the Transparency Council No. 113/2019 of 16 December 2019 on the evaluation of Afstyla (lonoctocog alfa) under the following drug programme: "Prevention of bleeding in children with haemophilia A and B (ICD-10 D 66, D 67)".

2. Reimbursement application for Afstyla (lonoctocog alfa) to be available under the following drug programme: "Prevention of bleeding episodes in children with haemophilia A and B (ICD-10 D 66, D 67)". Verification analysis No. OT.4331.51.2019. Completion date: 05/12/2019