Recommendation No. 10/2020

of 29 January 2020

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

on whether Hizentra (human normal immunoglobulin) should be reimbursed in the following indication: "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)"

The President of the Agency recommends reimbursing the following medicinal product:

- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 50 ml per vial, EAN: 05909991067380;
- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 20 ml per vial, EAN: 05909990869657;
- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 5 ml per vial, EAN: 05909990869541;
- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 10 ml per vial, EAN: 05909990869572,

indicated in treatment under a drug programme: "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)" **on condition** that the drug price is reduced to the level of the cheapest intravenous immunoglobulin product or that an appropriate risk-sharing scheme is introduced.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the available scientific evidence and results of pharmacoeconomic analyses, the President of AOTMiT is of the opinion that financing of the health technology in question from public funds is justified, on condition that the drug price is reduced to the level of the cheapest intravenous immunoglobulin product or an appropriate risk-sharing scheme is introduced.

An assessment of the efficacy and safety of use of human normal immunoglobulin (SCIg) for subcutaneous injection as a therapeutic option in treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) was conducted based on an indirect comparison with immunoglobulins administered intravenously (IVIg) using a common comparator: placebo (PLC). The above-mentioned analysis was based on two studies: RCT – PATH which compared SCIg vs PLC and ICE which compared IVIg vs PLC. The clinical analysis also included lower-class scientific evidence (observational studies, case studies).

Results of the indirect comparison indicate the lack of statistically significant differences between SCIg vs IVIg in terms of efficacy, with regard to the "risk of relapse" endpoint. Similarly, no statistically significant difference between SCIg vs IVIg in terms of safety of use of the drugs with regard to the "risk of adverse events resulting in exclusion from the study" endpoint have been identified.

However, it should be underlined that conducting an indirect comparison was possible only for the two above-mentioned endpoints, which results in limited possibilities of drawing conclusions in the scope in question. The main limitation of the clinical analysis is the fact that no studies which directly compare the assessed technology with intravenous immunoglobulins in CIDP treatment have been found. The RCTs included in the clinical analysis differed in terms of the study population characteristics, as well as the study methodology.

The results of the included observational studies and case studies are convergent with the RCT results.

In line with results of the economic analysis conducted using the cost-minimisation method, the use of Hizentra (SCIg) instead of IVIg *[information protected as a trade secret]*.

[*information protected as a trade secret*].

Results of the budget impact analysis indicate that in the case of a positive reimbursement decision for Hizentra in CIDP treatment, incremental expenditure from the NHF's perspective [*information protected as a trade secret*].

[*information protected as a trade secret*].
It should be emphasised that the population of CIDP patients eligible for SCIg therapy might be greater than assumed by the applicant, which constitutes a limitation of the presented estimates. At the same time, it should be noted that in the basic variant of the applicant's calculations [*information protected as a trade secret*].

Furthermore, the AOTMiT finds taking into account remarks of clinical experts on the drug programme to be justified, in particular with regard to the frequency of monitoring the patient's condition.

Subject of the application

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

- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 50 ml per vial, EAN: 05909991067380 with the net ex-factory price of PLN [*information protected as a trade secret*];
- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 20 ml per vial, EAN: 05909990869657 with the net ex-factory price of PLN [*information protected as a trade secret*];

- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 5 ml per vial, EAN: 05909990869541 with the net ex-factory price of PLN [*information protected as a trade secret*];
- Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 10 ml per vial, EAN: 05909990869572 with the net ex-factory price of PLN [*information protected as a trade secret*];

indicated in treatment under the following drug programme: "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)".

The proposed reimbursement availability category – drug available as part of a drug programme. The proposed patient's co-payment level – free-of-charge. The drug is to be available as part of an existing limit group – 1066.1, human normal immunoglobulin for subcutaneous use. No risk-sharing scheme was proposed.

Health problem

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic or recurrent autoimmune process which causes demyelination in the nerve trunks, roots, and nerve plexuses. The etiology of CIDP remains unclear.

CIDP symptoms develop over a longer period of time – from several (>8) weeks to many months. They include paresis of the extremities, paraesthesia, absence of deep reflexes, cranial nerve symptoms, vegetative and (very rarely) respiratory dysfunctions. EMGs depict slowing of conduction velocity, prolongation of latency, lack of F wave. Cerebrospinal fluid testing depicts increased protein concentration in 95% of patients. The course of the disease may be progressive, relieving/exacerbating or relapsing. The prognosis is good, symptoms subside completely in 40% of patients, while 50% of patients are left with slight defects.

CIDP is diagnosed based on imaging of slow growth of flaccid paresis with progressive absence of reflexes, increased concentration of protein in the cerebrospinal fluid, as well as conduction block, slowing down of the speed of conduction of impulses and extending the F-wave latency, all found in neurophysiological examinations.

CIDP is classified as a rare disease (Orphanet 2018). The prevalence of CIDP is estimated to be 1-5 cases per 100,000 residents of different ages (the estimates vary depending on the adopted diagnosis criteria – using older criteria might lead to underestimation of CIDP prevalence), whereas approx. 10% of patients are children. The disease might be preceded by infections or vaccinations. CIDP can occur in pregnant women, with symptoms becoming more severe in the third trimester or directly after delivery. The prevalence of the disease is estimated to be 1 in 300,000 (and occurs very rarely in infants).

Pursuant to NHF data, between 3,465 and 4,637 patients a year were qualified for the B.67 drug programme, i.e. "Immunoglobulin infusion treatment in neurological disorders" in the years 2016-2018. Of that, between 313 and 367 patients were diagnosed with ICD-10 G61.8 (other inflammatory polyneuropathies) and between 2,165 and 3,098 patients diagnosed with ICD-10 G62.8 (other specified polyneuropathies). In line with the applicant's analysis, CIDP is classified using either of those two ICD codes. 484, 611 and 616 patients with those diagnoses, respectively, received human immunoglobulin in subsequent years.

Alternative health technologies

Clinical guidelines do not mention subcutaneous immunoglobulins (SCIg) as a therapeutic option in treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), however, it should be underlined that they were published prior to Hizentra obtaining marketing authorisation in the

indication in question. Clinical guidelines recommend intravenous immunoglobulins (IVIg), corticosteroids or plasmapheresis for first-line treatment of CIDP patients. In the event of treatment failure, immunosuppressive and immunomodulating drugs (rituximab, cyclosporin, interferon, azathioprine, cyclophosphamide, methotrexate) are used in the next treatment line.

Pursuant to the Announcement of the Minister of Health of 20 December 2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices, currently, under the B.67 drug programme "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G 70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)", the following substances are financed from public funds:

- human normal immunoglobulin
    - Flebogamma DIF, solution for infusion,
    - Privigen, solution for infusion,
- human normal immunoglobulin
    - Kiovig, solution for infusion,
- human normal immunoglobulin for intravenous use
    - Ig VENA, solution for infusion,
    - Octagam, solution for infusion,
    - Octagam 10%, solution for infusion.

As comparators for the assessed intervention in the indication in question, the applicant selected intravenous immunoglobulins and no active treatment/placebo.

AOTMiT finds adopting intravenous immunoglobulins as a comparator to be a justified choice. However, placebo can be treated only as an additional comparator for assessing the safety profile of the therapy in question and as part of the indirect comparison between SCIg and IVIg.

Description of the proposed intervention

The mechanism of action of Hizentra (subcutaneous human normal immunoglobulin, SCIg) in indications other than replacement therapy is not completely clear, however it also includes immunomodulatory activity. Human normal immunoglobulin contains IgG antibodies found in the normal population. It is usually created from plasma pools obtained from at least 1,000 donors. The distribution of immunoglobulin G subclasses is similar to that found in the plasma of healthy humans. The right doses of that product can restore correct immunoglobulin G concentration.

In line with the summary of product characteristics (SPC), Hizentra's registered indications include:

- Replacement therapy in adults, children and adolescents (0-18 years) in:
    - Primary immunodeficiency syndromes with impaired antibody production,
    - Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contraindicated,
    - Hypogammaglobulinaemia and recurrent infections in multiple myeloma (MM) patients,
    - Hypogammaglobulinaemia in patients, pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT),
- Immunomodulatory therapy in adults, children and adolescents (0-18 years):

- Hizentra is indicated for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilisation obtained with IVIg therapy.

Currently Hizentra is reimbursed under drug programmes for treatment of primary immunodeficiency in children (B.17) and adults (B.62).

The indication specified in the reimbursement application for Hizentra regards the treatment of chronic inflammatory demyelinating polyneuropathy and is included in the marketing authorisation indication. It should be noted that the proposed drug programme covers also treatment of patients with multifocal motor neuropathy, myasthenia gravis, inflammatory myopathies, Guillain-Barré syndrome, Devic disease, paraneoplastic syndromes and encephalitis with antibodies against neuronal antigens. The above indications are not Hizentra's marketing authorisation indications and are not the subject of the reimbursement application.

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 efficacy and safety analysis of subcutaneous human normal immunoglobulin (SCIg) in CIDP includes only some of the studies identified by the applicant, i.e. RCTs on the following direct comparisons for the purpose of conducting an indirect comparison:

- subcutaneous human normal immunoglobulin (SCIg) vs placebo (PLC):
    - PATH (publications: Shaik 2016 and van Shaik 2018) – multicentre, double-blind, phase III randomised clinical trial; Study hypothesis: *superiority*; Interventions: SCIg – Hizentra in a dose of 0.2 g/kg body weight and 0.4 g/kg body weight; Comparator: PLC; Observation period: up to 52 weeks, (including 24 weeks of SCIg treatment); Number of patients: Hizentra 0.2 g/kg body weight arm – 57, Hizentra 0.4 g/kg body weight arm – 58, PLC arm – 57. Study quality assessment – the risk of bias assessed using the Cochrane Collaboration tool was found to be unclear in the "incomplete data" domain, and low in the remaining domains.
- Intravenous human normal immunoglobulin (IVg) vs placebo (PLC):
    - ICE (publication: Hughes 2008) – multicentre, double-blind, phase II randomised clinical trial; Study hypothesis: *superiority*; Interventions: IVIg – immunoglobulin (Gamunex) administered intravenously at a dose of 1 g/kg body weight on day 1 or 2, every three weeks over the course of 24 weeks of the study; Comparator: PLC; Observation period: 24 weeks (extension phase); Number of patients: IVIg arm – 43, PLC arm – 31. Assessment of the study quality – the risk of bias, assessed using the Cochrane Collaboration tool, was found to be low in all analysed domains.

Furthermore, in order to assess the product's effectiveness, results of the following observational studies on Hizentra were presented:

- prospective uncontrolled studies:

  - Cocito 2017 – 7 patients diagnosed with CIDP participated in the study (6 men and 1 women aged 35-82 years old), who, after the phase of disease stabilisation with IVIg treatment, received SCIg (Hizentra) in a monthly dose of 1 g/kg body weight over the course of subsequent 6 months. After 6 months of treatment, patients moved on to SCIg administered in bolus, however the results were not included in the analysis. The inclusion criterion for this study was recurrence of disease symptoms between subsequent IVIg administrations in the first treatment phase. The quality of the study was estimated at 6/8 points on the NICE scale.
  - Cirillo 2018 – the study assessed long-term (2-year) SCIg treatment (Hizentra) in 16 CIDP patients after previous 1 cycle of IVIg treatment who responded to that treatment. After that, patients commenced SCIg therapy in the dose of 0.4 g/kg body weight/week. The quality of the study was estimated at 5/8 points on the NICE scale.

- prospective controlled study:
  - Cocito 2014 (and Cohito 2016 – extension phase to Cocito 2014) – prospective, multi-centre study assessing 4-month SCIg treatment after a change from IVIg treatment among 66 patients with CIDP or multifocal motor neuropathy (MMN). IVIg therapy: IVIg in a dose of 1-2 g/kg body weight/month; SCIg therapy: SCIg, 16% solution in 6/87 (6.9%) or 20% solution in 81/87 (93.1%) (no breakdown into specific SCIg types separately for CIDP patients was presented). The quality of the study was estimated at 7/8 points on the NICE scale.

The following evidence was also taken into account in the clinical analysis:

- Case studies (Cocito 2016a, Hadden 2015, Markvardsen 2014 and Yoon 2015)
- Brill 2018 conference abstract which presented results of an assessment of electrophysiological parameters for patients participating in the PATH study.

The above studies constitute evidence characterised by the lowest reliability, and, therefore, it was decided against presenting their descriptions and results in the recommendation.

The following parameters were used to assess efficacy and safety:

- HR – hazard ratio;
- RR – risk ratio;
- IQR – interquartile range;
- MD – mean difference.

The following scales and questionnaires were used in the presented studies:

- CGS (Clinical Grading Scale) – the scale is used to assess disability. The possible score on the scale ranges from 0 to 10, where 0 means no sign of disability and 10 means death;
- INCAT (Inflammatory Neuropathy Cause and Treatment) – disability score used to monitor a patient's condition with regard to upper and lower extremities. Lower scores indicate improvement, higher scores indicate greater disability;
- R-ODS (Rasch-built Overall Disability Scale) – the scale is used to assess disability (e.g. impaired activity, social limitations in patients with peripheral immune neuropathies. R-ODS is a 24-item scale and each item can be scored 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform, without any difficulty).
- ODSS (Overall Disability Sum Score) – an arm and leg disability scale. The total score ranges from 0 to 12, where 0 means "no sign of disability" and 12 means "most severe disability";

- ONLS (Overall Neuropathy Limitations Scale) – the scale is designed to assess the limitations of patients with immune-mediated peripheral neuropathies and focuses on mobility issues of patients with neuropathies. It is based on the ODSS scale. In ONLS , the item on mobility difficulties was modified to include difficulties with climbing stairs and running. ONLS is the total of the Arm scale score (0-5) and Leg scale score (0-7);
- NIS (Neurological Impairment Scale) – the scale is used to assess the severity of neurological disorders in impairing disorders. NIS is made up of 10 items in the physical impairment domain and 7 items in the cognitive impairment domain. Each element can be assessed on a scale from 0 to 3, where 0 means correct functioning, no impairment, 1 – mild impairment with impairment only in the domain of higher activities, 2 – moderate impairment with significant limitations, 3 – severe impairment making normal functioning impossible, limiting chances for rehabilitation. The maximum total score is 50 points;
- MRC (Medical Research Council) scale – the scale is used to assess muscle power in clinical practice, with scores ranging from 0 (no muscle contraction) to 5 (normal power) depending on the muscle power assessment;
- mRS (modified Rankin Scale) – the scale was initially used in stroke patients to assess overall disability and strength deficit. The scale runs from 0-5, running from 0 (no symptoms) to 5 (severe disability).
- The hand grip strength assessment is used to measure disease progression in clinical practice and clinical trials. The Jamar hand dynamometer is used to measure grip strength, registered in PSIs (pounds per square inch). The patient is asked to squeeze his/her hand and hold the grip for 6 seconds. Then the procedure is repeated three times, with a 1-minute break between the rounds. The result is expressed in kilogrammes as the mean of three parameters;
- CDAS (*CIDP Disease Activity Status*) – the CDAS is used to monitor response to treatment and CIDP activity.

Efficacy

The SCIg vs IVIg indirect comparison was conducted using the Bucher method and a common comparator (PLC). Since conducting an indirect comparison was possible only for 2 endpoints (the risk of CIDP relapse and adverse events leading to withdrawal from the study), a comparison of results regarding the remaining endpoints used in both RCTs, which could not be used in an indirect comparison, was also presented.

<u>SCIg vs IVIg indirect comparison</u>

Results of the indirect comparison indicate that no statistically significant differences in the risk of CIDP relapse compared to IVIg were observed for both Hizentra doses.

<u>Summary of results</u>

The comparison of results for SCIg and IVIg includes data on the following endpoints:

- Quality of life

  In PATH, the quality of life was measured using the EQ-5D questionnaire (Schaik 2018 does not define the “improvement” and “deterioration” of quality of life as part of the presented domains). The majority of patients treated with Hizentra reported lack of changes in terms of quality of life in all 5 domains of that questionnaire. The largest percent of patients reporting an improvement rather than deterioration of quality of life were reported in the “self-care” domain for the low drug dose and in the “pain or discomfort” domain for the higher dose. According to van Schaik 2018, the results concerning the quality of life were generally better in both arms using SCIg than in the placebo arm.

The quality of life was not assessed in the ICE study.

- Change in the INCAT total score

  The total INCAT score ranges from 0 to 10, where a high score means that the patient's condition deteriorated. No change in the INCAT score among patients receiving Hizentra regardless of the dose size was reported in the PATH study.

  A slight deterioration of that score was reported in patients receiving IVIg in the ICE study.

- Change in grip strength

  In the PATH study, increased grip strength of the dominant hand compared to baseline was reported in patients treated with a low and high dose of SCIg, while decreased grip strength of the non-dominant hand was observed in both these arms.

  Reduced grip strength of both the dominant hand and non-dominant hand was reported for patients receiving IVIg.

- Change in MRC muscle power

  No increase with regard to increased MRC muscle power compared to baseline was observed in both SCIg arms in the PATH study.

  However, increased MRC muscle power was recorded in the IVIg arm of the ICE study.

Effectiveness

Studies on effectiveness, the results of which are coherent with results of the clinical trials, have been identified in the course of the analysis.

Cocito 2017

Results of the first, 6-month phase of conventional SCIg treatment indicate that patients treated with Hizentra have been observed to improve on the R-ODS in month 6 of observation, while no statistically significant changes in terms of MRC muscle power and the INCAT score have been observed. The average R-ODS score in month 6 of observation obtained by patients in this study was 36.1 points (SD: 9.67).

This study also presented findings on the quality of life of patients treated with SCIg, expressed using the LQI. The results were presented as the percentage of the minimum score appointed to each domain of the questionnaire completed by patients after 6 months of treatment. The average percentage of the score for the first three LQI domains (treatment interference, therapy-related problems, therapy setting) achieved by patients from the Cocito 2017 trial was similar (91.89%-96.49%), and lower for the "treatment costs" domain, i.e. 65.38%.

Cirillo 2018

Patients treated with SCIg in the Cirillo 2018 trial were observed to experience an improvement after 24 months of treatment in terms of:

- the mRS performance score – the score after 12 months of treatment was 2.83 (SD: 2.32), and after subsequent 12 months of treatment decreased to 1.91 (SD: 2.64),
- INCAT – after 12 months of treatment, the average INCAT score was 14.7 (SD: 17.2), and after 24 months of treatment, 12.9 (SD: 24.4),
- change in MRC muscle power – the mean score after 12 months of treatment was 43.9 (SD: 27.2), and after subsequent 12 months of treatment: 56.6 (SD: 28.8),
- ODSS – a reduction of the mean ODSS score (3.3 (SD: 6.4) vs 2.9 (SD: 6.0)) was reported between 12 and 24 months of treatment.

- neurophysiological parameters: a decrease in the percentage of nerve segments covered by conduction blocks or a decrease in the percentage of nerve segments with absent sensory action potential between 12 and 24 months of SCIg therapy.

Cocito 2014

Results of the study on CIDP patients indicate a slight improvement in MRC and ONLS performance assessment in the SCIg arm as compared to the IVIg arm.

In the extension phase of the study (published in Cocito 2016), the main analysed endpoint was the patient adherence percentage, whereas the results were presented collectively for CIDP and MMN patients.

In Cocito 2014 (and the extension phase to that study, published in Cocito 2016), a general increase in the quality of life measured using LQI after changing from IVIg to SCIg treatment was observed.

Safety

No deaths were reported in the studies (PATH and ICE) included in the clinical analysis.

SCIg vs IVIg indirect comparison

As part of an indirect comparison conducted using PLC, no statistically significant differences in the risk of adverse events leading to exclusion of patients receiving SCIg (in either dose) from the study as compared to patients receiving IVIg were observed.

Summary of results

Adverse events: total

In the PATH study, any treatment-requiring adverse events occurred in 58% of patients receiving a lower dose of Hizentra (the 0.2 g arm) and in 52% of patients receiving a higher dose of Hizentra (the 0.4 g arm). Severe adverse events occurred in 3 patients (5%) from the low-dose arm and in 2 patients (3%) from the high-dose arm. Severe treatment-related adverse events occurred in 2 patients in total (1 in either treatment arm).

The most common adverse events, occurring in at least 5% of patients treated with Hizentra in the PATH study include general disorders and site reactions, contagions or infections, as well as injection site reactions.

In the ICE study, the safety analysis was presented for all IVIg treatment phases (stabilisation and maintenance) with the exception of the endpoint for which an indirect comparison was carried out. Therefore, this analysis presents only results regarding the safety for IVIg taken from the ICE studying the scope of the indirect comparison.

Additional safety information

No alerts on the safety of use of Hizentra 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 Hizentra, very common adverse reactions (≥1/10) include: headache, rash and musculoskeletal pain (including muscle spasm). Common adverse reactions (≥1/100 to <1/10) include: dizziness, hypertension, diarrhoea, abdominal pain, nausea, vomiting, arthralgia, fever, fatigue (including malaise), chest pain and flu-like symptoms.

Some adverse reactions may be more common in patients who are administered human normal immunoglobulin for the first time, or in rare situations when this product is replaced by another treatment or treatment is discontinued for more than eight weeks.

Limitations of the analysis

The following aspects impact the reliability of the clinical analysis:

- no studies which directly compare the drug in question (SCIg) with its comparator (IVIg) have been identified. Therefore, on the basis of identified RCTs comparing SCIg with PLC and IVIg with PLC, an indirect comparison was conducted using the Bucher method and a common comparator (PLC). It should be kept in mind that indirect comparisons are characterised by limitations resulting from the adopted methodology;
- the indirect comparison was conducted only for two endpoints (risk of CIDP relapse and adverse events leading to withdrawal from the trial). In the case of the other endpoints (including i.a. quality of life), the comparison was not possible due to the different manner of result presentation. The studies included in the analysis did not assess survival ratios;
- results of single-arm studies should be interpreted with caution due to the possible transfer of treatment effects from the previous use of IVIg;
- The two RCTs – PATH and ICE – differ in terms of population and study methodology. It should be noted that in the period between the commencement of both trials, international CIDP diagnostic criteria (EFNS/PNS 2010) were developed, which might result in different assessments of disease severity in the study subjects.
- lack of high-quality evidence on the efficacy of the drug in question in the paediatric population, which can also be eligible for the proposed drug programme. Only adult patients were enrolled into the two RCTs: PATH and ICE. Patients < 18 years of age took part only in one, single-arm study (Cocito 2014).

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

- in some of the studies, some patients used SCIg in a 16%, and not 20% solution. Cocito 2014 does not provide information on whether the administered subcutaneous immunoglobulin was indeed Hizentra.

Proposals of risk-sharing schemes

No risk-sharing scheme was proposed.

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 conducted an economic analysis using the cost-minimisation analysis (CMA), comparing SCIg (Hizentra) with IVIg products reimbursed under the B.67 drug programme "Immunoglobulin infusion treatment in neurological disorders".

The estimates include the public payer's perspective (the National Health Fund) and the common perspective (the NHF and the patient), which is identical to the payer's perspective due to the proposed reimbursement terms (drug programme, drug available to the patient free of charge).

The analysis was conducted in a one-year time horizon.

[*information protected as a trade secret*].

In line with the applicant's estimations, the use of SCIg (Hizentra) instead of IVIg [*information protected as a trade secret*].

For the purpose of estimating the net ex-factory price at which the cost of using Hizentra would equal the cost of using IVIg [*information protected as a trade secret*].

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The applicant carried out a one-way, deterministic sensitivity analysis [*information protected as a trade secret*].

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Limitations of the analysis

In view of the available data, the selection of CMA as the analytic technique should be deemed justified.

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AOTMiT's own calculations

For the purpose of estimating the net ex-factory price at which the cost of using Hizentra would equal the cost of using IVIg [*information protected as a trade secret*].

As part of the AOTMiT's estimations, the net ex-factory price for Hizentra was calculated under Article 13 paragraph 3, with regard to immunoglobulins administered intravenously in the lowest price offered in a tender. The net ex-factory price calculated in that manner is [*information protected as a trade secret*].

The net ex-factory prices for specific packages of Hizentra are as follows:

- Hizentra, 1 vial of 50 ml – [*information protected as a trade secret*];
- Hizentra, 1 vial of 10 ml – [*information protected as a trade secret*];
- Hizentra, 1 vial of 20 ml – [*information protected as a trade secret*];
- Hizentra, 1 vial of 5 ml – [*information protected as a trade secret*];

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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)

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.

Pursuant to Article 13 paragraph 3 of the Act on reimbursement, the statutory ex-factory price of a drug must be calculated in a way ensuring that the cost of using the drug which is the subject of the reimbursement application is not higher than the cost of the health technology, as per the act on healthcare services, previously financed from public funds, characterised by the greatest cost-effectiveness ratio. In view of the above provision, threshold prices should be calculated with regard to the lowest-priced IVIg product [*information protected as a trade secret*].

As part of the AOTMiT's estimations, the net ex-factory price for Hizentra was calculated under Article 13 paragraph 3, with regard to immunoglobulins administered intravenously in the lowest price offered in a tender. The net ex-factory price calculated in that manner is [*information protected as a trade secret*].

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 impact of a positive reimbursement decision on the healthcare system budget regarding subcutaneous human normal immunoglobulin (SCIg) (Hizentra) in immunomodulatory therapy in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilisation obtained with immunoglobulins administered intravenously (IVIg) under a drug programme financed from public funds in Poland.

The analysis was carried out from the perspective of the NHF. Given the lack of patients' co-payment for the health technology in question, the common perspective (the NHF and the patient) is identical to the public payer's perspective.

The estimations were carried out in a 2-year time horizon.

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The number of patients eligible for the technology was estimated to be [*information protected as a trade secret*].

Results of the budget impact analysis indicate that in the case of a positive reimbursement decision regarding Hizentra [*information protected as a trade secret*] from the NHF's perspective will be approx. [*information protected as a trade secret*] in the first year and approx. [*information protected as a trade secret*] in the second year of reimbursement.

The applicant's sensitivity analysis includes one-way sensitivity analyses.

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Limitations of the analysis

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

The NHF data indicate that the population of CIDP patients eligible for SCIg treatment might be greater than assumed by the applicant. The applicant's starting point was the actual number of patients treated under the drug programme on immunoglobulin infusion treatment in neurological disorders in 2014 specified in an appendix to AOTMiT's 2014 analysis, i.e. 200 patients. According to NHF data, 3,465-4,637 patients a year were qualified for the B.67 programme, including between 313 and 367 patients diagnosed with ICD-10 G61.8 (other inflammatory polyneuropathies) and between 2,165 and 3,098 patients diagnosed with ICD-10 G62.8 (other specified polyneuropathies). According to the applicant's analyses, CIDP is classified under both ICD codes. From among patients with the above diagnoses, 484, 611 and 616 patients received human immunoglobulins in the subsequent years, which suggests that the starting point for estimating the population size should be presented as higher than in the applicant's variant, taking into account the maximum estimation of the actual number of patients treated under the drug programme on immunoglobulin infusion treatment in neurological disorders in 2014 specified in an appendix to the AOTMiT's 2014 analysis, i.e. 400 patients. At the same time it should be kept in mind that [*information protected as a trade secret*]. The results of the maximum population scenario as estimated by the applicant suggest [*information protected as a trade secret*] in the first year and [*information protected as a trade secret*] in the second year of the analysis. Adopting a mean number of CIDP patients treated in Poland under the drug programme (mean calculated based on the above-mentioned NHF data) results in [*information protected as a trade secret*] in the amount of [*information protected as a trade secret*] in the first year and [*information protected as a trade secret*] in the second year of the analysis.

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Remarks on the proposed risk-sharing instrument

Given the findings of the clinical analysis suggesting a similar therapeutic effect of using SCIg and IVIg, the costs of both therapies should be similar. According to the President of the AOTMiT, the assumptions of the conducted analysis favour SCIg, [*information protected as a trade secret*]. For that reason, financing of the technology in question is justified on condition that the price of Hizentra equals the cost of the cheapest intravenous immunoglobulins or that an appropriate risk-sharing scheme which would result in the reduction of treatment costs is introduced.

Remarks on the drug programme records

In line with opinions of clinical experts, including the following remarks in the drug programme is suggested:

- regarding the introduction of a monitoring scheme which would assume less frequent follow-up visits and less frequent diagnostic tests;
- establishing the rules of exercising care over patients participating in the programme in outpatient – home settings. According to an expert, the proposed drug programme should limit patients' visits in the neurological clinic (up to 1-2 a year) and eliminate patient hospitalisations in hospital wards;
- creating a mobile system of acquiring data on the course of the disease and creating a national, expert-supervised register of patients treated under the programme.

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.

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

The search resulted in the identification of 5 clinical guidelines regarding treatment of chronic inflammatory demyelinating polyneuropathy, including Polish guidelines:

- American Academy of Allergy, Asthma & Immunology AAAAI 2017 (USA);
- American Society for Apheresis ASA 2016 (USA);
- American Academy of Neurology AAN 2012 (USA);
- European Federation of Neurological Societies/Peripheral Nerve Society EFNS/PNS 2010 (Europe);
- Stępień 2011 Expert group position on the intravenous use of immunoglobulins in the treatment of the nervous system disorders (Poland).

None of the identified guidelines mention subcutaneous immunoglobulins (SCIg) as a therapeutic option in treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). Only the Polish guidelines mentioned that "there is certain hope with regard to subcutaneous administration of immunoglobulins in multifocal motor neuropathy (MMN)", i.e. a different indication than the currently assessed indication, while authors of the AAAAI 2017 guidelines mention SCIg as an alternative to IVIg in autoimmune, inflammatory and neuromuscular disorders. At the same time it should be underlined that the identified guidelines were published prior to Hizentra obtaining marketing authorisation in the indication in question.

Intravenous immunoglobulins (IVIg), corticosteroids or plasmapheresis is recommended as first-line treatment of CIDP patients. The identified guidelines indicate similar effectiveness of those therapies, however IVIg treatment is associated with a higher quality of life (AAAAI 2019). Additionally, EFNS/PNS 2010 guidelines point to worse tolerability of plasmapheresis. In the event of treatment failure, immunosuppressive and immunomodulating drugs (rituximab, cyclosporin, interferon, azathioprine, cyclophosphamide, methotrexate) are used in the next treatment line.

Furthermore, the conducted search identified 1 positive recommendation published by the French Haute Autorité de Santé (HAS) in 2019, regarding stabilisation treatment using Hizentra in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Authors of the recommendation have determined that the clinical benefit of using this drug in treatment of CIDP is high. However, they underlined that no clinical benefit over intravenous immunoglobulin therapy (Clairyg, Octagam, Privigen, Tegeline) in the indication in question has been demonstrated.

In line with the information presented by the applicant, Hizentra:

- is currently reimbursed in 5 ml, 10 ml and 20 ml vials in 8 out of 31 UE and EFTA member states, however none of those states has a GDP per capita similar to that of Poland,
- is currently reimbursed in a 50 ml vial in 4 out of 31 UE and EFTA member states, however none of those states has a GDP per capita similar to that of Poland.

Risk-sharing schemes are not used for the technology in question in any country reimbursing that product.

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 13/11/2019 (reference number: PLR.4600.857.2019.14.RB, PLR.4600.858.2019.14.RB, PLR.4600.859.2019.14.RB, PLR.4600.860.2019.14.RB), on preparing a recommendation of the President of the AOTMiT on reimbursement of Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, vial of 50 ml, EAN: 05909991067380; Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 20 ml per vial, EAN: 05909990869657; Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 5 ml per vial, EAN: 05909990869541; Hizentra, Human normal immunoglobulin (SCIg), solution for subcutaneous injection, 200 mg/ml, 10 ml per vial, EAN: 05909990869572, in the indication: under the following drug programme: "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)", 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. 10/2020 of 27 January 2020 on the evaluation of Hizentra (human normal immunoglobulin (SCIg)) under the drug programme "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)".

References

1. Position of the Transparency Council No. 10/2020 of 27 January 2020 on the evaluation of Hizentra (human normal immunoglobulin (SCIg)) under the drug programme "Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)".
2. Reimbursement application for Hizentra (human normal immunoglobulin) in the indication: »Immunoglobulin infusion treatment in neurological disorders (ICD-10: G61.8, G62.8, G63.1, G70, G04.8, G73.1, G73.2, G72.4, G61.0, G36.0, M33.0, M33.1, M33.2)«. Verification analysis No. OT.4331.64.2019; completion date: 17 January 2020