Recommendation No. 100/2019

of 08 November 2019

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

on whether to reimburse Signifor (pasireotide) under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)"

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

- Signifor (pasireotide), powder and solvent for suspension for injection, 10 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 07613421022365;
- Signifor (pasireotide), powder and solvent for suspension for injection, 20 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 05909991200305;
- Signifor (pasireotide), powder and solvent for suspension for injection, 30 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 07613421022372;
- Signifor (pasireotide), powder and solvent for suspension for injection, 40 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 05909991200312,

under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)" **provided that** the conditions offered in the risk-sharing scheme are enhanced.

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, has concluded that financing of the health technology in question from public funds is justified provided that the conditions offered in the risk-sharing scheme (RSS) are enhanced.

The efficacy and safety analysis of the assessed technology in the indication as specified in the application was based on 1 randomised study – Lacroix 2018 – evaluating pasireotide (PAS) administered intramuscularly at doses of 10 mg and 30 mg. In addition, Fleseriu 2019, a study

presenting the results from the open-ended, extension phase to study NCT01374906 (described in Lacroix 2018), was identified.

Furthermore, to compare the results for pasireotide and active comparators in terms of treatment-response endpoints, 4 observational studies concerning cabergoline (CAB) were included in the analysis: Ferriere 2017, Godbout 2010, Vilar 2010, Pivonello 2009, as well as 3 observational studies concerning ketoconazole (KET): Castinetti 2008, Castinetti 2014 and Esponosa des los Monteros 2017.

The results of the primary phase of Lacroix 2018 demonstrated that, in month 7, the total response to treatment was observed in approx. 40% of patients taking pasireotide, in month 12 – in 35% of patients from the PAS 10 mg arm and in 25% of patients from the PAS 30 mg arm, whereas in month 24 – in 23% of patients taking PAS in 10 mg or 30 mg doses.

At the same time, the total response to treatment for a 6-month follow-up was observed in 25-37% of patients in the observational studies on cabergoline, while for a 12-month follow-up, that percentage ranged between 40% and 50% and remained at 40% for a 24-month follow-up. In the case of observational studies on ketoconazole, for the 24-month follow-up, the total response to treatment occurred in 49% to 93% of patients, depending on the study.

In addition, a statistically significant change in favour of pasireotide in the assessment of quality of life measured using the CushingQoL against the baseline value was observed in Lacroix 2018. Furthermore, in patients taking pasireotide, a reduction of the ACTH plasma level as compared with the baseline values, a reduction of night salivary cortisol level and cortisol plasma level as compared with baseline values, as well as a reduction of the pituitary tumour volume by ≥20% in month 12 of follow-up in 43% of patients taking PAS in the 10 mg dose and 27% of patients taking PAS in the 30 mg dose, and a change of the tumour by<20% in 49% and 42% of patients, respectively, were observed.

The most common adverse events reported in the safety analysis included: hyperglycaemia, diarrhoea, cholelithiasis, diabetes and nausea.

The main limitation of the reliability of the clinical analysis is the lack of direct pasireotide vs. ketoconazole and pasireotide vs. cabergoline comparisons, as well as the lack of possibility of carrying out an indirect comparison. Furthermore, it was also not possible to compare the technology in question with metyrapone, which also constitutes a comparator for pasireotide.

The economic analysis was carried out using the cost-utility analysis (CUA) and cost-consequence analysis (CCA). In line with the results of the CCA, the use of PAS allows for achieving 11.30 QALY, whereas the use of KET, MET and CAB allows for achieving only 10.56 QALY, 10.09 QALY and 10.33 QALY, respectively. Due to the reservations as to the legitimacy of carrying out the CUA, its results should not constitute grounds for the decision taken.

The budget impact analysis conducted from the NHF's perspective indicates that, assuming that some of the patients do not receive active treatment, a positive reimbursement decision for pasireotide will result in *[information protected as a trade secret]*At the same time, the estimates might not reflect the actual costs, i.a. due to the adopted estimates of the population size; therefore, enhancing of the conditions offered in the risk-sharing scheme included in the applicant's proposal is recommended.

Subject of the application

The order of the Minister of Health concerns assessing whether the following medicinal products should be financed from public funds:

- Signifor (pasireotide), powder and solvent for suspension for injection, 10 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 07613421022365, for which the proposed net ex-factory price amounts to *[information protected as a trade secret]*
- Signifor (pasireotide), powder and solvent for suspension for injection, 20 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 05909991200305, for which the proposed net ex-factory price amounts to *[information protected as a trade secret]*
- Signifor (pasireotide), powder and solvent for suspension for injection, 30 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 07613421022372, for which the proposed net ex-factory price amounts to *[information protected as a trade secret]*
- Signifor (pasireotide), powder and solvent for suspension for injection, 40 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, EAN: 05909991200312, for which the proposed net ex-factory price amounts to *[information protected as a trade secret]*

under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)".

The proposed payment and reimbursement availability category: a free-of-charge drug available as part of the drug programme, within the existing 1174.0 Pasireotide limit group. The applicant has proposed a risk-sharing scheme.

Health problem

The Cushing's Syndrome is a condition associated with clinical symptoms resulting from the excess of corticosteroids in the patient's body. The excess of the hormone may be:

- endogenous – it covers all cases of excessive secretion of corticosteroids by the adrenal glands, regardless of the cause of this disorder. Endogenous disorders are divided into:
    - dependant on ACTH (secondary adrenal hyperfunction) – the following types are distinguished:
        - pituitary form (excessive production of ACTH by the pituitary gland) called the Cushing's disease;
        - ectopic ACTH secretion syndrome caused by a tumour developed outside the pituitary gland;
        - ectopic corticoliberin secretion syndrome;
    - ACTH-independent, as a form of suprarenal hyperfunction (primary adrenal hyperfunction);
- exogenous – caused by the use of corticosteroids.

Cushing's disease is the most common form of Cushing's syndrome, its aetiology is endogenous.

Hypercortisolaemia, typical of Cushing's disease, has a significant impact on the functioning of the entire body. The excessive cortisol level causes metabolic syndrome, obesity, diabetes, dyslipidaemia, hypertension, myopathy, hirsutism, osteoporosis and mental disorders. These disorders have a significant impact on the quality of life and everyday functioning of patients.

Cardiovascular disorders are among the main causes of poor prognosis in Cushing's disease. They are associated with abnormal functioning of the cardiovascular system and changes in its structure.

One of the more serious disorders accompanying CD is osteoporosis. Both mild and severe hypercortisolaemia affects the condition of bones, which leads to reduced osteoblast activity,

increased osteoclast activity and disorders of calcium absorption. It is estimated that more than 40% of CD patients suffer from spinal and pelvic osteopenia, whereas 70% of patients with Cushing's disease experience bone fractures due to osteoporosis caused by an excessive cortisol level.

Chronic excessive levels of cortisol affect also the smooth operation of the immune system. Patients with Cushing's disease are at risk for difficult-to-treat bacterial and fungal infections.

Cushing's disease is strongly associated with anxiety disorders and depression. It is estimated that depression occurs five times more frequently in the CD patient population than in the general population.

Untreated Cushing's disease carries a very high risk of death – 50% of patients who have not undergone effective treatment die within 5 years following the diagnosis. The most common causes of death include cardiovascular diseases (stroke and heart attack), untreated diabetes and difficult-to-treat infections of the body.

The prevalence of Cushing's disease in the European population is estimated to be 30/1 million, with an annual incidence of 23/1 million or 1-10/1 million. The peak onset is between 20 and 30 years of age. Women suffer from this disease 4-8 times more often than men.

According to the EMA's data, the prevalence of Cushing's disease is 0.9 per 10,000 inhabitants in the European population.

Alternative health technologies

On the basis of the identified guidelines, in addition to pasireotide, ketoconazole-, cabergoline- and metyrapone-based therapies are also used to treat Cushing's syndrome or disease.

In line with the opinions of clinical experts, the drugs used to treat patients with Cushing's disease, other than pasireotide, include ketoconazole, cabergoline, metyrapone, mitotane, etomidate, cabergoline, bromocriptine and mifepristone. In addition, other possibilities indicated by experts include radiotherapy, surgical treatment, as well as lack of active treatment.

Pursuant to the announcement of the Minister of Health of 30 August 2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices (Official Journal of the Minister of Health of 2019, item 65), no medicinal products indicated in Cushing's disease are reimbursed in Poland.

The applicant indicated ketoconazole, cabergoline and metyrapone as an alternative technology to Signifor (pasireotide). The above-mentioned medicinal products are not financed from public funds. Furthermore, due to their limited availability in Poland, in the Agency's opinion, lack of active treatment (BSC, Best Supportive Care) should also constitute a comparator.

Description of the proposed intervention

The active substance of Signifor is pasireotide; it is administered by intramuscular injection in the form of suspension for injection (the packaging contains powder and solvent for suspension for injection).

Pasireotide (PAS) is a somatostatin analogue. Like the natural peptide hormones, somatostatin-14 and somatostatin-28 (also known as somatotropin release-inhibiting factor [SRIF]) and other somatostatin analogues, pasireotide's pharmacological activity consists in binding to somatostatin receptors.

The indications of Signifor included in its marketing authorisation are as follows:

- treatment of adult patients with acromegaly for whom surgery is not an option or was unsuccessful and who are inadequately controlled by treatment with another somatostatin analogue;
- treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

In both indications, i.e. acromegaly and Cushing's syndrome, the drug has orphan drug status.

The indication included in the application corresponds to the indication specified in the drug's marketing authorisation. In line with the criteria of the drug programme in question, the drug is to be used in adult patients for whom surgery is not an option or for whom surgery has failed**.**

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 assessment of efficacy and safety of pasireotide was based on one randomised study: Lacroix 2018 – a phase III multi-centre, triple-blind clinical trial aimed at assessing the efficacy and safety of pasireotide (intramuscular administration) in patients with Cushing's disease. 150 patients were recruited to the study; 74 patients were included in the PAS 10 mg arm and 76 patients – in the PAS 30 mg arm. The follow-up was 12 months. The risk of bias in most domains assessed in line with the Cochrane Collaboration was deemed low. It was impossible to assess the "blinding of outcome assessment" domain.

What is more, the following were included in the analysis:

- observational studies concerning cabergoline:
    - Ferriere 2017 – retrospective, multi-centre study assessing cabergoline as monotherapy and cabergoline in combination therapy with steroidogenesis inhibitors. 62 patients were included in the study, of whom 9 received cabergoline in combination with steroidogenesis inhibitors. The median follow-up was 7 months. The quality score of the study was estimated at 7 out of 8 on the NICE scale;
    - Godbout 2010 – retrospective, multi-centre, international study assessing cabergoline in 30 patients with Cushing's disease. The follow-up was 6 months. The quality score of the study was estimated at 7 out of 8 on the NICE scale;
    - Vilar 2010 – prospective study in which, during the first six months, 12 patients with persistent Cushing's disease were given cabergoline, then 9 patients in whom normalisation of the UFC (urinary free cortisol) level was not achieved were given cabergoline in combination with ketoconazole for another 6 months. The follow-up was 6 months. The quality score of the study was estimated at 7 out of 8 on the NICE scale;
    - Pivonello 2009 – prospective study assessing cabergoline in 20 patients with persistent Cushing's disease. The follow-up was 24 months. The quality score of the study was estimated at 7 out of 8 on the NICE scale;
- observational studies concerning ketoconazole:
    - Espinosa-de-los-Monteros 2017 – retrospective study assessing ketoconazole in patients with endogenous Cushing's syndrome. 84 patients were included in the study. In the subgroup of 13 patients using KET in second-line treatment, the median therapy period was 26 months. The quality score of the study was estimated at 6 out of 8 on the NICE scale;

- Castinetti 2008 – retrospective study assessing ketoconazole. 38 patients with Cushing's disease were included in the study. The median follow-up was 23 months, and the median therapy period in the subgroup of patients who underwent surgery was 22.9 months. The quality score of the study was estimated at 6 out of 8 on the NICE scale;
- Castinetti 2014 – retrospective study. In the study, out of 200 patients, 160 (80%) used ketoconazole, including 31 as first-line treatment due to contraindications or lack of consent for surgical treatment, 93 (58.1%) as second-line treatment after ineffective surgery and 35 (21.9%) patients to reduce hypersecretion while awaiting surgery. The median therapy period was 24.8 months. The quality score of the study was estimated at 6 out of 8 on the NICE scale.

In addition, the results of Fleseriu 2019 – extension phase to NCT01374906 (published in Lacroix 2018) – were presented. Median pasireotide treatment period was 23.9 months. Patients with mUFC (median urinary free cortisol) level equal to or lower than upper limit of normal or who benefited clinically in the baseline study and who were able to continue treatment in the extension phase of the study, participated in the extension phase (N=81).

The quality-of-life outcomes were related to assessment using the following scales:

- CushingQoL scale – Cushing's Quality of Life questionnaire. The score in the questionnaire ranges from 0 (the worst) to 100 (the best). The assessment was made at baseline, and in months 2,4,7,10 and 12. Minimal relevant difference (MRD) is a change in relation to baseline that amounts to 10.1 points.
- The SF 12v2 (The 12-item Short Form General Health Survey version 2) questionnaire – an abridged quality-of-life assessment questionnaire consisting of 12 questions, version 2. In the analysis in question, mental component summary (MCS) and physical component summary (PCS) were assessed. Minimal relevant difference (MRD) is the change in relation to baseline that amounts to 3.0 points.

Efficacy

The analysis of the results for pasireotide (PAS) and its active comparators (CAB, KET) in terms of the frequency of occurrence of response to treatment based on mUFC (mean urine free cortisol) level demonstrated:

- the mean urinary free cortisol level equal to or less than the upper limit of normal, regardless of the previous change in dosing, was reported (Lacroix 2018):
  - in month 7 of follow-up:
    - in 41.9% of patients taking PAS 10 mg;
    - in 40.8% of patients taking PAS 30 mg;
  - in the month 12 of follow-up:
    - in 35.1% of patients taking PAS 10 mg;
    - in 25.0% of patients taking PAS 30 mg;
- the mean urinary free cortisol level equal to or less than the upper limit normal without previous reduction in dosing in month 7 of follow-up was reported (Lacroix 2018):
  - in 28.4% of patients taking PAS 10 mg;
  - in 31.6% of patients taking PAS 30 mg;

- the mean urinary free cortisol level equal to or less than the upper limit of normal and the reduction of mUFC level as compared to baseline level equal to or higher than 50% was reported:
    - in month 7 of follow-up (Lacroix 2018):
        - in 5.4% of patients taking PAS 10 mg;
        - in 13.2% of patients taking PAS 30 mg;
    - in month 12 of follow-up in 7.5% of patients taking CAB (Ferriere 2017);
    - in month 24.8 of follow-up (mean time) in 24.8% of patients taking KET (Castinetti 2014);
- the mean urinary free cortisol level equal to or lower than the upper limit of normal was reported:
    - in the month 6 of follow-up:
        - in 36.6% of patients taking KAB (Godbout 2010);
        - in 25.0% of patients taking KAB 2.0- 3.0 mg/week (Vilar 2010);
    - in month 12 of follow-up:
        - in 50% of patients taking KAB (Pivonello 2009);
        - in 39.6% of patients taking KAB (Ferriere 2017);
    - in month 24 of follow-up in 40% of patients taking CAB (Pivonello 2009);
    - in the month 22.9 of follow-up (mean time) in 58.8% of patients taking KET (Castinetti 2008);
    - in the month 24.8 of follow-up (mean time) in 49.4% of patients taking KET (Castinetti 2014);
    - in the month 26 of follow-up (median) in 93.3% of patients taking KET (Espinoza-de-los-Monteros 2017);

The analysis of the results concerning lack of response to treatment demonstrated that the mean urinary free cortisol level higher than the upper limit of normal in month 12 of follow-up was reported:

- in the arm of patients with total response to treatment in month 7 of follow-up (Lacroix 2018):
    - in 19.4% of patients taking PAS 10 mg;
    - in 41.9% of patients taking PAS 30 mg;
- in the arm of patients with no response to treatment in month 7 of follow-up (Lacroix 2018):
    - in 41.9% of patients taking PAS 10 mg;
    - in 48.9% of patients taking PAS 30 mg;
- in 52.8% of patients taking CAB (Ferriere 2017).

In Lacroix 2018, a statistically significant change in patients taking pasireotide was observed in favour of pasireotide in the assessment of quality of life measured using the CushingQoL questionnaire (mean score change as compared with the baseline value):

- in month 7 of follow-up:
    - the average change was 5.7 points (95%Cl: 1.4; 10.0) in the arm taking PAS 10 mg (clinically insignificant change);

  - the average change was 7.8 points (95%CI: 1.4; 10.0) in the arm taking PAS 30 mg (clinically insignificant change);
- in the month 12 of observation:
  - the average change was 6.4 points (95%CI: 1.4; 10.0) in the arm taking PAS 10 mg (clinically irrelevant change);
  - the average change was 7.0 points (95%CI: 1.4; 10.0) in the arm taking PAS 30 mg (clinically irrelevant change);

Furthermore, Lacroix 2018 also observed an improvement in the quality of life assessed according to MCS of the Sf12v2 questionnaire where the mean change as compared to the baseline value for both PAS arms in total exceed the set MRD of 3.0 points in months 4 and 7 of the study (clinically relevant change). No improvement has been observed in the physical component summary (PCS).

The results of Lacroix 2018 relating to the ACTH (adrenorticotropic hormone) level demonstrate that, in patients taking pasireotide, a reduction of ACTH level in plasma as compared to the baseline value was observed (no information on the clinical relevance of observed changes is available).

Furthermore, in Lacroix 2018, the following was observed in patients taking pasireotide:

- reduction of the ACTH level in plasma as compared to the baseline values (no information on the clinical relevance of observed changes is available);
- reduction of the late-night salivary cortisol level and cortisol level in plasma as compared to the baseline values (no information on the clinical relevance of observed changes is available);
- higher incidence of late-night salivary cortisol level values within the normal level as compared to baseline values (no information on the clinical relevance of the observed changes is available);
- in approx. 90% of patients, an improvement or no change in the clinical symptoms of Cushing's disease were observed;
- in month 7 of the study, an improvement of the parameters evaluating the clinical symptoms of Cushing's disease, which in most cases lasted until month 12 of the study, was observed;
- the percentage of patients with the reduction of pituitary tumour by ≥20% in month 12 amounted to:
  - 42.9% of patients taking PAS 10 mg;
  - 47.4% of patients taking PAS 30 mg;
- the percentage of patients with the change of pituitary tumour by <20% in month 12 amounted to:
  - 48.6% of patients taking PAS 10 mg;
  - 42.1% of patients taking PAS 30 mg.
- the reduction of the median tumour size as compared to the baseline value:
  - in month 7 of follow-up:
    - by 12% in the arm of patients taking PAS 10 mg;
    - by 11.4% in the arm of patients taking PAS 30 mg;
  - in month 12 of follow-up:
    - by 17.8% in the arm of patients taking PAS 10 mg;
    - by 16.3% in the arm of patients taking PAS 30 mg.

Safety

The results of Lacroix 2018 concerning safety in the 12-month follow-up demonstrated that:

- two deaths have been reported in patients receiving pasireotide at a dose of 30 mg;
- any adverse events were reported:
    - in 98.6% of patients taking PAS 10 mg;
    - in 100% of patients taking PAS 30 mg;
- serious adverse events were reported:
    - in 28.4% of patients taking PAS 10 mg;
    - in 22.4% of patients taking PAS 30 mg;
- as regards adverse events related to pasireotide, the following were reported:
    - in 7.3% of patients – reactions associated with a potential risk of an allergic reaction/immunogenicity;
    - In 2% of patients – adrenal insufficiency;
    - In 2.7% of patients – anaemia;
- as regards the adverse events with a suspected relation to pasireotide, the following were reported:
    - serious adverse events with a suspected relation to the drug in question in total:
        - in 10.8% of patients taking PAS 10 mg;
        - in 5.3% of patients taking PAS 30 mg;
    - in 93.3% of patients – serious adverse events with a suspected relation to the drug in question in total;
    - in 46.7% of patients – hyperglycaemia;
    - in 32% of patients – diarrhoea;
    - in 31.3% of patients – cholelithiasis;
    - in 20.7% of patients – diabetes;
    - in 14.7% of patients – nausea;
    - in 11.3% of patients – abdominal pain;
    - in 10% of patients – fatigue;

Additional safety and efficacy information

NCT01374906 demonstrated:

- the mUFC level higher than the upper limit of normal was achieved in 51.9% of patients;
- In month 24, the mUFC level was controlled in 64.3% of patients;
- the mUFC level was controlled in 72.2% of patients treated in the month 36 of the study.
- Among 35 patients with a measurable tumour at baseline and in month 24 of treatment, a reduction of the tumour size by ≥20% was observed in 34.2% of patients and by <20% – in 51.4% of patients;

- the adverse events occurred in 91.4% of patients, of which grade 3 or 4 adverse events were reported in 38.3% of patients;
- The most frequently reported adverse events were: hyperglycaemia (23.5%), nasopharyngitis (19.8%), cholelithiasis (18.5%) and diarrhoea (17.3%);
- one death due to cardiovascular causes has been reported (the death was deemed to be unrelated to treatment).

Additional safety information

In line with the summary of product characteristics (SPC) for Signifor, the following adverse events were observed following intramuscular administration:

- very common (≥ 1/10): metabolism and nutrition disorders: hyperglycaemia and diabetes; gastrointestinal disorders: diarrhoea, nausea, abdominal pain; hepatobiliary disorders: cholelithiasis; general disorders and administration site conditions: fatigue;
- common (≥ 1/100 to < 1/10): blood and lymphatic system disorders: anaemia; endocrine disorders: adrenal insufficiency; metabolism and nutrition disorders: type 2 diabetes, glucose tolerance impaired, decreased appetite; nervous system disorders: headache, dizziness; cardiac disorders: sinus bradycardia (the term covers both bradycardia and sinus bradycardia), QT prolongation; gastrointestinal disorders: flatulence, vomiting; hepatobiliary disorders: cholecystitis (the term covers cholecystitis, including acute and chronic cholecystitis), cholestasis; skin and subcutaneous tissue disorders: alopecia, pruritus; general disorders and administration site conditions: injection site reaction (the term covers: pain at injection site, nodule at injection site, discomfort at injection site, bruise at injection site, pruritus at injection site, reaction at injection site, hypersensitivity at injection site, as well as oedema at injection site); investigations: elevated glycosylated haemoglobin, elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated gamma-glutamyltransferase, elevated blood glucose, elevated blood creatine phosphokinase, elevated lipase;
- Uncommon (≥ 1/1,000 to < 1/100): investigations: elevated amylase, prolonged prothrombin time.

In line with the Summary of Product Characteristics for Signifor, these data were presented on the basis of studies concerning pasireotide administered intramuscularly in patients with acromegaly and Cushing's disease.

A notice for the period January-March 2019 concerning the possibility of ketoacidosis in patients treated with pasireotide was identified on the FDA's (Food and Drug Administration) website.

[information protected as a trade secret]

No additional safety information for the technology in question was identified on the websites of the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL) or the European Medicines Agency (EMA).

Limitations

The following aspects impact the reliability of the analysis:

- the pasireotide vs. ketoconazole and pasireotide vs. cabergoline comparisons were carried out solely by means of a qualitative comparison of results. Despite taking into account the best currently available scientific evidence, this comparison was drawn up on the basis of a randomised study (PAS) and observational studies for the comparators and is only of a qualitative nature. Therefore, drawing conclusions based on the above-mentioned comparison is subject to high risk;

- the observation periods in the studies concerning ketoconazole were presented as mean/medians and some patients have been undergoing this therapy for a longer period of time, thus drawing conclusions may be subject to significant risk of overestimating the extent of the health effect achieved in this patient group;
- the results concerning the response to treatment in the studies concerning comparators are subject to high risk of overestimation due to the difference in reporting of data in PAS vs. studies on the comparators;
- the analysis does not include a safety assessment for ketoconazole;
- no studies on metyrapone have been identified, therefore the efficacy and safety of PAS cannot be compared to this comparator;
- no studies on effectiveness which meet the inclusion criteria for the review have been identified.

The uncertainty of the analysis is impacted by:

- the fact that a collation of the safety results for pasireotide and cabergoline does not take into account hyperglycaemia which was reported in nearly half of the patients administered pasireotide in Lacroix 2018. Hyperglycaemia was not included in the list of adverse events which occurred in observational studies in patients administered cabergoline, which suggests that it affects only a small percentage of patients;

Proposals of risk-sharing schemes

The following solution was proposed as a 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 implementation of a new therapy and comparing them to the costs and effects of already reimbursed therapies allow to answer the question whether the health effect achieved as a result of a new therapy is associated with higher costs in comparison to already reimbursed therapies.

The achieved results of the health cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. A result which indicates that the wealth of our country (expressed in GDP), the maximum cost of a new therapy that should be associated with obtaining a unit health effect (1 LYG or 1 QALY), compared to treatments already available, should not exceed a triple of GDP per capita.

The estimated 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 economic assessment of the technology in question was carried out using a cost-utility analysis (CUA) and a cost-consequence analysis (CCA). The public payer's perspective and common perspective (the public payer and the patient) were taken into consideration. The *[information protected as a trade secret]* horizon, corresponding to life-long time horizon, was adopted.

The following costs were taken into account in the economic model: costs of drugs, costs of drug administration, costs of treatments, costs of qualification for treatment in the drug programme, costs of monitoring, costs of treating adverse events and complications, costs of co-morbidities.

Discounting in the amount of 5% for costs and 3.5% for health effects was taken into account.

In line with the results of the CCA, the use of PAS allows for achieving 11.30 QALY *[information protected as a trade secret],* whereas in the case of using KET, MET and CAB it is possible to achieve 10.56 QALY, 10.09 QALY and 10.33 QALY, respectively.

Results of the CCA demonstrated that the total cost of therapy amounts to:

- PAS therapy:
    - from the NHF's perspective *[information protected as a trade secret]* with the RSS *[information protected as a trade secret]* without the RSS);
    - from the common perspective – *[information protected as a trade secret]* with the RSS *[information protected as a trade secret]* without the RSS);
- KET therapy:
    - from the NHF's perspective – *[information protected as a trade secret]*
    - from the common perspective – *[information protected as a trade secret]*
- MET therapy:
    - from the NHF's perspective – *[information protected as a trade secret]*
    - from the common perspective – *[information protected as a trade secret]*
- CAB therapy:
    - from the NHF's perspective – *[information protected as a trade secret]*
    - from the common perspective – *[information protected as a trade secret]*

In line with the results of the CUA, from the NHF's perspective, the use of pasireotide in place of the comparator is *[information protected as a trade secret]*

The value of the incremental cost utility ratio (ICUR) from the NHF's perspective amounts to:

- for the PAS vs. KET comparison – *[information protected as a trade secret]*
- for the PAS vs. MET comparison – *[information protected as a trade secret]*
- for the PAS vs. CAB comparison – *[information protected as a trade secret].*

The estimated value of the ICUR is *[information protected as a trade secret]* of the cost-effectiveness threshold referred to in the Act on reimbursement.

From the common perspective, the results concerning the PAS vs. KET and PAS vs. CAB comparisons also demonstrate that using PAS in place of the comparators is *[information protected as a trade secret]* – ICUR was *[information protected as a trade secret]* in the variant with the RSS and *[information protected as a trade secret]* in the variant without the RSS. The values are *[information protected as a trade secret]* of the cost-effectiveness threshold referred to in the Act on reimbursement. In turn, for the PAS vs. MET comparison, the intervention in question is a therapy *[information protected as a trade secret]* in the variant without the RSS – ICUR is *[information protected as a trade secret]* and is below the cost-effectiveness threshold referred to in the Act on reimbursement. However, in the variant with the RSS, PAS is a therapy *[information protected as a trade secret]* than MET.

The results of threshold analysis demonstrate that from the common perspective, the net ex-factory price at which the ICUR would be equal to the cost-effectiveness threshold, compared to KET amounts to *[information protected as a trade secret]*, compared to MET *[information protected as a trade secret]*, however compared to CAB it amounts to *[information protected as a trade secret]* for each of the Signifor presentations.

The conducted sensitivity analysis has demonstrated the following:

- CCA:

[information protected as a trade secret]

- CUA:

[information protected as a trade secret]

Limitations

The economic analysis is based on the clinical analysis carried out by the applicant and therefore it should be assumed that the limitations relating to that analysis apply also to the economic assessment.

Since there are no studies which directly compare the intervention in question with comparators and it is not possible to make an indirect comparison, and thus it is impossible to reliably assess the efficacy and safety of PAS vs. KET, MET and CAB, limiting the economic analysis to the CCA only would be more appropriate.

Furthermore, the reliability of the application on the basis of the presented results is affected by the fact that:

- a life-long time horizon was adopted in the model, which is the correct approach. However, due to the lack of long-term data, the estimates in the life-long time horizon are subject to uncertainty;
- in Lacroix 2018, which constitutes the basis for information on efficacy, the patients were given doses of 10mg and 30mg, but the efficacy of 20mg and 40mg doses was not tested;
- the clinical analysis does not provide scientific evidence on the efficacy and safety of MET; thus the economic analysis is not based on clinical analysis as regards the health effects
- the prices of comparators adopted in the model were based on data obtained from pharmaceutical wholesalers. In addition, the study does not provide the names of medicinal products whose prices were used to estimate the cost of KET and MET therapies. Therefore, their verification was not possible;
- The analysis did not conduct a comparison with the lack of active treatment (with simultaneous use of the best supportive treatment (BSC)), which would correspond better to the Polish clinical practice.

In addition, in the context of the reliability of the CUA results, attention should also be paid to the results of the economic analysis enclosed in the application for KET reimbursement (AWA Ketoconazole HRA 2018), according to which KET is a dominant therapy (cheaper and more efficacious) than PAS, whereas KET was compared with PAS administered as subcutaneous injections twice per day.

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 apply (Journal of Laws of with 2019 item 784 as amended)

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 official selling price of the drug that must be calculated in such a way that the cost of using the drug applied for reimbursement is not higher than the cost of medical technology with the most favourable ratio of health effects to the cost of obtaining them.

The circumstances referred to in Article 13 of the Act on reimbursement do not apply in the present case.

Analysis of the effects on the healthcare system, including budget impact analysis (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 Signifor (pasireotide, PAS), used in the treatment of adults with Cushing's disease for whom surgery is not an option or for whom surgery has failed, is reimbursed, was carried out from the public payer's (National Health Fund, NHF) perspective and the common perspective (public payer and patient). The estimations were carried out in a life-long time horizon. The number of patients was estimated at *[information protected as a trade secret]* in the first year of reimbursement and approx. *[information protected as a trade secret]* in the second year of reimbursement.

The costs of drugs and their administration, the costs of treatment (reoperation of the pituitary gland, bilateral adrenalectomy, radiotherapy), costs of treating adverse events and complications, costs of treating co-morbidities, costs of qualification for the drug programme, as well as the costs of treatment monitoring (within the drug programme and beyond it) were taken into account in the analysis.

The results of the basic budget impact analysis indicate that, if Signifor is reimbursed, the public payer's expenditure will increase by:

- in the variant not taking the RSS into account:
  - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
  - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;
- in the variant taking the RSS into account:
  - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
  - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;

In the common perspective, total expenditure in the target population will increase in the variant not taking the RSS into account by *[information protected as a trade secret]* in the first year of reimbursement and by *[information protected as a trade secret]* in the second year of reimbursement. After a risk-sharing scheme is introduced, expenditure will decrease by *[information protected as a trade secret]* and by *[information protected as a trade secret]* *[information protected as a trade secret]* in the first and second year of reimbursement, respectively, which constitutes *[information protected as a trade secret]* change in the public payer's current expenditure.

The results of the sensitivity analysis indicate that the incremental expenditure will amount to:

- from the NHF's perspective:
    - in the minimum scenario:
        - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
        - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;
    - in maximum scenario:
        - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
        - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;
- from the common perspective:
    - in minimum scenario:
        - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
        - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;
    - in maximum scenario:
        - approx. PLN *[information protected as a trade secret]* in the first year of reimbursement;
        - approx. PLN *[information protected as a trade secret]* in the second year of reimbursement;

The sensitivity analysis also indicated that, in the variant which includes the public payer's perspective, both taking into account the RSS and not taking it into account, the change of parameters and the choice of the alternative scenario will not impact the conclusions drawn from the analysis. *[information protected as a trade secret]*

Furthermore, the sensitivity analysis demonstrated, that, assuming *[information protected as a trade secret]* of patients do not receive active treatment, a positive decision to reimburse pasireotide will result in *[information protected as a trade secret]* In the AOTMiT's opinion, the above results are the most reliable.

Limitations

The uncertainty associated with the estimation of the target population constitutes the main limitation of the analysis. In line with the opinion of clinical expert, the percentage of individuals who meet the inclusion criteria for the drug programme and in whom the drug in question would actually be used is approx. 70-80%. The population size in which Signifor will be used, adopted in the model, constitutes *[information protected as a trade secret]* of the target population estimated by the applicant. It may indicate a certain underestimation of the number of patients to be included in the drug programme.

In addition, the model includes the costs calculated using the model applied in the economic analysis. Therefore, the limitations of the economic analysis apply also to the budget impact analysis.

In addition, the reliability of the analysis is influenced by the fact that:

- active treatment (BSC) was not included among the comparators in the basic analysis. The results of the sensitivity analysis, assuming that some patients do not receive active treatment, seem to be more reliable;
- *[information protected as a trade secret]*

- according to the received expert opinion, due to financial reasons, less than 5% of patients with Cushing's disease currently use pharmacotherapy. The regional consultant estimated that the percentage of patients who do not use active treatment amounts to approx. 50% and should Signifor become reimbursed, "in most cases, inclusion in pharmacotherapy will occur". It is also worth noting that, according to one of the experts surveyed by the applicant, only complications (e.g. hypertension, osteoporosis and diabetes) are treated in approx. 50% of patients from the target population;
- the sensitivity analysis took into account the variant in which the average percentage of patients using pharmacotherapy without normalisation was used, and in which it was conservatively assumed that *[information protected as a trade secret]*

Remarks on the proposed risk-sharing instrument

[information protected as a trade secret]

Remarks on the drug programme stipulations

The expert's comments on the particular parts of the programme are as follows:

- testing during qualification for treatment – "test of visual fields in the case of pituitary macroadenoma (tumour diameter ≥ 1 cm)" should be required if the tumour occurs at the optic chiasma in the MRI examination;
- treatment monitoring – it was assumed that "after 6 and 12 months from the beginning of treatment, an MRI examination of the hypothalamo-hypophyseal complex. Starting from the second year of treatment, this examination should be carried out every 12 months, or immediately after new scotomata appear, and in the case of macroadenoma (tumour of >10 mm), every 6 months during the entire treatment period". The expert pointed out that in patients with invisible focal lesion in the MRI of pituitary gland, such frequent MRI checks are not necessary;
- inclusion criteria – carrying out INR and albumin tests is also suggested.

Furthermore, the drug programme does not specify whether it is possible to re-include patients who have completed treatment with pasireotide under the drug programme in question in line with exclusion criteria. The clinical experts indicate the possibility of re-inclusion of patients such as: patients with compression at optic chiasma following the neurosurgical decompression therapy; patients following surgical treatment of symptomatic cholelithiasis; after thyroid function compensation, achieving diabetes control in total in approx. 10% of patients.

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 in the analysed indications.

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, in which it is assumed that *[information protected as a trade secret].* The generated savings would cover the maximum incremental expenditure of the public payer resulting from the reimbursement of Signifor.

However, it should be underlined that sufficient justification has not been provided regarding the possibility of implementing the proposed solution in practice. Therefore, it can be concluded that the presented solution partially does meet the formal requirements, although it will probably not be implemented in practice.

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

The following 4 clinical guidelines on therapeutic treatment in patients with Cushing's disease have been identified:

- National Comprehensive Cancer Network (NCCN) 2019 (USA);
- Endocrine Society (ES) 2015 (USA);
- European Registry on Cushing's Syndrome (ERCUSYN) 2018 (Europe);
- European Society of Endocrinology (ESE) 2018 (Europe).

The American guidelines ES 2015 recommend cabergoline and pasireotide as pharmacological treatment directly affecting the secretory function of pituitary tumours in patients with Cushing's disease (CD) in whom surgery is impossible or for whom surgery has failed. The NCCN 2019 guidelines for the treatment of benign tumours recommend following the ES 2015 guidelines. The European ERCUSYN 2018 guidelines identify these therapies as still in the research phase. According to the European ESE guidelines, pasireotide is the only drug registered for the treatment of Cushing's disease which targets the secretory function of pituitary tumours. In the American ES 2015 guidelines, attention was drawn to the risk of hyperglycaemia in patients taking pasireotide.

The search also identified two recommendations on using pasireotide administered intramuscularly in Cushing's disease – one negative: HAS (Haute Autorite De Sante) 2018 for Signifor in that route of administration (and maintaining the positive recommendations issued for Signifor administered subcutaneously in 2012 and 2015), and HAS 2019 maintaining its 2018 the recommendation.

What is more, a notice was identified that in 2017, the All Wales Medicines Strategy Group (AWMSG) did not recommend using pasireotide administered intramuscularly (powder and solvent for suspension for injection) in the treatment of Cushing's disease in patients in whom surgery of pituitary tumour is impossible or for whom surgery has failed due to the MAH's failure to submit the application.

[information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 21/08/2019 (reference number: PLR.4600.803.2019.4.MN; PLR.4600.804.2019.4.MN; PLR.4600.805.2019.4.MN; PLR.4600.806.2019.4.MN), with regard to preparation of the recommendation of the President of the AOTMiT on whether to reimburse Signifor (pasireotide), powder and solvent for suspension for injection, 10 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter; Signifor (pasireotide), powder and solvent for suspension for injection, 20 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter; Signifor (pasireotide), powder and solvent for suspension for injection, 30 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter; Signifor (pasireotide), powder and solvent for suspension for injection, 40 mg, vial of powder + 1 pre-filled syringe, 2 ml of solvent + 1 needle + 1 vial adapter, 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. 102/2019 of 04 November 2019 on the evaluation of Signifor (pasireotide) under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)"

References

1. The Position of the Transparency Council No. 102/2019 of 04 November 2019 on the evaluation of Signifor (pasireotide) under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)"
2. Report No. OT.4331.47.2019 "Reimbursement application for Signifor (pasireotide) to be available under the following drug programme: "Treatment of Cushing's disease (ICD-10 E24.0)". Completion date: 25 October 2019.