Recommendation No. 14/2021

of 12 February 2021

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

on the assessment of Ozempic (semaglutide) for the indication:

type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m^2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking

The President of the Agency recommends the inclusion of the medicinal product Ozempic (semaglutide) in the reimbursement for the indication: type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m^2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking, **provided that** (trade secret)

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, considers the public financing of the technology applied for to be justified **provided that** (trade secret)

The indication covered by the order is included in the registration indication of the medicinal product Ozempic (semaglutide), at the same time the drug is currently on the list of reimbursed medicines and is financed in the (narrower than requested) population of patients with type 2 diabetes before insulin initiation, treated with at least two oral hypoglycaemic drugs for at least 6 months, with HbA1c ≥ 8%, with obesity defined as BMI ≥35 kg/m^2 and very high cardiovascular risk.

The results of clinical analysis, which indicate that the use of semaglutide in patients with type 2 diabetes significantly reduces HbA1c level and body weight compared to both placebo used together with insulin, metformin, and SGLT-2 inhibitors, were also taken into account.

It is undoubtedly a limitation that the available scientific evidence on which the application is based is not completely validated, mainly the lack of results of studies for the specific subpopulation of patients with type 2 diabetes indicated in the reimbursement application. This limitation is the primary reason

why it is justified to seek to equate the cost of Ozempic therapy to the cost of therapy with the cheapest of the SGLT-2 inhibitors.

Estimates in the economic analysis indicating that (trade secret) were taken into account. On the other hand, the results of the applicant's budget impact analysis indicate (trade secret)

The opinion also notes that most of the clinical indications recommend the use of GLP-1 receptor agonists in obese patients and in the presence or risk of cardiovascular co-morbidities. GLP-1 receptor agonists can also be used in further stages of treatment in the indications: two-drug therapy, three-drug therapy, and simple and combined insulin therapy.

Taking into account the above arguments, but also the proposed price of the requested technology, it seems reasonable to provide reimbursement for Ozempic (semaglutide) **provided that** (trade secret)

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public financing of a medicinal product:

- Ozempic, Semaglutidum, solution for injection using an injector, 0.25 mg, 1, 1.5 ml injector + 4 NovoFine Plus needles, EAN code: 05909991389901, net selling price (trade secret)
- Ozempic, Semaglutidum, solution for injection using an injector, 0.5 mg, 1, 1.5 ml injector + 4 NovoFine Plus needles, EAN code: 05909991389918, net selling price (trade secret)
- Ozempic, Semaglutidum, solution for injection using an injector, 1 mg, 1, 3 ml injector + 4 NovoFine Plus needles, EAN code: 05909991389956, net selling price (trade secret)

Proposed reimbursement payment and dispensing category: (trade secret), a drug available in a pharmacy by prescription for an indication defined by a clinical condition, in an existing joint-limit group.

(trade secret)

Health problem

Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from a defect in insulin secretion and/or activity. Chronic hyperglycaemia is associated with damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.

Type 2 diabetes is classified as E11 in the ICD 10 classification (Noninsulin-dependent diabetes mellitus), which includes the following disease entities:

- Diabetes mellitus (without obesity) (with obesity): adult-onset; young adult-onset (MODY); without ketosis; stable; type 2.
- noninsulin-dependent growth-onset diabetes

The prevalence of type 2 diabetes in Poland is about 9% in the population between 20 and 79 years of age. The annual incidence in Poland is estimated to be about 200/100,000 people. Age of onset is generally > 30 years. The incidence increases with age until 70 years of age, while it decreases above this age. The mortality rate in Poland is about 15/100,000 persons, while in the population > 75 years of age it rises up to 120/100,000 persons. 70% of deaths are due to cardiovascular complications.

The most important predictor is cardiovascular complications. Despite the important role of diabetes in the development of cardiovascular disease, when it occurs, hypoglycaemic treatment is not as effective as hypertension treatment. Therefore, the importance of early recognition of pre-diabetic state and prevention of diabetes is emphasised. Better glycaemic control in early diabetes has been shown to reduce the risk of myocardial infarction and death. Furthermore, hypoglycaemic treatment significantly reduces the risk of nephropathy, even in patients with advanced cardiovascular disease.

Alternative health technology

Given the clinical guidelines and currently publicly funded technologies, SGLT-2 (sodium-glucose cotransporter 2) inhibitors and placebo (insulin therapy adjustment) were identified as comparators for the technology in question.

It should be noted that these comparators partially reflect current clinical practice. Apart from SGLT-2 inhibitors and insulin therapy, dulaglutide can be considered an additional comparator.

Description of the benefit named in the application

Ozempic contains semaglutide, which acts as a GLP-1 receptor agonist; it selectively binds to the GLP-1 receptor by activating it, which is similar to native GLP-1. GLP-1 is a physiological hormone that demonstrates a considerable number of effects in terms of the regulation of appetite and blood sugar levels, as well as effects on cardiovascular function. Its effects on blood sugar levels and appetite are related to GLP-1 receptors in the pancreas and brain.

According to the Summary of Product Characteristics (SmPC), Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications,
- in addition to other medicinal products for the treatment of diabetes.

The indication applied for is included in the registration indication.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the assessment of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

The target population in the analyses consists of patients with type 2 diabetes treated with at least metformin±sulphonylurea derivative or basal insulin±metformin with baseline HbA1c ≥8%, BMI ≥ 30 kg/m^2 and a very high cardiovascular risk.

The following primary studies were included in the clinical analysis:

- SUSTAIN-5 – a randomised controlled trial that directly compares semaglutide (SEM) administered subcutaneously with placebo (PLA) plus (in both arms): insulin (INS) or insulin + metformin (INS + MET): SEM + INS ± MET vs PLA + INS ± MET;
- SUSTAIN 6 – a randomised controlled trial that compared the use of semaglutide administered subcutaneously with placebo plus (in both arms): standard treatment: 0-2 antihyperglycemic agents ± insulin, in a population of adult patients with type 2 diabetes with a high cardiovascular risk (as part of additional scientific evidence): SEM + 0-2 OAD ± INS vs PLA + 0-2 OAD ± INS. The trial assessed the effect of the intervention on the cardiovascular system.

No studies were found directly comparing the use of semaglutide in the analysed doses with the use of SGLT-2 inhibitors (in doses reimbursed in Poland), after the failure of metformin ± sulfonylurea derivative therapy.

A comparison between semaglutide and SGLT-2 inhibitors is based on the results of a published network meta-analysis:

- Kanters 2019 - A systematic review with network meta-analysis evaluating the efficacy of subcutaneously administered semaglutide compared with SGLT-2 inhibitors in a population of adult patients with type 2 diabetes with inadequate glycaemic control previously treated with 1-2 oral antidiabetic drugs.

In addition, 6 additional secondary sources were included in the analysis (Li 2018, Witkowski 2018, Avgerinos 2019, Zhu 2019, CADTH 2019, Hussein 2020).

The following primary endpoints were assessed in the primary studies:

- change in HbA1c over 30 weeks (SUSTAIN 5);
- time from randomisation to the first *major adverse cardiovascular event* (MACE): death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6).

The SUSTAIN 5 trial assessed the quality of life using the questionnaire: SF-36v2 and overall treatment satisfaction using the Diabetes Treatment Satisfacion Questionnaire (DTSQ).

The reliability of the SUSTAIN-5 trial was assessed using the JADAD scale criteria. The resulting score is 5 points. The quality of the Kanters 2019 review was assessed to be poor according to the AMSTAR quality rating scale.

Efficacy

SUSTAIN 5

Among patients with type 2 diabetes, statistically significantly greater reductions in glycated haemoglobin levels were observed in the SEM 0.5 mg and 1 mg groups used together with MET and INS after 30 weeks of treatment: HbA1c, fasting plasma glucose levels: FPG, plasma glucose by self-measurement: SMPG, body weight, BMI and waist circumference, and a greater reduction in postprandial glycaemic spikes compared with the group receiving PLA together with MET and INS:

- SEM 0.5 mg vs PLA (INS adjustment):
    - HbA1c: MD=-1.35 p.p . [95% CI: -1.61; -1.10], p<0.0001; MD=-14.79 mmol/mol [95% CI: -17.54; -12.03], p<0.0001;
    - FPG: MD=-1.14 [95%CI: -1.75; -0.54], p=0.0002;
    - SMPG: MD=-1.76 [95%CI: -2.32; -1.19], p<0.0001;
    - Post-meal glycaemic spikes: MD=-0.66 [95%CI: -1.10; -0.23], p=0.003;
    - Body weight: MD=-2.31 kg [95%CI: -3.33; -1.29], p<0.0001;
    - BMI: MD=-0.84 kg/m2 [95%CI: -1.20; -0.49], p<0.0001;
    - Waist circumference: MD=-1.46 cm [95%CI: -2.83; -0.09], p=0.0365.
- SEM 1 mg vs PLA (INS adjustment):
    - HbA1c: MD=-1.75 p.p . [95% CI: -2.01; -1.50], p<0.0001; MD= -19.18 mmol/mol [95% CI: -21.95; -16.42], p<0.0001;
    - FPG: MD=-1.88 [95%CI: -2.48; -1.28], p<0.0001;
    - SMPG: MD=-2.28 [95%CI: -2.84; -1.72], p<0.0001;
    - Post-meal glycaemic spikes: MD=-1.01 [95%CI: -1.44; -0.58], p<0.0001;
    - Body weight: MD=-5.06 kg [95%CI: -6.08; -4.04], p<0.0001;
    - BMI: MD=-1.82 kg/m2 [95%CI: -2.18; -1.47], p<0.0001;
    - Waist circumference: MD=-4.05 cm [95%CI: -5.42; -2.67], p<0.0001.

The SEM 1 mg group used together with MET and INS also had a statistically significant greater increase in heart rate and a statistically significant greater reduction in systolic blood pressure (SBP) values after 30 weeks of treatment compared to the group receiving PLA together with MET and INS:

- SBP: MD=-6.29 mmHg [95% CI: -9.91; -2.66], p=0.0007;
- Heart rate: MD=4.74 bpm [95% CI: 2.48; 7.01], p<0.0001.

In addition, the Rodbard 2018 publication (SUSTAIN 5 trial) reported in subpopulations separated by their baseline HbA1c, that the change in HbA1c relative to the baseline:

- in patients with baseline HbA1c≤8% taking SEM 0.5 mg, SEM 1 mg, and PLA together with MET and INS was respectively: -0.88% (SD, 0.94); -1.32% (SD, 0.71), and -0.04% (SD, 0.98);

- in patients with baseline HbA1c≥8% taking SEM 0.5 mg, SEM 1 mg and PLA together with MET and INS was respectively: -1.83% (SD, 1.00), -2.19% (SD, 0.86), and -0.28% (SD, 1.12).

In addition, post-hoc subgroup analysis indicated greater weight reduction in patients treated with semaglutide in comparison to placebo:

- in patients taking SEM 0.5 mg together with MET and INS with a baseline BMI between 30-35 kg/m2: -3.6 kg (absolute weight change from baseline) vs - 1.0 kg in the PLA group; with baseline BMI≥35 kg/m2: -3.9 kg (SEM 0.5 mg) vs -2.3 kg (PLA),
- in patients taking SEM 1 mg together with MET and INS and a baseline BMI in the range of 30-35 kg/m2: - 6.6 kg (absolute weight change from baseline) vs - 1.0 kg in the PLA group; with baseline BMI≥35 kg/m2: -7.5 kg (SEM 1 mg) vs -2.3 kg (PLA).

Evaluation of overall satisfaction with treatment and quality of life

In the SEM 0.5 mg and SEM 1 mg groups, a statistically significantly greater improvement in overall treatment satisfaction as assessed by the DTSQ specific questionnaire was observed after 30 weeks of treatment in comparison with PLA. For the quality of life assessed by the SF-36v2 questionnaire, no statistically significant differences were observed between the groups.

SUSTAIN-6

In comparison with PLA, treatment with semaglutide reduced the risk of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke by 26%:

- HR=0.74 [95%CI: 0.58; 0.95], p<0.001.

In addition, statistically significantly greater reductions in HbA1c and body weight were observed with respect to the average baseline values in the semaglutide 0.5 mg and 1 mg groups compared to the placebo group after 104 weeks of treatment.

Network meta-analysis of Kanters 2019

The use of semaglutide at doses of 0.5 mg and 1 mg was associated with statistically significant greater reductions in HbA1c, fasting glucose levels and body weight reduction than the use of SGLT-2 inhibitors (canagliflozin - CANA, empagliflozin - EMPA, and dapagliflozin - DAPA) in patients with type 2 diabetes:

SEM vs SGLT-2

- HbA1c:
  - SEM 0.5 mg vs CANA: MD=-0.45% [95%CI: -0.68; -0.21], p<0.05;
  - SEM 0.5 mg vs EMPA: MD=-0.53% [95%CI: -0.80; -0.27], p<0.05;
  - SEM 0.5 mg vs DAPA: MD=-0.55% [95%CI: -0.78; -0.29], p<0.05;
  - SEM 1 mg vs CANA: MD=-0.71% [95%CI: -0.92; -0.48], p<0.05;
  - SEM 1mg vs EMPA: MD=-0.79% [95%CI: -1.04; -0.53], p<0.05;
  - SEM 1 mg vs DAPA: MD=-0.80% [95%CI: -1.02; -0.57], p<0.05;
- fasting glucose levels:
  - SEM 0.5 mg vs CANA: MD=-0.35 mmol/L [95%CI: -0.68; -0.01], p<0.05;
  - SEM 0.5 mg VS EMPA: MD=-0.46 mmol/L [95%CI: -0.86; -0.07], p<0.05;
  - SEM 0.5 mg vs DAPA: MD=-0.64 mmol/L [95%CI: -1.01; -0.28], p<0.05;
  - SEM 1 mg vs CANA: MD=-0.78 mmol/L [95%CI: -1.10; -0.46], p<0.05;
  - SEM 1 mg VS EMPA: MD=-0.90 mmol/L [95%CI: -1.27; -0.53], p<0.05;
  - SEM 1 mg vs DAPA: MD=-1.08 mmol/L [95%CI: -1.42; -0.73], p<0.05;

- weight reduction:
    - SEM 0.5 mg vs CANA: MD=-0.62 kg [95%CI: -1.22; -0.01], p<0.05;
    - SEM 0.5 mg VS EMPA: MD=-0.88 kg [95%CI: -1.53; -0.23], p<0.05;
    - SEM 0.5 mg vs DAPA MD=-0.80 kg [95%CI: -1.42; -0.18], p<0.05;
    - SEM 1 mg vs CANA: MD=-1.98 kg [95%CI: -2.56; -1.40], p<0.05;
    - SEM 1 mg VS EMPA: MD=-2.24 kg [95%CI: -2.86; -1.61], p<0.05;
    - SEM 1 mg vs DAPA MD=-2.17 kg [95%CI: -2.75; -1.57], p<0.05.

The odds of HbA1c<7% were over 4.07, 2.53, and 2.70/5.52, 3.43, and 3.66 times higher in the SEM 0.5mg/SEM 1 mg group, compared to the group receiving canagliflozin, empagliflozin, and dapagliflozin, respectively.

Avgerinos 2019, Hussein 2020, Li 2018, Witkowski 2018, CADTH 2019, Zhu 2019

The results of the efficacy analysis of the other reviews are consistent with the results of the SUSTAIN 5 trial and also show, among other things, the efficacy of semaglutide in reducing HbA1c levels and body weight in patients with type 2 diabetes, but it should be noted that they also relate, among other things, to the same trials that were included in the clinical analysis.

Safety

SUSTAIN-5

The results of the safety analysis of SUSTAIN-5 indicate that moderate-to-severe and mild adverse events were statistically significantly more frequent (1.75 and 1.71 times, respectively) in the SEM 0.5 mg group compared to PLA used together with MET and INS (SUSTAIN-5). In contrast, adverse events leading to treatment discontinuation, vomiting and diarrhoea were statistically significantly more frequent in the SEM 1 mg group than PLA used together with MET and INS (8.59, 4.17 and 4.83 times more frequent, respectively). Nausea was statistically significantly more frequent in both the SEM 0.5 mg and 1 mg groups used together with MET and INS compared to PLA used together with MET and INS.

The percentage of patients who discontinued treatment was comparable in all groups analysed in the trial.

SUSTAIN-6

The results of SUSTAIN-6 on the safety of semaglutide in a population at high cardiovascular risk indicate that the use of semaglutide compared with placebo administered together with 0–2 OAD ± insulin statistically significantly increased the risk of complications of retinopathy, this event occurred in 3% and 1.8% of patients in the SEM and placebo groups, respectively.

There were no statistically significant differences in the semaglutide treated group compared with placebo when assessing the risk of death from any cause, death from a cardiovascular cause, non-fatal myocardial infarction, hospitalisation for unstable angina pectoris and hospitalisation for heart failure.

Kanters 2019

Safety outcomes were not presented due to the reporting of safety endpoints for SEM and SGLT2 inhibitors at different periods.

The authors of the meta-analysis indicate that the two groups of drugs differ in their safety profile due to the type of adverse events reported, which makes a reliable comparison in terms of the safety of drugs from these groups difficult.

Limitations

The main limitation of the reliability of the presented analysis is the fact that the analyses of efficacy and safety concern the general population of patients with diabetes. No results were extracted for the population indicated in the reimbursement application, i.e. patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30kg/m^2 and with very high cardiovascular risk defined as confirmed cardiovascular disease or damage to other organs

manifested by proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 for men, ≥ 60 for women, dyslipidaemia, hypertension, smoking.

In addition, the uncertainty of the presented results of the clinical analysis is affected by the following limitations, among others:

- no studies were found directly comparing the use of semaglutide at the doses analysed with the use of SGLT-2 inhibitors after the failure of metformin ± sulphonylurea derivative therapy;
- in SUSTAIN-5, the baseline proportion of patients with HbA1c ≥ 8% was 37% in each arm of the study; in the remaining patients, HbA1c < 8%;
- in SUSTAIN-5, the inclusion criteria do not take into account confirmed very high cardiovascular risk; therefore, it is unknown what proportion of patients in the trial corresponds to the population named in the application in terms of this parameter;
- in SUSTAIN-5, the baseline BMI of the patients includes a wider group than the population named in the application;
- based on the Kanters 2019 network meta-analysis, it was not possible to assess the safety of semaglutide compared to SGLT-2 inhibitors.

Proposed risk-sharing schemes

(trade secret)

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

The costs of therapy are estimated in the currency of our country, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

The cost-effectiveness evaluation included a cost-utility analysis (CUA) over a lifetime horizon (50 years), from the perspective of the public payer - the entity required to fund the benefits with public funds, i.e. the National Health Fund (NFZ) and from the shared perspective of the payer and the beneficiary.

The following differential medical costs were included in the analysis:

- Ozempic;
- comparators, i.e. canagliflozin, empagliflozin and dapagliflozin;
- oral antidiabetic drugs, i.e. metformin and sulphonylurea derivative (glimepiride);
- insulin and insulin therapy needles;
- lances and diabetes test strips
- treatment of diabetic complications.

The results are presented for two subpopulations:

- patients treated ineffectively with ≥ 2 OADs;
- patients treated ineffectively with basal insulin in combination with ≥ 1 OAD.

(trade secret)

Limitations

The following aspects of the economic model, among others, influenced the uncertainty of the presented results:

- lack of RCTs directly comparing the technology under assessment with comparators (SGLT-2 inhibitors);
- lack of placebo-compared studies (insulin therapy adjustment) in the defined target population;
- in the population of patients treated ≥ 2O AD compared to SGLT-2 inhibitors, canagliflozin was used as a comparator in the primary analysis due to the best numerical clinical results in terms of HbA1c reduction in the group of SGLT-2 inhibitors. The other SGLT-2 inhibitors (empagliflozin and dapagliflozin) were included only in the sensitivity analysis;
- semaglutide at 0.25 mg was not included;
- a narrow range of safety data on semaglutide treatment was considered;
- the design of the presented model precludes its complete verification (no possibility to edit input data/track calculations);
- (trade secret).

Agency's own calculations

Additional own calculations were carried out to estimate threshold prices in relation to the current profitability threshold of PLN 155,514/QALY.

(trade secret)

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended);

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

In the absence of a demonstration of the superiority of semaglutide therapy over reimbursable alternative therapy in the population named in the application, in a randomised clinical trial, the circumstances referred to in Art. 13 sec. 3 of the Reimbursement Act.

(trade secret)

Assessment of the impact on the healthcare system, including the impact on the budget of the public payer

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

Estimates of expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating a health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources to treat a given health problem or is associated with savings in the payer's budget.

A budget impact assessment determines whether a payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The results of the applicant's budget impact analysis are presented over a two-year horizon. The analysis was conducted from a public payer (NHF) and a shared payer perspective.

The analysis included:

- cost of active substances (semaglutide, insulin, metformin, sulphonylurea derivative),
- insulin administration costs (needle costs),
- blood glucose monitoring costs (cost of test strips and lancets).

The applicant has estimated the number of patient-years i.e. full 12-month treatments to be:

- (trade secret)

The results of the base-line analysis indicate that including Ozempic (semaglutide) in the reimbursement for the indication named in the application will entail (trade secret)

Limitations

The uncertainty in the results presented is affected by the inability to accurately estimate the proportion of patients using Ozempic (semaglutide) in the target population. Available data on the number of patients with coexisting diabetes and obesity do not allow to estimate future sales of the medicinal product in the indication named in the application. At the same time, data from the NFZ indicate that the market share of the assessed technology has not yet stabilised.

Because the reimbursement indication of semaglutide partially covers the population already treated with the assessed drug (i.e. patients with HbA1c ≥ 8% and BMI ≥ 35 kg/m^2 and very high cardiovascular risk), this population was omitted from the analysis indicating that it is already "drug-secure". However, it should be noted that given this, the public payer's expenditure in the entire population covered by the reimbursement in the indication named in the application was not determined.

Agency's own calculations

No additional own calculations were performed.

Comments on the proposed risk-sharing scheme

(trade secret)

Comments on the drug programme

Not applicable.

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on reimbursement of the health technology named in the application.

A rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding shows an increase in reimbursement costs.

(trade secret)

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

Twelve clinical recommendations related to the indication named in the application were found, issued by:

- Polish Diabetes Association (PTD 2020);
- European Society of Cardiology and European Association for the Study of Diabetes (ESC/EASD 2019);

- National Institute for Health and Care Excellence (NICE 2020);
- World Health Organisation (WHO 2020);
- American Diabetes Association (ADA 2020);
- American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE 2020);
- Australian Diabetes Society (ADS 2020);
- American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD 2019);
- American College of Physicians (ACP 2017/2018);
- Diabetes Canada (DC 2018);
- Scottish Intercollegiate Guidelines Network (SIGN 2017);
- International Diabetes Federation (IDF 2017).

Recommendations agree on the basic principles of type 2 diabetes treatment. The basis for improvement of health status is non-pharmacological treatment – body weight reduction, increasing physical activity. The primary oral first-line medication for the treatment of type 2 diabetes remains metformin. All recommendations indicate that the choice of drug should take into account concomitant conditions.

Most of the above guidelines refer to the possibility of using GLP-1 receptor agonists in obese patients.

According to the current Polish PTD 2020 guidelines, the first-line treatment in diabetes is metformin monotherapy, and if metformin is ineffective, it is recommended to add an SGLT-2 inhibitor, incretin-based drug (DPP-4 inhibitor or GLP-1 receptor agonist), sulphonylurea derivative or PPAR-ɣ agonist. After treatment with two antiglycaemic drugs has failed, three-drug therapy with metformin (always) and two other drugs with different mechanisms of action (SGLT-2 inhibitors, GLP-1 receptor agonists, sulphonylurea derivatives, acarbose, DPP-4 inhibitors, PPAR-ɣ agonist) is recommended. It is also possible to include metformin with basal insulin.

BMI was referenced in two recommendations – SIGN and NICE.

SIGN recommends GLP-1 in patients with a body mass index ≥ 30 kg/m^2 in combination with oral glucose-lowering drugs or basal insulin (or both) as third- or fourth-line therapy when adequate glycaemic control has not been achieved with these drugs. In contrast, NICE recommends the use of a GLP-1 receptor agonist when three-drug therapy with other drugs is ineffective, intolerant or contraindicated, in combination with metformin and a sulphonylurea derivative in patients with BMI ≥ 35 kg/m^2 or other obesity-related health problems or BMI < 35 kg/m^2, and for patients in whom insulin therapy would have significant work-related consequences, or weight loss would benefit other significant obesity-related comorbidities.

The guidelines found also address the role of GLP-1 receptor agonist therapy in the presence or risk of cardiovascular comorbidities.

In addition, GLP-1 receptor agonists also find a place in downstream treatment in two- (PTD, SIGN, AACE/ACE) and tree-drug therapy (PTD, AACE/ACE) and simple and combined insulin therapy (PTD, AACE/ACE 2020, ADS 2020, SIGN 2017) in the recommendations found. GLP-1 receptor agonist therapy should also be considered an alternative to insulin in patients in whom combination treatment with oral glucose-lowering drugs has been insufficient (SIGN 2017). The ADA 2021 guidelines also indicate that a GLP-1 agonist is preferred to insulin.

Only 2020 WHO recommendations do not refer to the use of GLP-1 receptor agonists in diabetes therapy. The recommendations only stated that if further treatment was needed, specialist consultation was recommended.

Reimbursement recommendations

Four favourable recommendations were found: SMC 2019, TLV 2018, ZIN 2018, and two conditionally favourable: CADTH 2019 and PBAC 2019. In addition, AWMSG 2018 and HAS 2019 recommendations were found, which were favourable in the parts concerning the use of SEM in selected combination therapies and unfavourable for SEM in monotherapy. The HAS 2019 recommendation was unfavourable also for the combination of SEM with insulin.

The favourable recommendations mainly point out that SEM is not less effective compared to dulaglutide. All favourable reimbursement recommendations are for indications narrower than the registration indication and include the use of SEM in a two- or three-drug combination. Of the five recommendations relating to earlier

insulin use, four were favourable (SMC 2019, AWMSG 2018, TLV 2018, ZIN 2018) and one was unfavourable (HAS 2019).

Most recommendations do not address use in patients with a specific BMI, except for HAS 2019 and ZIN 2018. HAS concluded that the medicinal product Ozempic combined with metformin, with or without sulphonylurea derivatives (SUL), can be considered as an additional alternative for the treatment of type 2 diabetes in patients with BMI ≥30 kg/m^2. The ZIN 2018 recommends SEM for patients with BMI ≥ 30 kg/m^2 after unsuccessful three-month treatment with optimally adjusted dose basal insulin in combination with metformin, with or without SUL, at the highest tolerated doses. The ZIN 2018 introduced an additional restriction of BMI ≥ 35 kg/m^2 in patients treated unsuccessfully with the highest tolerated doses of metformin and SUL if insulin is not used.

The conditional recommendations referred to the need to equate the cost of therapy with the cheapest available alternative (in the case of PBAC, dulaglutide; CADTH, n.d.), based on the insufficient added clinical value in terms of efficacy and safety.

According to the information provided by the applicant, the medicinal product Ozempic (semaglutide) is funded in (trade secret) EU and EFTA countries (out of 31 indicated). (trade secret)

PRESIDENT

dr n. med. Roman Topór-Mądry

/document signed electronically/

Basis for the recommendation

The recommendation was prepared under an order dated 6 November 2020 of the Minister of Health (reference number: PLR.4500.802.2020.5.KK, PLR.4500.803.2020.5.KK, PLR.4500.807.2020.5.KK) regarding the preparation of the President's recommendation on the evaluation of Ozempic (semaglutide) for the indication: type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking, pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended), upon receipt of the Position of the Transparency Board No. 14/2021 of 8 February 2021 on the evaluation of the drug Ozempic (semaglutide) for the indication: type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking

References

1. Position of the Transparency Board No. 14/2021 of 8 February 2021 on the evaluation of the drug Ozempic (semaglutide) for the indication: type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking
2. Report No. OT.4330.18.2020 Application for reimbursement of the medicinal product Ozempic (semaglutide) for the indication: type 2 diabetes, for patients using at least two oral hypoglycaemic agents or basal insulin in combination with at least one oral hypoglycaemic agent, with HbA1c ≥ 8%, with obesity defined as BMI ≥ 30 kg/m2 and with very high cardiovascular risk defined as: confirmed cardiovascular disease or damage to other organs manifested by: proteinuria or left ventricular hypertrophy, or retinopathy, or the presence of 2 or more major risk factors among the following: age ≥ 55 years for men, ≥ 60 years for women, dyslipidaemia, hypertension, smoking