Recommendation No. 112/2019

of 19 December 2019

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

on the evaluation of Repatha (evolocumab) under the following drug programme: "Treatment of patients with very high risk of cardiovascular disease in secondary prevention"

The President of the AOTMiT recommends reimbursing Repatha (evolocumab) under the following drug programme: "Treatment of patients with very high risk of cardiovascular disease in secondary prevention" **on condition that** the proposed risk-sharing scheme is enhanced and a risk-sharing scheme is introduced to ensure the maximum expenditure on the part of the payer is not exceeded.

Statement of reasons for the recommendation

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

As part of the clinical analysis, one primary randomised study, FOURIER, was presented, in which evolocumab was compared with placebo, while patients from both arms underwent basic lipid-lowering therapy using statins ± ezetimibe.

In line with the results of FOURIER, the use of the therapy in question resulted in a statistically significantly lower risk of death due to cardiovascular (CV) causes, occurrence of a myocardial infarction (MI), hospitalisation due to unstable angina pectoris, stroke or coronary revascularisation. Furthermore, the risk of myocardial infarction and stroke was demonstrated to be lower. On the other hand, no statistically significant differences in terms of mortality due to cardiovascular diseases have been identified. However, it should be borne in mind that the population indicated in the application is not fully compatible with the population included in the study. The application involves patients with a very high risk of cardiovascular events in secondary prevention, in populations of patients who meet the following criteria:

[information protected as a trade secret].

The results of the economic analysis indicate that *[information protected as a trade secret]*.

The budget impact analysis indicates an increase in the public payer's expenditure by *[information protected as a trade secret]*.

The identified reimbursement recommendations support the funding of the intervention in question, but they underline the high cost of treatment.

Taking the above into account, the President of the AOTMiT believes that financing of the technology in question is justified, on condition that the risk-sharing scheme in question is enhanced and a risk-sharing scheme is introduced to ensure the maximum expenditure on the part of the payer is not exceeded.

In addition, similarly to the Transparency Council, the President of the Agency suggests that the development of a single drug programme which would include the drug in question and alirocumab financed in familial hypercholesterolaemia, should be considered.

Subject of the application

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

- Repatha (evolocumab), solution for injection, 140 mg, 2 pre-filled pens, EAN: 05909991224370 – the proposed net ex-factory price of PLN *[information protected as a trade secret]*.
- Repatha (evolocumab), solution for injection, 140 mg, 1 pre-filled pen, EAN: 05909991224363 – the proposed net ex-factory price of PLN *[information protected as a trade secret]*.

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

Health problem

Myocardial infarction, multivascular coronary heart disease

Ischaemic heart disease is a broad term covering all states of myocardial ischaemia regardless of their pathomechanism. Coronary artery disease includes myocardial ischaemia related to changes in the coronary arteries.

The annual mortality rate in a diverse population of patients with stable angina pectoris amounts to 1.2-3.8%. The prognosis is better in patients with unstable angina pectoris (30-day mortality rate <2%) than in patients with myocardial infarction without ST segment elevation (30-day mortality rate: approx. 5%). Before the introduction of fibrinolytic treatment, in-hospital mortality rate due to ST-elevation myocardial infarction amounted to 18% on average. Currently in Europe, it is estimated that the in-hospital mortality rate due to ST-elevation myocardial infarction amounts to 8.4%, and in patients eligible for reperfusion therapy – to 6%.

Ischaemic stroke

According to the definition proposed by the World Health Organisation in 1970, "stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin. This definition was modified in 2013, when it was agreed that stroke should also be diagnosed when the typical clinical stroke symptoms last less than 24 hours, but the ischaemic focus was clearly documented by neuroimaging.

The age-standardised prevalence of stroke in people >65 years of age amounts to 46-73/1,000, including 32-61 in women and 59-99 in men (there are no relevant data for this age group in Poland). In Poland, the incidence rate for the first stroke, standardised in relation to the European population, amounts to 111/100,000 people. The mean age of onset is approx. 70 years of age.

The risk of death and disability depends on the type of stroke. The risk of recurrent stroke also depends on its type and is the highest in patients with embolic strokes of cardiac origin and in cases of significant carotid artery occlusion. In the case of ischaemic stroke, the risk of recurrent stroke amounts to 10-12% in the first year and 5-8 in each subsequent year following the stroke.

Peripheral artery disease

Peripheral artery disease (PAD) represents a group of disease units of different symptoms and course, but with a common origin associated with the development of atherosclerosis.

The total prevalence of patients with peripheral artery disease, based on objective studies, has been assessed in several epidemiological studies. It amounts to 3-10% and increases to 15-20% in people over 70 years of age.

In the systematic review of 17 studies in 11,391 patients with asymptomatic carotid artery occlusion of > 50%, 63% of late deaths were associated with cardiac events and the mean cardiac mortality amounted to 2.9%/year. In many studies, increased risk of death, as well as of mortality and morbidity from cardiovascular causes (myocardial infarction, stroke) have been demonstrated in patients with symptomatic or asymptomatic lower extremity artery disease (LEAD), even when conventional risk factors were considered. The ankle-brachial index (ABI) of ≤ 0.90 is associated with an over twofold increase in the 10-year incidence rate of coronary events, cardiovascular mortality and general mortality.

Alternative health technologies

Pursuant to the announcement of the Minister of Health of 23/10/2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices (Official Journal of the Minister of Health, item 88), the following products are currently financed from public funds in Poland:

- drugs from the 46.0 limit group, drugs affecting lipid metabolism – HMG-CoA reductase inhibitors (atorvastatin, lovastatin, rosuvastatin, simvastatin) and
- drugs from the 48.0 limit group, Drugs inhibiting the absorption of cholesterol from the gastrointestinal tract (ezetimibe and rosuvastatin+ezetimibe).

On the basis of clinical guidelines and the drugs financed in the indication in question, continuation of therapy with maximum tolerated doses of statins in combination with ezetimibe should be considered as a comparator. This choice is in line with that made by the applicant.

Description of the proposed intervention

Evolocumab selectively binds to PCSK9 (proprotein convertase subtilisin/kexin type 9). Thus, it inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the hepatocyte surface, preventing PCSK9-mediated LDLR degradation. Increasing the density of LDLRs results in a decrease of LDL cholesterol fraction in blood serum.

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

- in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
    - in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
    - as monotherapy or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
- in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

- in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
    - in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
    - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The indication included in the application is included in the above list. In line with the indication in question, the population was narrowed down to patients meeting the following criteria:

- *[information protected as a trade secret]*.

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.

FOURIER, a primary randomised study was presented as part of the clinical analysis; in that study, evolocumab was compared with placebo, while patients from both arms underwent basic lipid-lowering therapy using statins ± ezetimibe. Median follow-up time – 26 months. 27,564 patients were included in the study. The risk of bias using the Cochrane Collaboration tool was assessed to be low for most domains (only for "other factors" the risk was assessed to be unknown).

One observational study was included in the analysis – *[information protected as a trade secret]*, which was aimed to assess the clinical practice in Europe in the field of the prescription of evolocumab and compliance. 1,186 patients were included in the analysis; the baseline period was 26 weeks before the EVO therapy was included and the follow-up period was 30 weeks after its inclusion. The quality of the study [*information protected as a trade secret]* was estimated at 7 out of 8 on the NICE scale. The score was lowered by one point due to the lack of information about consecutive arm selection.

The following parameters were used to assess efficacy:

- HR – hazard ratio;
- NNT– *Number Needed to Treat*, the estimated number of people in whom the assessed intervention should be used instead of the comparator to obtain additional incidence or to avoid the occurrence of the given event within a specified time horizon;
- RR – risk ratio;

Efficacy

Death due to cardiovascular causes, myocardial infarction, hospitalisation due to unstable angina pectoris, stroke or coronary revascularisation

In line with the results of the FOURIER study, the use of EVO vs. PLC resulted in a statistically significantly lower risk of death due to cardiovascular causes (CV), myocardial infarction (MI), hospitalisation due to unstable angina pectoris, stroke or coronary revascularisation:

- By 15% in the general population – HR=0.85 (95% CI: 0.79; 0.92), and NNT=63 (95% CI: 44; 116);
- *[information protected as a trade secret]*

For the general population in FOURIER, the risk reduction of the primary endpoint in the first and subsequent year of treatment was also determined, where in the first year it amounted to 12% (HR=0.88 [95%CI: 0.8; 0.97]), and in the subsequent year of treatment it amounted to 19% (HR=0.81 [95%CI: 0.73; 0.89]).

Death due to cardiovascular causes, myocardial infarction or stroke

In line with the results of the FOURIER study, the use of EVO vs. PLC was associated with a lower risk of death due to CV causes, MI or stroke:

- By 20% in the general population – HR=0.80 (95% CI: 0.73; 0.88), and NNT=70 (95% CI: 50; 119);
- *[information protected as a trade secret]*

No statistically significant differences in the risk of death due to CV causes, MI or stroke have been demonstrated *[information protected as a trade secret]*

For the general population of the FOURIER study and for the population with at least 1 high-risk factor, risk reduction in the first and subsequent year of treatment was also determined. The risk reduction in the general population amounted to 16% in the first year (HR=0.84 [95%CI: 0.74;0.96]) and 25% in the subsequent year of treatment (HR=0.75 [95%CI: 0.66; 0.85]), whereas in the population with at least one high-risk factor, it amounted to 19% and 27%, respectively.

Death due to cardiovascular causes

No statistically significant differences were identified for the comparison of EVO vs. PLC in terms of risk of death from: cardiovascular causes, acute myocardial infarction, stroke, cause other than MI/stroke CV.

Myocardial infarction

In line with the results of the FOURIER study, the use of EVO vs. PLC was associated with a lower risk of myocardial infarction:

- By 27% in the general population – HR=0.73 (95% CI: 0.65; 0.82), and NNT=83 (95% CI: 59; 129);

[information protected as a trade secret]

For the general population in FOURIER, the risk reduction of myocardial infarction in the first and subsequent year of treatment was also determined; in the first year it amounted to 20% (HR=0.80 [95%CI: 0.68; 0.94]), and in the subsequent year of treatment it amounted to 35% (HR=0.65 [95%CI: 0.55; 0.77]).

Stroke

In line with the results of FOURIER, the use of EVO vs. PLC was associated with a lower risk of:

- Stroke in general:
    - By 21% in the general population – HR=0.79 (95% CI: 0.66; 0.95);
    - *[information protected as a trade secret]*
- Ischaemic stroke:
    - By 25% in the general population – HR=0.75 (95% CI: 0.62; 0.92);

- *[information protected as a trade secret]*

For the general population in FOURIER, the following has also been determined:

- the reduction of the risk of stroke in the first and subsequent year of treatment; however, significant statistical results were observed only in the subsequent year of treatment, where the risk reduction of stroke amounted to 24% (HR=0.76 [95%CI: 0.6; 0.97]).
- risk of fatal or non-fatal ischaemic stroke (IS) or transient ischaemic attack – the observed differences are statistically significant (HR=0.77 [95%CI: 0.65; 0.92]).

Coronary revascularisation

In line with the results of FOURIER, the use of EVO vs. PLC was associated with a statistically significant lower risk of the need to perform:

- coronary revascularisation in general:
  - by 22% in the general population – HR=0.78 (95% CI: 0.71; 0.86), and NNT=67 (95% CI: 48; 107).
- urgent coronary revascularisation:
  - by 27% in the general population – HR=0.73 (95% CI: 0.64; 0.83), and NNT=96 (95% CI: 68; 163).
- planned coronary revascularisation:
  - by 17% in the general population – HR=0.83 (95% CI: 0.73; 0.95), and NNT=42 (95% CI: 36; 49).

[information protected as a trade secret]

For the general population of the FOURIER study, the reduction of the risk of revascularisation in the first and subsequent year of treatment was also determined. In the first year of treatment, statistically significant results were observed only for coronary revascularisation in general (HR=0.96 [95%CI: 0.74; 0.96]), whereas in the subsequent year of treatment also for urgent and planned revascularisation.

Hospitalisation due to unstable angina pectoris

The results concerning hospitalisation due to unstable angina pectoris were available only for the general population of the study – however, no statistically significant differences between the study arms were observed. For the general population in FOURIER, a reduction of the risk of hospitalisation due to UA in the first and subsequent year of treatment was also determined, but the results were not statistically significant.

Cardio-vascular diseases (CVD)

[information protected as a trade secret]

The Cholesterol Treatment Trialists Collaboration (CTTC)

The results concerning the occurrence of a composite CTTC endpoint, made up of sudden coronary death, the occurrence of a non-fatal MI , stroke or coronary revascularisation, were available only for the general population of the study, where the risk of this endpoint being reached was significantly lower by 17% in favour of the EVO vs. PLC arm – HR=0.83 (95%CI): 0.77; 0.90), and NNT=57 (95% CI: 41; 97).

For the general population in FOURIER, the risk reduction for CTTC in the first and subsequent year of treatment was also determined. The differences between the study arms were statistically significant in both the first and the subsequent year (HR=0.87 [95%CI: 0.87; 0.97] and HR=0.78 [95%CI: 0.71; 0.86]).

Major adverse limb events (MALE)

The FOURIER study analysed major adverse limb events (MALE) – a composite endpoint made up of the following endpoints i.e. acute limb ischaemia (ALI), severe amputations (below or above the knee) and urgent revascularisation.

In line with the results of the FOURIER study, the use of EVO vs. PLC was associated with a statistically significant lower risk of:

- MALE:
    - by 42% in the general population – HR=0.58 (95% CI: 0.38; 0.88);
    - *[information protected as a trade secret]*
- ALI or significant amputation:
    - by 48% in the general population – HR=0.52 (95% CI: 0.31; 0.89);
- ALI:
    - by 45% in the general population – HR=0.55 (95% CI: 0.31; 0.97).

There were no statistically significant differences in the incidence of:

- *[information protected as a trade secret]*
- ALI or significant amputation:
    - *[information protected as a trade secret]*
- ALI:
    - *[information protected as a trade secret]*
- significant amputation:
    - In the general population,
    - *[information protected as a trade secret]*
- Peripheral limb revascularisation – urgent:
    - In the general population,
    - *[information protected as a trade secret]*

Peripheral revascularisation

In the event that peripheral revascularisation is necessary *[information protected as a trade secret]*

Death due to CV causes, occurrence of MI, stroke, MALE

In line with the results of the FOURIER study, the use of EVO vs. PLC was associated with a statistically significantly lower risk of death due to CV causes, occurrence of MI, stroke, MALE:

- by 21% in the general population – HR=0.79 (95% CI: 0.72; 0.87);
- *[information protected as a trade secret]*

Death from any cause

The incidence of death due to any cause was analysed in the general population of the FOURIER study, the patient population *[information protected as a trade secret]*

Change in the LDL-C level

In the arm of patients taking evolocumab, after 48-week follow-up period, LDL-C concentration was on average 59-61% lower than in the control arm. Median absolute reduction of LDL-C concentration in

the EVO arm in comparison to the PLC arm amounted to 56-58 mg/dL. The observed differences are statistically significant.

The LDL-C concentration in the EVO arm was decreased *[information protected as a trade secret]* and remained at a similar level throughout the study. *[information protected as a trade secret]*

In the general population in FOURIER, after a 48-week follow-up period, 87% of patients from the EVO arm and 18% of patients from the PLC arm reached LDL-C level ≤ 70 mg/dL, 67% of patients from the EVO arm and 0.5% of patients from the PLC arm reached LDL-C level ≤ 40 mg/dL, and LDL-C level C ≤ 25 mg/dL was reached by 42% of patients from the EVO arm and < 0.1% of patients from the PLC arm. The identified differences are statistically significant.

Safety

The safety profile in the FOURIER study was analysed only in the general population of the study *[information protected as a trade secret]*

The results of the safety analysis indicate that the safety profile of EVO is similar to that of PLC administered as adjunct to standard hypolipidaemic therapy. However, the use of EVO is associated with a statistically significant reduction of cataract risk and laboratory parameters concerning the level of creatine kinase, *[information protected as a trade secret]*

Statistically significant differences to the detriment of EVO were observed only in the case of injection site reactions (RR=1.35 [95%CI: 1.14; 1.61]) in the general population of the study.

Effectiveness and safety

- *[information protected as a trade secret]*

Additional safety information

During the search of the Food and Drug Administration website, the applicant identified 3 alerts on the safety of use of Repatha. The alerts come from the FDA's Adverse Event Reporting System (FAERS).

- Influenza-like illnesses (FAERS: 07-09.2018)

  The leaflet of Repatha was supplemented by data concerning adverse events obtained after the drug had been authorised. These events include influenza-like illnesses, but it has been pointed out that, due to the voluntary reporting of adverse events by patients and the unknown size of the population receiving the drug, it is not possible to estimate the risk of the event in detail or to establish a connection between receiving the drug and the incidence of influenza-like diseases.

- angioedema (FAERS: 04-06.2018) – FDA is currently assessing the need for regulatory actions;
- bacterial infections of the skin and subcutaneous tissue (FAERS: 04-06.2017) – FDA is currently assessing the need for regulatory actions.

On the WHO Uppsala Monitoring Centre website (www.vigiaccess.org), the applicant identified a database of suspected adverse events in patients using evolocumab. The most frequent events concerned: general disorders and reactions at the administration site, injuries, poisoning and complications related to procedures and disorders of breathing, chest and mediastinum. In total, 74,488 events were reported.

Limitations

The following factors impact the uncertainty of the presented results:

- The patients with a baseline LDL-C level of ≥ 70 mg/dL were qualified for the FOURIER study, whereas the subject of the application is the population of patients with baseline LDL-C level *[information protected as a trade secret]*

- Data for all *[information protected as a trade secret]* of the FOURIER study were available only for the primary endpoint and key secondary - endpoint.
- The FOURIER study did not assess the quality of life.
- The age criterion in the drug programme (DP) is at least 18 years of age, whereas the patients included in the FOURIER study were aged >40 to ≤85 years, with the mean age being 62.5 years.
- The FOURIER study was originally planned as a 5-year study; however, the final median of the follow-up period was 26 months.
- The observation period in the FOURIER study was relatively short, which may have a key impact on the possibility of obtaining statistically significant results in terms of death due to CV causes.
- A part of the results comes from *[information protected as a trade secret]*

Proposals of risk-sharing schemes

As part of the proposed risk-sharing scheme (RSS), the applicant undertakes to:

- *[information protected as a trade secret]*

Economic analysis, including a cost-effectiveness estimation

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

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

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

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

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

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

The applicant presented a cost-utility analysis (CUA) and a cost-effectiveness analysis (CEA). The analysis was conducted in a lifelong time horizon (modelling of the treatment course was conducted *[information protected as a trade secret]* from the NHF's perspective and the common perspective (NHF+patient) which was tested as part of the sensitivity analysis, in a lifelong time horizon, in which evolocumab (EVO) in combination with statins at maximum tolerated doses (MTD STA) and ezetimibe (EZE) was compared with continuation of statin and ezetimibe therapy.

The analysis considered the direct medical costs which differ between the compared technologies:

- costs of drugs (evolocumab, statins and ezetimibe) and their administration;

- cost of diagnostics of patients qualified for evolocumab therapy;
- costs of treatment monitoring;
- costs related to *[information protected as a trade secret]*

In line with the applicant's estimations, the use of evolocumab in combination with statins and ezetimibe in place of statin therapy in combination with ezetimibe is *[information protected as a trade secret]* Estimations for the EVO + MTD STA + EZE vs. MTD STA + EZE comparison:

- for the 1. population *[information protected as a trade secret]*:
    - without taking the proposed RSS into account:
        - incremental cost-utility ratio (ICUR) was *[information protected as a trade secret]*
        - incremental cost-effectiveness ratio (ICER) was *[information protected as a trade secret]*
    - taking the proposed RSS into account:
        - ICUR was *[information protected as a trade secret]*
        - ICER was *[information protected as a trade secret]*
- for the 2. population *[information protected as a trade secret]*:
    - Without taking the proposed RSS into account:
        - ICUR was *[information protected as a trade secret]*
        - ICER was *[information protected as a trade secret]*
    - taking the proposed RSS into account:
        - ICUR was *[information protected as a trade secret]*
        - ICER was *[information protected as a trade secret]*.

In the adopted time horizon, the net ex-factory price for a single EVO packaging, at which the cost of one additional quality-adjusted life year when using EVO in combination with MTD STA + EZE instead of a comparator is equal to the cost-effectiveness threshold, amounts to:

- *[information protected as a trade secret]*

The results of the probabilistic analysis indicate that *[information protected as a trade secret]*

In line with the results of the one-way sensitivity analysis, even taking the RSS into account, no change is made to the conclusion on the cost-effectiveness of the assessed technology against the comparator as compared to the baseline scenario in any of the analysed scenarios.

The highest increase in ICUR value *[information protected as a trade secret]*
Whereas the highest decrease in the value *[information protected as a trade secret]*

Limitations

As in the case of the clinical analysis, the key limitation consists in the lack of published research results directly corresponding to the population included in the application. The analysis was based on results concerning the general population *[information protected as a trade secret]*

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

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

Given the fact that the clinical analysis included FOURIER, a randomised clinical study which demonstrated the advantage of using the technology in question (EVO) in combination with MTD STA and EZE over the comparator (MTD STA + EZE), the circumstances referred to in Article 13 of the Act on reimbursement do not apply.

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 aim of the budget impact analysis was to estimate changes in public payer's expenditure (National Health Fund) in the event of a positive decision on public funding of Repatha under the new drug programme in patients with a very high risk of cardiovascular events in secondary prevention, meeting the following criteria:

[information protected as a trade secret].

The estimations were carried out from a public payer's perspective and common perspective (NHF+patient) in a 2-year time horizon.

In line with the applicant's estimations, the number of patients using the intervention in question will amount to:

- *[information protected as a trade secret]*

Direct medical costs were considered in the budget impact analysis, i.e.

- costs of drugs (evolocumab, statins and ezetimibe) and their administration;
- cost of diagnostics when qualified for treatment with evolocumab;
- costs of treatment monitoring;
- costs related to *[information protected as a trade secret]*

In line with the above assumptions, the financing of the intervention in question will involve an increase in the payer's expenditure by:

  - *[information protected as a trade secret]*

Limitations

The following factors impact the uncertainty of the presented results:

- It was assumed in the budget impact analysis that evolocumab would take over the analysed market *[information protected as a trade secret].* However, it is uncertain whether these values will correspond to the reality of the payer.
- *[information protected as a trade secret]*.

Remarks on the proposed risk-sharing scheme

[information protected as a trade secret]. Taking into account that no statistically significant differences were identified for the comparison of EVO vs. PLC in terms of mortality risk resulting from: cardiovascular causes, acute myocardial infarction, stroke, other cause than MI/stroke CV, reduction of the costs of the intervention in question is justified.

In addition, it is possible that the population in question will be larger than that presented in the budget impact analysis. Therefore, introducing a risk-sharing scheme which would ensure the maximum expenditure on the part of the payer is not exceeded should be considered.

Remarks on the drug programme

No remarks

Review of the solutions proposed in the rationalisation analysis

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

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

The rationalisation analysis refers to the results of the budget impact analysis regarding the reimbursement of Repatha (evolocumab).

In the rationalisation analysis, the applicant proposed solutions to release funds in the budget for the reimbursement of Repatha:

- reduction of the financing limit due to the entry of first equivalents or expiry of the market exclusivity period in limit groups *[information protected as a trade secret]*,
- reduction of the real prices of reimbursed drugs in hospital treatment by *[information protected as a trade secret]* when a subsequent administrative decision is issued.

The introduction of the presented solutions will result in the release of funds which will compensate the NHF's expenditure related to the reimbursement of evolocumab in the indication in question (the savings indicated in the rationalisation analysis are higher than the additional public payer's expenditure estimated in the basic budget impact analysis).

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

Thirteen clinical guidelines relating to the indication in question have been identified:

- Polish Cardiac Society Cardiovascular Pharmacotherapy Section (PTK SFSN) 2018
- Polish Lipid Association/College of Family Physicians in Poland/Polish Cardiac Society (PTL/KLRwP/PTK) 2016

- PTK 2016
- American Heart Association (AHA), American College of Cardiology (ACC), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), American Association Academy of Physician Assistants (AAPA), Association of Black Cardiologists (ABC), American College of Preventive Medicine (ACPM), American Diabetes Association (ADA), American Geriatrics Society (AGS), American Pharmacists Association (APhA), American Society for Preventive Cardiology (ASPC), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA) 2018;
- American Heart Association /American Stroke Association (AHA/ASA) 2018;
- American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE) 2017;
- National lipid association (NLA) 2017 and 2015;
- European Society of Cardiology (ESC) 2016
- European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) 2016
- National Institute for Health and Care Excellence (NICE) 2016
- Canadian Cardiovascular Society (CCS) 2016
- ACC 2016

All of the above guidelines recommend the use of PCSK9 inhibitors, including evolocumab, in the indication in question.

Three reimbursement recommendations which relate to the technology in question have been identified:

- Two positive recommendations:
    - Haute Autorité de Santé (HAS) 2018;
    - Canadian Agency for Drugs and Technologies in Health (CADTH) 2018;
- One document with a recommendation postponement:
    - Pharmaceutical Benefits Advisory Committee (PBAC) 2019.

In the case of one positive recommendation (HAS), no justification has been given, whereas the other one (CADTH) quotes the results of the FOURIER study. In the PBAC recommendation, where the decision to issue the recommendation was postponed, it was indicated that, although there is a clinical benefit associated with the use of evolocumab in the population of patients at high cardiovascular risk, the result of the cost-effectiveness analysis is not acceptable and a reduction of the price of Repatha is required. In addition, one document of the Scottish Medicines Consortium (SMC) 2018 was identified, which indicated that, due to the absence of a request by the entity responsible for the reimbursement of Repatha in the indication in question, the SMC may not issue a positive recommendation for this medicinal product.

According to the information provided by the applicant, Repatha is reimbursed in:

- packagings containing 1 pre-filled pen – *[information protected as a trade secret]*
- packagings containing 2 pre-filled pens – *[information protected as a trade secret]*

[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 03/10/2019 (reference numbers: PLR.4600.643.2019.14.JKB, PLR.4600.644.2019.15.JKB), with regard to preparation of the recommendation of the President of the AOTMiT on Repatha (evolocumab) under the following drug programme: "Treatment of patients with very high risk of cardiovascular disease in secondary prevention" 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. 112/2019 of 16 December 2019 on the evaluation of Repatha (evolocumab) under the following drug programme: "Treatment of patients with very high risk of cardiovascular disease in secondary prevention"

References

1. The Position of the Transparency Council No. 112/2019 of 16 December 2019 on the evaluation of Repatha (evolocumab) under the following drug programme: "Treatment of patients with very high risk of cardiovascular disease in secondary prevention"
2. Report No. OT.4331.57.2019. Reimbursement application for Repatha (evolocumab) to be available under the following drug programme: "Treatment of patients *[information protected as a trade secret]*. Verification analysis