Recommendation No. 8/2020

of 30 January 2020

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

on whether Mevalia PKU Motion (a foodstuff for particular nutritional use)

should be reimbursed in the following indication: phenylketonuria

The President of AOTMiT recommends reimbursement of Mevalia PKU Motion, a foodstuff for particular nutritional use, in the following indication: phenylketonuria **– on condition that** the product price is reduced.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the President of AOTMiT believes that reimbursement of Mevalia PKU Motion (a foodstuff for particular nutritional use) in the indication specified in the application is justified.

The clinical analysis includes one unpublished study on Mevalia PKU Motion which provides information on the product's tolerability and acceptability. It does not include studies assessing endpoints related to the course of the disease. However, it should be kept in mind that the limited availability of clinical data is a common problem applicable to most foodstuffs for particular nutritional uses.

Results of the cost-minimisation analysis indicate that the intervention in question is more expensive than three of the selected comparators and cheaper than one comparator. The budget impact analysis suggests that the decision to reimburse the technology in question would result in an additional burden for the public payer's budget.

In view of the fact that both clinical practice guidelines and experts indicate the use of phenylalanine-free amino acid mixtures as the basis for dietary treatment in the indication in question, a positive reimbursement decision is justified despite the limitations of the clinical analysis. However, given the high cost of the product and the fact that currently a number of similar foodstuffs for particular nutritional uses intended in the indication in question are reimbursed, a reduction of the price of Mevalia PKU Motion is warranted.

Subject of the application

The order of the Minister for Health concerns assessing whether the following foodstuffs for particular nutritional uses should be financed from public funds:

- Mevalia PKU Motion Red Fruits 10, liquid mixture, 30x70 ml, EAN: 8008698021323, net ex-factory price: *[information protected as a trade secret]*
- Mevalia PKU Motion Red Fruits 20, liquid mixture, 30x140 ml, EAN: 8008698021309, net ex-factory price: *[information protected as a trade secret]*
- Mevalia PKU Motion Tropical 10, liquid mixture, 30x70 ml, EAN: 8008698021286, net ex-factory price: *[information protected as a trade secret]*
- Mevalia PKU Motion Tropical 20, liquid mixture, 30x140 ml, EAN: 8008698015476, net ex-factory price: *[information protected as a trade secret]*
- Mevalia PKU Motion Yellow 20, liquid mixture, 30x140 ml, EAN: 8008698024331, net ex-factory price: *[information protected as a trade secret]*

The proposed co-payment and category of reimbursement availability: lump sum as part of a new joint-limit group. The application does not include a proposed risk-sharing scheme.

Health problem

Phenylketonuria (PKU) is an inherited metabolic disease (ICD-10: E70.0 - Classical phenylketonuria, in line with the International Statistical Classification of Diseases and Related Health Problems (ICD). It is inherited in an autosomal recessive fashion. PKU is caused by the absence or significant decrease in the activity of phenylalanine hydroxylase, an enzyme conditioning the transformation of phenylalanine (Phe), an exogenous amino acid, into tyrosine. This disorder results in an excessive accumulation of Phe and phenylketones (hyperphenylalaninemia, HPA) in blood, body fluids and other tissues leading to irreversible damage to the central nervous system, manifested by mental retardation and various neurological disorders.

The increase of Phe concentration in blood exceeding 120 µmol/l (2 mg/dl) is referred to as hyperphenylalaninemia, and its most frequent form is classical phenylketonuria (approx. 97% of hyperphenylalaninemia cases).

Phenylketonuria is a rare disease. In Poland, PKU prevalence is approx. 1:7,500 live births, which means that approx. 60 children with PKU are born every year, and 1 in 46 adults is a carrier of the mutated gene. In the south-eastern part of Poland, prevalence is slightly higher and amounts to approx. 1:6,500, while in the Greater Poland region the prevalence rate is 1:10,000.

Better prognosis in phenylketonuria depends on the earliest possible diagnosis of the disease and the introduction of an elimination diet from the very first days of life – low-phenylalanine diet. Maintaining the recommended Phe values in blood allows for achieving life expectancy comparable to that of healthy people. Untreated PKU can lead to permanent intellectual disabilities, in untreated people the intelligence quotient usually does not exceed 20-40 IQ.

All newborns in Poland are obligatorily screened for PKU, which enables the diagnosis of the disease in the asymptomatic period and reduction of phenylalanine intake at an early stage, which prevents progressive brain damage.

Alternative health technologies

All identified guidelines recommend the use of phenylalanine-free amino acid mixtures in patients (they do not, however, refer to specific products).

Pursuant to the Announcement of the Minister of Health of 20 December 2019 on the reimbursement list of drugs, foodstuffs for particular nutritional uses and medical devices as at 01 January 2020 (Official Journal of the Minister of Health, item 105), currently a number of foodstuffs for particular nutritional uses indicated in phenylketonuria are financed from public funds in Poland.

In its reimbursement application, the applicant indicated the following alternative technologies:

- Main comparator (form: liquid): PKU Lophlex LQ 10, PKU Lophlex LQ 20, PKU Cooler 10, PKU Cooler 15, PKU Cooler 20;
- Additional comparators (form: powder): PKU Express 15, PKU Express 20, PKU Gel 10.

The selection of alternative technologies was deemed correct.

Description of the proposed intervention

Mevalia PKU Motion products are foodstuffs for particular nutritional use.

The indication which is the subject of the reimbursement application is a narrower indication than the marketing authorisation indication for Mevalia PKU Motion and covers dietary treatment of phenylketonuria. In line with the documents provided by the applicant, it can be used in dietary treatment of phenylketonuria and hyperphenyloalaninemia in patients aged ≥ 3 years old, however, the indication provided for in the reimbursement application does not restrict the age of patients.

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 systematic review included [*information protected as a trade secret*].

Two cross-over studies have been identified for the adopted comparators; they compared PKU Cooler with powdered products, mainly PKU Gel and PKU Express (Gokmen-Ozel 2011, MacDonald 2006 and MacDonald 2008). The two studies involved 14 and 27 subjects, respectively, and the observation period was 5 and 6 weeks, respectively.

Furthermore, a single-arm retrospective observation study assessing PKU Cooler (Gokmen-Ozel 2009), with the observation period of 2.4 years and 34 subjects was included into the review.

[*information protected as a trade secret*] The risk of bias as described in the Cochrane Handbook in the RCTs was found to be high.

Efficacy

A study on the assessed intervention [*information protected as a trade secret*].

[information protected as a trade secret].

RCTs for comparators (Gokmen-Ozel 2011, MacDonald 2006 and MacDonald 2008)

In the study described in Gokmen-Ozel 2011 and MacDonald 2008 conducted for a comparison of PKU Cooler 10 (n=14) vs PKU Gel (n=10) for a 7-day treatment period, no statistically significant

differences between the arms have been observed in terms of blood phenylalanine levels, body mass changes or energy, protein, carbohydrate and fat supply from natural food sources. A statistically significant difference in the amount of consumed energy from the protein substitute in favour of PKU Cooler was demonstrated; it provided less energy ($p<0.001$). Full independence in the consumption of the product was observed in all patients consuming a ready-to-drink liquid protein substitute, as compared to 58% of subjects using the powdered product. The differences between the arms was statistically significant.

In MacDonald 2006, a study which compared PKU Cooler 15 (n=27) with PKU Express (n=23) and other powdered products (n=4), a statistically significant difference in favour of the liquid protein substitute, i.e. PKU Cooler, was demonstrated in terms of blood phenylalanine levels ($p=0.027$). Furthermore, statistically significant differences in favour of PKU Cooler with regard to more efficient use of the product portions, a greater share of patients assessing the product as easier and more convenient for use (including outside of home settings), a greater share of patients reporting lack of embarrassment in connection with the use of protein substitutes have been reported.

Observational study on the comparator (Gokmen-Ozel 2009)

Long-term effects of using PKU Cooler were assessed in Gokmen-Ozel 2009, a retrospective, single-arm observational study, where the median observational time was 2.4 years, and the observation range was between 6 months and 4.1 years. The study looked at the change in blood phenylalanine levels, nutrition markers and anthropometric parameters. The efficacy analysis was broken down into patients below and above 18 years of age.

In the <18 years of age arm, the blood phenylalanine level was the same at baseline and in the course of the study (no statistically significant differences have been observed). In terms of biochemical parameters, a statistically significant increase in median calcium, albumin, haemoglobin and haematocrit, and a decrease in blood selenium were found. All parameters were normal. Anthropometric parameters did not change.

In the > 18 years of age arm, a statistically significant reduction of the plasma phenylalanine level as compared to baseline was observed. Increased biochemical parameter concentration values were reported for vitamin B12, calcium and albumin. In adult patients using PKU Cooler, the median BMI increased, however that difference was not statistically significant.

Comparison of the composition of the Mevalia PKU Motion vs. PKU Cooler and PKU Lophlex LQ

In terms of single portions of protein substitutes, there are only slight differences with regard to carbohydrate, amino acid, vitamin, mineral and trace element content between the analysed intervention and its comparators. Mevalia PKU Motion provides less energy than PKU Cooler, PKU Lophlex and PKU Gel. With regard to the most caloric product version – Mevalia PKU Motion Red Fruits, the differences in terms of energy, when compared to relevant products containing 10 g and 20 g of protein substitutes, are:

- 11% for PKU Cooler 10;
- 17% for PKU Cooler 20;
- 7% for PKU Lophlex 10;
- 8% for PKU Lophlex 20;
- 36% for PKU Gel 10.

When compared to PKU Express 20, Mevalia PKU Motion Red Fruits 20 provides 14% of energy more. Excessive caloric content of the product can lead to increased body mass, and thus providing less calories by the protein substitute is favourable.

Mevalia PKU Motion does not include: preservatives, artificial flavours, soy lecithin (allergen), acesulfame K (sweetener), artificial Carmine dyes (cochineal red, which is used in PKU Cooler and PKU Lophlex QL), corn (glucose-fructose) syrup and powdered glucose syrup, modified starch.

Mevalia PKU Motion contains fruit juice from concentrate (which is used also in PKU Lophlex QL). The product also contains glutamic acid, it does not however contain taurine and fats, including docosahexaenoic acid (DHA), which in turn is an ingredient of PKU Cooler and PKU Lophlex LQ.

Safety

The study [*information protected as a trade secret*]

[*information protected as a trade secret*]

Additional safety information

The leaflet for Mevalia PKU Motion contains the following information:

- The product is intended for use under medical supervision.
- The product is intended for PKU / HPA patients aged ≥ 3 years old.
- The product is not intended for people not suffering from phenylketonuria and hyperphenylalaninemia.
- The product is not intended as the sole source of nutrition.
- The product is not intended for parenteral use.

Effectiveness

No studies on the effectiveness of the health technology have been identified.

Limitations of the analysis

The main limitation of the clinical analysis is the fact that no clinical trials which assess the effect of using Mevalia PKU Motion, a protein substitute product, have been identified. The clinical analysis, included [*information protected as a trade secret*].

Furthermore, due to the different nature of individual studies, as well as the discrepancies in the assessed endpoints and the manner of presenting results, the possibility of comparing results of the study on the intervention which is the subject of the application (PKU Motion), i.e. PKU Cooler, PKU Express and PKU Gel, was limited.

Additionally, the uncertainty of results of the clinical analysis is impacted by the following aspects:

- In the following publication: [*information protected as a trade secret*], the following inaccuracies and errors have been identified:
    - *[information protected as a trade secret]*
- Studies on the comparators are also subject to various limitations:
    - Gokmen-Ozel 2011-MacDonald 2008 and MacDonald 2006 were non-blinded RCTs which covered only a small number of subjects (14 and 27, respectively), while the products in question were used for a period of 2 weeks.
    - Not all patients of the comparator arms in RCTs comparing PKU Cooler with powdered protein substitutes used the selected comparators: Gokmen-Ozel 2011, MacDonald 2008, 10 of 14 patients (71.4%) used PKU Gel, while in MacDonald 2006, 23 of 27 patients (85.2%) used PKU Express.

- Gokmen-Ozel 2009, a study which assessed the long-term effects of using PKU Cooler did not make references to the optimal (individual) psychomotor development, which the clinical expert indicated as a significant endpoint.
- No clinical studies which would assess the effects of using PKU Lophlex LQ, a liquid, ready-to-drink protein substitute product constituting a comparator to the intervention which is the subject of the application have been identified.

- With regard to the comparison of the product ingredients and the properties of the intervention in question and the selected comparators, the applicant's analysis stated that "unlike PKU Cooler, PKU Lophlex QL as well as PKU Express and PKU Gel, the product in question, i.e. PKU Motion, does not contain fats and taurine", however it has not been determined what meaning that might have in the context of meeting the body's demand for nutrients and ensuring its proper growth and development. The lack of omega-3 fatty acids: EPA and DHA was also not referred to, which is a shortcoming pointed out by the clinical expert.

Proposals of risk-sharing schemes

The application does not include a proposed risk-sharing scheme.

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.

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 cost-effectiveness analysis for the technology in question was conducted in relation to comparators using the cost minimisation technique in a monthly time horizon from the public payer's (NHF) perspective and a common perspective (NHF + the patient). The economic analysis of the applicant took into account solely costs of using the analysed foodstuffs for particular nutritional uses, i.e. Mevalia PKU Motion and the selected comparators.

In line with the applicant's estimations, the use of Mevalia PKU Motion [*information protected as a trade secret*].

In line with the applicant's estimations, the net ex-factory prices for individual variants of the intervention in question are as follows (whereas the difference between the cost of use of that intervention and the cost of use of the cheapest alternative technology equals zero):

[information protected as a trade secret]

Findings of the sensitivity analysis indicate that [*information protected as a trade secret*]

Limitations of the analysis

Lack of evidence on the efficacy of Mevalia PKU Motion constitutes the fundamental, significant limitation of the economic analysis. (In line with the guidelines, the cost-minimisation analysis should be conducted provided that the efficacy of the analysed intervention and its comparator is on a similar level).

The uncertainty of results of the economic analysis is also impacted by available information on the average consumption of the analysed foodstuffs for particular nutritional uses in clinical practice in Poland. Verification of the correctness of the adopted assumptions is difficult.

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.

The analysed decision problem does not apply to a drug technology, and therefore 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 assessment of the impact on the public payer's budget was conducted in a 2-year horizon from the NHF's perspective and the common perspective (which is comparable to NHF's perspective). The estimated population size (presented as person-years) which will be using the technology in question after a positive reimbursement decision is made is*[information protected as a trade secret]* person-years in the first year and *[information protected as a trade secret]*person-years in the second year

of the product being covered by reimbursement. Only direct medical costs differentiating between the compared treatment regiment, i.e. the cost of analysed foodstuffs for particular nutritional uses, have been taken into account.

Results of the applicant's basic analysis indicate that the decision to reimburse Mevalia PKU Motion would result *[information protected as a trade secret]* in of the expenses of the public payer by approx. *[information protected as a trade secret]* in the first year of reimbursement and by approx. *[information protected as a trade secret]* in the first year of reimbursement. Results of the analysis conducted from a common perspective are similar – the decision to reimburse Mevalia PKU Motion would result *[information protected as a trade secret]* of the expenses from the common expenses by approx. *[information protected as a trade secret]* in the first year of reimbursement and by approx. *[information protected as a trade secret]* in the first year of reimbursement.

[information protected as a trade secret]

Limitations of the analysis

The uncertainty of results of the budget impact analysis impacts the fact that there are no reliable epidemiological data on the Polish population of patients who could use the health technology which is the subject of the application, and therefore the results of the analysis might not reflect the actual reimbursement expenses of the payer.

Remarks on the proposed risk-sharing instrument

Not applicable.

Remarks on the drug programme records

Not applicable.

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 two different solutions – the first assumes the reduction of prices of fingolimod-containing medicinal products by 15% when the reimbursement decision is extended to a subsequent period; the second solution assumes that selected generic and biosimilar drugs are reimbursed. In line with the applicant's estimates, the use of the above-listed solutions would help generate [*information protected as a trade secret*]. The saved resources will help cover the estimated maximum reimbursement costs of Mevalia PKU Motion incurred by the public payer over the course of two years.

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

The following clinical recommendations regarding the analysed indication, published by the following institutions, have been identified:

- European guidelines on PKU – van Wegberg 2017;
- Australasian consensus 2017;
- American College of Medical Genetics and Genomics 2014.

All of the above guidelines recommend using phenylalanine-free amino acid mixtures in patients suffering from phenylketonuria. The above-listed guidelines do not refer to specific products. Phenylalanine-free amino acid mixtures constitute a basis for dietary treatment.

No reimbursement recommendations have been identified in the course of the conducted search.

According to the information presented by the applicant, Mevalia PKU Motion is financed *[information protected as a trade secret]* (of the 31 indicated ones), *[information protected as a trade secret].* In all countries, the level of reimbursement from public funds *[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 13.11.2019 (reference number: PLR.4600.1430.2019, PLR.4600.1431.2019, PLR.4600.1432.2019, PLR.4600.1433.2019, PLR.4600.1434.2019), with regard to preparation of the recommendation of the President of the AOTMiT on whether to reimburse the following foodstuffs for particular nutritional uses: Mevalia PKU Motion Red Fruits 10, liquid mixture, 30x70 ml, EAN: 8008698021323, Mevalia PKU Motion Red Fruits 20, liquid mixture, 30x140 ml, EAN: 8008698021309, Mevalia PKU Motion Tropical 10, liquid mixture, 30x70 ml, EAN: 8008698021286, Mevalia PKU Motion Tropical 20, liquid mixture, 30x140 ml, EAN: 8008698015476, Mevalia PKU Motion Yellow Fruits 20, liquid mixture, 30x140 ml, EAN: 8008698024331pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of Laws of 2019, item 784, as amended.) after having read the Position of the Transparency Council No./2020 of 27 January 2020 on the assessment of Mevalia PKU Motion (a foodstuff for particular nutritional use) in the indication: phenylketonuria.

References

1. Position of the Transparency Council 8/2020 of 27 January 2020 on the assessment of Mevalia PKU Motion (a foodstuff for particular nutritional use) in the indication: phenylketonuria
2. Report no. OT.4330.18.2019 “Application for reimbursement of Mevalia PKU Motion (a foodstuff for particular nutritional use) in the indication: Phenylketonuria”. Completion date: 17 January 2020