Recommendation No. 18/2021

of 19 February 2021

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

on the evaluation of the foodstuff intended for particular nutritional uses

PKU GMPro for the indication:

phenylketonuria in patients over the age of 12 years

The President of the Agency does not recommend the reimbursement of the foodstuff intended for particular nutritional uses PKU GMPro in the indication: phenylketonuria in patients over the age of 12 years.

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 named in the application to be **unjustified**.

Consideration was given to the fact that phenylketonuria is a rare disease and that the choice and availability of low-phenylalanine dietary preparations, especially those that are well tolerated and accepted, are particularly important for the individual adaptation of the management of this disease entity.

Nevertheless, a clinical analysis is important in the assessment, but it does not present studies evaluating the technology applied for - PKU GMPro. The conducted evaluation of efficacy and safety was based only on results for other glycomacropeptide (GMP)-based formulations. It should be noted that these were products that differed from the requested product both in composition, formulation and taste.

Moreover, the results of the analysis of (trade secret) were taken into account. Therefore, the obtained results, which determine the impact on the public payer's budget, should be interpreted with caution.

Taking into account the importance of the health problem and the results of trials that suggest a higher acceptability of GMP-based products compared to L-AA, the President of the Agency indicates that the possible inclusion in reimbursement of the therapy in question could be justified after submission of scientific evidence regarding the technology applied for, confirming its efficacy and safety, and with a change in the proposed reimbursement conditions (trade secret)

Subject of the application

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

- PKU GMPro (vanilla flavour), powder, 532.8 grams (33.3 x 16 sachets), EAN code: 8716900590252, net selling price: (trade secret)

Proposed payment and reimbursement availability category: at the pharmacy on prescription for a flat fee, in a new limit group.

(trade secret)

Health problem

Phenylketonuria (PKU) is an inborn metabolic disease (ICD-10: E70.0 - Classic phenylketonuria, according to the International Classification of Diseases and Related Health Problems).

The disease is inherited in an autosomal recessive manner. It is caused by a lack of, or a significant reduction in the activity of phenylalanine hydroxylase, an enzyme involved in the conversion of the essential amino acid phenylalanine (Phe) into tyrosine. The consequence of the disorder is an excessive accumulation of Phe and phenylketones (hyperphenylalaninemia, HPA) in the blood, body fluids and other tissues leading to irreversible damage to the central nervous system manifested by mental retardation and various neurological disorders.

Phenylketonuria is a rare disease. In Poland the prevalence of PKU is about 1:7500 live births, which means that every year about 60 children with PKU are born, and every 46th adult is a carrier of the mutated gene. In the south-eastern part of the country the frequency is slightly higher at around 1:6 500, while in Wielkopolska it is 1:10 000.

The basic treatment of patients with classic phenylketonuria is a low phenylalanine diet, introduced as early as possible, optimally on day 7-10 of life. An elimination diet should be followed throughout life, or at least in infants, children and women of childbearing age. In cases of mild hyperphenylalaninemia, treatment is often not necessary. Atypical forms of PKU require nutritional treatment and administration of pharmacological agents.

The prognosis in phenylketonuria depends on the earliest possible diagnosis of the disease and the introduction of an elimination diet - low in phenylalanine - from the first days of life. Maintaining recommended blood Phe levels results in a life expectancy comparable to that of healthy individuals. Untreated PKU leads to permanent intellectual disability.

Alternative health technology

Considering clinical guidelines and technologies currently financed from public funds, non-condensed and condensed protein replacers (Milupa PKU 2 mix, Comida PKU B Formula, Milupa PKU 2 shake, Milupa PKU 3 tempora, Phenyl Free 2 HP, Phenyl Free 2, Easiphen, XP Maxamamum, Milupa PKU 3 advanta, Milupa PKU 3, Milupa PKU 2 prima, Milupa PKU 2 secunda, Lophlex, PKU Lophlex LQ, PKU Cooler 10, PKU Cooler 15, PKU Cooler 20, PKU Express 15, PKU Express 20).

Description of the benefit named in the application

The PKU GMPro product is an oral preparation with the following composition: casein glycomacropeptide (GMP) isolate (24.9%) (from cow's milk), sugar, refined vegetable oils (rapeseed oil, safflower oil, coconut oil, soybean oil, high oleic acid sunflower oil), dextrin, maltodextrin, modified corn starch, L-leucine, calcium phosphate, L-tyrosine, flavours, magnesium hydrogen phosphate, L-arginine, L-histidine, potassium chloride, L-valine, choline dihydrate, calcium hydrogen phosphate, L-cystine, L-tryptophan, dry glucose syrup, oil from the micro-algae Schizochytrium sp. , anti-caking agent (silicon dioxide), sodium chloride, L-ascorbic acid, taurine, inositol, iron(II) sulphate, L-carnitine,

DL-alpha-tocopherol acetate, nicotinamide, zinc oxide, stabiliser (sodium polyphosphate), copper(II) gluconate, manganese sulphate, calcium D-pantothenate, D-biotin, thiamine hydrochloride, pyridoxine hydrochloride, riboflavin, retinyl palmitate, pteroylmonoglutamic acid, beta-carotene, potassium iodide, chromium(III) chloride, sodium molybdate, sodium selenate, phytomenadione, cholecalciferol, cyanocobalamin.

The application indicates that the consumption dose and dilution of the product must be determined solely by the physician and depends on the patient's age, body weight and clinical condition.

Dissolve the contents of one sachet (33.3 g) in 80 ml of water to obtain a final volume of 100 ml. Depending on individual preference and product tolerance, a lower concentration may be required. The product should be consumed with water or additional liquids to ensure adequate fluid supply.

The foodstuff was approved by GIS in 2019 for the dietary management of confirmed phenylketonuria (PKU) in children over 3 years of age. However, the requested indication concerns patients with phenylketonuria over 12 years of age.

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 is phenylketonuria patients ≥ 12 years of age. Results for glycomacropeptide (GMP)-based formulations compared with phenylalanine-free (L-AA) protein replacers were included.

Clinical analysis included:

- 4 randomised trials (Ahring 2018, Ney 2016, Daly 2019b, Tiele 2019);
- 8 non-randomised controlled group trials (Daly 2020, Daly 2017, Daly 2019a, Daly 2019c, MacLeod 2010, Zaki 2016, van Calcar 2009, Daly 2012);
- 2 single-arm trials: Browne 2018 (abstract and conference poster only), (trade secret)
- 3 observational trials on practical effectiveness (Lim 2007, Proserpio 2018, Pinto 2017).

In addition, 1 secondary research was included - the Pena 2018 systematic review evaluating the efficacy of glycomacropeptide (GMP).

None of the above trials evaluates the foodstuff for particular nutritional uses applied for, i.e. PKU GMPro vanilla flavour. Two of the included trials deal with the evaluation of products similar to the one applied for ((trade secret) they evaluate a product with a coinciding name, i.e. PKU GMPro LQ - ready-to-drink liquid formulation with vanilla flavour, and Browne 2018 trial, which evaluates PhenylAde GMP Drink Mix powder formulation similar in composition).

The trials mainly assessed endpoints relating to changes in laboratory parameters and acceptability of the diet.

The reliability ratings of the Browne 2018 and (company secret) trials were rated 5/8 on the NICE scale and (trade secret) respectively

Efficacy

Laboratory parameters

Statistically significant results in favour of GMP over L-AA were noted for:

- albumin concentration, uric acid excretion, urinary calcium excretion, urinary sulphate excretion (Ney 2016).

Statistically significant results to the disadvantage of GMP against L-AA were noted for:

- a decrease in blood tyrosine concentrations (Ahring 2018);
- higher blood phenylalanine concentrations (Ney 2016, Daly 2019b trials).

Nutrient intake

Statistically significant results in favour of GMP over L-AA were noted for:

- the average daily energy value derived from the diet and the number of portions taken by the patient per day (Ney 2016).

Acceptability

Statistically significant results in favour of GMP over L-AA were noted for:

- preference of the product, preference of taking the product 3 times a day, comfort of taking the product in public situations, ease of use outside the home (Ney 2016);
- the impact of dietary intake on breath smell (Tiele 2019).

(trade secret)

Browne 2018 trial

- the final value of mean blood tyrosine concentration (µmol/L) was higher than the initial value - mean (SD): 57 (14) vs 45 (9); (p=0.02);
- there were no statistically significant differences between the initial and final values of mean plasma phenylalanine concentration and the assessment of the phenylalanine to tyrosine ratio.

Safety

Ney 2016

No adverse events were reported in either the GMP or L-AA groups.

(trade secret)

Safety information based on the PKU GMPro product leaflet:

- The product is not intended for parenteral use;
- Use under medical supervision;
- It must not be the only source of food;
- Do not use in people allergic to cow's milk;
- Product suitable for persons over 3 years of age. Do not use in children under 3 years of age. Use with caution in children 3-6 years of age;
- Only for use in phenylketonuria (PKU);
- The product must not be the only source of protein;

- The health of the patient depends on strict adherence to the directions for preparation, use and storage of the product.

Limitations

The main and key limitation of the analysis presented here is that no studies evaluating the PKU GMPro product were found, which translates into the need to make inferences based on the results of studies conducted on the entire group of GMP preparations.

Proposed risk-sharing schemes

Not applicable.

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 cost minimisation analysis in a monthly time horizon, from the perspective of the public payer - the entity obliged to finance the benefits from public funds, i.e. the National Health Fund (NHF), and from the joint perspective of the payer and the beneficiary. The results of the analysis from both perspectives were similar.

Due to the adopted analytical technique, only the cost of the evaluated intervention and the cost of other protein replacement products (i.e. comparators and products used to supplement the daily protein intake) were considered.

(trade secret)

According to estimates, the use of PKU GMPro from the NHF perspective is (trade secret)

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Limitations

The uncertainty of the presented results is mainly influenced by the lack of studies on the effectiveness of the evaluated intervention. Consequently, the performance of the cost minimisation analysis is questionable - the therapeutic equivalence of the juxtaposed options has not been demonstrated on a scientific evidence basis.

The lack of studies on the efficacy of PKU GMPro is a serious limitation to the economic analysis as none of the analytical techniques (i.e. cost-utility analysis, cost minimisation analysis or cost consequence analysis) are applicable in such a case. However, according to the minimum requirements regulation, the Agency's verification analysis must include economic analysis, so in this situation, a cost minimisation analysis seems to be the only solution and fulfilment of a formal prerequisite, although there are significant limitations in drawing conclusions on the basis of its results.

Own calculations of the Agency

No additional own calculations were performed.

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.

Not applicable.

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 results of the analysis from both perspectives were consistent.

The number of patients using the proposed technology in the new scenario was estimated to be:

(trade secret)

The results of the primary analysis indicate that the issuance of a positive decision on public funding of the foodstuff for particular nutritional uses, PKU GMPro, will result in (trade secret) expenditure by:

(trade secret)

Limitations

The main limitations of the budget impact analysis stem from, inter alia, uncertainties in the estimation of the population size, the assumed compliance rate or the inclusion of preparations indicated for a different subpopulation than the population applied for (under 12 years of age). Given the arbitrary use of available data, the presented results should be interpreted with caution.

Own calculations of the Agency

As part of the Agency's own calculations, an incremental cost comparison was conducted taking into account the average cost of 1 g of PE in the estimation excluding formulations that are not indicated for patients ≥ 12 years of age.

The estimated change in the average cost per gram of PE did not significantly affect incremental costs.

Comments on the proposed Risk Sharing Scheme (RSS)

Not applicable.

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.

In the framework of the submitted rationalisation study, the applicant proposed a solution comprising the following

(trade secret)

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

Four medical management recommendations relating to the requested indication were provided by:

- Institute of Mother and Child (Polish recommendations presented in a review paper - IMiD 2015);
- Australasian Society of Inborn Errors of Metabolism (ASIEM 2017);
- European Society for Phenylketonuria and Allied Disorders (ESPKU 2017);
- American College of Medical Genetics (ACMG 2016).

All of the found guidelines recommend the use of phenylalanine-free amino acid mixtures in patients with phenylketonuria, at the same time no reference was made to any specific formulation. Products containing a mixture of phenylalanine-free amino acids are a mainstay of dietary therapy.

Reimbursement recommendations

The search resulted in 1 reimbursement recommendation relating to the use of PKU GMPro for the phenylketonuria indication.

The Australian recommendation - PBAC 2018 was positive conditionally and indicated the need to reduce the cost of PKU GMPro to that of the primary comparator - PKU Glytactin RTD 10.

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

PRESIDENT

dr n. med. Roman Topór-Mądry

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Basis for the recommendation

The recommendation was prepared under an order dated 25 November 2020 Of the Minister of Health (reference number: PLR.4500.1036.2020) regarding the preparation of the President's recommendation on the evaluation of foodstuff for particular nutritional use PKU GMPro in the indication: phenylketonuria in patients over the age of 12 years 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), following Transparency Council Position No. 18/2021 of 15 February 2021 on the evaluation of the foodstuff for particular nutritional uses PKU GMPro in the indication: phenylketonuria in patients in patients over the age of 12 years

References

1. Position of the Transparency Board No. 18/2021 of 15 February 2021 on the evaluation of the foodstuff for particular nutritional uses PKU GMPro in the indication: phenylketonuria in patients over the age of 12 years.
2. Report No. OT.4330.20.2020 Application for reimbursement of the foodstuff for particular nutritional uses PKU GMPro in the indication: phenylketonuria in patients in patients over the age of 12 years.