

# Insight into PKU sphere™ – A GMP-based protein substitute

## Results from UK surveys of teens and adults with phenylketonuria and their dietitians

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Despite the recognised importance, poor dietary adherence and diet discontinuation remain common and serious issues in phenylketonuria (PKU). Vitaflo launched an innovative protein substitute, PKU sphere\*, in 2017. Surveys were conducted in 2019 with an objective of understanding the impact of PKU sphere on dietary adherence from the perspective of individuals with PKU and their dietitians. This article shares the findings.

### Background

PKU is a rare genetic disorder which, if untreated, leads to irreversible neurodevelopmental delay due to neurotoxic accumulation of the amino acid phenylalanine (Phe) and depletion of tyrosine.<sup>1</sup> Newborn screening for PKU is common: international guidelines recommend that a PKU diet (protein substitutes typically consumed three times daily alongside Phe/protein restriction) is initiated at diagnosis and maintained lifelong.<sup>2,3</sup> Protein substitutes supply up to 80% of protein requirements.<sup>2</sup>

Dietary management, whilst effective at preventing Phe toxicity and cognitive impairment, still has shortcomings. Some individuals struggle to accept the taste, smell, mouthfeel and daily volume, whilst others report gastrointestinal (GI) disturbance and breath malodour associated with traditional Phe-free amino acid-based formulations of protein substitutes.<sup>4-7</sup> These issues, combined with low social acceptance of the diet, are associated with deterioration in adherence and diet discontinuation.<sup>5</sup> Estimates indicate 43% of adults with PKU in Europe have poor or very poor adherence to the PKU diet.<sup>8</sup>

Poor adherence to the PKU diet leads to poor metabolic control; associated with increased blood Phe, low blood tyrosine levels, and nutritional deficiencies.<sup>2,9-13</sup> Poor metabolic control is correlated with reduced mood, IQ, cognitive ability, sustained attention and reaction times.<sup>14-18</sup>

### Next generation of protein substitutes

Glycomacropeptide (GMP) is derived from a natural protein source and is suitable for the dietary management of PKU due to its unique amino acid profile. Unmodified GMP has very low amounts of Phe, arginine, methionine, histidine, tryptophan and tyrosine and high amounts of threonine and isoleucine.<sup>19,20</sup> It requires supplementation with the limiting amino acids (apart from Phe) to produce a protein substitute for PKU which at least meets the World Health Organization (WHO) minimum safe intakes of essential amino acids.<sup>21-23</sup> GMP-based protein substitutes have been rated as more palatable<sup>24,25</sup> and preferred over amino acid-based

protein substitutes, particularly by those with poor adherence to, or who have discontinued the PKU diet.<sup>26,27</sup> All GMP-based protein substitutes contain small amounts of residual Phe.

PKU sphere is Vitaflo's innovative GMP-based protein substitute. Extensive research conducted during its development revealed that the ratio of amino acids added to a GMP-based protein substitute can significantly influence blood Phe concentration in children with good metabolic control.<sup>28</sup> This evidence informed the development of the product, ensuring optimisation of the GMP and amino acid blend for metabolic control<sup>29</sup> and palatability, whilst limiting volume, calories and the addition of sugar. In 2017, PKU sphere was launched in the UK and many individuals with PKU and their dietitians shared informal feedback that it particularly met the needs of teens and adults with difficulty adhering to their protein substitutes.

### Project scope

Online surveys distributed in 2019 aimed to evaluate the experience of using PKU sphere both from individuals with PKU and their dietitians and investigate factors related to adherence to protein substitutes. The surveys were distributed, collected and analysed by Clinical Outcomes Solutions, an independent clinical outcomes research organisation. UK metabolic dietitians, managing individuals over 13 years of age consuming PKU sphere, were contacted via the British Inherited Metabolic Disease Group. Participating dietitians chose if they also distributed a separate survey to eligible individuals on their caseload. Individuals with PKU were also made aware of the survey via a Facebook post. Eligibility for individuals with PKU:

- Aged >13 years (caregivers could complete the survey on behalf of <18-year-olds).
- Consuming PKU sphere:
  - For at least 1 month.
  - To provide at least 50% of their protein substitute intake.
  - As their first GMP-based protein substitute.

An exemption was provided by UK ethical committee after reviewing the protocol.

\*PKU sphere is a powdered, low phenylalanine protein substitute containing a balanced mix of casein GMP isolate, essential and non-essential amino acids, carbohydrate, fat, vitamins, minerals, and the long chain polyunsaturated fatty acid DHA. It is available in 3 flavours, red berry, chocolate, and vanilla and is packaged in individual serving sachets providing either 15g or 20g protein equivalent.



## Responses from dietitians

In total, 19 dietitians participated. Ninety-five per cent ( $n = 18$ ) reported that prior to the availability of GMP-based protein substitutes they had experienced cases in which they had exhausted all amino acid-based protein substitute options. Advantages of GMP-based compared to amino acid-based protein substitutes most commonly cited were:

1. Improved taste/palatability
2. Improved aftertaste
3. Improved smell.

When asked about individuals who switched to PKU sphere, 84% of dietitians ( $n = 16$ ) stated that adherence to protein substitute improved. None reported that adherence deteriorated with PKU sphere.

Advantages of PKU sphere reported by dietitians included sensory properties (84%,  $n = 16$ ), low energy content (74%,  $n = 14$ ), provision of docosahexaenoic acid (DHA) (58%  $n = 11$ ), and its low volume (69%  $n = 13$ ). Forty-two per cent ( $n = 8$ ) stated that the powdered format was a disadvantage.

### Comment from a dietitian:

*"PKU sphere offers a great low calorie, low sugar, low volume supplement. I believe it has greatly helped compliance to the PKU diet, and in turn, improved Phe levels, without having to always change exchanges"*

Dietitians were asked if, in their experience of teenagers and adults, blood Phe control is affected when PKU sphere is introduced. Answers provided in **Table 1**.

### Comment from a dietitian on their experience of the effect PKU sphere had on blood Phe for this age group:

*"It depends - if a patient has good control already, their Phe tends to increase slightly but if they have poor control their control seems to improve due to increased palatability hence improved compliance"*

## Responses from individuals with PKU

Three caregivers and 33 individuals with PKU completed the survey providing a total of 36 responses for individuals with PKU - see **Figure 1**.

All respondents chose to take PKU sphere. Eighty-nine per cent ( $n = 32$ ) reported taking PKU sphere for at least a year at the time of the survey. Eight participants (22%) took PKU sphere in combination with an amino acid-based protein substitute and of these, 75% ( $n = 6$ ) opted for a liquid product.

Prior to starting PKU sphere, 34 reported taking amino acid-based protein substitutes. Fifty-eight per cent ( $n = 21$ ) took a liquid option: PKU Lophlex LQ, Nutricia Ltd  $n = 11$ ; PKU cooler, VitaFlo Ltd  $n = 6$ ; PKU air, VitaFlo Ltd  $n = 5$ ; PKU Lophlex Sensation, Nutricia Ltd  $n = 2$ . Twenty-five per cent ( $n = 9$ ) took a powdered/tablet option: PKU express, VitaFlo Ltd  $n = 6$ ; Phlexy-10 tablets, Nutricia Ltd  $n = 3$ ; Phlexy-10 drink mix, Nutricia Ltd  $n = 2$ ; PKU Maxamum, Nutricia Ltd  $n = 1$ ; PKU Lophlex powder, Nutricia Ltd  $n = 1$ ; Phlexy-10 capsules, Nutricia Ltd  $n = 1$ . Four (11%) took a combination of liquid and powdered protein substitutes. Two reported not taking any product.

Ninety-two per cent ( $n = 33$ ) stated that the taste of PKU sphere was better than their previous protein substitutes, and 8% ( $n = 3$ ) stated that the taste was the same.

### Comments from individuals with PKU:

*"I was going back on diet and sampled a number of options. PKU sphere was the best tasting"*

*"the flavours are much more tasteful without the bitterness usually associated with amino acid-based supplements"*

Respondents were asked to comment on aspects of their protein substitute. PKU sphere compared more favourably to amino acid-based protein substitutes in every category (**Table 2**), in addition 58% ( $n = 21$ ) reported that PKU sphere improved their ability to adhere to the PKU diet.

Ninety-one per cent ( $n = 31$ ) of individuals with PKU stated that physical properties of PKU sphere supported adherence, including being supplied with a sports shaker (65%,  $n = 22$ ), easy to transport (59%,  $n = 20$ ), and low in volume (56%,  $n = 19$ ). Two individuals (6%) indicated that it was difficult to transport. Forty-seven per cent ( $n = 16$ ) reported that 'appearance similar to normal protein shakes/less self-conscious' aided adherence.

Fifty-six per cent ( $n = 20$ ) of PKU individuals reported that they were adherent to their protein substitute (taking >80% of recommended protein substitute) prior to switching to PKU sphere. When taking PKU sphere this figure improved to 89% ( $n = 32$ ), suggesting that PKU sphere enabled an increased level of adherence, compared to amino acid-based protein substitutes for 33% ( $n = 12$ ) of individuals with PKU. This is illustrated in **Figure 2**.

Sixteen individuals (44%) were classified as non-adherent to amino acid

protein substitutes (taking <80% of their recommended amount), reasons stated were poor sensory properties, GI symptoms and breath malodour. All these individuals reported the taste of PKU sphere was better than amino acid-based protein substitute options. Of this group, over 75% ( $n = 12$ ) self-reported PKU sphere had improved their ability to adhere to the PKU diet, and that they consumed >80% of their recommended amount of PKU sphere and so classified as adherent to PKU sphere. Over two-thirds of these 16 individuals had been taking PKU sphere for at least a year at the time of the survey. Four of these 16 reported they remained non-adherent after switching to PKU sphere, reasons selected were forgetting and difficult to transport.

## Discussion

GMP-based protein substitutes have provided individuals with PKU and their dietitians with alternatives to support dietary management. Prior to GMP-based protein substitutes being available, 95% of dietitians surveyed had experienced cases where they had not been able to find an accepted protein substitute option. Palatability was the main advantage of GMP-based protein substitutes reported by individuals and their dietitians, which corresponds with the findings of other publications.<sup>22, 24-26</sup>

In addition to taste, other properties of PKU sphere rated highly included: nutritional (low calorie, DHA content) by dietitians, and physical (low volume, appearance similar to a protein shake and provision of a sports shaker) by individuals with PKU. Some dietitians shared that the powdered format of PKU sphere was a disadvantage, which corresponds with some individuals choosing to take a PKU sphere and liquid protein substitute combination.

All GMP-based protein substitutes contain a small amount of Phe. Caution is recommended when introducing to children and individuals with a low Phe tolerance.<sup>28-30</sup> The dietitians' responses, combined with their comments, indicated that this additional Phe may affect blood Phe control for a small number of teenagers and adults. Most dietitians reported that blood Phe control was maintained or improved after switching to PKU sphere with comments that teenagers and adults with poor adherence benefit most.

In a study, children with PKU self-reported more breath malodour with amino acid- over GMP-based protein substitutes and were more self-conscious about breath odour compared to controls. This research found no significant difference in volatile organic compounds linked to breath malodour, measured 30 minutes after protein substitute consumption.<sup>4</sup>

Sixty-seven per cent of teens and adults with PKU in this survey self-reported breath malodour improved after switching to PKU sphere.<sup>4</sup> GI symptoms of diarrhoea, constipation, heartburn, nausea, and abdominal pain associated with amino acid-based formulations have been documented,<sup>6, 7</sup> high osmolality has been considered a contributor.<sup>31</sup> Over half of the individuals with PKU in the survey reported an improvement in GI symptoms after switching to PKU sphere - further research would be beneficial. Interestingly, most of the individuals with PKU reported benefits to breath malodour and GI symptoms, which wasn't well represented in dietitian's responses. This may indicate that these issues aren't highlighted at dietetic appointments.

Selection bias, self-reported measures and small sample sizes are limitations of the surveys. Individuals with PKU who responded had higher than UK average academic achievements and had chosen to take PKU sphere as their first GMP-based protein substitute.

It is, however, encouraging that 89% of individuals self-reported adherence to PKU sphere, which was consistent with the experience of 84% of dietitians who reported adherence improved after switching to PKU sphere.

### Conclusion

Individuals with PKU and their dietitians reported that PKU sphere offers sensory advantages compared to amino acid-based protein substitutes, including improved taste, aftertaste and smell. Individuals with PKU reported improved breath malodour and GI symptoms when taking PKU sphere and stated its taste, low volume, looking similar to a protein shake and provision of a sports shaker were advantages over amino acid-based protein substitutes. Most dietitians and individuals with PKU surveyed agreed that these attributes can promote adherence to protein substitutes, which may in-turn support improved clinical outcomes.

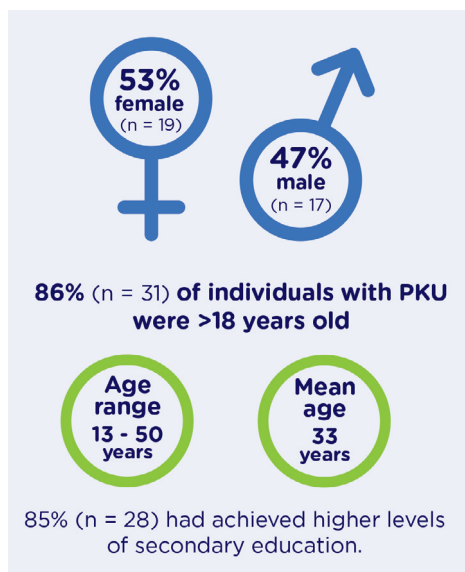
**Table 1: Dietitian's reported changes in blood Phe**

In your experience, when a patient changes from another product to PKU sphere does blood Phe control:	
	% of responders
Improve	42 (n = 8)
Remain the same	16 (n = 3)
Worsen	5 (n = 1)
Unknown	32 (n = 6)
Incomplete data	5 (n = 1)

**Table 2: Percentage of individuals who selected reasons which enabled them to consume their protein substitute (Participants could select more than one option)**

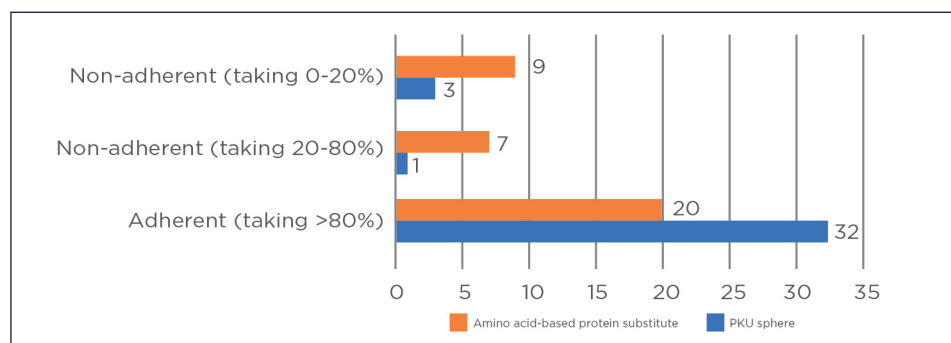
Why are you able to take your protein substitute regularly every day?	Amino acid-based protein substitutes (n = 36)	PKU sphere (n = 34**)
Like the taste	8 (n = 3)	79 (n = 27)
Like the smell	3 (n = 1)	42 (n = 14)
Like the flavour options	11 (n = 2)	50 (n = 17)
Low in calories	17 (n = 6)	35 (n = 12)
Low sugar content	6 (n = 2)	21 (n = 7)
Low volume	14 (n = 5)	56 (n = 19)
Easy to transport	42 (n = 15)	59 (n = 20)
Appearance similar to normal protein shakes/less self-conscious	0	47 (n = 16)
Preparation options and recipes	3 (n = 1)	21 (n = 7)
No stomach upset	3 (n = 1)	53 (n = 18)
Less breath odour	0	47 (n = 16)

**Figure 1: Individuals with PKU**



\*\* Survey participants were only prompted to answer this question if reported they were able to take PKU sphere every day.

**Figure 2: Reported degree of adherence to recommended amount of protein substitute**



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