

A practical guide to PKU sphere®



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dietary management of rare diseases



Important information

PKU sphere is a low phenylalanine (Phe) protein substitute containing a blend of glycomacropeptide (GMP), essential and non-essential amino acids (AA), carbohydrate, fat, vitamins, minerals and docosahexaenoic acid (DHA).

Purpose

This practical guide is for the use of PKU sphere in the dietary management of children and adults with phenylketonuria (PKU).

Intended users

This practical guide is:

- for use by **health care professionals** working with individuals with PKU.
- **not** for use by individuals with PKU or their parents/caregivers.
- for **general information** only and must not be used as a substitute for professional medical advice.

Product information

PKU sphere is a food for special medical purposes.

PKU sphere must be used under medical supervision.

Not for use as a sole source of nutrition.

PKU sphere is suitable over 3 years of age.

PKU sphere must only be consumed by people with Phenylketonuria (PKU). Diet must be supplemented with natural protein, water and other nutrients in prescribed quantities to supply phenylalanine, fluid and general nutritional requirements.

Protein substitutes based on GMP are a source of Phe.

For enteral use only.

Any product information contained in this practical guide, although accurate at the time of publication, is subject to change. The most current product information may be obtained by referring to product labels and www.vitafloweb.com. Please refer to these sources for information regarding allergens.

Introducing and adjusting PKU sphere is dependent on the individual patient. Practical examples are given in this guide; however, it is the responsibility of the managing health care professional to use clinical judgement to introduce and adjust PKU sphere in the most appropriate way for individual patients and it may not always be appropriate to use the practical guide.

Disclaimer

The information contained in the practical guide is for general information purposes only and does not constitute medical advice. The practical guide is not a substitute for medical care provided by a licensed and qualified healthcare professional and Vitaflo does not accept any responsibility for any loss arising from reliance on information contained in this guide. This practical guide should be read in conjunction with local, national and international guidelines and best practice for the dietary management of PKU. Information contained within the guide is based on the most recent scientific evidence available on the use of GMP-based protein substitutes/PKU sphere in PKU as of June 2022.

This practical guide does not establish or specify particular standards of medical care for the treatment of any conditions referred to in this practical guide. Vitaflo® International Limited does not recommend or endorse any specific tests, procedures, opinions, clinicians or other information that may be included or referenced in this practical guide.

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Abbreviations

AA	Amino acids.
DHA	Docosahexaenoic acid.
GI	Gastrointestinal.
GMP	Glycomacropeptide.
GMP-Protein substitute	GMP-based protein substitutes supplemented with the limiting free amino acids +/- micronutrients and essential fatty acids. May vary in format - powder, liquid, or bar.
AA-Protein substitute	Phenylalanine free protein substitutes based on synthetic amino acids +/- micronutrients and essential fatty acids. May be powder, liquid, bar, or tablet.
LNAAs	Large neutral amino acids.
PE	Protein equivalent.
Phe	Phenylalanine.
PKU	Phenylketonuria.
Unmodified GMP	Glycomacropeptide as a raw material isolated from cheese whey.
WHO	World Health Organisation.



Introduction

Professor Anita MacDonald PhD, BSc, OBE

A lifelong phenylalanine (Phe)-restricted diet is the primary treatment for Phenylketonuria (PKU) ⁽¹⁾. Over recent years dietary management has progressed to enable better quality of life and long-term health outcomes for individuals with PKU ⁽²⁾. Protein substitutes are the cornerstone of the dietary management, essential to promote normal growth, prevent protein deficiency, provide a source of tyrosine and help to optimise blood Phe control ^(1,3).

Since the 1980's protein substitutes for PKU have been based on synthetic Phe-free L-amino acid (AA) mixtures ⁽²⁾. In 2008 commercial protein substitutes using glycomacropeptide (GMP) were made available in USA ⁽⁴⁾. All GMP-based protein substitutes for PKU are made using a combination of GMP and single L-AAs, with GMP contributing between 1 and 2 mg of Phe per 1 g of protein equivalent (PE). GMP has been associated with improved taste and palatability ^(2, 5-11) and further potential advantages of GMP compared to AA-based protein substitutes in PKU dietary management have been reported in scientific literature ^(1, 12).

PKU sphere is Vitaflo's first GMP-based protein substitute for PKU. PKU sphere is the only GMP-based protein substitute which has been evaluated over a long-term (3 years) in children and teenagers ⁽¹³⁻¹⁵⁾. This research, and subsequent publications, have increased the knowledge and evidence available for GMP-based protein substitutes particularly in relation to the influence on metabolic control, biochemical status, growth, body composition and bone status in children and teenagers with PKU ⁽¹³⁻¹⁸⁾.

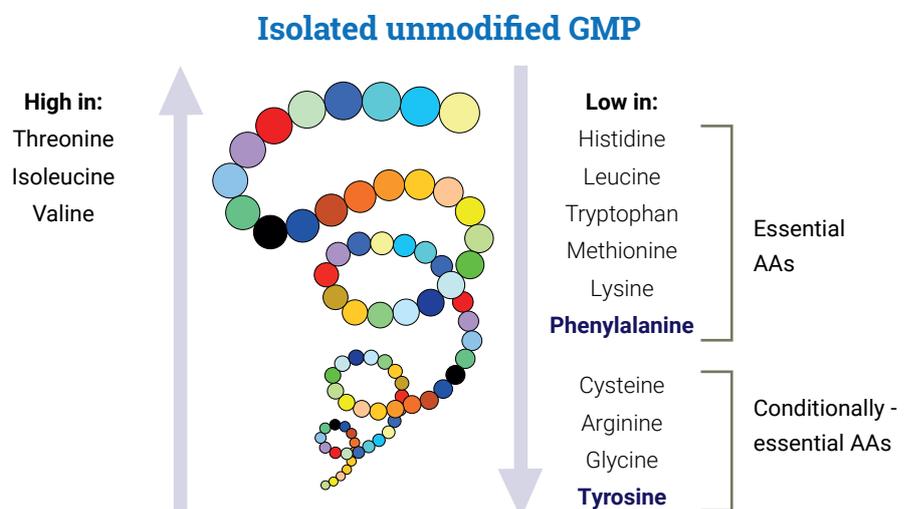
This practical guide was developed to support the use of PKU sphere through sharing knowledge and experience gained from its development, clinical trials, use in clinical practice and further research.

1.1 What is GMP and how is it produced?

GMP is a macropeptide, derived from a natural protein source and is a by-product of the cheese-making process. To be suitable for the use in PKU, GMP must be isolated, passed through a fractionation process and then further purified ⁽¹⁹⁻²¹⁾. During this isolation process, small amounts of other proteins that contain Phe become present in the isolated GMP ^(22, 23) therefore all GMP-based protein substitutes for PKU contain some residual Phe.

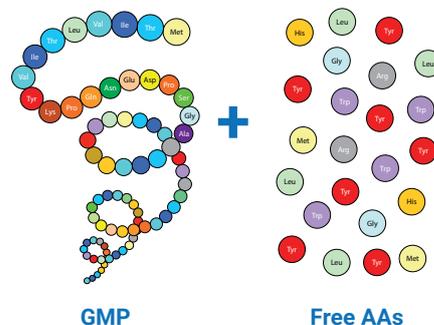
AA profile of GMP

Isolated, unmodified GMP has a unique AA profile. It is low in essential L-AAs including Phe, histidine, leucine, tryptophan, methionine and lysine and conditionally essential L-AAs cysteine, arginine, glycine and tyrosine. It also contains high amounts of threonine, valine and isoleucine ⁽²⁴⁾.



To be suitable for a protein substitute for PKU, GMP requires supplementation with L-AAs to:

- at least meet World Health Organisation (WHO) requirements of essential AAs ^(13, 18, 25).
- prevent essential AA deficiencies that would be rate limiting for protein synthesis, particularly tyrosine which is conditionally-essential in PKU ⁽³⁾.
- ensure an overall good quality protein for growth, development and tissue repair ⁽²⁶⁾.



1.2 Physical and functional properties of GMP

Physical and functional properties have been attributed to GMP's unique chemical structure ⁽²⁷⁾.



GMP is associated with improved palatability including taste, aftertaste, smell and mouthfeel, when compared to AA-based protein substitutes ^(2, 5-11).

Increasing evidence suggests GMP could offer benefits for:



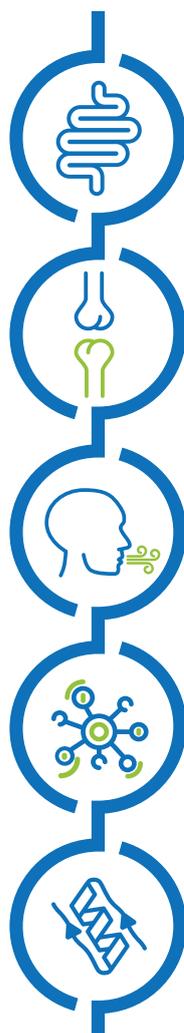
adherence to protein substitute recommendations ^(5, 7, 11)

growth and body composition ⁽¹⁴⁾

blood Phe variability ⁽¹⁷⁾

reduction of Phe in the brain ^(4, 33-35)

dental health ^(27, 37-39)



less constipation and abdominal discomfort ^(5, 27-31)

bone health ⁽¹⁵⁾

perceived breath malodour ^(5, 32)

enhanced absorption or bioavailability of specific micronutrients ^(13, 36)

protein absorption and utilisation ^(8, 16, 17, 40)

Further information can be found in Appendix 1.

2.2 PKU sphere format

PKU sphere's powdered and liquid formats have been designed to maximise protein equivalent delivery in a low volume. Low volume protein substitutes play an important role in supporting adherence to prescribed daily intake ⁽⁴³⁾.

In a UK survey of teenagers and adults with PKU and their dietitians:

- 92 % (n=33) of teenagers and adults with PKU said that the physical properties of PKU sphere powder supported their adherence, including the appearance being similar to a protein shake, being supplied with a sports shaker, easy to transport and low in volume.
- 84 % of dietitians (n=16) stated that their teenage and adult patients' adherence to protein substitute improved after switching to PKU sphere powder. Advantages of PKU sphere rated highest by dietitians included sensory (taste, smell, mouthfeel and aftertaste), low energy content, provision of DHA and its low volume ⁽⁵⁾.

PKU sphere powder

PKU sphere powder is packaged in pre-measured sachets, no weighing or measuring is required.

PKU sphere15



PKU sphere20



PKU sphere liquid

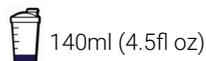
PKU sphere liquid is ready-to-drink in a resealable bottle. In PKU, ready-to-drink protein substitutes have been associated with better convenience and adherence ⁽⁴⁴⁾.

PKU sphere20 liquid



PKU sphere powder is indicated from 4 years.

PKU sphere liquid is indicated from 3 years.



237ml (8fl oz)

	Powder 15g PE	Powder 20g PE	Liquid 20g PE	
Calories (kcal)	91	120	120	Same
Fat (g)	1.3	1.6	1.2	Minor difference
Carbohydrate (g)	4.9	6.3	6.6	Minor difference
Protein equivalent (g)	15	20	20	Same
GMP: AA blend				Same
Phe (mg)	28	36	30	Minor difference
DHA (mg)	85	110	109	Minor difference
Micronutrient profile*				Minor differences

* For further information or resources see Appendix 2.

2.3 Introducing or transitioning to PKU sphere

GMP-based protein substitutes contain between 1 and 2mg of Phe per 1g PE.

Some individuals with PKU can quickly and easily commence or transition to PKU sphere as their sole source of protein substitute ^(1, 11).

This could include individuals:

- Who are teenagers or adults (excluding pregnant women) with a higher Phe tolerance or higher target blood Phe levels.
- With hyperphenylalaninemia/mild PKU.
- Returning to a Phe-restricted diet.
- With poor adherence to currently prescribed protein substitutes.
- Already established on a GMP-protein substitute.
- Requiring a protein substitute alongside PKU medications (sapropterin or pegvaliase-pqpz).

For others, a more gradual approach may be advised, and the transition to PKU sphere may only be partial ⁽¹³⁾.

This could include individuals:

- With a lower Phe tolerance
- With lower target blood Phe levels

Children and women with PKU who are pregnant or trying to conceive have strict target blood Phe levels with European ⁽³⁾ and American ⁽⁴⁵⁾ guidelines advising blood Phe levels no higher than 360µmol/L.

The additional Phe from GMP is likely to be clinically significant for these individuals and a gradual and systematic introduction with close monitoring, outlined in 2.4, is likely to be beneficial.



PKU sphere is the only GMP-based protein substitute to be evaluated in a long-term (3 years) clinical trial in children and teenagers with PKU ⁽¹⁴⁾. Clinical findings included:

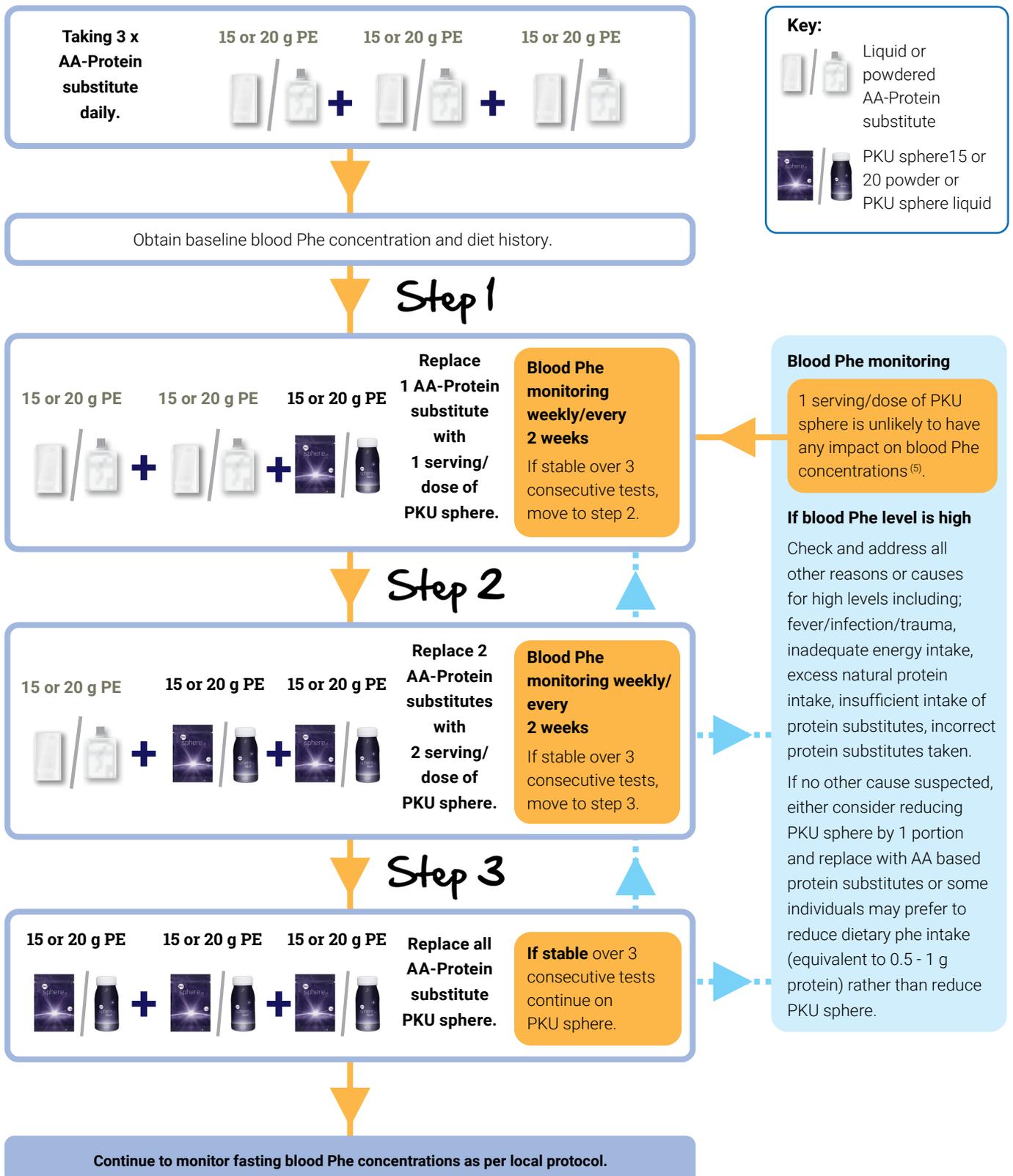
- With careful dietary management, all participants maintained blood Phe levels within their target range ^(13, 14).
- All participants were able to replace at least 1 AA-based protein substitute with 1 sachet of PKU sphere powder, providing 20 g PE and 36 mg Phe, without compromising metabolic control ⁽¹³⁾.
- ~50 % (n=14) of participants were able to transition to PKU sphere to provide 100% of their daily protein substitute requirement ⁽¹³⁾.
- Even those with a low Phe tolerance were able to take up to 75 % of their daily protein substitute requirement from PKU sphere, without adjustment of dietary Phe, or compromising metabolic control, when introduced gradually and systematically ⁽¹³⁾.

A summary of the clinical development of PKU sphere is available.



Introducing GMP-based protein substitutes/PKU sphere gradually, in a systematic way, allows monitoring of metabolic control and discussion with the patient/caregiver at each step. A decision can be made as to continue to increase PKU sphere, remain on a combination of PKU sphere and AA-based protein substitutes or consider reducing dietary Phe, depending on blood Phe control and individual preference.

The following step-by-step diagram is based on the protocol and results of Daly et al, 2019 ⁽¹³⁾.



Considering individuals with PKU:

Taking PKU medications

In recent years, pharmaceutical options have been licensed for PKU including sapropterin dihydrochloride and pegvaliase. Both medications aim to reduce blood Phe concentrations and can be used as a single therapy or in combination with a Phe-restricted diet ⁽⁴⁶⁾.

Approximately half of all individuals with long-term sapropterin responsiveness continued to require protein substitutes to meet their protein requirements and to achieve adequate metabolic control ⁽⁴⁶⁾. Individuals taking pegvaliase, mean protein substitute intake reduced from 26.3g at baseline to 24.2g at 12 months and 18.4g at 24 months ⁽⁴⁷⁾.

One of the main concerns of long-term pharmaceutical options is the nutritional adequacy of a the diet when protein substitute is reduced or stopped ⁽⁴⁶⁾. PKU sphere offers a palatable, nutritionally comprehensive product ⁽⁵⁾.

Individuals with low adherence to protein substitutes or returning to dietary management

Some adults patients acknowledge the benefits of maintaining lower blood Phe concentrations but find it too challenging and impractical to sustain dietary management. Individuals with low adherence to protein substitutes may include adults who discontinued diet in childhood by direction of their medical team prior to recommendation of lifelong treatment, those who have stopped their dietary management in part or completely despite diagnosis by new born screening, and those who were late diagnosed and treated ⁽⁴⁸⁾.

Two studies identified that improvements in overall palatability of protein substitutes have enabled many individuals return to ⁽⁶⁾, and maintain dietary management ^(6, 11). Improved palatability of GMP has been linked to enhanced protein substitute adherence, particularly for those individuals with poor adherence ^(5, 7).

The additional Phe from GMP is unlikely to be clinically significant for these individuals ^(1, 11). Individuals undergoing sapropterin responsive testing may still need to count the additional Phe from GMP.

GMP-based protein substitutes have been popular with individuals with poor adherence or accustomed to a higher natural protein intake ^(5-7, 11). PKU sphere offers a palatable option to support engagement and adherence with protein substitutes making it an ideal product to support dietary adherence for those taking PKU medications or returning to the PKU diet ^(5, 6).

Maternal PKU

Published clinical research on the use of GMP-based protein substitute during preconception and pregnancy (maternal PKU) is limited. Clinical experience of including GMP-based protein substitutes in maternal PKU is increasing ^(49, 50).

Factors which would be considered when assessing the appropriateness of a GMP-based protein substitute/PKU sphere for this group include: Phe tolerance (likely to be low prenatally and high in the third trimester ⁽⁴⁵⁾); severity of pregnancy associated nausea and vomiting; blood AA concentrations; adherence to current protein substitute; and variability of blood Phe concentrations.

Adherence with protein substitutes during pregnancy is critical. Improved metabolic control and intake of protein, energy, vitamin B₁₂ and folate are associated with adherence to protein substitutes and have been correlated with good foetal outcomes ⁽⁵¹⁻⁵³⁾.

If the use of GMP-based protein substitutes have been identified to be appropriate by the clinical team a gradual and systematic introduction with close monitoring, outlined in 2.4, is likely to be beneficial.

A case study series is available detailing dietitians' experiences of introducing PKU sphere with a child, teenager, and adult with PKU including during preconception and pregnancy.





When considering individuals for PKU sphere

Discuss PKU sphere as an alternative protein substitute including:

- Potential benefits of GMP for PKU – see section 1 and appendix 1 for further information.
- Phe content.

Taste test:

- Little, frequent tastes over several days or weeks might be preferred. Feedback from clinicians who conducted the clinical trial included that some children took a week or so to initially adjust from their AA-based protein substitute to the taste of PKU sphere.
- Some children may benefit from peer support at a group event for encouragement and reward or sticker charts to support the change to a new protein substitute.



If interest to start PKU sphere expressed

- Discuss individual preference to fully or partially transition to PKU sphere.
- Identify any significant Phe or calorie difference between current protein substitute and PKU sphere and if any dietary change is needed to compensate.
- A baseline blood Phe concentration, diet and gastrointestinal (GI) symptom history (frequency, consistency, discomfort) is recommended.



When starting PKU sphere

It is recommended for protein substitutes to be taken:

- At regular intervals, evenly spread throughout the day.
- Alongside regular meals.
- Followed by a permitted drink ⁽¹⁾.

Advise on keeping the natural protein intake stable.

When transitioning to PKU sphere, emphasize the importance of following the advice of their clinical team and to continue to take all prescribed amounts of protein substitute.



GMP is associated with improved palatability

- including taste, aftertaste, smell and mouthfeel; compared to AA-based protein substitutes ^(2, 5-10, 24).
 - GMP-based protein substitutes have been rated as more palatable and acceptable than AA-based protein substitutes by individuals with PKU with regard to their taste, odour, appearance and texture ^(7, 9, 11). This was particularly noticeable for those with poor adherence to protein substitutes ⁽⁷⁾.
 - 81% (n=13) of PKU adults who returned to diet opted for a GMP-based protein substitute ⁽⁶⁾.
 - 10 out of 11 adults with PKU reported that GMP-based protein substitutes had superior sensory properties compared to their previous AA-based products ⁽⁸⁾.
 - When investigating a GMP “cheese” spread, which was not supplemented with free AAs and so could only contribute 50% of their protein substitute requirements, all 10 participants preferred the GMP-based regimen due to a better taste compared to AA-based protein substitutes ⁽¹⁰⁾.
 - Palatability was the main advantage of GMP-based protein substitutes reported by individuals with PKU and their dietitians in a UK survey. Ninety-two per cent (n = 33) of individuals with PKU stated that the taste of PKU sphere was better than their previous protein substitutes and 84% of dietitians (n = 16) reported that sensory properties of PKU sphere were an advantage ⁽⁵⁾.

Increasing evidence suggests GMP could also offer benefit for:



Adherence to protein substitute intake

- A sensory study linked improved palatability of GMP-based protein and enhanced dietary adherence, particularly those with poor adherence ⁽⁷⁾.
- 2 studies identified that improvements in overall palatability of protein substitutes enabled many individuals return to ⁽⁶⁾, and maintain dietary management ^(6, 11).
- In a UK survey, 56% (n = 20) of PKU individuals reported that they were adherent to their 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 AA-based protein substitutes for 33% (n = 12) of individuals with PKU. This was consistent with the experience of 84% (n=16) of UK dietitians who reported adherence to protein substitute improved after adults and teenagers switched to PKU sphere ⁽⁵⁾.



Less constipation and abdominal discomfort

- GMP has been found to have prebiotic ^(30, 31) and anti-inflammatory properties ^(27, 29).
- Reduced constipation and abdominal discomfort was observed in children with tyrosinemia 7 days after starting TYR sphere ⁽²⁸⁾.
- Adults and teenagers with PKU self-reported an improvement in GI symptoms after switching to PKU sphere ⁽⁵⁾.

3.1 Appendix 1: Scientific references: clinical benefits of GMP



Growth and body composition

- A trend towards improved growth and body composition was observed in children consuming GMP-based protein substitutes (PKU sphere) long term as their sole source of protein substitute when compared AA- or a combination of both AA- and GMP-based protein substitutes ⁽¹⁴⁾.



Bone health

- Children and teenagers with good metabolic control were found to have bone density in the normal range and long-term consumption of GMP-based protein substitutes (PKU sphere) was found to support normal bone growth and density consistent with AA-based protein substitutes ⁽¹⁵⁾.
- Adherence to protein substitute intake, especially one fortified with a comprehensive nutrient profile, have been linked to improvements in markers of bone health ⁽⁵⁴⁻⁵⁶⁾.
- [Click here for an overview of the evidence around GMP potential benefits in bone.](#)



Blood Phe variability

- In a randomised controlled study, PKU sphere was associated with stabilisation of blood Phe concentrations with less fluctuation over 24 hours compared to AA-based protein substitutes ⁽¹⁷⁾.



Perceived breath malodour

- Children with PKU self-reported less breath malodour with GMP- than AA- based protein substitutes, however there wasn't a significant difference in volatile organic compounds measured 30 minutes after protein substitute consumption ⁽³²⁾.
- In a survey, 67% (n=24) of teenagers and adults with PKU self-reported breath malodour improved after switching to PKU sphere ⁽⁵⁾.



Reduction of Phe in the brain

- LNAA supplementation has been found to reduce brain Phe concentrations ^(33,34). GMP-based protein substitutes are higher than AA-based versions in certain LNAA ⁽¹³⁾.
- In PKU mouse models, a GMP supplemented diet was associated with lower brain Phe concentrations compared to an AA supplemented diet ^(4,35).

3.1 Appendix 1: Scientific references: clinical benefits of GMP



Enhanced absorption or bioavailability of specific micronutrients

- Including selenium ⁽¹³⁾ and zinc ⁽³⁶⁾.



Dental health

- GMP has been found to reduce or prevent enamel erosion ⁽³⁷⁾, dental caries and has been incorporated into some commercial toothpastes ^(38, 39).

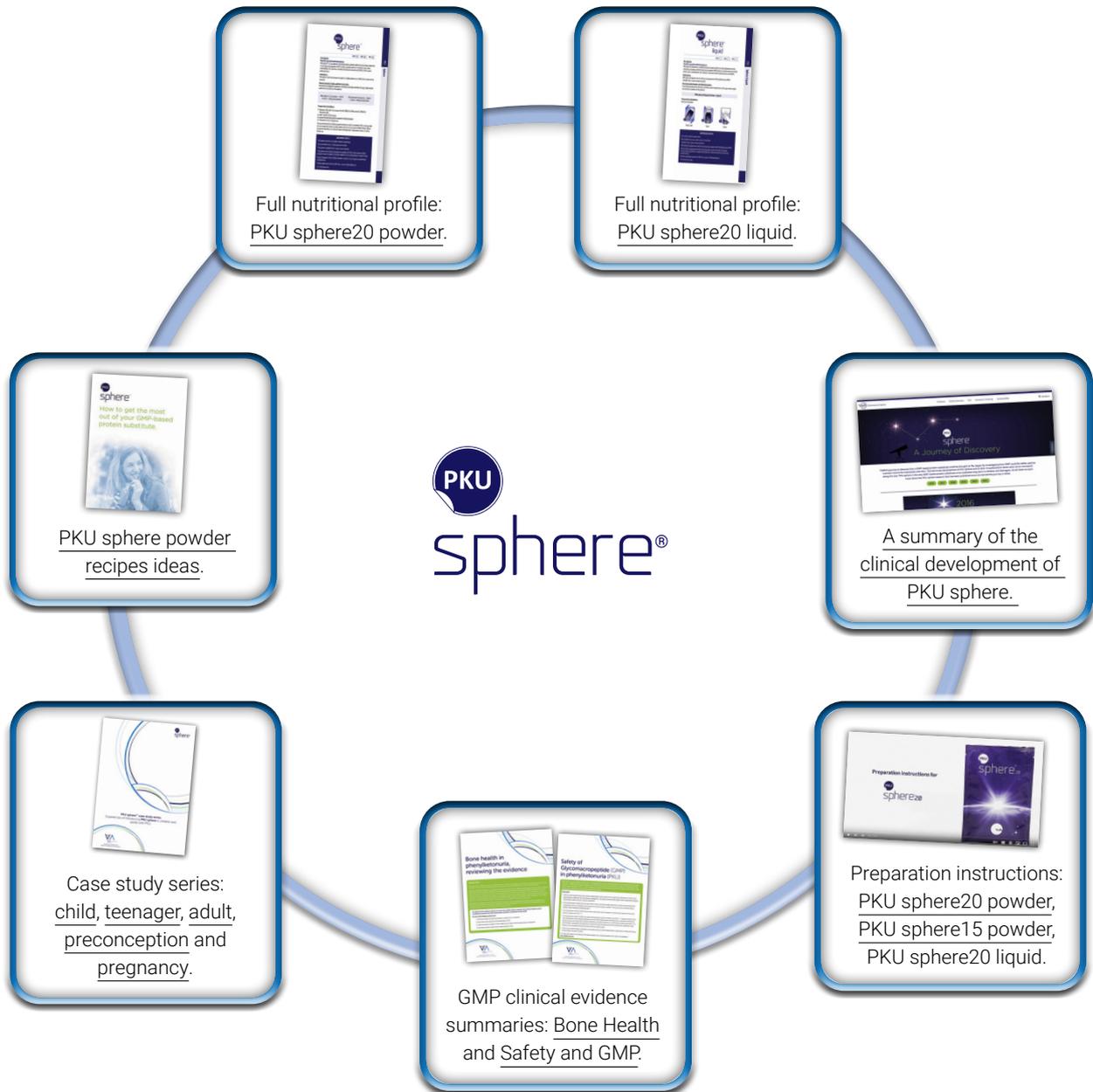


Protein absorption and utilisation

- As a macropeptide, GMP is closer in structure to intact dietary protein than free AAs and therefore may be a more physiological way to meet protein requirements. Some studies in PKU have indicated that GMP-based, compared to AA-based protein substitutes, may have a slower rate of AA absorption and therefore lead to improved protein utilisation ^(8, 40).
- Daly *et al*, concluded that GMP-based protein substitutes appear to give less Phe variability, which could lead to improvement in whole body protein balance and skeletal muscle synthesis, however the Phe present in GMP products may mask this effect ⁽¹⁷⁾.
- A preliminary investigation compared the impact of GMP-based and AA-based protein substitutes on pre and post prandial blood AA profiles in children with PKU showed a post-prandial rise in AAs which was reflective of the protein substitute AA profile. This study indicated that GMP-based protein substitutes are absorbed similarly to those which are AA-based ⁽¹⁶⁾.

More research could help to understand if GMP offers additional benefits for individuals with PKU.

3.2 Appendix 2: Further information and resources



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