



A practical guide to **PKU sphere™**.



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Supporting education in the
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Disclaimer

This practical resource should be **read in conjunction with local guidelines** for the dietary management of phenylketonuria (PKU). It is based on the most recent scientific evidence available on the use of glycomacropeptide (GMP) based protein substitutes in PKU. PKU sphere is a protein substitute consisting of a blend of GMP and free amino acids (**GMP based protein substitutes**) for use in the dietary management of children 4 years + and adults with PKU.

This guide is **for use by health care professionals** working with children and adults diagnosed with PKU.

It is **not for use by parents/caregivers of children or adults with PKU**.

It is for general information only and must not be used as a substitute for professional medical advice.

Any product information contained in this 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.

PKU sphere is a food for special medical purposes (FSMP) to be used under medical supervision. The term protein substitute is used throughout this guide. Protein substitutes might also be known as medical formulas, PKU medical food or PKU protein supplements.

PKU sphere is not suitable as a sole source of nutrition and is designed to supplement a low phenylalanine (Phe) diet. A low phe diet should provide essential phe requirements, protein, energy, nutrients and water to supply fluid and general nutritional requirements.

PKU sphere contains Phe - 36mg per 20g PE and 28mg per 15g PE; this must be taken into consideration when introducing PKU sphere into the dietary management of PKU.

The example for introducing **PKU sphere** in section 2.5 is based on data from a clinical trial Daly et al. 2017 where natural protein/exchanges remained the same throughout introduction of **PKU sphere**. Introducing **PKU sphere** gradually, in a systematic way, allows monitoring of metabolic control and discussion with patient/caregiver at each step.

It is the responsibility of the managing health care professional to use their clinical judgment to introduce PKU sphere in the most appropriate way for their individual patients.

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Foreword

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Abbreviations

AA	Amino acids.
GMP	Glycomacropeptide.
GMP based protein substitutes	Protein substitutes based on GMP supplemented with the limiting free amino acids +/- micronutrients and essential fatty acids. May vary in format - powder, liquid or bar.
AA based protein substitutes	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.
Unmodified GMP	Glycomacropeptide as a raw material isolated from cheese whey.



In the 1950's, the first protein substitute, which was based on protein hydrolysate, was developed to treat the first patient with PKU managed with diet therapy¹. For the last 30 years, the most commonly used protein substitutes have been amino acid (AA) based protein substitutes. They were originally developed using human breast milk as the reference protein.

Dietary treatment of PKU is multifaceted, challenging and lifelong²⁻⁴. Key dietary behaviours associated with optimal control of blood Phe levels include the avoidance of high protein foods plus evenly-distributed consumption of the AA based protein substitutes throughout the day³⁻⁵. PKU is a chronic condition, and although it is not unusual for adherence to be poor⁶ particularly in teenagers and adults, it is essential that treatment is lifelong in order to achieve optimal neuropsychological functioning. Common issues with protein substitute adherence in patients of all ages is their palatability, smell, taste, texture and aftertaste^{2, 7, 8}.

Individuals with PKU have rated GMP based protein substitutes as more palatable and acceptable than amino acid based protein substitutes with regard to taste, odour, appearance and texture^{9, 10}. Any new dietary option that offers an alternative to AA based protein substitutes should be considered as it may help to improve adherence and quality of life for individuals with PKU^{11, 12}.

Glycomacropeptide (GMP) is a well-researched protein that offers an alternative approach to protein substitutes provision in PKU. GMP is a natural protein that is produced as a by-product of the cheese making process. Unmodified, it has an incomplete amino acid profile; it is not only low in Phe, but it is also low in other important amino acids in PKU such as tyrosine, leucine and tryptophan¹³⁻¹⁵. Thereby, GMP requires measured and appropriate supplementation of these amino acids (apart from Phe) in order to aid attainment of satisfactory blood Phe levels as well as have potential to correct some large neutral amino acid (LNAAs) deficiencies in the brain¹⁶. GMP combined with these limiting essential amino acids and additional micronutrients ensure its suitability as an alternative to AA based protein substitutes^{12, 17, 18}. In addition to meeting requirements, the blend of amino acids used to supplement GMP has a significant impact on metabolic control¹⁷.

Due to its structure, GMP may also have other potential health benefits (see Appendix 1). The vast majority of evidence is from animal studies, however short-term cohort studies and case studies have been reported^{9, 12, 19}.

Vitaflo has carefully developed and researched a new GMP based protein substitute (**PKU sphere**) suitable for PKU. The blend of amino acids added to GMP in PKU sphere has been developed with controlled, clinical research^{17, 20, 21}. We now have over 4 years' experience of using this product in children and teenagers with PKU in the UK; we have assessed its acceptability and tolerance plus its effects on plasma amino acid profiles, micronutrient levels and growth when compared with conventional AA based protein substitutes.

Vitaflo have developed this guide on the use and introduction of **PKU sphere** in children over the age of 4 years and adults. Like any GMP based protein substitutes, it does contain some Phe (36 mg/20g protein equivalent), so it is essential that every patient with PKU is assessed individually taking into account their current adherence to protein substitutes and diet, Phe tolerance, metabolic control and this residual amount of Phe within **PKU sphere**. Following the suggested step wise system (illustrated in section 2.5) for introducing **PKU sphere** will aid its successful introduction without loss of metabolic control. Some patients may be able to fully or partially replace their conventional AA based protein substitutes with **PKU sphere**²¹.

Anita MacDonald

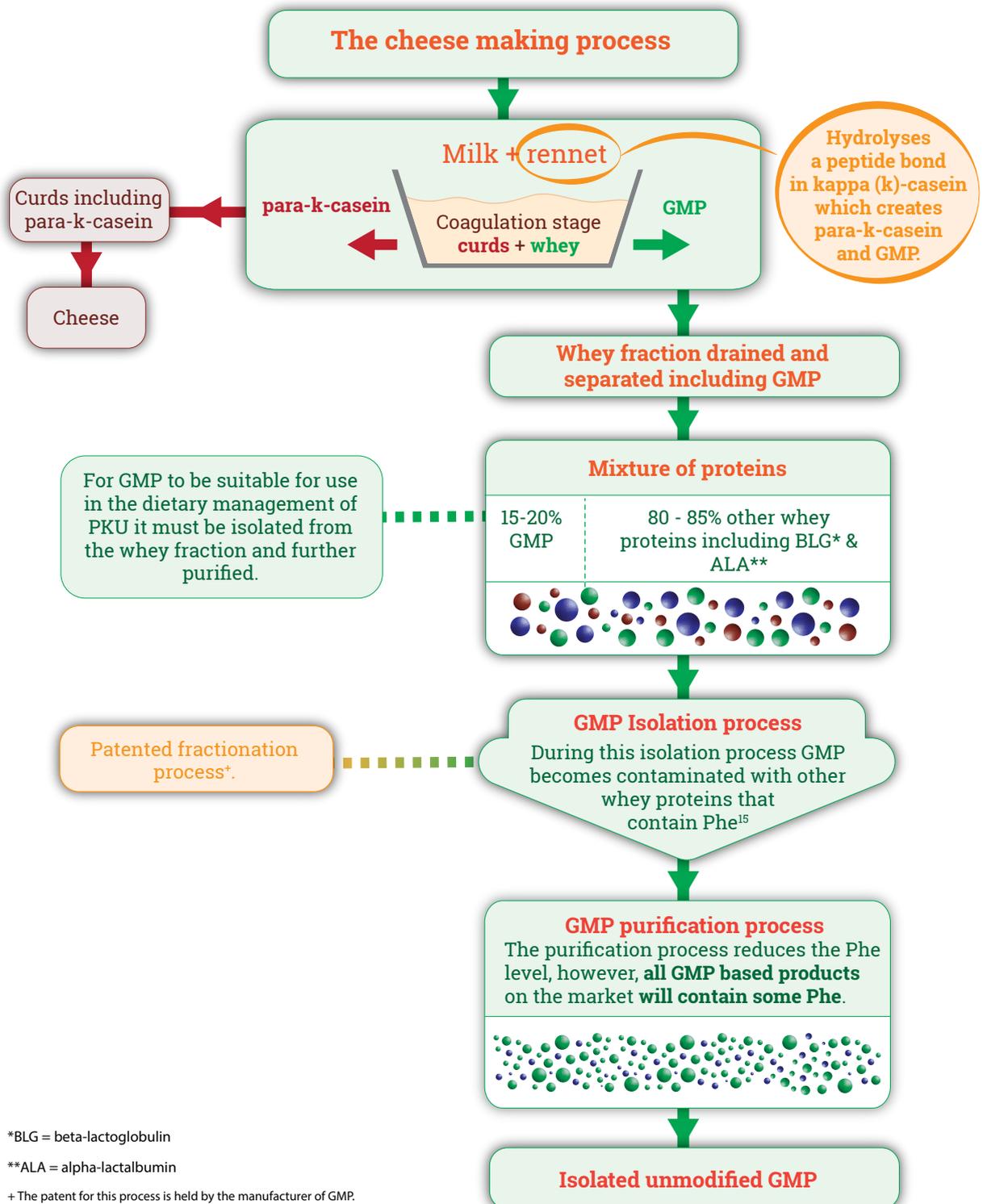
1.0 GMP

- ①.1 What is GMP and how is it produced?
- ①.2 What is PKU sphere?
- ①.3 Features of PKU sphere

1.1 What is GMP and how is it produced?

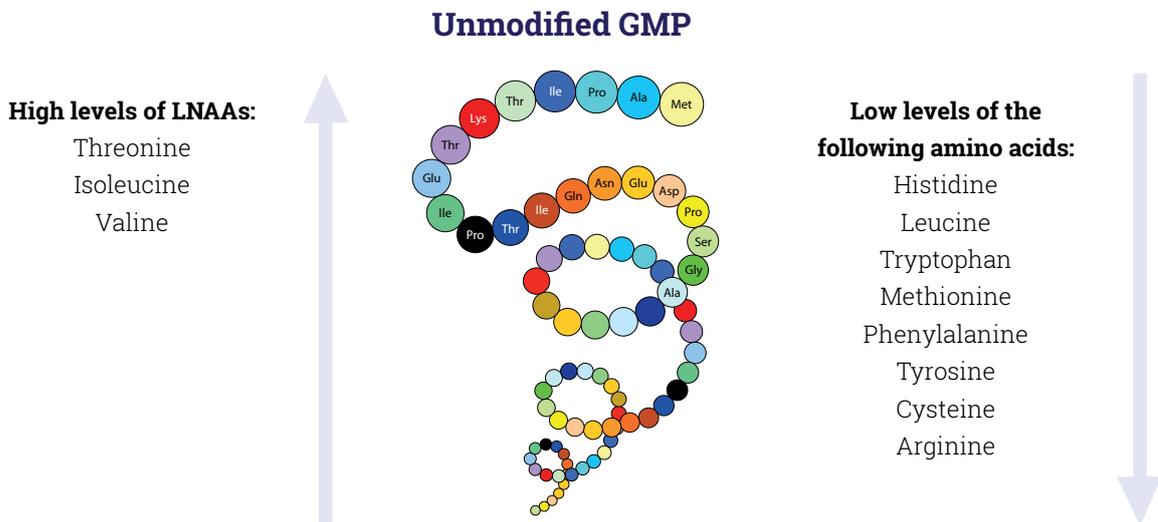
GMP is a macropeptide derived from a natural protein during the cheese making process. GMP is formed at the coagulation stage when rennet (a complex of enzymes) is added to the milk, to produce a mixture of curds and whey. An enzyme in rennet specifically hydrolyses kappa (k)-casein (a protein in milk) at the peptide bond between the Phe 105 and methionine 106 amino acid residues. It therefore splits into para-k-casein containing Phe, which remains in the cheese curd, the GMP drains off with all the whey proteins forming the whey fraction¹³ (see figure 1).

Figure 1. illustrates how GMP is formed and isolated through the cheese making process.



Amino acid profile of isolated, unmodified GMP

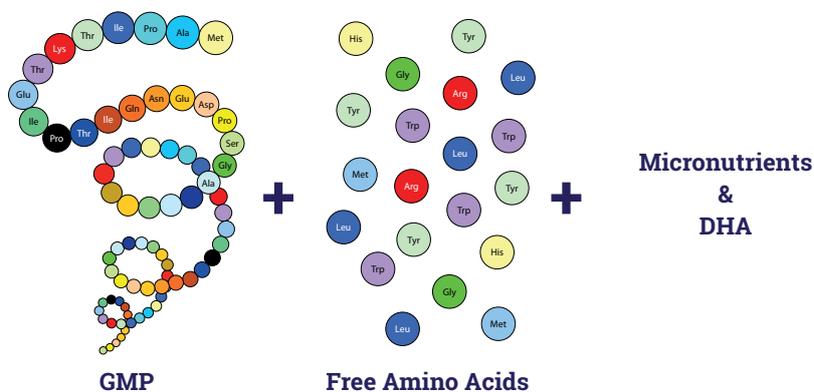
Isolated, unmodified GMP has an unusual amino acid profile. It contains low levels of Phe and other aromatic amino acids and has two to three times the amount of the LNAA's threonine and isoleucine compared to other proteins^{14, 18}.



Addition of free amino acids

Isolated, unmodified GMP must be supplemented with the limiting indispensable amino acids (apart from Phe) to ensure it is a viable alternative to AA based protein substitutes in PKU.

GMP supplemented with the limiting essential amino acids provides a **low-Phe protein source** for individuals with PKU. The inclusion of micronutrients and DHA in a GMP based protein substitute provides a nutritionally comprehensive product. In addition to meeting requirements, the blend of amino acids used to supplement GMP has a significant impact on metabolic control²⁰. The optimal blend of amino acids added to GMP in PKU sphere has been developed with controlled, clinical research²¹.



All commercial GMP based protein substitutes contain Phe and therefore partial or full replacement of the AA based protein substitutes will depend on an individual's blood Phe control.

1.2 What is PKU sphere?

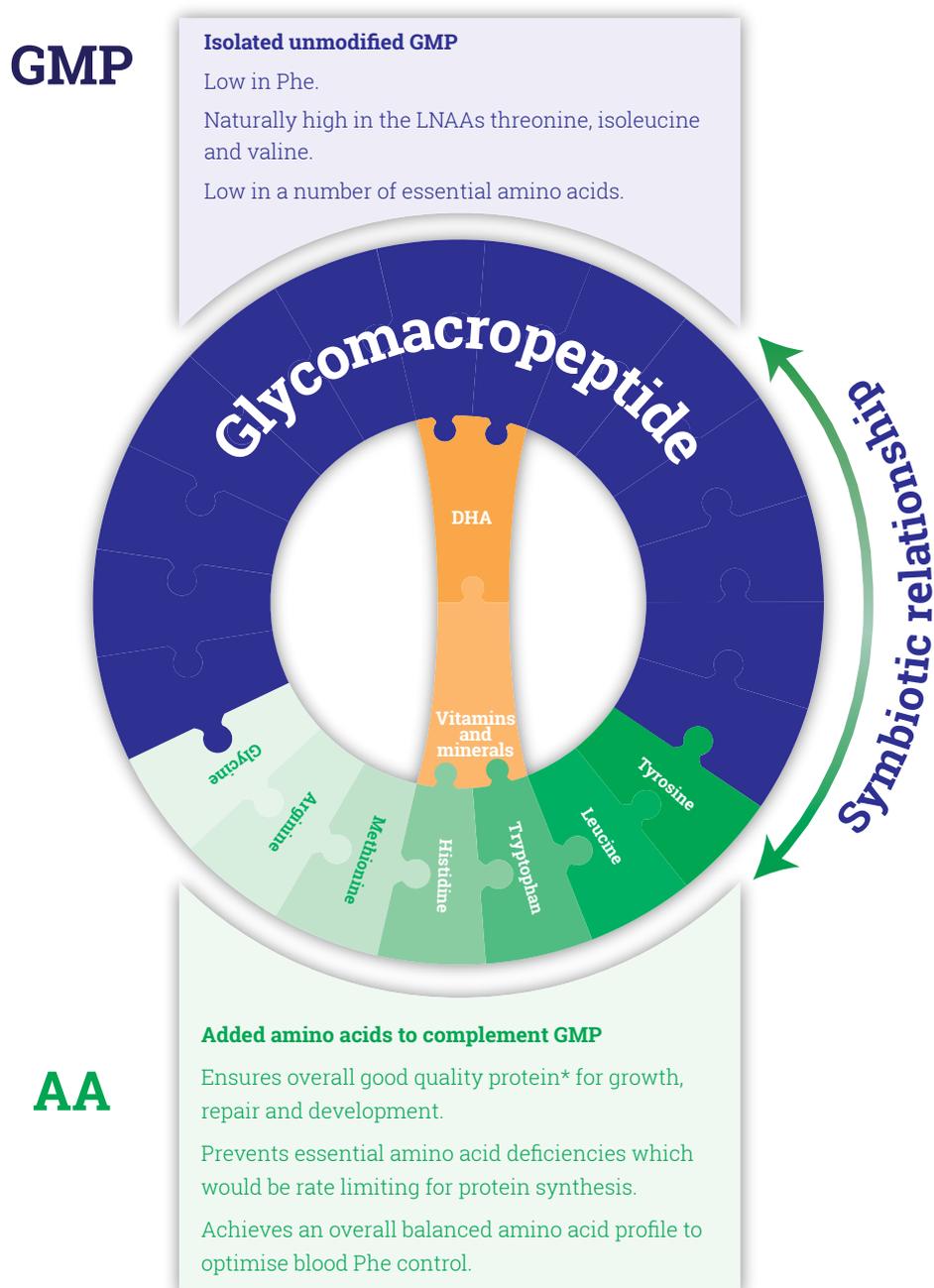
PKU sphere is a blend of isolated unmodified GMP and free amino acids with added micronutrients and DHA.

Amino acid profile - PKU sphere is formulated using the latest nutritional science to ensure the combination of the added LNAAs and GMP are in balance to **optimise blood Phe control** as well as meeting WHO minimum amino acid recommendations²⁰.

The added LNAAs in PKU sphere are key and may compete with Phe both at the blood brain barrier and in the gut.

Contains DHA (110mg per 20g PE). If a patient is taking DHA supplements in addition to AA based protein substitutes, these may no longer be required once initiated on **PKU sphere**.

Comprehensive micronutrient profile which is **interchangeable** with the Vitaflo range including PKU cooler, PKU express and PKU air.



* When coupled with tolerated Phe allowance.

1.3 Features of PKU sphere

Low volume

PKU sphere has been designed to deliver a set protein equivalent in a low volume to help aid adherence.

High volumes of protein substitute can be difficult to manage especially in addition to maintaining a healthy food intake.

Low volume of **PKU sphere** allows it to fit easily into a '3-a-day' protein substitute approach.

1 sachet PKU sphere20 + 120ml water = 140ml

1 sachet PKU sphere15 + 100ml water = 120ml

Low in energy

PKU sphere has been designed to be comparatively low in calories and sugar.

PKU sphere20 contains 120 calories and 2.2g sugar*. PKU sphere15 contains 91 calories and 1.7g sugar*.

The energy content is similar to AA based protein substitutes such as PKU express, PKU cooler and PKU air.



PKU sphere



PKU cooler20

Obesity is a global issue and is as prevalent in the PKU population as the general population²². The calorie content and overall nutritional intake should be monitored closely in PKU. Advice and encouragement to maintain a healthy weight is an important aspect of dietetic management particularly in teenage and adult patients. It is expected that most of the energy requirements will be met by low Phe food.

Palatable

PKU sphere offers an alternative tasting product to AA based protein substitutes.

PKU sphere is available in 3 different flavours: Vanilla, Red berry and Chocolate.

Due to its palatability, **PKU sphere** could improve adherence in a patient group where it may waver¹⁷.

Convenient

PKU sphere is presented in a convenient pre-measured sachet which can be made up accurately, quickly and easily.

A sports beaker is provided with **PKU sphere** to 'normalise' the product, appearing similar to a protein shake. The individual can decant the **PKU sphere** powder into the shaker before going out. This ensures it is quick and easy to prepare, even on the go.

* Sugar content for vanilla and red berry.

2.0

Application of PKU sphere

- 2.1 Who is PKU sphere for?
- 2.2 An individual with a higher phe tolerance, on a relaxed or non-adherent diet or with poor tolerance of current protein substitutes and seeking to regain metabolic control
- 2.3 Individuals with a low phe tolerance especially children aged 4 to 11 years
- 2.4 Special considerations
- 2.5 How to introduce PKU sphere
- 2.6 Practical Tips

2.0

2.1 Who is PKU sphere for?

PKU sphere is ideal for individuals with PKU:

- 
- Aged 12 years and above
 - With hyperphenylalaninemia/mild PKU who require dietary treatment from the age of 4 years
 - On sapropterin
 - With poor adherence of AA based protein substitutes
 - Returning to a phe-restricted diet, or who could not tolerate the full recommended amount of AA based protein substitutes
 - Already established on an alternative GMP based protein substitute

The **potential impact the extra Phe** from **PKU sphere** will have on blood Phe levels will likely **be less in an individual with a higher natural protein/exchange tolerance and/or a higher maximum target Phe level.**

See section [2.2](#) more information.

PKU sphere is safe to be used with care in:

- 
- Children with PKU aged 4-11 years

Target Phe range is lower in this group, therefore it may be more challenging to introduce a product containing Phe without compromising Phe control.

The introduction of a GMP based protein substitutes requires additional consideration in these children and **careful monitoring is required.**

See section [2.3](#) more information.

PKU sphere/GMP based protein substitutes have very limited or no evidence to inform dietary management of:

- 
- Young children under the age of 4 years
 - Pregnancy (maternal PKU)

See section [2.4](#) for more information.

For all groups PKU sphere offers an alternative to AA based protein substitutes for individuals experiencing taste fatigue or struggling with adherence.

For patients with an interest in the potential health benefits of GMP a summary of evidence to date is available in the Appendix.

All individuals who wish to try PKU sphere need to be assessed on an individual basis. Progressing with PKU sphere will depend on metabolic control, adherence to the phe restricted diet and the clinical judgement of the managing health care professional.

An individual with a higher phe tolerance, on a relaxed or non-adherent diet or with poor tolerance of current protein substitutes and seeking to regain metabolic control



- **The amount of Phe in PKU sphere is less likely to be as much of a concern in an individual with a higher natural protein/exchange tolerance and/or a higher maximum target phe level.**

The introduction and increase of **PKU sphere** could therefore be much quicker, or the full required amount started at once should the individual desire and the health professionals feel appropriate.

- It is not unusual for adherence to be challenging in life-long conditions⁶, such as PKU²³. Poor adherence is indicated by Phe levels above target range²⁵ and/or low key plasma micronutrients such as vitamin B₁₂, iron or DHA²⁵⁻²⁷.
- Common issues with adherence to protein substitutes, found in patients of all ages, are the palatability, smell, taste, aftertaste and texture^{2,7,8}. Also often through teenage years, with growing independence, changes at school, peer pressure, condition resentment, **adherence with diet and protein substitutes may deteriorate**⁸.
- Published studies reveal patients may prefer GMP based protein substitutes^{9,12,17,19}.
- For patients struggling with adherence the perceived enhanced palatability may enable them to increase their daily consumption of protein substitute^{9,12,19}.

PKU sphere offers a new palatable option and may help individuals to successfully return to diet and / or regain control of blood Phe levels.

Consider the below points when introducing **PKU sphere**:

- How **PKU sphere** is introduced will **depend on the individual's ability** to cope, tolerance of the product and motivation.
- In those individuals who are non-adherent, when they start taking **PKU sphere, blood phe levels may significantly improve.**
- **Ideally the amount of PKU sphere, coupled with the natural protein from food, would meet protein requirements.**
 - However, this may be unrealistic for some and therefore aiming for 1 or 2 **PKU sphere** sachets per day may be more manageable which would still be beneficial.
- **A gradual systematic introduction could aid adherence and tolerance.**
 - Gastrointestinal (GI) side effects have been reported by PKU individuals taking AA based protein substitutes^{4,19}. Research literature and anecdotal reports indicate that GI symptoms may improve in some individuals who choose to change from AA based protein substitutes to GMP based protein substitutes^{19,28}.
 - GI side-effects are more likely to be experienced by those who have not taken protein substitutes routinely for some time whether AA based protein substitutes or GMP-based. It should be considered that someone with pre-existing, or a history of, GI symptoms might experience worsening of symptoms with a new dietary change, such as introducing or changing protein substitutes.



2.3 Individuals with a low phe tolerance

Individuals with a low phe tolerance especially children aged 4 to 11 years

Target Phe range is lower in this group, therefore it may be more challenging to introduce a product containing Phe without compromising blood Phe control.

In addition, the **potential impact the extra Phe** from **PKU sphere** will have on blood Phe levels will likely **be higher in an individual with a low natural protein/exchange tolerance**.

Individuals with a low Phe tolerance

During the trial nearly 50% of children are able to transition to PKU sphere in full to provide 100% of their protein substitute requirement without compromising metabolic control. Even those with a low phe tolerance were able to take up to 75% of their daily protein substitute requirement without adjustment of dietary phe, or compromising metabolic control, when introduced gradually and systematically²¹.

Introducing **PKU sphere** gradually, in a systematic way, allows monitoring of metabolic control and discussion with 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 natural protein/exchanges depending on blood Phe control, individual preference and circumstance.

See section 2.5 for more information.



2.4 Special considerations

Young children under the age of 4 years

The micronutrient profile for **PKU sphere** is suitable from 3 years of age however as yet there is no published evidence of GMP based protein substitutes use in young children under the age of 4 years. Research is ongoing in children from the age of 3 years to understand the impact of the Phe content of GMP based protein substitutes on metabolic control.

Long term data is required to enable evidence based guidelines to be written for the use of GMP based protein substitutes in the younger population under the age of 4 years.



Pregnancy (maternal PKU)

GMP based protein substitutes have been used widely in the management of PKU in North America for approximately 8 years²⁹. However, so far very little has been published to provide guidance on dietetic management of PKU using GMP based protein substitutes during preconception and pregnancy.

Summary of research

A conference poster reported outcomes in 19 PKU pregnancies, 7 of which were managed with either a combination of GMP based protein substitutes and AA based protein substitutes or GMP based protein substitutes and sapropterin³⁰. No concerns were highlighted relating to GMP based protein substitutes and results appeared to be associated with positive birth outcomes in the group managed with a combination of GMP based protein substitutes and AA based protein substitutes.

A single case report has been published describing a PKU pregnancy managed with a combination of GMP based protein substitutes and AA based protein substitutes. The authors concluded by stating that more data is essential to examine the impact of using GMP based protein substitutes in maternal PKU particularly with respect to pregnancy associated nausea and vomiting severity, maternal weight gain, blood amino acid concentrations and variability of blood Phe concentrations³¹.

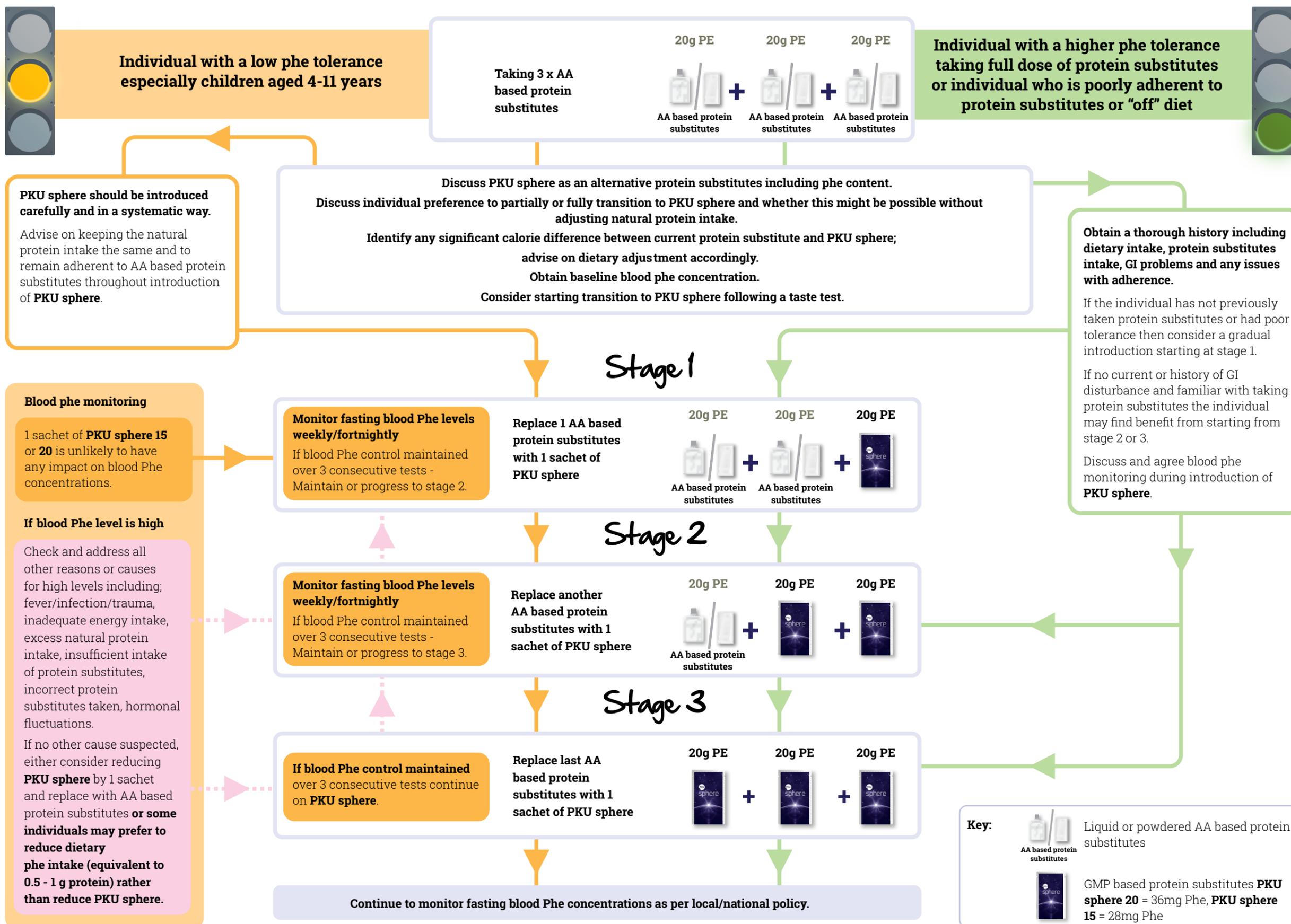
Natural protein/exchange tolerance is likely to be extremely low prenatally and during the first trimester of pregnancy³. This requires the individual to be consistent with adhering to phe-restricted diet and their full recommended amount of protein substitutes. **PKU sphere** contains some Phe (36mg/20g PE) which would need to be accounted for, and the introduction appropriately monitored. Based on the phe content, the suitability of the GMP based protein substitutes should be determined by the managing healthcare professional for each individual particularly for maternal PKU.

Improved adherence with protein substitutes during pregnancy is associated with improved outcomes for the foetus related to improved protein, energy, vitamin B₁₂ and folate intake³²⁻³⁴. For those individuals who are struggling to adhere to AA based protein substitutes during pregnancy or prefer the taste of GMP based protein substitutes, **PKU sphere** may be an alternative choice. **PKU sphere** could provide partial or full protein substitute requirements depending on the opinion of the managing healthcare professional. Improved adherence to a protein substitutes when intake was previous suboptimal is likely to improve phe tolerance and metabolic control⁷.

Vitaflo is committed to supporting research and health care professional education

Case studies have been written by metabolic dietitians who have successfully used **PKU sphere** in maternal PKU patients which are available on the VIA website.

A **Practical Guide to maternal PKU** has been developed and contains more information about dietary management during a PKU pregnancy.



2.6 Practical Tips

Tips for health care professionals:

- Take a **good dietary history** including symptoms and history of GI disturbance to allow **tailoring of advice** to best promote tolerance and adherence.
- Introduce aspects of the diet **gradually**. Work with individuals/families to set their own goals and strategies; encourage them to set **realistic, achievable** goals.
- Encourage taking protein substitutes in a variety of ways to limit taste fatigue. **PKU sphere** shake recipes are available.
- Emphasise the importance of continuing to take the usual protein substitute whilst building up the amount of **PKU sphere** taken, particularly at the stage where only 1 AA based protein substitutes is being taken. Explain that dropping off any AA based protein substitutes can affect blood Phe control and could also delay progression with **PKU sphere**.

If blood phe levels are high:

- Check **PKU sphere** has not been increased of the patient's own accord
- Check adherence (at home, school, work, out socialising). Routine may have changed e.g. on holiday, eating out more, protein substitutes not spread evenly through the day
- Check understanding/calculation of exchanges/Phe allowance, dietary adherence and hidden sources of natural protein
- Check which protein substitutes are being taken. Occasionally the wrong protein substitutes may be prescribed or delivered
- When necessary recalculate protein substitutes requirements and adjust dosage appropriately
- Check any special products used are low protein and not gluten free by mistake

Tips for individuals:

- Seek **support or encouragement** from family, friends or work colleagues to achieve specific goals.
- When introducing, choose a time each day when you have **time** to prepare and consume the protein substitutes.
- Place protein substitutes in an obvious place to **remind** you to take it, keep a small supply at your place of study, work, friends/family houses which you visit regularly.
- **Use apps or mobile devices to set reminders** for ordering repeat supplies for protein substitutes and low protein foods, bloodspot monitoring and taking protein substitutes.

Some general reminders before commencing any new protein substitutes, including **PKU sphere**:

- Introduce any dietary change gradually
- Take smaller doses of protein substitutes regularly through-out the day
- Ensure to have regular meals
- Try to drink afterwards
- Take the protein substitutes along with food

3.0 Practical guide references

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4.0 Appendix

4.1 Summary of references related to GMP potential benefits

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GMP scientific evidence summary

GMP has a unique chemical structure. Many of the biological properties of GMP are attributed to this unique structure. Since the 1970's GMP has been of interest for its potential benefits in many population groups and conditions. Specific investigations into GMP for use in the management of PKU first arose because of the natural low levels of Phe.

Further potential benefits of GMP have been proposed and reported, mainly in relation to bone and gut health, but also its impact on overall nitrogen metabolism. The following is a summary of evidence listing the **potential benefits of GMP**. References marked in bold font denote research directly linked to GMP whereas references marked in non-bold font denote research that, whilst not directly linked to GMP, are of relevance to the highlighted issue.

Potential GMP benefits directly related to PKU

The vast majority of evidence is from animal studies, however short-term cohort studies and case studies have been reported.

Reduction of phe in the brain

Ney et al 2008¹, Pietz et al 1999², Sanjuro et al 2003³, van Spronsen et al 2010⁴

Increased efficacy of protein utilisation / improved nitrogen retention

Ney et al 2014⁵, van Calcar et al 2009⁶, Ahring et al 2018⁷

Improved long term bone health

Solverson et al 2012⁸

Better palatability

Lim et al 2007⁹, van Calcar et al 2009⁶, **Ney et al 2016¹⁰**, **Zaki et al. 2016¹¹**, **Daly et al. 2017¹²**

Oral hygiene

White et al 2010¹³, **Aimutis 2004¹⁴**, **Brody 2000¹⁵**

Other potential GMP related benefits

Prebiotic effect

Brody 2000¹⁵, **Chen et al 2012¹⁶**, **Sawin et al 2015¹⁷**, **Ntemiri et al. 2017¹⁸**

Anti-inflammatory effect

Jia et al 2011¹⁹, **Sprong et al 2010²⁰**, **Requena et al 2008²¹**, **Wang et al 2012²²**, **Daddaoua et al 2005²³**, **Hvas et al 2016²⁴**, **Solverson et al 2012²⁵**

Binds to enterotoxins & inhibits bacterial and viral adhesion

Kawasaki et al 1992²⁶, **Nakajima et al 2005²⁷**, **Hermes et al 2013²⁸**, **Dziuba et al 1996²⁹**

Improved satiety

Burton-Freeman et al 2008³⁰, **Macleod et al 2010³¹**, **Ney et al. 2016¹⁰**, **Zaki et al. 2016¹¹**

Role in weight management

Xu et al 2013³², **Royle et al 2008³³**

Improvement of zinc absorption

Kelleher et al 2003³⁴

Stimulation of brain development

Wang et al 2007³⁵

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