PKU sphere®

A practical guide to **PKU sphere®**.

Vitaflo in Association With You

Supporting education in the dietary management of rare diseases

Important information

This practical resource should be read in conjunction with local guidelines for the dietary management of phenylketonuria (PKU). It is based on recent scientific evidence available on the use of glycomacropeptide (GMP) based medical foods in PKU.

PKU sphere® is a low Phenylalanine (Phe) medical food containing a blend of whey protein isolate **(glycomacropeptide — GMP)**, essential and non-essential amino acids, carbohydrate, fat (including docosahexaenoic acid — DHA), vitamins and minerals for use in the dietary management of PKU from 1 year of age (**PKU sphere liquid**) and from 3 years of age (**PKU sphere powder**).

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.**

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 medical food intended for use under medical supervision. It is commonly referred to as PKU formula.

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

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

Health care professionals are encouraged to use this practical guide as an evidenced-based and best-practice resource to inform clinical decision-making, but always exercise clinical judgment to determine what is appropriate for individual patients.

*__PKU sphere 15__ only available in powder

Disclaimer

The information contained in this 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® International Ltd does not accept any responsibility for any loss arising from reliance on information contained in this guide.

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 Ltd does not recommend or endorse any specific tests, procedures, opinions, clinicians, or other information that may be included or referenced in this practical guide.

Collaborators

Vitaflo dietitians in collaboration with:

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Contents

Abbreviations

AA	Amino acids.
GMP	Glycomacropeptide.
GMP-MF	GMP-based medical foods supplemented with the limiting free amino acids +/- micronutrients and essential fatty acids. May vary in format - powder, liquid, or bar.
AA-MF	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.

Background

Dietary management for PKU began in the 1950's when the first medical food, based on protein hydrolysate, was developed[1]. Since that time, AA-MF have been used as the primary protein source in the dietary management of PKU. Medical food consumption, in combination with a diet low in natural protein, is the key to blood Phe control. However, PKU diet sustainability is multifaceted, challenging, and lifelong[2-4]. As with many chronic conditions, adherence to the PKU diet often decreases as individuals age, and with it metabolic control and neuropsychological functioning[5-7].

Medical food has come a long way since the 1950's with differences in nutritional composition, a variety of flavor profiles, and packaging variations for convenience. However, individuals with PKU of all ages have challenges with palatability, smell, taste, texture, and aftertaste of the traditional AA-MF[2, 8, 9]. These challenges make adhering to the recommended total amount and spacing of medical foods even more challenging.

GMP is the third most abundant protein in cheese whey, and in its theoretical pure form, contains no aromatic AA, including Phe[10-13]. Moreover, in its unmodified form, GMP is also higher than the reference protein in the large neutral AA threonine, isoleucine, and valine. GMP was first developed as an alternative protein source for AA-MF for PKU at the University of Wisconsin, through collaborations between research and clinical teams[10, 14-16]. Now it is used widely across the world, and following more than 15 years of clinical research in the US and Europe, GMP is safe, more palatable than AA-MF, and has potential for a host of other health benefits, outlined in Appendix 1 of this guide. GMP consistently outperforms traditional AA-MF when clinically tested for taste, odor, appearance, and texture[14, 17-20]. Some of the most interesting areas of research of GMP include connections with improved bone health, the potential to enhance satiety, and its prebiotic properties for improved gut health[17, 21-27].

GMP must be supplemented with limiting AA to make it suitable as a primary protein source for the dietary management of PKU[10, 19, 28, 29]. The blend of AA to be added to GMP for **PKU sphere** has been optimized for blood Phe control using clinical research[19, 29, 30].

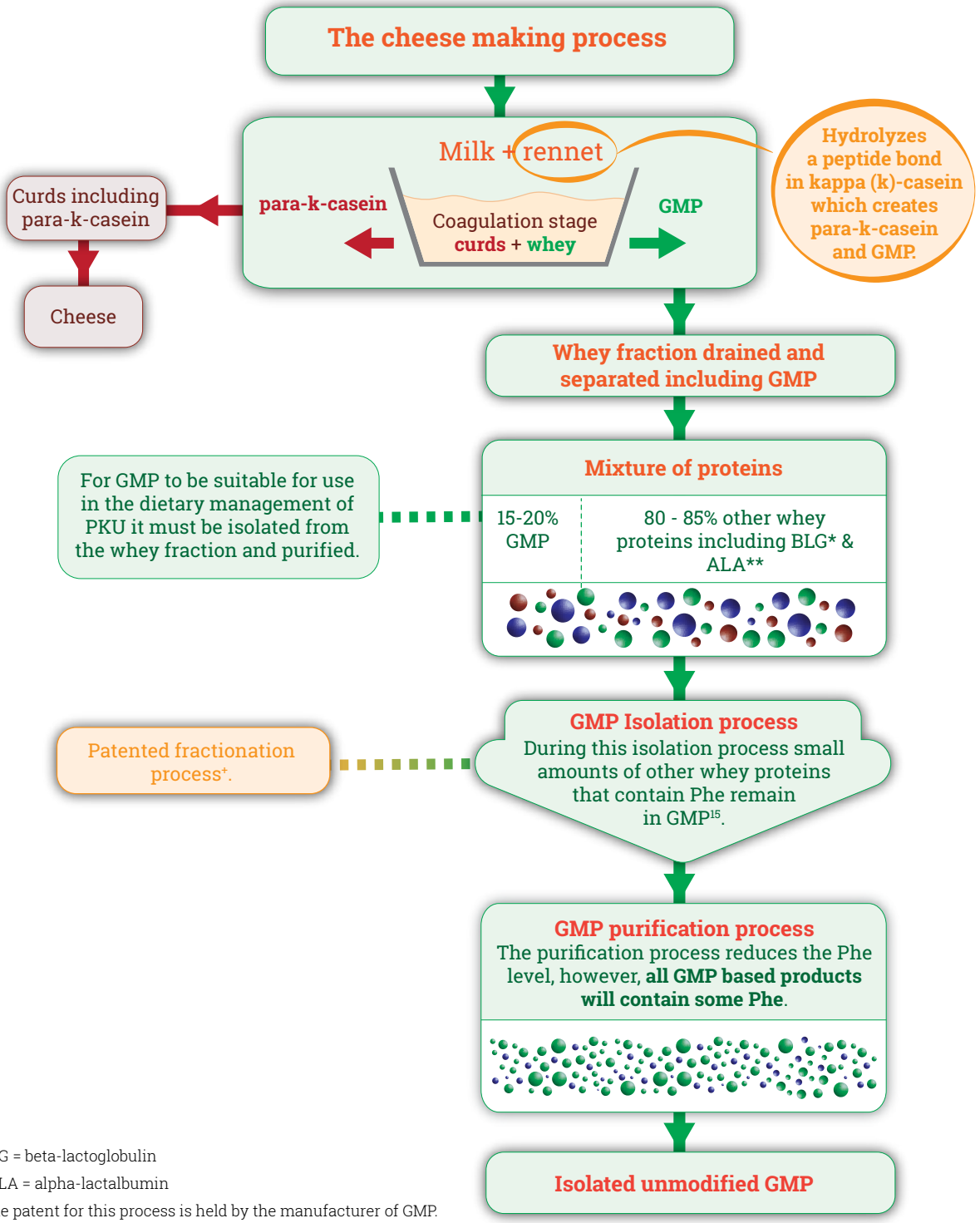
Vitaflo has developed this guide on the use and introduction of **PKU sphere** in children and adults. Like any GMP-MF, it does contain some Phe (36 mg/20 g protein equivalent), so it is essential that every individual with PKU be assessed based on their own Phe tolerance, metabolic control, and current medical food intake. Any transition can be challenging. Following the suggested step wise process (illustrated in section 2.2 and 2.3) for introducing **PKU sphere** will aid in a successful sustainable medical food regimen without loss of metabolic control. **PKU sphere** provides more options for those with PKU currently struggling with the PKU diet, those intrigued by the potential health benefits of PKU, or simply looking for something different.

Erin MacLeod

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 and GMP which drains off with all the whey proteins forming the whey fraction[11] (see figure 1).

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



* BLG = beta-lactoglobulin

** ALA = alpha-lactalbumin

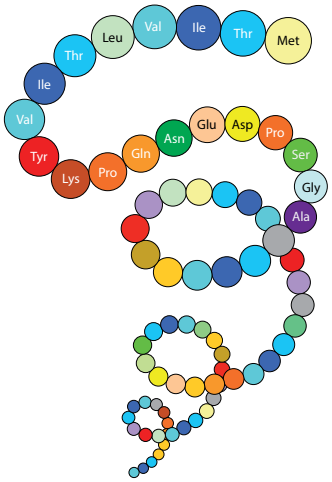
+ The patent for this process is held by the manufacturer of GMP.

Amino acid profile of isolated, unmodified GMP

Isolated, unmodified GMP has a unique AA profile. It contains low levels of Phe and other aromatic AA and has two to three times the amount of the LNAAs threonine and isoleucine compared to other proteins[10, 12].

Unmodified GMP

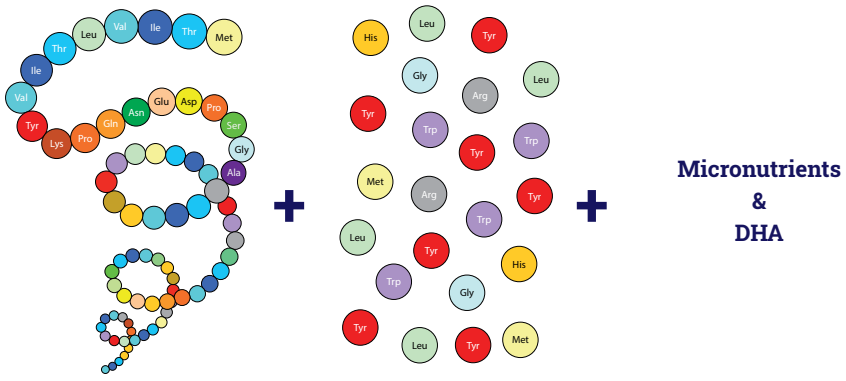
High levels of LNAAs:
Threonine
Isoleucine
Valine



Low levels of the following amino acids:
Histidine
Leucine
Tryptophan
Methionine
Phenylalanine
Tyrosine
Cysteine
Arginine

Addition of free amino acids

Isolated, unmodified GMP must be supplemented with the limiting AA (apart from Phe) to make it suitable as a primary low Phe protein source for the nutrition management of PKU[10, 19, 28, 29]. In addition to meeting requirements, the blend of AA used to supplement GMP has a significant impact on metabolic control[19, 29, 30]. The inclusion of micronutrients and DHA in a GMP-MF provides a nutritionally "well-rounded" product.



Micronutrients & DHA

GMP **Free Amino Acids**

The blend of AA added to PKU sphere has been developed and optimized over time with controlled, clinical research[19, 29, 30].

1.2 What is PKU sphere?

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

AA profile - PKU sphere is formulated using the latest nutritional science to ensure the combination of the added LNAAs and GMP are in balance to **optimize blood Phe control**[19, 29, 30], and meet World Health Organization (WHO) minimum AA recommendations[31].

The added LNAAs in **PKU sphere** may play an important role in PKU by competing with Phe both at the blood brain barrier and in the gut[32].

Contains DHA to support adequate intake which is lacking in the typical PKU diet[33].

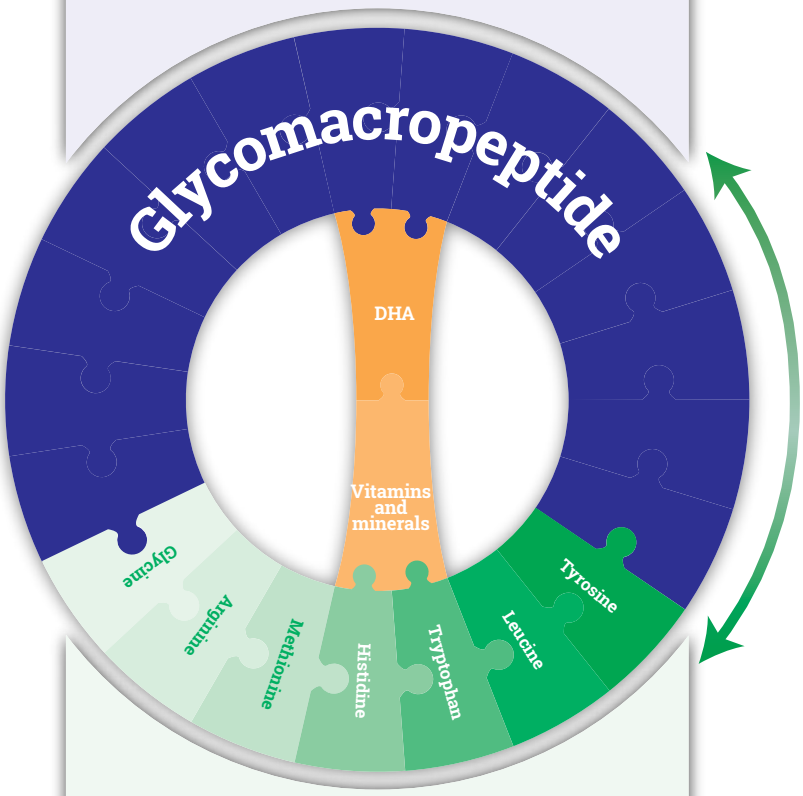
Comprehensive micronutrient profile which is **interchangeable** with the Vitaflo range including PKU cooler, PKU express, and PKU air.

PKU sphere liquid is suitable from 1 year of age and **PKU sphere powder** is suitable from 3 years of age.

GMP

Isolated unmodified GMP

- Low in Phe.
- High in the LNAAs threonine, isoleucine, and valine.
- Low in certain essential amino acids.



AA

Added AA to complement GMP

- Ensures overall good quality protein* for growth, development, and tissue repair.
- Prevents essential AA deficiencies which would be rate limiting for protein synthesis.
- Achieves an overall balanced AA profile to optimize blood Phe control.

* When coupled with tolerated Phe allowance.

1.3 Features and benefits of PKU sphere

Taste

PKU sphere is formulated with GMP from a natural whole protein source, offering a different taste profile to AA-MF which may be preferred by some individuals with PKU[14, 15, 17, 20].

PKU sphere powder is available in 3 flavors: Vanilla, Red Berry, and Chocolate to offer flavor variety.

PKU sphere liquid is available in Vanilla flavor and can be taken as is or easily customized with permitted flavorings.

Low volume

PKU sphere is designed to maximize protein equivalent delivery in a low volume and support diet sustainability.

Low volume medical foods play an important role in supporting adherence to prescribed daily intake[34].

PKU sphere supports a '3-a-day' medical food approach.

	**1 packet PKU sphere15**	**+**		**120 ml (4 fl oz) water**	**=**	 **140 ml (4.5 fl oz)**
	**1 packet PKU sphere20**	**+**		**120 ml (4 fl oz) water**	**=**	 **140 ml (~4.5 fl oz)**
	**1 bottle of PKU sphere20 liquid**				**=**	 **237 ml (8 fl oz)**

Convenience

PKU sphere powder is available in convenient **pre-measured packets** for quick and easy mixing. No weighing or measuring is required. The **PKU sphere** shaker bottle is similar to other commonly used protein shakers to "normalize" the experience for those with PKU taking their medical food throughout the day in public.

PKU sphere liquid is available in a small 8 fl oz **resealable bottle** which is easy to take on-the-go to daycare, school, work, or when traveling to support adherence to the recommended total amount and spacing of medical food.

Lower calorie

120 kcal per 20 g PE to help support an overall healthy diet without excess intake of calories.

A full nutrient profile

Provide a wide range of vitamins, minerals, and DHA to support adequate intake of nutrients lacking in the typical PKU diet.

Flexibility

Can be used in combination with other Vitaflo products, offering more choices and allowing gradual introduction to the diet if needed to support adherence.


PKU explore

PKU trio


PKU express


PKU cooler


PKU air

PKU sphere powder and PKU sphere liquid are nutritionally equivalent

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

* For full micronutrient profile click here: **PKU sphere 20 powder**, **PKU sphere 20 liquid**

2.1 Who is PKU sphere for?

2.1.1. PKU sphere is ideal for individuals with PKU:

- With hyperphenylalaninemia/mild PKU.
- On sapropterin.
- With poor adherence to currently prescribed medical food.
- Returning to a Phe-restricted diet.
- Already established on a GMP-MF.
- Those opting out of, OR those who would benefit from using PKU sphere in conjunction with pegvaliase-pqpz treatment.

The potential impact the Phe in **PKU sphere** will have on blood Phe levels will likely be less in the above mentioned groups. These individuals may choose to transition to **PKU sphere** without a gradual introduction. Section 2.2 provides an illustration.

A gradual and systematic introduction of PKU sphere may be helpful in the following circumstances:

- A history of gastrointestinal (GI) intolerance with AA-MF. Positive reports of improved GI symptoms have been documented when switching to a GMP-MF[17,18].
- A prolonged history of non-adherence to prescribed medical food - any new dietary change, including introduction of a new medical food, may trigger unwanted GI symptoms.
- For those who may have a more difficult time transitioning to a medical food with a different taste profile than AA-MF.

2.1.2. PKU sphere is safe for use in children with some considerations:

- A gradual systematic introduction of **PKU sphere** may be advantageous as it allows monitoring of metabolic control. A clinical trial[29] including children with good metabolic control (ages 5-16 years) demonstrated that when **PKU sphere** is introduced gradually and systematically without adjustment of dietary Phe:
  - on average, children could take 75% of their daily medical food prescription without compromising metabolic control, including those with low Phe tolerance.
  - almost 50% of children were able to transition to 100% **PKU sphere** for their medical food requirement.

Based on a combination of factors such as metabolic control, individual preferences, dietary quality, and lifestyle, the metabolic dietitian and patient/caregiver should decide whether the goal of dietary management is a complete transition to **PKU sphere** or a combination of AA-MF and **PKU sphere**.

Section 2.2 provides a step-by-step introduction of **PKU sphere** based on the protocol and results of Daly et al 2019[29].

2.1.3. PKU sphere/GMP-MF may be used in the following groups with some considerations:

- **Children under the age of 4.**

  Clinical research on the use of **PKU sphere**/GMP-MF in children under the age of 4 is lacking. However, anecdotal clinical experience suggests that early and partial introduction of GMP may be of interest to some metabolic dietitians and some families. **PKU sphere liquid** is indicated from 1 year of age. Section 2.3 provides a step-by-step example of how to incorporate **PKU sphere liquid** into the diet of a child under the age of 4 based on clinical practice experience.

- **Pregnancy (maternal PKU)**

  Clinical research on the use of GMP-MF during preconception and pregnancy is limited.

  A scientific poster highlighting 19 PKU pregnancies, 7 of which were managed with either a combination of GMP-MF and AA-MF or GMP-MF and sapropterin showed positive results* with respect to birth outcomes[30].

  Pregnancy associated nausea and vomiting is a common problem. GMP-MF are less acidic and have a lower osmolality than AA-MF[17]. This may be beneficial for some women experiencing nausea or heartburn.
  A single case study scientific poster reported reduced exacerbation of pregnancy associated nausea with use of a GMP-MF in a mother with classical PKU, who achieved good metabolic control throughout pregnancy[36].

  Factors such as:

  - severity of pregnancy associated nausea and vomiting;
  - blood AA concentrations;
  - variability of blood Phe concentrations;
  - Phe tolerance (likely to be low prenatally and high in the third trimester).

  must be considered when assessing appropriateness of a GMP-MF in maternal PKU diet management. Adherence with medical food during pregnancy is critical and associated with good outcomes for the fetus related to improved protein, energy, vitamin B_{12}, and folate intake[37-39]. For women struggling to adhere to AA-MF during pregnancy, **PKU sphere** may be an alternative choice providing partial or full medical food requirements.

  * One infant with low birth weight despite average Phe levels within treatment range throughout pregnancy; mother started treatment at 6 weeks of pregnancy.

Additional healthcare professional resources

Case studies written by metabolic dietitians who have successfully used **PKU sphere** in maternal PKU patients which are available at **www.vitaflo-via.com**.

The **Practical Guide to maternal PKU** contains more information about dietary management during a PKU pregnancy and is available at **www.vitaflousa.com/via**.

2.2 How to introduce PKU sphere

Individuals in section 2.1.1

15 or 20 g PE + 15 or 20 g PE + 15 or 20 g PE

AA-MF + AA-MF + AA-MF

Discuss PKU sphere as an alternative
Discuss individual preference to fully
Obtain baseline blood
Consider starting transition to

Obtain a thorough history including dietary intake, medical food intake, GI problems and any issues with adherence.

Introduction may start from step 1, 2, or 3 depending on the individual. Discuss and agree on blood Phe monitoring schedule during introduction of **PKU sphere**.

15 or 20 g PE + 15 or 20 g PE + 15 or 20 g PE

AA-MF + AA-MF + PKU sphere

15 or 20 g PE + 15 or 20 g PE + 15 or 20 g PE

AA-MF + PKU sphere + PKU sphere

15 or 20 g PE + 15 or 20 g PE + 15 or 20 g PE

PKU sphere + PKU sphere + PKU sphere

Continue to monitor fasting blood P

Taking 3 x AA-MF daily.

Individuals in section 2.1.2 and 2.1.3

medical food including Phe content.
or partially transition to PKU sphere.
Phe concentration.
PKU sphere following a taste test.

PKU sphere should be introduced in a systematic way.

Advise on keeping the natural protein intake the same and to remain adherent to AA-MF throughout introduction of **PKU sphere**.

Step 1

Replace 1 AA-MF with 1 packet/bottle of PKU sphere.

Blood Phe monitoring weekly/every 2 weeks
If stable over 3 consecutive tests, move to step 2.

Blood Phe monitoring

1 packet or bottle of **PKU sphere** is unlikely to have any impact on blood Phe concentrations[29].

Step 2

Replace another AA-MF with 1 packet/bottle of PKU sphere.

Blood Phe monitoring weekly/every 2 weeks
If stable over 3 consecutive tests, move to step 3.

If blood Phe level is high

Troubleshoot - see page 14.

If no other cause identified, replace 1 **PKU sphere** packet/ bottle with AA-MF or consider reducing dietary Phe intake by 0.5-1 g protein.

Step 3

Replace last AA-MF with 1 packet/bottle of PKU sphere.

If stable over 3 consecutive tests continue on **PKU sphere**.

Phe concentrations as per local protocol.

Key:

Liquid or powdered AA-MF

PKU sphere powder 15 = 28 mg Phe
or
PKU sphere powder 20 = 36 mg Phe

PKU sphere liquid 20 = 36 mg Phe

2.3 Introducing PKU sphere liquid from 1 year of age

Starter tips:

- Consider offering **PKU sphere liquid** separate from higher calorie AA-MF, as depicted here. Or, for a slow taste transition, mix **PKU sphere liquid** into current formula, decreasing final volume with each decrease of current AA-MF.

  If **PKU sphere liquid** is offered separate:
- Discuss when toddler eats best and consider which higher calorie formula bottle to remove first.
- Remember to take into consideration energy difference between formulas and advise dietary adjustment as needed.
- Provide expectation that toddler may be unusually cranky due to hunger.
- Offer additional water by straw or sippy cup.

5 g PE	5 g PE	5 g PE	5 g PE / 2 fl oz
AA-MF	AA-MF	AA-MF	PKU sphere liquid
5 g PE	5g PE	5 g PE / 2 fl oz	5 g PE / 2 fl oz
AA-MF	AA-MF	PKU sphere liquid	PKU sphere liquid
5 g PE	5 g PE / 2 fl oz	5 g PE / 2 fl oz	5 g PE / 2 fl oz
AA-MF	PKU sphere liquid	PKU sphere liquid	PKU sphere liquid
5 g PE / 2 fl oz	5g PE / 2 fl oz	5 g PE / 2 fl oz	5 g PE / 2 fl oz
PKU sphere liquid	PKU sphere liquid	PKU sphere liquid	PKU sphere liquid

Monitor blood phe and dietary intake for adequate

Discuss PKU sphere as an alternative medical food including Phe content.

Obtain baseline blood Phe concentration.

At each step evaluate metabolic control, dietary intake, lifestyle and decide with family if it is appropriate to move to the next step.

Key:

Higher calorie AA-MF

PKU sphere liquid
2 fl oz = 9 mg Phe

Step 1

Replace 5 g PE of current AA-MF with 2 fl oz of PKU sphere liquid, give in a cup for at least 1 week.

Monitor blood Phe
If stable and wish to progress move to **step 2**.

Step 2

Replace another 5 g PE of current AA-MF (total 10 g PE).

Give 2 fl oz of PKU sphere liquid twice a day for at least 1 week.

Monitor blood Phe
If stable and family feels comfortable with feeding move to **step 3**.

Step 3

Replace another 5 g PE of current AA-MF (total 15 g PE).

Give 2 fl oz of PKU sphere liquid 3 times a day for at least 1 week.

Monitor blood Phe
If stable and family feels comfortable with feeding move to **step 4**.

Step 4

Give 2 oz of PKU sphere 4 times a day in a cup.

calories and Phe to ensure appropriate growth.

Elevations in blood Phe

- Evaluate calorie intake.
- Give free food/snack suggestions.
- Suggest healthy fat add ins*.
- Try larger "meal like" snacks.
- Re-evaluate Phe goal and intake, may need adjustment with higher free food intake and addition of Phe from GMP-MF.

Assess metabolic control, dietary intake, and lifestyle on a case-by-case basis, and decide with the family if full or partial transition to **PKU sphere liquid** is appropriate. For example, some children may be getting a significant amount of their daily phe allowance from solid foods, or not getting enough calories and will **stay at 2 or step 3**. Reassess as needed.

*Ask your Vitaflo representative about a helpful resource on healthy fat add ins.

2.4 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 promote tolerance and diet sustainability.
- Identify any significant calorie difference between current medical food and **PKU sphere**;
- Introduce aspects of the diet **gradually**.
- Encourage setting realistic goals and work with families to develop strategies to achieve them.
- Starting from stage 2 or 3 may be appropriate for those in the green light groups, if there is no history of GI disturbance and the individual is familiar with taking medical food.
- Encourage taking medical foods in a variety of ways to limit taste fatigue. **PKU sphere** recipes are available at **www.vitaflousa.com/recipes**.

If blood Phe levels are high, check:

- ☑ Adherence to prescribed medical food (at home, school, work, out socializing). Routine may have changed e.g. on vacation, eating out more, medical foods not spread evenly through the day.
- ☑ Adherence to Phe allowance and hidden sources of protein.
- ☑ If any recent fever/infection/trauma.
- ☑ If energy intake is adequate.
- ☑ Medical food prescription, recalculate requirements and if necessary adjust dosage.
- ☑ Pubertal stage and whether hormonal fluctuations may be occurring.
- ☑ **PKU sphere** has not been increased of the patient's own accord.

Tips for success to share with individuals:

- Seek **support or encouragement** from family, friends, or work colleagues to achieve specific goals.
- In the beginning, choose a time each day when you have **time** to prepare and consume the medical foods.
- Place medical food in an obvious place to **remind** you to take it.
- Keep a small supply at your place of study, work, and friends/family houses which you visit regularly.
- **Use apps or mobile devices to set reminders:**
    - To order repeat supplies of medical foods and low protein foods
    - To do your blood spots
    - To take your medical food.

Some general reminders before commencing any new medical foods, including **PKU sphere**:

- ☑ Take smaller doses of medical foods regularly through-out the day.
- ☑ Ensure to have regular meals.
- ☑ Take the medical foods along with food.
- ☑ Try to drink afterwards.

3.1 Scientific references: potential benefits of GMP

GMP scientific evidence summary

GMP has a unique chemical structure. Many of the biological properties of GMP are attributed to its 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.

Potential GMP benefits directly related to PKU

The vast majority of evidence is from animal studies, however

Reduction of Phe in the brain

Ney et al 2008[32], Pietz et al 1999[40], Sanjuro et al 2003[41], van Spronsen et al 2010[42]

Increased efficacy of protein utilization / improved nitrogen retention

Ney et al 2014[43], van Calcar et al 2009[14], Ahring et al 2018[44,] Daly et al. 2019[45]

Improved long term bone health

Solverson et al 2012[21]

Better taste

Lim et al 2007[15], van Calcar et al 2009[14], Ney et al 2016[17], Zaki et al. 2016[18], Daly et al. 2017[19,] Properpio et al. 2018[20]

Oral health

White et al 2010[46], Aimutis 2004[47], Brody 2000[22,] Tiele et al. 2019[48]

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**.

Other potential GMP related benefits

short-term cohort studies and case studies have been reported.

Prebiotic effect

Brody 2000[22], Chen et al 2012[23], Sawin et al 2015[24], Ntemiri et al. 2017[25]

Anti-inflammatory effect

Jia et al 2011[49], Sprong et al 2010[50], Requena et al 2008[51], Wang et al 2012[52], Daddaoua et al 2005[53], Hvas et al 2016[54], Solverson et al 2012[21]

Antibacterial properties

Kawasaki et al 1992[55], Nakajima et al 2005[56], Hermes et al 2013[57], Dziuba et al 1996[58]

Improved satiety

Burton-Freeman et al 2008[26], Macleod et al 2010[27], Ney et al. 2016[17], Zaki et al. 2016[18]

Role in weight management

Xu et al 2013[59], Royle et al 2008[60]

Improvement of zinc absorption

Kelleher et al 2003[61]

Stimulation of brain development

Wang et al 2007[62]

4.0 References

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