# Safety of Glycomacropeptide (GMP) in phenylketonuria (PKU)

**GMP has an excellent safety record and it is incorporated into foods, including infant formula [1, 2]. GMP-based protein substitutes were first made available for the dietary management of phenylketonuria (PKU) in North America in 2010 [3] and in the past several years in Europe and UK. In this evidence summary we highlight a selection of the published research on the safety of GMP-based protein substitutes used with individuals with PKU.**

**Key points:**

- GMP-based protein substitutes are a safe low phenylalanine (Phe)-nitrogen source as an alternative to amino acids-based protein substitutes in the dietary management of PKU [4].
- Due to its nature GMP must be supplemented with limiting indispensable amino acids to be an appropriate alternative to amino acid-based protein substitutes for individuals with PKU. The amino acid profile varies between GMP-based protein substitutes [4], but it is known that the blend of amino acids added to GMP significantly impacts Phe-control in children with PKU [5].
- GMP-based protein substitutes have been shown to be a safe and suitable alternative to amino acid-based protein substitutes in terms of growth and micronutrient status in adults [3, 6] and growth and nutritional status in children when introduced systematically [7, 8, 9].
- The residual Phe content of GMP-based protein substitutes does not appear to significantly impact the blood Phe control of adults with PKU [3, 10, 11].
- The residual Phe content of GMP can impact the blood Phe control of children with PKU [4, 6, 7, 10]. Target blood Phe levels were maintained, without adjusting dietary Phe, when GMP-based protein substitutes are introduced carefully and systematically with nearly half of children tolerating a complete transition to a GMP-based protein substitute [7]. For some children, adjustment of dietary Phe to account for Phe provided by the GMP-based protein substitute might enable a more consistent blood Phe profile within the target range [8].
- There is no current evidence published on the safety and use of GMP-based protein substitutes in infancy and young children below the age of 5 years.

For more information on introducing PKU sphere please see: A practical guide to PKU sphere, available at **www.vitaflo-via.com**

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## Ney *at al.*

**Study:**
Case report of an individual taking a GMP-based protein substitute with run-in and washout period taking amino-acid based protein substitute.

**Length:**
15 weeks, 10 weeks taking GMP-based protein substitute.

**Subjects:**
1 PKU adult patient.

**Findings:**
Blood Phe levels 10% lower whilst taking GMP-based protein substitutes [12].

**2009**

## Van Calcar *et al.*

**Study:**
Clinical trial comparing intakes of amino acid-based protein substitutes and GMP-based protein substitutes.

**Length:**
8 days (Two 4-day study periods).

**Subjects:**
11 PKU patients (aged 11-31 years).

**Findings:**
The study found there was no significant difference in the post prandial plasma Phe levels. No adverse reactions and no significant difference in blood Phe concentrations were detected. Concluded that GMP-based protein substitutes are a safe and suitable alternative to amino acid-based protein substitutes [13].

## Ney *et al.*

**Study:**
A two stage, randomised crossover trial.

**Length:**
9 weeks: 3 weeks taking each GMP and amino acid- based protein substitutes separated with a 3-week wash-out.

**Subjects:**
30 early treated PKU subjects (aged 15-49 years).

**Findings:**
The study found there was no significant difference in the post prandial plasma Phe levels over time [10].

**2016**

**2017**

## Daly *et al.*

**Study:**
Prospective, longitudinal, parallel pilot study.

**Length:**
6 months.

**Subjects:**
PKU subjects (aged 5-16 years) 12 taking GMP-based protein substitutes and 9 taking amino acid-based protein substitutes.

**Findings:**
The amino acid group took 100% of their protein equivalent from amino acid-based protein substitutes. In the GMP group median intake of protein equivalent was 50% from GMP-based protein substitutes and 50% from amino acid-based protein substitutes after 6 months. Blood Phe control declined in the GMP group however, by titrating the dose of GMP-based protein substitute, blood Phe levels remained within target range. The blend of amino acids added to GMP-based protein substitutes significantly impacts Phe-control in children with PKU [5].

## Pinto *et al.*

**Study:**
Retrospective review of annual clinical assessments.

**Subjects:**
1 patients (mean age 27 +/- 10 years) who consumed amino acid-based protein substitutes at baseline and then consumed GMP-based protein substitutes.

**Findings:**
Average time on GMP-based protein substitutes was 13 +/- 5 months and mean intake provided 57% (27 to 100%) of protein substitute intake. Nutritional intake, anthropometry, body composition, blood pressure and blood biochemistry were similar in both groups (except HbA1C which significantly decreased with GMP-based protein substitutes). Median blood Phe did not change (p=0.594) and tyrosine levels significantly (p=0.033) increased. Study concluded that although GMP-based protein substitutes contain residual Phe, they can contribute partially to total protein substitute intake without any negative effects on nutritional status of PKU patients [3].

**2018**

## Pena *et al.*

**Study:**
Systematic review and meta-analysis for the dietary management of PKU with GMP-based protein substitutes.

**Subjects:**
Systematic review: 152 PKU subjects.
Meta-analysis: 72 PKU subjects.

**Findings:**
Focused on the use of GMP in PKU and the effect of residual Phe and impact on Phe control, biochemical status and palatability. The meta-analysis included 2 randomised, controlled trials (RCT) [10,11]. The pooled results showed GMP-based protein substitutes were well accepted and no significant effect was found for all outcome measures, including Phe control [6].

## Ahring *et al.*

**Study:**
Randomised, cross-over, short-term trial comparing 4 different formulations of protein substitutes (2 GMP-based and 2 amino acid-based) to assess absorption and short-term effects on plasma AA, biomarkers related to food intake, taste and satiety.

**Length:**
4 hours.

**Subjects:**
8 PKU patients (aged 15-48 years).

**Findings:**
All patients received each protein substitute formulation and intake was followed by blood sampling at 15, 30, 60, 120 and 240 minutes. It was found that residual Phe in the GMP-based protein substitute did not significantly influence plasma Phe in the short-term when compared to an identical formulation of Phe-free amino acid-based protein substitute. Scores for satiety and taste were non-significant [11].

**2019**

## Daly *et al.*

**Study:**
Randomised controlled cross over study to examine 24-hour blood Phe variability under 3 controlled dietary regimens using 2 different protein substitutes GMP-based or amino acid-based protein substitutes.

**Length:**
6 weeks.

**Subjects:**
16 children with PKU (aged 6-16 years).

**Findings:**
The median Phe concentrations over 24 hours showed statistically significant difference between each arm of the study. GMP-based protein substitute without dietary Phe adjustment led to higher blood Phe concentrations in children with PKU, however blood Phe remained within the target treatment range. These findings indicate that reducing the dietary Phe to compensate for Phe contained in GMP-based protein substitutes enables a more consistent blood Phe profile, although the difference did not reach statistical significance [8].

## Daly *et al.*

**Study:**
Prospective, longitudinal, parallel, controlled trial.

**Length:**
12-months.

**Subjects:**
48 children with PKU (aged 5-16 years, 29 taking GMP-based protein substitutes and 19 taking amino acid-based protein substitutes); none treated with sapropterin dihydrochloride.

**Findings:**
Almost 50% of children were able to transition to GMP-based protein substitute in full to provide 100% of their daily protein substitute requirement without compromising metabolic control. On average children could take 75% of their daily protein substitute requirement as GMP-based without adjustment of dietary Phe, or compromising metabolic control, when introduced gradually and systematically. GMP-based protein substitute maintained adequate nutritional status and growth in children when compared to amino acid-based protein substitutes [7].

**2021**

## Daly *et al.*

**Study:**
Prospective, longitudinal study comparing the impact of protein substitutes (GMP- and amino acid (AA)-based) on body composition and growth.

**Length:**
36-months.

**Subjects:**
48 children with PKU (aged 5-16 years; 13 taking GMP-based protein substitutes, 16 taking a combination of GMP- and AA-based protein substitutes, 19 taking AA-based protein substitutes). 2 patients had mild PKU, 46 patients had classical PKU. All of them were on dietary treatment only.

**Findings:**
No statistically significant difference between all three groups for lean body mass, fat mass, % body fat and height after 36 months could be found. A trend for improved growth and body composition was noted in children only taking GMP as sole source of protein, though it did not reach statistical significance [9].

Additionally, a second publication from this study shows that long-term consumption of GMP-based protein substitutes supports normal bone growth consistent with AA-based protein substitute consumption in patients with good metabolic control [14].

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Vitaflo International Ltd
Suite 1.11, South Harrington Building, 182 Sefton Street, Brunswick Business Park, Liverpool, L3 4BQ, UK.
**+44 (0)151 709 9020 vitaflo@vitaflo.co.uk www.vitafloweb.com**



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