PDE reach™ 5

A practical guide to PDE reach™ 5

Vitaflo in Associatio With You

Supporting education in the dietary management of rare diseases

Overview

PDE reach5 is a lysine-free protein substitute with tryptophan, formulated in collaboration with expert clinicians to be used as part of the management of Pyridoxine dependent epilepsy (PDE).

This practical guide was produced to support Healthcare professionals (HCPs) with the use of PDE reach5 supported by the knowledge and experience gained during the development and clinical trial of PDE reach5.

PDE reach5 was successfully evaluated in 11 individuals with PDE aged 2-15 years. The study took place in two centres: Great Ormond Street Hospital for Children, United Kingdom (UK) and Radboud University Medical Centre in The Netherlands.

Important information

PDE reach5 is a food for medical puposes for the dietatary management of PDE.

Use under medical supervision.

Not suitable for use as a sole source of nutrition.

Suitable from 1 year of age .

For enteral use only.

PDE reach5 must only be consumed by individuals with proven PDE under supervision by the managing clinician or dietitian.

Natural protein must be given in prescribed amounts to meet requirements.

This information is intended for use by Healthcare professionals only.

Allergen information

PDE reach5 contains **fish (tuna)**.

Collaborators

This document was written by Vitaflo dietitians in collaboration with:

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Contents

Abbreviations

AA	Amino acid
AASA	α-aminoadipic semialdehyde
DHA	Docosahexaenoic acid
FAO	Food and Agriculture Organization of the United Nations
GA1	Glutaric aciduria type-1
HCP	Healthcare professional
IEM	Inborn error of metabolism
P6C	Δ-1-piperidene-6-carboxylate
PDE	Pyridoxine dependent epilepsy
PE	Protein equivalent
PLP	Δ-1-piperidene-6-carboxylate
P/S	Protein substitute
UNU	United Nations University
WHO	World Health Organisation

1.0 Background

Pyridoxine Dependent Epilepsy due to ALDH7A1 Deficiency

PDE is an inborn error of metabolism (IEM) in the lysine catabolism pathway, caused by mutations in ALDH7A1 gene. There is decreased activity of the enzyme, α-aminoadipic semialdehyde dehydrogenase which results in accumulation of α-aminoadipic semialdehyde (AASA), Δ-1-piperidene-6-carboxylate (P6C) and pipecolic acid. Lysine does not accumulate. Increased levels of P6C deactivates pyridoxial-5-phosphate (PLP), the active form of pyridoxine, a co-factor for many enzymes in the central nervous system. Depletion of PLP causes epileptic seizures and encephalopathy [1-3].

Most PDE patients present in the first days of life with seizures which are resistant to standard anti-epileptic drugs but are highly responsive to treatment with high dose pyridoxine (vitamin B6) [4]. Despite good seizure control with pyridoxine, global developmental delay and/or intellectual disability is seen in 75% of patients [4]. To address the long term risk of developmental delay, which is hypothesised to be caused by elevated neurotoxic metabolites such as AASA and P6C, lysine reduction therapies have been established in the last 10 years [4-6]. Management options for individuals with PDE include monotherapy (pyridoxine only), double therapy (pyridoxine and either lysine restricted diet or L-arginine supplementation) or triple therapy (all three; pyridoxine, lysine restricted diet and L-arginine supplementation) [4].

The 2021 International PDE consortium consensus guidelines recommends that lysine reduction therapies be initiated as early as possible in newly diagnosed newborns and infants with PDE to help optimise developmental outcomes [4]. It also recommends children, adolescents and adults with PDE be offered lysine reduction therapies [4]. There is some emerging evidence to support improved developmental outcomes for patients who initiated lysine reduction therapies early, within the first 6 months of life [5].

With the absence of newborn screening for PDE, diagnosis and commencement of treatment, including the lysine-restricted diet and a protein substitute, may be delayed [7-9]. Establishing a lysine-restricted diet and protein substitute at an older age can pose significant challenges in acceptance and tolerance [10]. Experience of supporting patients with accepting a protein substitute is outlined in section 3.

The 2014 International PDE consortium consensus guidelines provide the most recently published recommendations for dietary management [6], these are currently under review. For further information on PDE, lysine reduction therapies, and advice for emergency management during episodes of illness, please see the PDE Consortium's website: **www.PDEonline.org**.

Protein substitute development

Where there is an absence of a PDE specific protein substitutes patients have been managed with products designed for Glutaric aciduria type-1 (GA1), another IEM in the lysine pathway. Dietary management of GA1 requires supplementation with a lysine-free, low tryptophan protein substitute. Tryptophan is an essential AA and does not need to be limited in PDE, therefore use of a GA1 protein substitute poses possible risk of tryptophan deficiency [4, 6]. Tryptophan is the sole precursor of the neurotransmitter serotonin.

The 2014 PDE Consortium consensus guidelines [6] advise when GA1 protein substitutes are used, tryptophan should be supplemented if dietary intake is inadequate according to the FAO/WHO/UNU [11] recommendations. However, provision of tryptophan as a single dose AA is not easily feasible.

Healthcare professionals (HCPs) identified the need for a lysine-free protein substitute containing tryptophan for individuals with PDE, which led to the development of **PDE reach5**.

Clinical evaluation*

PDE reach5 was shown to be efficacious for the dietary management of PDE. **PDE reach5** was well tolerated, accepted and rated easy to use. Metabolic control was maintained throughout the study. Tryptophan levels were maintained within the reference range during the study period. Five individuals took **PDE reach5** made with water and six mixed it with a permitted food or drink. There were no withdrawals during the study and all patients continued to take **PDE reach5** at the end of the 8 week evaluation period.

* Data on file.

2.0 What is PDE reach5?

- **Disorder specific AA profile**
  - including essential AA tryptophan
- **Suitable from 1 year of age**
  - and throughout childhood, adolescence and adulthood
- **Convenient pre-measured 5g protein equivalent (PE) servings in 18g sachets**
  - to facilitate accurate intake
- **Mild raspberry-vanilla flavour with no colours or artificial sweeteners**
  - investment in sensory during development to optimise acceptance and adherence to the product
- **Designed to provide a source of micronutrients and DHA**
  - which are likely to be low in a lysine-restricted diet
- **Flexible presentation**
  - can be taken as a semi-solid by spoon or a low volume drink depending on individual preference
- **Low volume**
  - to facilitate acceptance and adherence

Table 1: Nutritional overview

	Units	Per 100g	Per 18g sachet
Energy	kJ	1477	266
	kcal	348	63
Fat	g	0.40	0.07
of which saturates	g	0.10	0.02
DHA	mg	90	16
Carbohydrate	g	58	10
of which sugars	g	17	3.1
Protein Equivalent	g	28	5.0
Lysine**	mg	-	-
Tryptophan	mg	0.66	0.12

** No added lysine. Trace amounts may still be present from other ingredients (<10mg per 100g/<2mg per serving).

For full nutritional information see product label.

3.0 How to introduce PDE reach5

Introduction for individuals already established on a protein substitute

Individuals who were already established on a protein substitute before entering the clinical study were able to incorporate PDE reach5 into their diet quickly and easily.

Individuals were advised to swap out one serving of their previous protein substitute and replace with the equivalent amount of PDE reach5 each week. For the clinical study, this was to ensure any tolerance or gastrointestinal disturbance could be monitored.

The study dietitians reported patients adapted to PDE reach5 without difficulty, and a quicker introduction may be tolerated outside the clinical study*.

Example

Replacing current protein substitute given 3 times/day				
Stage 1				replace 1 serving of current P/S with equivalent serving of PDE reach5
Stage 2				replace 2 serving of current P/S with 2 equivalent servings of PDE reach5
Stage 3				replace all current P/S with equivalent amount of PDE reach5

Introduction for individuals who have not been on a protein substitute as part of their management

Individuals who had not been established on a protein substitute prior to the clinical study required more encouragement and support strategies for them to accept and take PDE reach5.

In the clinical study the strategy for introduction varied for these individuals:

- some individuals were able to introduce 1 sachet of PDE reach5 at one mealtime and build up to full requirements quickly
- others needed a slower introduction. Starting with a few spoonfuls and gradually building up to full requirements, this could take about a month
- positive feedback, patience and/ or a reward system was used to help during this process.

* Data on file.

Key strategies to support the introduction and adherence of protein substitute

These are based on experience introducing protein substitutes with other IEM and may be helpful for use with **PDE reach5**.

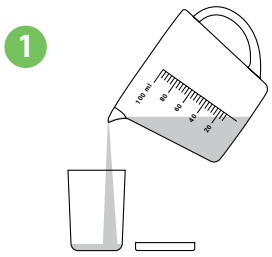
- **Treat protein substitutes with the same importance as a medicine** [12]
- **Supervise the child until the protein substitute is finished** [10]
- **Best given with main meals (providing natural protein)** [12]
    - the rest of the family might try to have a special drink at the same time
- **Establish a routine -** always give protein substitute at the same time each day [12]
- **Be persistent, and encouraging**
    - Increasing familiarity with the taste of a food increases the likelihood of acceptance. Offer new foods several times, even if initially rejected [12]
    - Star charts and rewards may help
- **Seek peer support from nursery, school or clinic tasting events where children may be more receptive to new foods**
- **Keep to the minimum time possible (ideally less than 5 minutes)**
    - timer games may be helpful
- **Continue to offer even when refused or the child is unwell** [6]

4.0 Preparation of PDE reach5

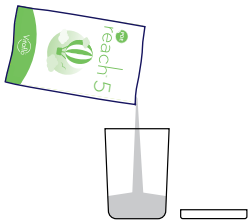
Mixing instructions:

PDE reach5 can be taken as a semi-solid spoonable consistency or a low volume drink.

For a semi-solid spoonable consistency:



1. Add 20ml of cold water into a beaker.

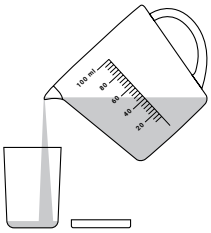


2. Empty the contents of the sachet into the beaker.

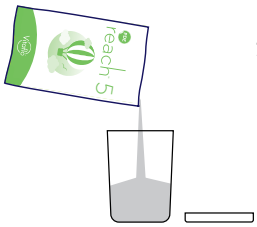
3. Secure lid and shake well for 10 – 15 seconds.

4. Leave to stand for 1 - 2 minutes, allowing a smooth semi-solid consistency to form. Consume immediately with a spoon.

For a low volume drink:

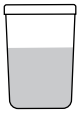


1. Add 80 ml of cold water into a beaker.



2. Empty the contents of the sachet into the beaker.

3. Secure lid and shake well for 10 – 15 seconds.



4. Drink immediately.

Water or permitted drinks should be taken after PDE reach5.

The product should be prepared immediately prior to feeding and any remaining product must be discarded if not used within 1 hour.

PDE reach5 **can be mixed with permitted foods and drinks to aid acceptance or offer more variety.**

5.0 References

1. Coughlin CR, 2nd, Swanson MA, Spector E, Meeks NJL, Kronquist KE, Aslamy M, et al. The genotypic spectrum of ALDH7A1 mutations resulting in pyridoxine dependent epilepsy: A common epileptic encephalopathy. J Inherit Metab Dis. 2019; 42(2): 353-61.
2. Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, Baumgartner M, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med. 2006; 12(3): 307-9.
3. Struys EA, Jakobs C. Alpha-aminoadipic semialdehyde is the biomarker for pyridoxine dependent epilepsy caused by alpha-aminoadipic semialdehyde dehydrogenase deficiency. Mol Genet Metab. 2007; 91(4): 405.
4. Coughlin CR, 2nd, Tseng LA, Abdenur JE, Ashmore C, Boemer F, Bok LA, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to α-aminoadipic semialdehyde dehydrogenase deficiency. J Inherit Metab Dis. 2021; 44(1): 178-92.
5. Coughlin CR, Tseng LA, Bok LA, Hartmann H, Footitt E, Striano P, et al. Association Between Lysine Reduction Therapies and Cognitive Outcomes in Patients With Pyridoxine-Dependent Epilepsy. Neurology. 2022; 99(23): e2627–36.
6. van Karnebeek CD, Stockler-Ipsiroglu S, Jaggumantri S, Assmann B, Baxter P, Buhas D, et al. Lysine-Restricted Diet as Adjunct Therapy for Pyridoxine-Dependent Epilepsy: The PDE Consortium Consensus Recommendations. JIMD Rep. 2014; 15: 47-57.
7. Al Teneiji A, Bruun TUJ, Cordeiro D, Patel J, Inbar-Feigenberg M, Weiss S, et al. Phenotype, biochemical features, genotype and treatment outcome of pyridoxine-dependent epilepsy. Metab Brain Dis. 2017; 32(2): 443-51.
8. Wempe MF, Kumar A, Kumar V, Choi YJ, Swanson MA, Friederich MW, et al. Identification of a novel biomarker for pyridoxine-dependent epilepsy: Implications for newborn screening. J Inherit Metab Dis. 2019; 42(3): 565-74.
9. Coughlin CR, 2nd, Tseng LA, van Karnebeek CDM. A case for newborn screening for pyridoxine-dependent epilepsy. Cold Spring Harb Mol Case Stud. 2022; 8(2).
10. Dixon M, MacDonald A, White FJ. Disorders of amino acid metabolism, organic acidaemias and urea cycle disorders. In: Shaw V, ed. Clinical Paediatric Dietetics, 5th edition. Wiley Blackwell. 2020. [513-98].
11. Food and Agriculture Organization of the United Nations F, World Health Organization W, United Nations University U. Protein and Amino Acid Requirements in Human Nutrition: Report of a Joint WHO/FAO/UNU Expert Consultation. FAO/WHO/UNU; 2007. Report No.: 0512-3054 (Print) 0512-3054 Contract No.: 935.
12. MacDonald A, van Wegberg A, Ahring K, Beblo S, Bélanger-Quintana A, Burlina A, et al. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis. 2020; 15(1): 1-21.

Notes

Notes

Vitaflo™

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All information correct at the time of publication.

This information is intended for Healthcare professionals.

Nov 2023