EE656

Challenges in Health Economic Modeling of Phenylketonuria (PKU): A Targeted Review of HTA Evaluations

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1. Background & Objectives:

PKU is an inherited, genetic condition leading to elevated blood phenylalanine (Phe) causing neurological damage and cognitive disability.[1]

- Disease management involves stringent, lifelong dietary management to maintain low blood Phe levels,[2] but adherence to Phe-restricted diets is challenging, leading to suboptimal disease management and potential neurological damage from uncontrolled Phe.[3]
- Two regulatory-approved treatments, sapropterin dihydrochloride and pegvaliase, are currently available as pharmacological options for PKU.

However, these may be associated with inadequate efficacy or adverse events, such as the low responder rate of sapropterin, particularly in more severe PKU cases,[4] and the potentially serious side effects and anxiety linked to pegvaliase's subcutaneous mode of administration.[5]

- Various cost-effectiveness analysis (CEA) approaches for health technology assessment (HTA) have been used for the reimbursement evaluations of sapropterin and pegvaliase.

An understanding of historical health economic modeling challenges may inform CEA for future interventions for PKU.

In this study, the modeling approaches used in CEAs for HTA evaluations of sapropterin and pegvaliase, and the challenges associated with these approaches, were characterized as well as HTA committees' critiques and recommendations.

2. Methods:

Targeted Review

- A targeted review was conducted to identify HTA evaluations for sapropterin and pegvaliase for the treatment of PKU from HTA agency websites (see Supplementary Materials for full list of HTA agencies).
- Publicly available HTA materials were downloaded, and relevant information was extracted, including country and year of the evaluation/CEA, model structure and key inputs / assumptions, health states used to model disease progression, and limitations and critiques from HTA agencies.

Expert Panel

- A panel of 8 medical experts in PKU was invited to provide clinical expertise and context that may be important to modeling the disease.
- Given the potential for heterogeneity in clinical perspectives on PKU, a purposive sampling method was used to recruit an international, multidisciplinary sample of medical experts across pediatrics, metabolic, dietetics, and genetics specialties.
- Summaries of key modeling challenges were presented to confirm relevance and considerations for economic modeling of treatments for PKU.

3. Results:

Overview of CEA approaches

- A targeted search of HTA evaluations for sapropterin and pegvaliase identified 10 CEAs (**Table 1; Supplementary materials**).
  - Approaches included lifetime-horizon Markov models (6 evaluations), microsimulations (2 evaluations), and 1 year horizon decision trees (2 evaluations; **Figure 1**).
  - The searches of HTA agencies in France (HAS), Germany (GBA), and Netherlands (ZIN) did not identify sufficiently detailed descriptions of economic modeling of PKU to be included in the models summarized below.

Table 1. CEAs identified in the targeted search of HTA evaluations

Country	Australia	Canada	England	Ireland	Scotland
Sapropterin (n=7 evaluations)	2018/2022	2016	2021*	2017	2018
Pegvaliase (n=3 evaluations)	2022	2023	-	2022	-

*Two models were identified in this evaluation (the manufacturer's and the Evidence Review Group's)

Figure 1. CEA approaches used in HTA evaluations identified

Lifetime-horizon Markov models (6 evaluations)

Microsimulations (2 evaluations)

1 year horizon decision trees (2 evaluations)

- Markov models included 4-5 alive health states. Health states were variously defined, typically considering blood Phe ranges and/or disease control.
  - 4 evaluations shared 3 health states ("controlled", "partially-controlled", "uncontrolled"), and further included "controlled+Phe tolerance" or "asymptomatic" as a 4th state.
  - 1 evaluation included 5 blood Phe-range health states.

Critiques by HTA committees for sapropterin and pegvaliase CEAs

- HTA committees critiqued that CEAs did not fully address clinical dimensions of the decision problem (**Figure 2**).
- Committees also noted the absence of modeling of PKU-associated comorbidities; in maternal PKU, impacts on mothers and/or unborn children; and caregiving impacts.

Expert panel

- Clinical experts from the multidisciplinary panel agreed with the limitations cited by HTA committees for economic models that have been conducted to assess the cost-effectiveness of sapropterin and pegvaliase.
- Input from the panel informed the development of materials for a subsequent Delphi panel.[6]

Figure 2. Major critiques of CEAs from HTA committees

Impacts of uncontrolled Phe on long-term outcomes were not captured

[The committee] concluded that the costs of long-term brain damage after uncontrolled Phe levels in childhood, cost of potential comorbidities, and costs of caregiving and carer disutilities may be substantial and need to be considered [but] cannot be included in a model with a 1-year time horizon.

The PBAC considered that the submission did not adequately address the range of important benefits for adults associated with lowering and stabilising Phe levels. […] The PBAC considered that while not well-demonstrated in the clinical data, consumer input assisted in establishing the degree of benefit to patients from blood Phe-lowering treatment.

Raised Phe levels in pregnant women with PKU can cause severe birth defects in their unborn children. This could increase maternal anxiety, with the additional burden of the even more restrictive diet that is needed during pregnancy [...] The model is not appropriate to capture the effects of PKU in pregnancy.

Health state definitions did not align with utility/cost impacts

No reliable clinical evidence was presented to quantify a symptomatic or clinically meaningful benefit in adult patients initiating sapropterin or even clear benefits associated within specific Phe ranges.

None of the descriptions of the seven Swedish health states [informing utilities] accurately reflect any of the company model health states. […] Clinical advice to the ERG is that many patients with PKU have blood Phe concentration levels outside of the optimum controlled ranges yet are free from clinically relevant symptoms.

The health-state utility values lack face validity […] For example, a utility score of 0.171 for severe PKU symptoms requiring dietary restriction and medical food is substantially lower than utility score norms reported for mood disorders (0.643), effects of a stroke (0.581), and Alzheimer disease or other dementia (0.374) […] [CADTH clinical experts] considered patients with a mood disorder to be more appropriate proxies for uncontrolled PKU.

Modeling of discontinuation was lacking or implausible

The model structure does not adequately capture the condition in that […] blood Phe control was not related to adherence to therapy in the model, and discontinuation was not considered [absence of modelling discontinuation rates for ineffective treatments], greatly inflating the costs of sapropterin and pegvaliase.

Patients who discontinued treatment with sapropterin are not permitted to receive sapropterin at a later time […] In the company base case [baseline age: 4 months], by the time this cohort of patients is 18 years old, only 2.6% will still be taking sapropterin, with 97.4% never taking sapropterin (despite it being effective) […] such a scenario is implausible.

Once a patient moves into the controlled state they are assumed to cease treatment and no further medicine cost is incurred. [...] However, it also appears that it is assumed there would be no loss of subsequent benefit (i.e. QALYs) when patients move into the controlled state but no longer receive sapropterin treatment, which seems unlikely.

Diet liberalization modeling was unsupported/likely overstated

The committee noted that sapropterin did not replace the need for diet in most people but had been shown to be effective in combination with a protein restrictive diet (PRD) in trials. Ideally this would allow people to consume more natural protein, relax the diet to a varying degree and need less low-protein food and supplements. However, the committee concluded that the cost savings related to a reduction in protein-restricted diet are uncertain.

The estimated natural protein intake and reduction in the use of protein supplements and hence cost of diet in the sapropterin arm leads to significant cost offsets. There is uncertainty over the cost reduction estimated and the extent to which such cost savings can be realised in practice.

In the company model, it is assumed that patients taking sapropterin who have controlled blood Phe concentration levels are able to relax their PRD through a 71.2% reduction in protein supplements and low protein food. [...] The ERG was not able to verify that the methods employed to derive the value of 71.2% were robust. [...] Furthermore, clinical advice to the ERG is that it is likely that even if patients could reduce their intake of low-protein foods, they would be advised to maintain their intake of protein supplements.

4. Discussion & Conclusions:

This review of 10 CEAs conducted in HTA evaluations of PKU treatments found, in common with other rare diseases, considerable challenges in health economic modeling for PKU.

In PKU, approaches that were previously used have been inadequate for capturing the full clinical picture of the disease, including long-term outcomes.

Key aspects that could contribute to increased costs and worse clinical consequences were often overlooked, such as comorbidities and caregiver impact.

Models based on blood Phe levels had inconsistent definitions for disease control and were limited by potential Phe variability, which must be interpreted alongside the patient's diet and treatment adherence.

Limitations identified in these CEAs may stem in part from data availability, and the complexity of disease management.

For example, in the Australian evaluations for both treatments, clinical data was found to be lacking to support a microsimulation approach with a lifetime horizon.[6-8]

The heterogeneity of existing CEA models (both modeling approaches and time horizons) reflects a significant lack of consensus on how to model PKU in a clinically accurate manner.

This review identifies limitations of health economic modeling in PKU and offers insights on important components for future approaches to ensure clinical accuracy of modeling of disease presentation and management.

Economic models previously used in HTA evaluations for PKU did not accurately represent the presentation and impacts of the disease, nor certain aspects of its management. Future modeling approaches should seek to address these limitations. Building from this review, a Delphi process is being conducted to inform clinically-accurate economic modeling of PKU.

6. References:

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