

Sapropterin (Kuvan) for the treatment of phenylketonuria (PKU)



Summary

1. Sapropterin, a synthetic form of tetrahydrobiopterin (BH4), is the natural co-factor for the enzyme phenylalanine (Phe) hydroxylase that catalyses the breakdown of phenylalanine. It is licensed for the treatment of hyperphenylalaninaemia (HPA) in patients ≥ 4 years of age with phenylketonuria, and for the treatment of HPA in patients with BH4 deficiency who have been shown to be responsive to such treatment. Sapropterin is a soluble 100mg oral tablet. Sapropterin is not a cure for PKU. It is an add-on agent and will not replace standard care completely. Duration of therapy is unknown and it is possible that patients may be treated both long-term and short-term.
2. One phase III randomised, double-blind, clinical trial in patients with PKU has been published, PKU003 which included 42 patients treated with sapropterin and 47 with placebo for 6 weeks. These patients were recruited into the trial following an open-label screening study of 480 patients, who were ≥ 8 years with elevated blood Phe levels of ≥ 600 $\mu\text{mol/l}$ who received a 10mg/kg dose. After 6 weeks of treatment, patients given sapropterin had a decrease in mean Phe levels of 236 (± 257) $\mu\text{mol/l}$ as compared with a 3 (± 240) $\mu\text{mol/l}$ increase in the placebo group ($p < 0.001$). Blood Phe levels < 600 $\mu\text{mol/l}$ at week six were seen in 54% (22/41) and 23% (11/47) of patients in the sapropterin and placebo groups respectively. After 6 weeks, 44% of patients in the sapropterin group and 9% in the control group had a reduction of Phe levels of $\geq 30\%$.
3. No significant differences in adverse events were noted between the two groups in the PKU003 six week trial and the subsequent 22 week open-label extension study. The most commonly reported adverse effects were gastrointestinal, neurological (dizziness, headache) and rhinorrhoea.

4. The acquisition cost of a 100mg tablet of sapropterin is €21.50. The PKU diet which includes low protein food supplements (currently available on the LTI or GMS community drugs schemes) must be continued, even with sapropterin therapy. The additional costs of sapropterin are difficult to estimate due to variations in weights of adults and children. Estimates of additional costs to existing therapy range from €15,695 for a child of 15-24kg to €62,780 for an adult of 75-84kg, based on 10mg/kg dosing regimen. Depending on the uptake of sapropterin, the budget impact could range from €2.66 million to €9.88 million per year.
5. The efficacy outcome marker used in the clinical trial is a surrogate marker of effectiveness i.e. $\geq 30\%$ reduction in Phe levels, and does not allow extrapolation to a valid therapeutic gain for PKU patients. Cost per QALY data is unavailable due to the paucity of quality of life data in the literature. The appropriate comparator for an economic evaluation would be the current protein restricted diet and protein supplements but clinical trial data is lacking.
6. On the basis of the available evidence and in the absence of a demonstration of cost-effectiveness, the NCPE review cannot recommend sapropterin as an add-on treatment for patients with PKU. Current dietary management with a phenylalanine-free diet remains the intervention of choice.