Seth, diagnosed at birth with PKU

MANAGEMENT OF PAH DEFICIENCY/PKU:

A Summary of the ACMG Treatment Guidelines

Julie, adult with PKU

Bailey, young adult with PKU

Recommendations from the experts

PKU experts with the American College of Medical Genetics and Genomics (ACMG) released the "Phenylalanine Hydroxylase (PAH) Deficiency: Diagnosis and Management Guideline" in 2014. These recommendations represent a tremendous step forward in ensuring patients receive the highest quality treatment in the management of PAH deficiency.

A summary of the ACMG treatment guidelines[1]

The ACMG Guidelines
The guidelines refer to PKU as phenylalanine hydroxylase (PAH) deficiency. PAH deficiency refers to the underlying enzyme defect.

Begin treatment early
Treatment should be started as early as possible, preferably within the first week of life.

Aim for the range
Blood Phe levels should be maintained within 120-360 µmol/L (2-6 mg/dL) throughout life.

Use every tool in your toolbox
Any combination of therapies that help to keep blood Phe levels within the recommended range is appropriate.

Intellectual and mental health
Appropriate intellectual and mental health assessments are an important part of PKU care.

Every PKU patient deserves a trial*
Every patient should be offered a response trial of KUVAN® (sapropterin dihydrochloride) Tablets.

Health Canada approved
KUVAN Tablets is the only approved medication for the treatment of PKU.

It's not too late!
Patients returning to therapy may see an improvement in symptoms.

*Except those with 2 null mutations in *trans*.

Reference: 1. Vockley J, et al; for the American College of Medical Genetics and Genomics Therapeutic Committee. *Genet Med*. 2014;16(2):188-200.

Questions to help get the most out of your patient's next clinic visit

Discussing the ACMG management guidelines with individuals with PKU will help you provide the best possible care for your patients. Below are questions to assist your healthcare team in advocating for improved patient care:

- ☐ **Are blood Phe levels within 120-360 µmol/L (2-6 mg/dL)?**
- ☐ **What can be done to keep blood Phe levels in better control?**
- ☐ **Are there any tips to help stay on diet and are there any foods that are off-limits?**
- ☐ **What amounts of formula and Phe or protein should be consumed each day?**
- ☐ **Is there anything else to try to help with Phe control?**
- ☐ **How often should blood Phe levels be tested?**
- ☐ **Should any intellectual or mental health assessments be conducted?**

Please see back cover for Important safety Information

KUVAN® (sapropterin dihydrochloride) Tablets are indicated in conjunction with a phenylalanine- (Phe-)restricted diet to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-)responsive phenylketonuria (PKU).

Important Safety Information for KUVAN® (sapropterin dihydrochloride) Tablets:

Treatment with KUVAN® (sapropterin dihydrochloride) Tablets should be directed by physicians knowledgeable in the management of PKU. Prolonged elevations in blood Phe levels in patients with PKU can result in severe neurologic damage, including severe mental retardation, microcephaly, delayed speech, seizures, and behavioural abnormalities. This may occur even if patients are taking KUVAN but not adequately controlling their blood Phe levels within the recommended target range. Neurocognitive outcomes with KUVAN treatment have not been established in long-term clinical studies. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and protein breakdown. Active management of dietary Phe intake while taking KUVAN is required to ensure adequate Phe control and nutritional balance.

Not all patients with PKU respond to treatment with KUVAN. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with KUVAN [see CLINICAL TRIALS section of the product monograph]. Response to treatment cannot be pre-determined by laboratory testing (e.g., genetic testing), and should only be determined by a therapeutic trial of KUVAN [see DOSAGE AND ADMINISTRATION section of the product monograph].

Patients with PKU who are being treated with KUVAN should also be treated with a Phe-restricted diet. The initiation of KUVAN therapy does not eliminate the need for appropriate monitoring by trained professionals to assure that blood Phe control is maintained in the context of ongoing dietary management.

Monitor patients when co-administering KUVAN with medications known to inhibit folate metabolism, or with levodopa. Monitor patients for hypotension when co-administering KUVAN with medications known to affect nitric oxide-mediated vasorelaxation.

Monitor patients for signs and symptoms of gastritis (see ADVERSE REACTIONS).

KUVAN has not been studied in patients with liver or renal impairment. Patients who have these conditions should be carefully monitored when receiving KUVAN.

KUVAN is contraindicated in patients with a history of anaphylaxis to KUVAN (see CONTRAINDICATIONS). Hypersensitivity reactions, including anaphylaxis and rash, have occurred [see ADVERSE REACTIONS]. Discontinue treatment with KUVAN in patients who experience anaphylaxis and initiate appropriate medical treatment. Continue dietary Phe restrictions in patients who experience anaphylaxis.

Monitor patients for hyperactivity. Frequent blood monitoring is recommended in the pediatric population.

Some patients receiving KUVAN can experience significant drops in blood Phe levels. Patients should be monitored closely to ensure that blood Phe levels do not fall too low.

Patients should be advised to notify their physicians in cases of overdose.

The most commonly reported adverse reactions (in ≥ 4% of the KUVAN-treated patients) were: headache, diarrhoea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea.

Reporting Suspected Adverse Reactions: You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by any of the 3 following ways:

- Report online: www.healthcanada.gc.ca/medeffect
- Call toll-free: 1-866-234-2345
- Complete a Consumer Side Effect Reporting Form and fax it toll-free to 1-866-678-6789, or mail it to:
  Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

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