Management of PAH deficiency/PKU:

A summary of the ACMG treatment guidelines

Management of PAH deficiency/PKU: **Recommendations from the experts**[1]

The American College of Medical Genetics and Genomics (ACMG), released guidelines in 2014 titled "Phenylalanine Hydroxylase (PAH) Deficiency: Diagnosis and Management Guideline". These recommendations ensure that all PKU patients receive the highest quality of care.

A summary of the ACMG treatment guidelines

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

PKU treatment should be started as early as possible, preferably within the first week of life

Blood Phe levels should be maintained within 120-360 µmol/L (2-6 mg/dL) in patients of all ages throughout life
Blood phenylalanine and tyrosine should be monitored on a regular basis

KUVAN® (sapropterin dihydrochloride) is the only FDA-approved medication for the treatment of PKU

Every patient should be offered a trial of KUVAN*
Response must be determined by a "test for response" or trial period

Any combination of therapies (medical foods, KUVAN, and diet) that improve a patient's blood Phe levels is appropriate and treatment should be individualized

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

Those who return to therapy may see an improvement in symptoms – It's not too late to take control

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

Please see Important Safety Information on back cover.

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

It's important to do all you can to protect your (or your loved one's) brain from the toxic effects of high or unstable Phe. Discuss the ACMG management guidelines with your PKU treatment team to help you get the best possible care for managing PKU. These questions are intended to support you in advocating for yourself or your child.

- [ ] **Should my blood Phe levels be within 120-360 µmol/L?**
- [ ] **What can I do to keep my blood Phe levels in better control?**
- [ ] **Do you have any tips to help me stay on diet and are there any foods that are off-limits?**
- [ ] **Can we discuss KUVAN® (sapropterin dihydrochloride)? I would like to try it to see if I respond.**
- [ ] **How often should I have my blood Phe levels tested?**
- [ ] **Should all PKU patients receive intellectual or mental health assessments?**
- [ ] **If I have not been closely managing my PKU, will it help me to start therapy again? What can I do to get started?**

Indication

KUVAN® (sapropterin dihydrochloride) Tablets for Oral Use and Powder for Oral Solution are approved to reduce blood Phe levels in people with a certain type of Phenylketonuria (PKU). KUVAN is to be used with a Phe-restricted diet.

Important Safety Information

It is not possible to know if KUVAN will work for you without a trial of the medicine.
Your doctor will check your blood Phe levels when you start taking KUVAN to see if the medicine is working.

Starting KUVAN does not eliminate the need for ongoing dietary management. Any change to your diet may impact your blood Phe level. Follow your doctor's instructions carefully. Your doctor and dietitian will continue to monitor your diet and blood Phe levels throughout your treatment with KUVAN **to make sure your blood Phe levels are not too high or too low**. If you have a fever, or if you are sick, your Phe level may go up.
Tell your doctor and dietitian as soon as possible so they can make any necessary changes to your treatment.

Children younger than 7 years old treated with KUVAN doses of 20 mg/kg per day are at an increased risk for low levels of blood Phe compared with children 7 years and older. Frequent blood monitoring is recommended in this population to ensure that blood Phe levels do not fall too low.

Tell your doctor if you have ever had liver or kidney problems, have poor nutrition or have a loss of appetite, are pregnant or plan to become pregnant, or are breastfeeding or plan to breastfeed.

KUVAN is a prescription medicine and should not be taken by people who are allergic to any of its ingredients. KUVAN and other medicines may interact with each other. Tell your doctor about **all the medicines you take**, including prescription and over-the-counter medicines, vitamins, herbal and dietary supplements.

If you forget to take your dose of KUVAN, take it as soon as you remember that day. Do not take 2 doses in a day. If you take too much KUVAN, call your doctor for advice.

The most common side effects reported when using KUVAN are headache, runny nose and nasal congestion, sore throat, diarrhea, vomiting, and cough. Additional adverse reactions reported in connection with worldwide marketing include sore throat, heartburn or pain in the esophagus, inflammation of the lining of the stomach, indigestion, stomach pain, and nausea. These are not all the possible side effects seen with KUVAN. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

KUVAN can cause serious side effects, including:

- **Severe allergic reactions.** Stop taking KUVAN and **get medical help right away** if you develop any of these symptoms of a severe allergic reaction:
  - Wheezing or trouble breathing
  - Lightheadedness or fainting
  - Nausea
  - Coughing
  - Flushing
  - Rash
- **Inflammation of the lining of the stomach (gastritis).** Gastritis can happen with KUVAN and may be severe. **Call your doctor right away if you have any:**
  - Severe upper stomach-area discomfort or pain
  - Black, tarry stools
  - Blood in your vomit or stool
  - Nausea and vomiting
- **Too much or constant activity (hyperactivity) can happen with KUVAN.** Tell your doctor if you have any signs of hyperactivity, including fidgeting, moving around or talking too much.

For more information, call BioMarin RareConnections™ at 1-888-863-3361.

Please read the attached full Patient Information.

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

KUVAN®
(sapropterin dihydrochloride)
Tablets or Powder for Oral Solution

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