

Comparison of Criteria for reimbursing KUVAN (sapropterin dihydrochloride) 100 mg tablets for the treatment of Phenylketonuria (PKU)

	ON	SK	Calgary	QC	AB Children's Hospital	The American College of Medical Genetics and Genomics (ACMG) Practice Guidelines
Payment length of time covered by manufacturer	6 months	6 months	1-2 months	NA	4 weeks	
Initial Criteria for payment of therapy by manufacturer	<p>Initial 6 month, with ALL of the following criteria:</p> <ol style="list-style-type: none"> Compliance with a low protein diet and formulas Baseline blood Phe levels >360 µmol/L despite compliance with low protein diet (require at least 2 levels during 3 to 6 month time frame) Baseline protein intake assessment by a dietitian Ability to comply with medication regimen Managed by a physician specialized in metabolic/biochemical diseases 	<p>Non-Pregnant Patients and Patients actively planning pregnancy:</p> <ul style="list-style-type: none"> For the management of patients with the diagnosis of PKU who meet ALL of the following criteria: <ol style="list-style-type: none"> Compliance with low protein diet and formulas Baseline blood Phe levels > 360 µmol/L despite compliance with low protein diet (require at least 2 levels during 3 to 6 month time frame) Baseline protein intake assessment by a dietitian Ability to comply with medication regimen Managed by a physician specialized in metabolic/biochemical diseases 	<p>for each patient with HPA/PKU</p> <ol style="list-style-type: none"> Available through the "KUVAN Assistance Program" Requires patient registration by clinic or pharmacy Staff to supervise / assist patients / measure PHE if required 		<p>for a responsiveness, according to the following terms:</p> <ol style="list-style-type: none"> A free 30 day supply of KUVAN will be provided to patients: this includes patients either enrolled in the KAP or not KUVAN will be delivered to the in-hospital retail pharmacy for dispensing to patients. Patients are to be assigned a number by the treating clinic or pharmacy If after 30 days a response has not been determined, an additional supply of KUVAN can be obtained on a per patient basis Patients deemed responsive to KUVAN by the clinic physician (responsive patients will be given a letter to that effect) and wish to continue on therapy can purchase KUVAN from a retail pharmacy or enroll in the KAP and utilize the reimbursement services provided in order to receive free drug while a reimbursement assessment is performed. Upon completion of the reimbursement status, patients will be transitioned to either compassionate use (for patients that have no access to reimbursement) or commercial product (for patients that have access to reimbursement). If reimbursement is denied or discontinued due to lack of information supplied to the payer, the KAP will assume that the patients are non-responders and will discontinue therapy 	
Pregnant Patients	Initial funding available also for pregnant patients	For pregnant patients: points 2 & 5		After the trial period (see below), physician will have to		

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			<p>provide the following proof:</p> <ol style="list-style-type: none"> 5. A response to KUVAN defined by an average decrease of serum Phe concentration of at least 30%; and 6. A serum Phe concentration >360µmol/l despite a low Phe diet <p>Authorization will be granted for the period during which the women actively attempt to procreate, up to the end of their pregnancy</p>		
<p>Additional clarifying criteria for initial coverage</p>	<p><i>For children less than 4 years of age, clinically validated age-appropriate neuro-behavioural, neuro-cognitive, or developmental tests may be selected at the clinician's discretion rather than PKU specific tests</i></p>		NA		
<p>Exclusion criteria for initial funding coverage</p>	<ol style="list-style-type: none"> 1. Known hypersensitivity to KUVAN 2. Any other contraindications 3. Baseline Phe levels < 360 µmol/L 4. Women who are nursing/breast feeding 5. Patients who are not on the special diet or who are not compliant with their special diet 	<ol style="list-style-type: none"> 1. Known hypersensitivity to KUVAN 2. Any other contraindications 3. Baseline Phe levels < 360 µmol/L 4. Women who are nursing/breast feeding 5. Patients who are not on the special diet or who are not compliant with their special diet 	NA		
<p>Identifying "Responders" - Eligibility Test</p> <p><u>Test for Eligibility: 72 hour "KUVAN" Challenge</u></p> <ul style="list-style-type: none"> ○ 72 hour challenge with KUVAN at 20 mg/kg/day ○ Blood Phe concentrations are measured at 48 hours, 24 hours, and time "0" PRIOR TO the KUVAN dose and THEREAFTER at 4, 12, 24, 48, and 72hours following the dose; OR as per clinic's protocol <p><i>Note that the recommended dose of</i></p>	<p>Exact same as ON</p> <p>But with additional clarification:</p> <p><i>Note: Baseline Phe tolerance level must be documented as well as Phe tolerance levels documented at</i></p>	<p>Responsiveness to be confirmed by clinic,</p> <ol style="list-style-type: none"> 1. Baseline visit <ol style="list-style-type: none"> a. Protocol review with patient b. Prescription for KUVAN 2. Weekly PHE levels (4 blood dots) <ol style="list-style-type: none"> a. Dietary - PHE intake to be adjusted weekly if appropriate 3. Weekly diet three day intake records 4. Post trial <ol style="list-style-type: none"> a. Analysis of dietary intake and PHE levels b. Assessment of responsiveness 	<p>For women suffering from PKU who wish to procreate, a 2-month trial period is authorized to determine those responding to KUVAN</p>	<p><i>Patients need to indicate that they are responders to KUVAN by providing a letter of documentation from the metabolic clinic</i></p> <p>Protocol to Determine PKU Patient Responsiveness to KUVAN</p> <ol style="list-style-type: none"> 1. Patients PKU of any age can participate in this trial but typically would have been on PKU diet and formula for at least 1-2 years to demonstrate stability of treatment 2. Patients or their caregivers/parents (if <18 years) 	<p>General guidelines</p> <ul style="list-style-type: none"> • Newborn screening for PAH deficiency • Initiation of treatment for PKU should be undertaken as early as possible, preferably within the first week of life • Dietary therapy with restriction of dietary PHE intake remains the mainstay of therapy for PAH deficiency

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<p><i>KUVAN to establish clinical benefit is 20 mg/kg/day</i></p> <p>Responders to the 72 hour "KUVAN" Challenge</p> <ul style="list-style-type: none"> • For Non-Pregnant patients and patients actively planning pregnancy, responders to the KUVAN challenge are those who meet the following criteria: <ul style="list-style-type: none"> ○ Reduction in Phe blood level of at least 30% compared to baseline; AND ○ Patient must have a baseline assessment of neuro-behavioural or neuro-cognitive impairment and quality of life assessment due to PKU after the 72 hr KUVAN challenge but before start of KUVAN therapy (this assessment does not apply to pregnant women) 	<p><i>months 1-2 and 4-6 while on KUVAN therapy</i></p>	<p>by clinic staff</p> <ol style="list-style-type: none"> 5. Appointment +Letter to patient re: outcome <ol style="list-style-type: none"> a. Compliance with trial b. Change in PHE levels (> 30% decline) and clinically relevant c. Increase in dietary PHE tolerance where appropriate <p>If patient is responsive and patient is considered compliant with diet:</p> <ol style="list-style-type: none"> 1. Assist with private insurance application 2. Provide ongoing support for drug via "KUVAN Assistance Program if other sources of funding not available 		<p>must submit an application to the Metabolic program to have this done</p> <ol style="list-style-type: none"> a. Once this is received, the patient / parents/caregivers will be seen in clinic to discuss the "trial of responsiveness" including the options for therapy if they do demonstrate that they are responsive. This will require that the patient or parents/caregivers to sign a form indicating that they are aware that without provincial reimbursement, neither the clinic, Alberta Health Services of Alberta Children's Hospital can assume the costs of reimbursement for the drug b. If the patient choses have testing done after step a, is completed, a date for the trial to begin will be planned and the patient will be allocated a patient number which will be used by the physician to order a supply of KUVAN for their use in this trial <ol style="list-style-type: none"> 3. Prior to the trial with KUVAN, the patient must be on stable treatment with the phenylalanine-restricted diet and demonstrate stable phenylalanine levels. A documented phenylalanine tolerance determined by the metabolic clinical dietitian is required and needs dietary intake records from the patient for this to be calculated. Regular measurement of plasma phenylalanine levels will be obtained. Once the PKU treatment is stable, the administration of KUVAN will be started. Typically, this will take 3 weeks. 	<ul style="list-style-type: none"> • Monitor blood PHE levels <p>Pharmacotherapy</p> <ul style="list-style-type: none"> • Test for responsiveness to KUVAN by change in PHE blood levels (at 24h, 1,2, up to 3 and 4 weeks) • Response is considered <ul style="list-style-type: none"> ○ 30% PHE reduction ○ An improvement in neuropsychiatric symptoms or increase in PHE tolerance without a decrease in blood PHE in any patient constitutes sufficient justification to continue therapy

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4. Blood work will be necessary just prior to the first dose of KUVAN and will be repeated weekly during the test. This will include measurements of plasma levels of Phe and tyrosine on a weekly basis and a CBC, electrolytes, urea and creatinine and liver function tests such as AST, ALT, alkaline phosphatase, enzymes and protein and albumin levels will be done at the beginning and the end of the test
 5. The dosage of KUVAN prescribed will be 20 mg per kg body weight (based on a weight measured during the stabilization period just prior to the 28 day trial). This dosage will be taken once daily orally usually with the first meal (natural food &/or formula) of the day
 6. During the 28 day "KUVAN challenge" the diet must remain stable (about the same amount of Phe, protein and calories daily) as prior to beginning KUVAN
 7. During the 4 week trial, the patient must keep regular and accurate dietary intake records as required by the dietitian. It is necessary to demonstrate that there has been no significant change in phenylalanine and nutrition intake in order to accurately determine whether or not there has been a response. These will be assessed in relationship to the blood phenylalanine levels as part of determining whether responsiveness has been adequately demonstrated
 8. During the trial, blood Phe levels and the results of the nutritional records assessment by the
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- metabolic dietitian will not be made available to the patient.
9. Patients and/or parents will also be asked to complete several questionnaires (before, at 1 and 6 months) related to behavior and social-emotional functioning.
 10. Following the 28 day trial, responsiveness to KUVAN will be determined by the metabolic dietitian and the metabolic physician and the results discussed with the patient or their parents (if patient is a minor)

Patients with PKU need to be assessed therapeutically with a trial of tetrahydrobiopterin to determine whether they may benefit from use of this medication as part of their treatment program for their PKU

In those who do respond, public funding to continue receiving KUVAN after the clinical trial through provincial drug programs is not yet available, and so the drug is available in only the following ways:

- Personal funding
- Private insurance (the company will help to assess the details of your personal health insurance provider's policy and will help with your application)
- Manufacturer sponsors a "KUVAN Assistance Program" for patients who need financial assistance to continue ongoing treatment with KUVAN, once they have been shown to be "responders". Patients need to indicate that they are responders to KUVAN (provide a letter of documentation from your metabolic clinic) and that they do not have the financial

Above all, treatment of phenylalanine hydroxylase deficiency must be life long, with a goal of maintaining blood phenylalanine in the range of 120–360 µmol/l

Ongoing funding of KUVAN will be considered through the EAP for non-pregnant patients and patients actively planning pregnancy who have a diagnosis of PKU and who have demonstrated a response to the initial 6 month trial of KUVAN (reimbursed through the manufacturer) and who meet ALL of the following criteria:

1. Compliance with low protein diet, formulas, and treatment with KUVAN; AND
2. Has achieved
 - a. Normal sustained blood Phe levels ($> 120 \mu\text{mol/L}$ and $< 360 \mu\text{mol/L}$) - at least 2 levels measured at least 1 month apart); OR
 - b. Sustained blood Phe reduction of at least 30% (at least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is $< 1200 \mu\text{mol/L}$ OR
 - c. Sustained blood Phe reduction of at least 50% (at least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is > 1200

AFTER INITIAL 6-MONTH TRIAL DEMONSTRATING RESPONSE TO KUVAN THERAPY

Non-Pregnant Patients and Patients actively planning pregnancy:

For the management of patients with the diagnosis of PKU who meet ALL of the following criteria:

1. Compliance with low protein diet, formulas, and KUVAN; AND
2. Achieve:
 - a. Normal sustained Blood Phe levels [$> 120 \mu\text{mol/L}$ and $< 360 \mu\text{mol/L}$] (at least 2 levels measured at least 1 month apart); OR
 - b. Sustained blood Phe reduction of at least 30% (at least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is $< 1200 \mu\text{mol/L}$; OR
 - c. Sustained blood Phe reduction of at least 50% (At least 2 levels measured at least 1 month apart) compared to baseline if the Phe baseline level is $> 1200 \mu\text{mol/L}$; AND

1. Any patient stable on dietary treatment
2. Letter of application to clinic – interest & scheduling
3. Meeting with patient / parents
 - a. Discuss conduct of trial – physician & dietician
 - b. Commitment to compliance during trial by patient or parent(s)
 - c. Disclosure regarding long-term financing concerns - signed by patient or parent(s) after reading & informed discussion
4. 3 weeks close monitoring before responsiveness trial
 - a. Blood PHE levels weekly
 - b. Two diet intake records
 - c. Behavioral, social & emotional questionnaires

**Reimbursement
Criteria**

- μmol/L; AND
3. Demonstrated increase of dietary protein tolerance based on targets set between the clinician and patient; AND
 4. Clinically meaningful age-appropriate improvement in:
 - a. Neuro-behavioural or neuro-cognitive function or impairment for patients with such impairments as determined by peer reviewed clinically validated scales; OR
 - b. Demonstrated improvement in QoL using peer reviewed validated scales; AND
 5. Managed by a physician specialized in metabolic/biochemical diseases

For pregnant patients: points 2 & 5

KUVAN is only considered through the EAP for responders to an initial 6 month trial period funded through the manufacturer

3. Demonstrated increase of dietary protein tolerance based on target set between the clinician and patient; AND
4. Clinically meaningful age-appropriate improvement in:
 - a. Neurobehavioural or neurocognitive function or impairment for patients with such impairments as determined by peer reviewed clinically validated scales; OR
 - b. Demonstrated improvement in Quality of Life using peer reviewed validated scales; AND
 - c. Managed by a physician specialized in metabolic/biochemical diseases

Dosage: Up to a maximum of 20 mg/kg per day.

Approval Duration: 1 year

Caution

1. Taking medication known to inhibit folate synthesis (e.g., methotrexate)
2. Any condition requiring treatment with levodopa or any PDE-5 inhibitor (e.g., sildenafil)

resources to purchase KUVAN from personal or insurance sources, until provincial programs will be in place

Protocol for Ongoing Therapy of BH4 – responsive PKU Patients with KUVAN

- Once the diagnosis of BH4-responsive phenylalanine hydroxylase deficiency is made (on the basis of a demonstrated response to KUVAN) and availability of funding is clarified, drug treatment can begin
- If necessary, the Phe intake and amount of formula in the diet may need to be adjusted by the dietitian at this time or during the monitoring of your Phe blood levels
- The recommended dosage range for KUVAN when started is 20 mg/kg/day
- Phe levels must be monitored frequently after starting KUVAN with diet adjustments being made by the metabolic dietitian ,to maintain safe phenylalanine levels and adequate nutritional intake
- Behavior and social-emotional functioning will continue to be monitored. Questionnaires will be provided after one month, and after 6 months of treatment. Further monitoring and follow-up will be provided on an as-needed basis
- Once treatment goals and diet and/or medication adjustments are established, the frequency of monitoring will be similar to those when on diet therapy only