FOR HEALTHCARE PROFESSIONALS

NUTRICIA
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GUIDELINES FOR THE USAGE OF PhenylAde® PheBLOC™

For the dietary management of PKU
To be used under medical supervision

DISCLAIMER:

PhenylAde® PheBLOC™ LNAA is a PKU medical food intended for use in the dietary management of certain phenylketonuria (PKU) individuals ages 12 and over. Not intended for use during pregnancy. Should be used only under medical supervision. The following guidelines are provided to help support healthcare professionals involved in the dietary management of PKU patients. Practices may vary from clinic to clinic, and this booklet should serve as guidance, not as strict protocol.

ACKNOWLEDGEMENTS:

Nutricia North America would like to thank Kathryn Moseley, MS, RD, University of Southern California, for her input and review of these guidelines.

GUIDELINES FOR THE USAGE OF **PHENYLADE® PheBLOC™**

Table of Contents:

Introduction

Phenylketonuria (PKU) is an inherited, genetic disorder caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH). PAH helps the body break down the amino acid phenylalanine (PHE) into tyrosine (TYR).[1] A person with PKU is unable to break down PHE. Consuming too much PHE will result in an accumulation of PHE in the blood and brain[2] of a person with PKU, and if not managed over time can cause severe developmental delay.[3-4] Dietary management has been the cornerstone of disease management since the 1950's.

In the dietary management of PKU, early institution and maintenance of a strict low-PHE diet has been shown to be essential to improve outcomes and avoid the potential consequences of poor metabolic control, e.g. low IQ and behavioral problems.[4-5] Protein-rich foods must be eliminated from the diet, and a PKU formula must be given to compensate for the resulting deficiencies in the other essential and non-essential amino acids.[4-5]

It is generally accepted that even early-managed PKU adults who have relaxed their diet may be exposing themselves to developing neurological impairments, which may have a negative impact on quality of life.[1,6] Recurrent headaches, neurological abnormalities, hyperactivity and lethargy are among the symptoms that may result when plasma PHE concentrations remain elevated.[3]

Current guidelines recommend management for life.[1,4,5] However, compliance with formula is not ideal with reports that less PKU formula is taken than the amount actually prescribed in older children, teens and adults.[2,7]

Many individuals with PKU relax dietary control as they get older,[2,7] or they no longer come to clinic,[3] forming a so-called 'off-diet' population in which PHE concentrations are high and nutritional status may be compromised. Individuals often self-restrict protein-rich foods when they come off diet, which can lead to a diet low in essential amino acids and micronutrients.[8-9]

Nutricia North America supports Diet-For-Life for all individuals with PKU. Traditionally, adherence to a well-managed diet plan has had the best possible clinical outcomes for individuals with PKU. However, dietary adherence continues to be a major issue among older individuals with PKU, often starting in preadolescence.[4] Please refer to Genetic Metabolic Dietitians International (GMDI) for the most recent clinical practices on the management of PKU.[10]

What are Large Neutral Amino Acids (LNAAs)?

LNAAs are a group of single amino acids, which include tyrosine, tryptophan, threonine, methionine, valine, isoleucine, leucine, histidine and phenylalanine.[11] The concept of LNAAs for use in the dietary management of PKU (excluding phenylalanine) is not new. In the late 1970's, research emerged about a new approach in PKU management incorporating LNAAs into the diet plan of individuals with PKU.[11,12] Incorporation of LNAAs may allow for some individuals with PKU to consume a more liberalized diet.[13] Since then, LNAAs have addressed the population of those with PKU who are no longer following a PHE-restricted diet; or who significantly struggle with this diet resulting in possible chronic elevation of plasma and brain PHE. PhenylAde PheBLOC is a PKU medical food created with the concept of LNAAs. This booklet is intended to help guide clinicians on how to incorporate PhenylAde PheBLOC into their patient's diet plan.*

Please see page 18 for a list of publications regarding the concept, safety and efficacy of LNAAs.

*NOTE: Individuals with PKU who are successfully managing their diet through the traditional PHE-restricted diet are advised to continue using their current regimen. A traditional PHE-restricted diet has been shown most effective in reducing plasma PHE concentrations and promoting good clinical outcomes.

Product Presentation

Target Group

PhenylAde PheBLOC is indicated for individuals with proven PKU over 12 years of age[11] who are not planning a pregnancy, are pregnant or nursing.[4,5,13] PhenylAde PheBLOC should always be used under medical supervision.

Who Should Consider Taking PhenylAde PheBLOC?

PKU individuals who may be:

- Having difficulty consuming prescribed amount of medical food
- Currently using sapropterin dihydrochloride and still requiring medical food
- Returning to the PKU diet after a period of time
- Struggling with obtaining low protein foods and prefer increased food choices, such as regular bread and pasta
- Late-diagnosed or have never been on-diet

Cautions and Considerations

Pregnancy

PhenylAde PheBLOC is NOT RECOMMENDED for women who are either planning a pregnancy, are pregnant or nursing. It is generally used with a "relaxed" low-PHE diet. Plasma PHE levels tend to be elevated with this alternative approach. Women of childbearing age who use this alternative approach must be counseled about family planning and the need to be on a traditional PHE-restricted diet prior to conception and throughout pregnancy. High blood PHE levels during pregnancy are known to lead to irreversible brain damage and other severe injuries to the fetus.[4-5]

Drug Interactions

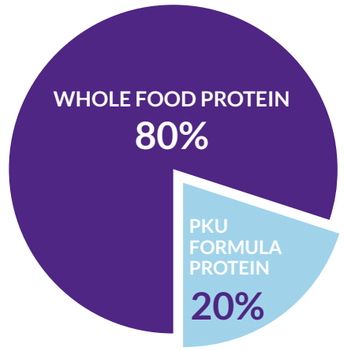
PhenylAde PheBLOC contains a relatively large amount of tryptophan, an essential amino acid and precursor for the neurotransmitter serotonin; which is the pharmacological target of many selective serotonin reuptake inhibitors (SSRIs).[14-15] Mental health professionals should be aware that the amount of tryptophan in PhenylAde PheBLOC may interact with SSRIs, e.g., for depression/anxiety. Combination of PhenylAde PheBLOC and these SSRIs may result in over-stimulation of brain serotonin systems. It is recommended all psychotropic medications be monitored by a mental health professional while a patient is using PhenylAde PheBLOC.

Consideration for a daily MULTIVITAMIN is suggested when using PhenylAde PheBLOC.

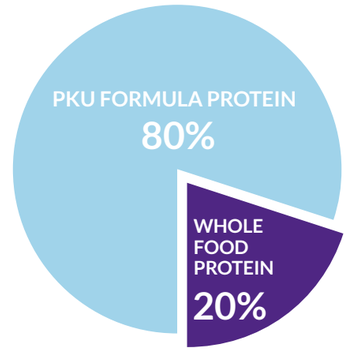
The PhenylAde PheBLOC Diet

PhenylAde PheBLOC is designed to work in combination with a "relaxed" low-PHE diet, where 70-80% of a patient's protein requirements will come from whole food protein, and the remaining 20-30% from PhenylAde PheBLOC.[1] Some individuals may combine PhenylAde PheBLOC with traditional PKU formula. Please see further details on these approaches later in this booklet.

PhenylAde PheBLOC Diet



Traditional PKU Diet



How to calculate PhenylAde PheBLOC:

Protein requirements are calculated based on ideal body weight (IBW).

1. Determine patient's IBW.
2. Calculate total recommended daily protein intake. Recommendations are 120-140% of DRI for patients > 4 years of age.[4] For adults, this amounts to approximately 1 g protein/kg IBW.
3. Calculate 20-30% of total recommended protein intake. This is the amount of protein equivalent (PE) the patient will take per day from PhenylAde PheBLOC.
4. To calculate:
   Tablet dose, take calculated PE from step 3 and divide by 0.44 g PE.
   Pouch dose, take calculated PE from step 3 and divide by 2.2 g PE.
5. Review that PhenylAde PheBLOC is to be consumed throughout the day at meals with PHE-containing foods.

Quick Calculation Reference Tables:

The following tables provide guidance based on 80/20 and 70/30 diet approaches.

20% of protein needs from PhenylAde PheBLOC

Ideal Body Weight, kg	g Protein/kg	Protein per day	80% of total protein from food	20% of total protein from LNAA	Suggested number of **PhenylAde PheBLOC Pouches per day**	Suggested number of **PhenylAde PheBLOC Tablets per day**
50	1	50	40	10	4.5	23
55	1	55	44	11	5	25
60	1	60	48	12	5.5	27
65	1	65	52	13	6	30
70	1	70	56	14	6.5	32
75	1	75	60	15	7	34
80	1	80	64	16	7.5	36

30% of protein needs from PhenylAde PheBLOC*

Ideal Body Weight, kg	g Protein/kg	Protein per day	70% of total protein from food	30% of total protein from LNAA	Suggested number of **PhenylAde PheBLOC Pouches per day**	Suggested number of **PhenylAde PheBLOC Tablets per day**
50	1	50	35	15	7	34
55	1	55	39	16	7.5	36
60	1	60	42	18	8	41
65	1	65	45	20	9	45

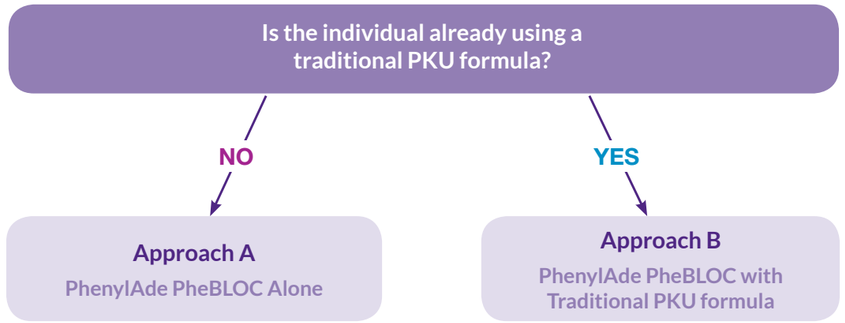
*It is suggested not to exceed 45 tablets (or 9 pouches) per day.

Approaches to Using PhenylAde PheBLOC

PhenylAde PheBLOC can be used as nutrition management in a few ways. It can be used (1) by itself without additional PKU formulas, (2) in combination with traditional PKU formula, or (3) with sapropterin dihydrochloride drug therapy. Please refer to page 14, the Sample Meal Plan section, for examples on these approaches.

Below are detailed explanations for the two most common ways to use PhenylAde PheBLOC.

Which approach best fits your patient?



Approach A: *PhenylAde PheBLOC Alone*

Use this nutrition management approach for individuals who

- are not using any traditional PKU formula,
- are using traditional PKU formula, however non-adherent and not in good control,
- are not on any form of PHE-restricted diet, e.g. "off diet" individuals, late diagnosed/never managed, or
- either have not, or only partially, responded to sapropterin dihydrochloride drug therapy and are not currently on any traditional PKU formula

The table below shows step-by-step instructions. It reviews how to calculate the amount of PhenylAde PheBLOC needed and how to introduce it into the diet for both powder and tablet form.

	PhenylAde PheBLOC, powder	**PhenylAde PheBLOC, tablets**
Step 1	Calculate total recommended daily protein intake based on ideal bodyweight. Recommendations are 120-140% of DRI for patients > 4 years of age.[4] For adults, this amounts to approximately 1 g protein/kg IBW	
Example	Establish and fill daily prescription for 27 yo male, 70 kg ideal body weight 70 kg x 1 g = 70 g total protein	
Step 2	Determine amount of PhenylAde PheBLOC powder per day. Provide 20-30% of total protein from PhenylAde PheBLOC. One pouch PhenylAde PheBLOC provides 2.2 g PE. Energy contribution from PhenylAde PheBLOC is minimal.	Determine amount of PhenylAde PheBLOC tablets per day. Provide 20-30% of total protein from PhenylAde PheBLOC. Each tablet provides 0.44 g PE. Energy contribution from PhenylAde PheBLOC is minimal.
Example	70 g total protein x 20% = 14 g PE from PhenylAde PheBLOC powder. 14 g PE PhenylAde PheBLOC = ~6 pouches	70 g total protein x 20% = 14 g PE from PhenylAde PheBLOC powder. 14 g PE PhenylAde PheBLOC = ~32 tablets
Step 3	The remainder (70-80%) of protein requirement will come from regular foods.	
Example	70 g total protein – 14 g PE from PhenylAde PheBLOC powder = 56 g protein from regular foods	70 g total protein – 14 g PE from PhenylAde PheBLOC tablets = 56 g protein from regular foods
Introduction	Introduce PhenylAde PheBLOC gradually into the diet. As always, consider patient preferences. Divide the calculated dose among meals and snacks according to the individual's preferred meal pattern. Give higher doses of PhenylAde PheBLOC at meals with more protein and less amounts of PhenylAde PheBLOC at smaller protein containing meals. It is not necessary to take PhenylAde PheBLOC with protein-free snacks. *Phases below are broken down to just 3 meals – please alter based on individual preferences/meal patterns.*	
Phase 1	Start with 1 pouch per meal for one week. Counsel on healthy food choices.	Start with 5 tablets per meal for one week. Counsel on healthy food choices.
Phase 2	After one week, increase to 2 pouches PhenylAde PheBLOC powder per meal.	After one week, increase to 11 tablets of PhenylAde PheBLOC per meal.
Phase 3	After 2 weeks, analyze food intake, obtain plasma amino acids and assess for any nutritional deficiencies. Based on evaluations further modifications may be necessary to increase or reduce whole protein or increase or reduce traditional PKU formula.	

Approach B: *PhenylAde PheBLOC with Traditional PKU formula*

Use this nutrition management approach for individuals who are on some form of a traditional PKU diet, however are not completely compliant, and who

- want to reduce traditional PKU formula intake, or
- want to add more "normal" food choices into their diet

The table below is step-by-step instruction guide on how to use PhenylAde PheBLOC and traditional PKU formula together. Refer to established diet prescription and consider patient preferences. Introduce PhenylAde PheBLOC into the diet gradually.

Below is based off the example of:
70 g total protein – 14 g PE from PhenylAde PheBLOC = 56 g protein from regular foods

Phase	**PhenylAde PheBLOC, powder**	**PhenylAde PheBLOC, tablets**
1	Add 1 pouch of PhenylAde PheBLOC powder at 2-3 meals to the current diet prescription without changing prescription for whole protein or traditional PKU formula. Increase to 2 pouches of PhenylAde PheBLOC powder at 2-3 meals within about one week.	Start with 5 tablets per meal for one week, continue on prescribed amount of traditional PKU formula.
2	After 1-2 weeks, and if patient is feeling well, consider cutting back on 10 g protein from traditional PKU formula prescription at 2-3 meals and replace with whole protein.	Increase PhenylAde PheBLOC to 11 tablets three times each day with meals. Reduce traditional PKU formula by 50%. Replace with prescribed whole protein. Counsel on healthy food choices.
3	After 2 weeks, analyze food intake, obtain plasma amino acids and assess for any nutritional deficiencies. Based on evaluations further modifications may be necessary to increase or reduce whole protein or increase or reduce traditional PKU formula.	After 2 weeks, analyze food intake, obtain plasma amino acids and assess for any nutritional deficiencies. Based on evaluations further modifications may be necessary to increase or reduce whole protein, or increase or reduce traditional PKU formula.

Individuals using psychotropic medication may want to start more slowly. Depending on the patient, consider starting with 2 tablets (or 1/2 pouch) per meal for 5 days, then increase 2 more tablets (or 1/2 pouch) per meal for 5 days, repeat until full dose is reached.

Response to Management

Response to management is based on the patient reporting "feeling better". Relying on patient's feedback is essential to knowing if management is working as plasma PHE levels may remain elevated and are not a good indicator in this form of dietary management.[16]

Follow clinic protocol on testing plasma amino acids as well as monitoring protein intake with dietary recalls to avoid essential amino acid deficiencies. Some individuals may not be accustomed to consuming higher amounts of whole protein so it is important to monitor protein intake and watch for protein deficiency.

Monitoring

It is imperative that all individuals on PKU dietary management continue to be monitored carefully by their metabolic team. You should always follow clinic guidelines, or the PKU guidelines from GMDI,[10] on what to monitor for someone with PKU. Some suggestions on what should be obtained before an individual starts on PhenylAde PheBLOC, as well as throughout this type of management, are:

- Routine blood biochemistry including plasma PHE, TYR, other amino acid concentrations and prealbumin
- Nutritional assessment including dietary intake, especially total protein, body weight, BMI, etc.
- Behavioral assessment (see next section)

The frequency of monitoring will depend on the clinic and any other specific protocol for managing the 'relaxed' or less restricted PKU diet. Additional assessments might be required depending on each clinic's guidelines for management.

Genetic Metabolic Dietitians International (GMDI) offers MetabolicPro, the only web-based nutrient analysis software program designed for use by metabolic dietitians. All foods in the database contain complete amino acid data, making it a valuable tool for analyzing diets of patients with amino acid and organic acid disorders. More information can be found at www.gmdi.org.

Behavioral assessment:

Several healthcare professionals advocate or report using behavioral assessment tools for monitoring metabolic patients. Behavioral assessment tools, such as Behavior Rating Inventory of Executive Function® (BRIEF®), may be useful to use in monitoring the effects of PhenylAde PheBLOC on PKU patient(s).[17]

Comparative Food Chart

PhenylAde PheBLOC Diet ● / Traditional PKU Diet ●	UNLIMITED	PARTIALLY RESTRICTED	VERY RESTRICTED	TOTALLY AVOID
DAIRY				
Cow's Milk		●		●
Soy Milk		●		●
Rice Dream®	●	●		
Yogurt		●		●
Ice Cream		●		●
Cheese		●		●
Imitation Low Protein Cheese	◐			
MEAT/PROTEIN				
Beef			●	●
Pork			●	●
Chicken			●	●
Fish/Shellfish			●	●
Beans/Nuts			●	●
Peanut Butter			●	●
BREADS/GRAINS				
Bread/Cereal/Muffins	●			●
Pasta	●			●
Rice	●			●
Low Protein Bread/Cereals/Muffins	◐			
Low Protein Pasta	◐			
Low Protein Rice	◐			
FRUITS/VEGETABLES				
Potatoes	●	●		
French Fries	●		●	
Corn	●		●	
Peas	●		●	
Lettuce	◐			
Green Leafy Vegetables	●	●		
Tomatoes	●	●		
Fruits	●	●		
Fruit Juice	●	●		
SNACKS				
Potato Chips	●		●	
Cookies	●			●
Low Protein Cookies	◐			
Chocolate		●		●
Candy	◐			
Jelly/Jam	◐			
FATS				
Butter	●	●		
Margarine from Vegetable Sources	◐			
Oils	◐			
ASPARTAME				◐

Appropriateness of foods are based on individual patient needs.

Sample Meal Plans

	OFF DIET **Meal Plan 1** Just PhenylAde PheBLOC - No Traditional PKU Formula	NON-ADHERENT **Meal Plan 2** PhenylAde PheBLOC + PKU formula	LNAAs WITH PKU FORMULA AND SAPROPTERIN DIHYDROCHLORIDE **Meal Plan 3** PhenylAde PheBLOC + PKU Formula + Sapropterin Dihydrochloride
Breakfast	· PhenylAde PheBLOC · Cereal with coconut milk, rice milk or Flax milk · Banana	· PhenylAde PheBloc · PhenylAde 60 (1 pouch or scoop) · Oatmeal with coconut milk or Flax milk · Applesauce	· PhenylAde PheBLOC · Scrambled eggs (2) · Hash browns · Banana · Sapropterin Dihydrochloride
Lunch	· PhenylAde PheBLOC · Rice with vegetables and tofu · Tossed green salad · Roll with butter · Apple · Coconut milk, rice milk or Flax milk	· PhenylAde PheBLOC · PhenylAde 60 (1 pouch or scoop) · Portobello mushroom burger with bun · Tossed green salad · Strawberries	· PhenylAde PheBLOC · Bean and cheese burrito · Guacamole · Tortilla chips · Blueberries
Dinner	· PhenylAde PheBLOC · Burrito with beans and cheese · Tossed green salad · Broccoli · Pear · Coconut milk, rice milk or Flax milk	· Phenylade PheBLOC · PhenylAde 60 (1 pouch or scoop) · Low protein spaghetti with marinara sauce · Mixed vegetables · Garlic bread · Peaches	· PhenylAde PheBLOC · PhenylAde 60 (1 pouch or scoop) · Cheese Pizza · Tossed green salad · Grapes
Total	**Protein 70 g** *(15 g from PhenylAde PheBloc, 54 g whole protein)*	**Protein 70 g** *(30 g from PKU formula, 15 g from PhenylAde PheBLOC, 25 g whole protein)*	**Protein 70 g** *(10 g from traditional PKU formula, 15 g from PhenylAde PheBLOC, 45 g whole protein)*

Patients will differ in their tolerance to higher protein foods and LNAAs. All patients should be monitored closely and diet tailored to their specific needs.

Product Information

	PhenylAde PheBLOC Powder	PhenylAde PheBLOC Tablets
Nutrients	**Per Pouch** (3 g Powder)	**Per Tablet** (750 mg)
Calories	10	3
Protein Equivalent, g	2.2	0.44
Carbohydrate, g	0.34	0.2
Fat, g	Nil Added	0.02
MINERALS		
Calcium, mg	Nil Added	43.5
Sodium, mg	0.03	0.82
Chloride, mg	28	5.5
AMINO ACIDS, mg		
L-Arginine	170	34
L-Histidine	156	31.3
L-Isoleucine	158	31.5
L-Leucine	154	30.8
L-Lysine	115	23
L-Methionine	249	49.7
L-Threonine	164	32.8
L-Tryptophan	306	61.1
L-Tyrosine	984	197
L-Valine	160	32
Ingredients	L-Tyrosine, Maltodextrin, L-Tryptophan, L-Methionine, L-Arginine, L-Threonine, L-Valine, L-Isoleucine, L-Histidine, L-Leucine, L-Lysine Monohydrochloride	L-Tyrosine, Calcium Carbonate, L-Tryptophan, L-Methionine, Microcrystalline Cellulose, L-Arginine, L-Threonine, L-Valine, L-Isoleucine, L-Histidine, L-Leucine, L-Lysine Monohydrochloride, Hydroxypropyl Methylcellulose, Stearic Acid, Croscarmellose Sodium, Magnesium Stearate, Silicon Dioxide.

Patient Resources

Your Partner in Helping PKU Adults Back to Diet

In addition to offering PhenylAde PheBLOC as an option for patients struggling to return to the PKU diet, here are an array of additional services to aid this special population:

DIET-FOR-LIFE CARE COORDINATOR

A free service for your patients that connects them with a support coordinator who will help implement your recommended use of Nutricia products and care plan.

PKU FORMULA FOR ADULTS

Providing the widest range of PKU products to meet adult needs. Choices range from low calorie/ low volume powders and liquids to smooth and easy to drink shake-like formulas. Nutricia's sample program allows patients the opportunity to taste at home and find the right formula for them.

DIETFORLIFE.COM

An easy to navigate web page with 1-click connections to tools and services to support diet-for-life.

MY PKU USA APP

A simple app to help patients return to diet by setting reminders to drink formula, track protein intake, log blood levels and more. Available for iOS only.

RECIPES

Find over 50 great tasting and easy to make low protein recipes all in one place at MedicalFood.com/Recipes.

BE INSPIRED

Patients can get to know other adults who returned to the PKU diet, watch formula mixing videos and low protein cooking in action at YouTube.com/LowProLiving

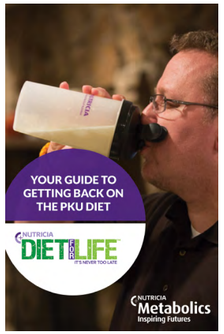
REIMBURSEMENT SUPPORT

Connect your patients with reimbursement experts to help review their insurance coverage and find product suppliers.

OVER **90%** SUCCESS RATE!

9 OUT OF 10 PEOPLE GAINED PKU FORMULA COVERAGE!

Send your patient a ***Guide to Getting Back on the PKU Diet*** Today.



https://shop.medicalfood.com/PatientSamples.aspx

GUIDELINES FOR THE USAGE OF **PHENYLADE® PheBLOC™**

Nutricia Learning Center

Tools & Support for You and Your Patients

The **Nutricia Learning Center** (NLC) is a community hub of trusted resources for healthcare providers managing patients with special nutritional needs. It provides a wealth of information on a variety of topics including Inborn Errors of Metabolism (IEM). These resources are comprised of webinars led by specialists in the presented topic, transition tools and calculators, educational materials for your patients, and guidelines, such as this one, written with input and review of an expert in the metabolic community.

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