

The format of this leaflet was determined by the Ministry of Health and its contents were inspected and approved in 12/2015 and updated in accordance with the instructions of the Ministry of Health in 02/2019.

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATION) - 1986**

This medicine requires a doctor's prescription

Kuvan[®] Soluble Tablets

Active ingredient:

Each soluble **tablet contains 100 mg of**

Sapropterin dihydrochloride (**equivalent to 77 mg sapropterin**)

Inactive ingredients - See Section 6.

Please read the entire leaflet carefully before using this medicine. This leaflet contains information that is important for you.

- Keep this leaflet. You may want to read it again.
- This leaflet contains concise information about the medicine. If you have any further queries, contact a doctor or pharmacist.
- This medicine has been prescribed for your treatment. Do not pass it on to others. It may cause them harm, even if it seems to you that their medical condition is similar to yours.

In this leaflet:

1. What is the intended use of the medicine?
2. Before using the medicine
3. How should this medicine be used?
4. Side-effects
5. How to store the medicine
6. Additional information

1. What is the intended use of the medicine?

Kuvan[®] is intended for the treatment of high blood levels of the amino acid phenylalanine in adults and children of all ages. High blood levels of phenylalanine can be harmful. These conditions are called hyperphenylalaninaemia (HPA) or phenylketonuria (PKU). **Kuvan** decreases these levels in patients who respond to BH4. This makes it possible for these patients to increase the amount of phenylalanine in their diet.

Kuvan can also treat a genetic disease known as BH4 deficiency in adults and children of all ages, where the body is unable to produce enough BH4. Because of the low BH4 level, the phenylalanine consumption is abnormal, its level rises, and the phenylalanine accumulation is harmful. Administering **Kuvan**, which is a substitute for the BH4 that the body cannot produce, reduces the damage caused by the excess phenylalanine in the blood and increases the tolerance to phenylalanine in the diet.

Therapeutic group:

Kuvan belongs to a group of preparations that are basic substances for metabolism in the body.

Kuvan contains an active ingredient which is a synthetic copy of a natural substance found in the body called cofactor of tetrahydrobiopterin-BH4. The body requires BH4 in order to convert the amino acid phenylalanine into another amino acid called tyrosine.

2. Before using the medicine

X Do not use Kuvan:

- If you are hypersensitive (allergic) to sapropterin or to any of the additional ingredients that the medicine contains (see Section 6).

! Special warnings regarding the use of Kuvan

Before using Kuvan, tell the doctor if:

- You are 65 years old or older
- You have problems with your liver or kidneys
- You are ill. Consulting a doctor is recommended, because during the course of the illness, the phenylalanine level in the blood is likely to rise
- You have a tendency for convulsions

During **Kuvan** treatment, your doctor will recommend tests to determine the phenylalanine and tyrosine levels in your blood. This is done in order to adjust the therapeutic dosage of **Kuvan** you receive or to adjust your diet.

You must always follow the diet recommended by the doctor. Do not change your diet without consulting your doctor.

Even if you are taking **Kuvan**, if the phenylalanine level in the blood is not controlled properly, you could develop severe neurological problems. The doctor will continue monitoring the phenylalanine levels in the blood frequently during the **Kuvan treatment, in order to ensure that the phenylalanine levels are not too low or too high.**

Using Kuvan Together with Other Medicines

If you are taking, will take, or have recently taken any other medications, including nonprescription drugs and nutritional supplements, report this to the doctor or pharmacist.

You should consult your doctor specifically if you are taking any of the following medicines:

- Levodopa - treatment for Parkinson's disease
- Medicines for cancer treatment (such as methotrexate)
- Medicines for treating bacterial infections (such as trimethoprim)
- Preparations for dilating blood vessels (such as (GTN) glyceryl trinitrate, isosorbide dinitrate (ISDN), sodium nitroprusside (SNP), molsidomin and Minoxidil

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, or you think you might be pregnant or are planning to become pregnant, consult your doctor or pharmacist before using the medicine.

If you are pregnant, your doctor will explain how to control your phenylalanine levels properly. If these levels are not controlled tightly before and during your pregnancy, this could be harmful to you and your baby.

The first choice treatment is medical supervision of the diet to limit the absorption of phenylalanine before and during pregnancy. Your doctor will consider treatment with

Kuvan if strict management of your diet is insufficient to reduce the phenylalanine levels in the blood.

If you are breast-feeding, do not use this medicine.

Driving and using machinery

The use of **Kuvan** is not expected to have any effect on the ability to drive or use machinery.

Important information regarding one of the medicine's ingredients:

This medicine contains less than 1 mmol (23 mg) of sodium per tablet. Consequently, it is considered to be "sodium-free."

3. How should this medicine be used?

Always use **Kuvan** according to the doctor's instructions. Check with your doctor or pharmacist if you are not sure.

The dosage and manner of treatment must be determined by the doctor only.

Do not exceed the recommended dose.

Dosage

Phenylketonuria (PKU)

The usual initial dose for adults and children is 10 mg for each kilogram of body weight. The dose of soluble tablet(s) should be taken as a single dose with a meal, in order to increase absorption. The dose should be taken at the same time every day, preferably in the morning.

Your doctor may adjust your dose between 5-20 mg per kilogram of body weight per day, according to your condition.

BH4 deficiency

The usual initial dose in adults and children is 2-5 mg per kilogram of body weight. Take Kuvan with a meal in order to increase absorption. Divide the total dose into 2-3 portions, to be taken over the course of the day. Your doctor may adjust your dose up to 20 mg per kilogram of body weight per day, according to your condition.

The following table provides an example of how the appropriate dose is calculated:

Body weight (kg)	Number of tablets (Kuvan dose of 10 mg/kg)	Number of tablets (Kuvan dose of 20 mg/kg)
10	1	2
20	2	4
30	3	6
40	4	8
50	5	10

Direction for use

For PKU patients, the entire daily dose should be taken once a day, at the same time every day, preferably in the morning.

For patients with BH4 deficiency, the total daily dose should be divided into 2-3 portions.

Use in all patients

Place the number of tablets prescribed for you in a glass of water, as detailed below, and stir until dissolved.

It may take several minutes to dissolve **Kuvan**. If you wish to speed up the process, you can crush the tablet. You may notice particles in the solution, but these do not make any difference to the effectiveness of the medicine.

Drink the **Kuvan** solution together with your meal within 15-20 minutes after beginning its preparation.

Do not swallow the desiccant capsule in the bottle.

Use by patients weighing more than 20 kg

Dissolve the tablet(s) in a glass with 120-240 ml of water and stir until dissolved.

Use by children weighing up to 20 kg

The **Kuvan** dose is based on the body weight and will vary as your child grows. Your doctor will offer guidance regarding:

- The number of **Kuvan** tablets necessary for one dose
- The amount of water necessary for mixing one dose of **Kuvan**
- The amount of the solution that you must give to your child in order to give the prescribed dose.

Your child should drink the Kuvan solution with a meal, at the same time every day, preferably in the morning. Give the solution to your child within 15-20 minutes after preparation. If you are unable to administer the dose within 15-20 minutes after dissolving the tablets, discard the medicine. You will have to prepare a new solution, because the solution must not be used after 20 minutes.

*Equipment required to prepare and give your child a dose of **Kuvan***

- The number of **Kuvan** tablets necessary for one dose
- A measuring cup with graduations of 20, 40, 60 and 80 ml
- Glass
- A small teaspoon or a clean utensil for mixing
- A syringe for oral administration with graduations of 1 ml (a 10 ml syringe for administering volumes of up to 10 ml or a 20 ml syringe for administering volumes exceeding 10 ml)

Ask the doctor for a measuring cup for dissolving the tablets and 10 ml or 20 ml syringes for oral administration, if you do not have this equipment.

Steps to prepare and take the dose

- Place the number of tablets prescribed for your child in the measuring cup. Pour the volume of water into the measuring cup according to the doctor's instructions. (For example: The doctor told you to use 20 ml in order to dissolve one tablet of **Kuvan**.) Ensure that the volume of liquid matches the volume that your doctor instructed. Stir with a small teaspoon or clean utensil until the tablets have dissolved.
- If the doctor told you to administer only part of the solution, insert the end of the syringe for oral administration into the measuring cup. Slowly extract the plunger in order to draw up the quantity instructed by the doctor.
- Transfer the solution to a glass by pushing the plunger slowly until all the solution in the syringe has been transferred to the glass for administration. (For example: If the doctor told you to dissolve 2 tablets of **Kuvan** in 40 ml of

water and to give your child 30 ml, use the 20 ml syringe for oral administration twice in order to draw up 30 ml (i.e. 20 ml + 10 ml) of the **Kuvan** solution and transfer it to a cup for administration). Use the 10 ml syringe for oral administration for administering volumes of up to 10 ml or the 20 ml syringe for oral administration for administering volumes exceeding 10 ml).

- If your child is too small to drink from a cup, you can administer the **Kuvan** solution using the syringe for oral administration. Draw up the prescribed volume of the solution prepared in the measuring cup and insert the end of the syringe into the baby's mouth. Push the plunger down slowly, a small amount at a time, until all the solution in the syringe has been administered.
- Discard any remaining solution. Remove the plunger from the syringe for oral administration. Wash both parts of the syringe and the measuring cup with warm water and allow to dry in the open air. When the syringe for oral administration is dry, return the plunger to the syringe. Store the syringe and the measuring cup for the next use.

If you have taken a larger dose accidentally

If you have mistakenly taken a larger dose, you must call your doctor or pharmacist immediately. You may experience side-effects including headaches and dizziness. If you have taken an overdose, or if your child has mistakenly swallowed some of the medicine, contact a doctor or hospital emergency room immediately and bring the medicine package with you.

If you forgot to take the medicine

Do not take a double dose in order to replace the dose that you forgot. Take the next dose at the scheduled time.

If you stop using Kuvan

Even if your health condition has improved, do not discontinue the treatment without first consulting your doctor, because the phenylalanine level in the blood may rise.

If you have any further questions about the use of this preparation, consult your doctor or pharmacist.

How can you help the success of the treatment?

- Continue the treatment as recommended by the doctor
- Do not take medicines in the dark! Check the label and dose each time you take a medicine. Wear your glasses if you need them.

4. Side-effects

Like all medicines, the use of **Kuvan** may cause side-effects in some patients. Do not be alarmed by the list of side-effects. It is possible that you will not suffer from any of them.

Consult a doctor immediately:

A few cases of allergic reactions (such as skin rashes and severe reactions) have been reported. Their frequency is not known.

If swollen, red and irritated areas appear on your skin (urticaria), or if you develop a runny nose, rapid or irregular pulse, swelling of the tongue and throat, sneezing, wheezing, serious breathing problems or dizziness, you might be experiencing a

serious allergic reaction to the medicine. If you notice these symptoms, you must consult a doctor immediately.

Additional side-effects:

Very common side-effects (effects that appear in more than 1 patient out of 10): Headache and runny nose.

Common side-effects (effects that appear in up to 1 patient out of 10): Sore throat, nasal congestion or stuffy nose, coughing, diarrhea, vomiting, abdominal pain, excessively low phenylalanine level in blood tests, indigestion and feeling sick (nausea).

Not known side effects (frequency cannot be estimated from the available data)
Gastritis (inflammation of the lining of the stomach), oesophagitis (inflammation of the lining of the gullet)

Reporting side-effects

If one of the side-effects appears, becomes worse, or if you suffer from any side-effect not mentioned in the leaflet, you must consult your doctor, pharmacist or nurse. Reporting side-effects is recommended so that you can assist in gathering additional information on the safety of the medicine.

Side-effects can be reported to the Ministry of Health by clicking on the link "Reporting side-effects following medicinal treatment" on the Ministry of Health homepage on the Ministry of Health website (www.health.gov.il) that links to an online form for reporting side-effects, or by clicking the link:
<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>

5. How should the medicine be stored?

Avoid poisoning! This medicine, and all other medicines, must be stored in a safe place out of the reach of children and/or infants. Doing so will prevent poisoning.

Do not induce vomiting without explicit instructions from a doctor.

- Do not use the medicine after the expiration date (EXP.) specified on the packaging. The expiration date refers to the last day of that month.
- Store at temperatures under 25°C.
- Keep the vial/package well sealed in order to protect the contents against moisture.
- After the initial opening, it can be used for 2 months.
- Do not throw medicines into the sewer system or household waste. Consult a pharmacist as to how to discard medicine that you no longer need. This will help protect the environment.

6. Additional information

What does Kuvan contain?

In addition to the active ingredient, the medicine also contains:

Ascorbic acid
Crospovidone
Dibasic calcium phosphate anhydrous
Mannitol
Sodium stearyl fumarate
Riboflavin

What does Kuvan look like and what does the package contain?

Kuvan is supplied as soluble tablets. The soluble tablets are off-white to light yellow and the number "177" is embossed on one side.

The packages are available in bottles with a child-resistant cap (30 or 120 soluble tablets). Each bottle contains a desiccant capsule (silica gel).

Not all the packaging sizes are marketed.

Manufacturer: BioMarin International Ltd., Cork, Ireland

Registration holder and its address: Medison Pharma Ltd., 10 Hashiloach St., P.O.B. 7090, Petach Tikva, Israel

This leaflet was inspected and approved by the Ministry of Health in 12/2015 and updated in accordance with the instructions of the Ministry of Health in 02/2019

Registration number of the medicine in the National Drug Register of the Ministry of Health: 144 23 33052 00.