Abbreviated Prescribing Information (PI) (INTL): KUVAN®
Refer to Summary of Product Characteristics for full information.
Presentation: KUVAN® 100 mg soluble tablets. Each soluble tablet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin) + excipients (mannitol (E421), calcium hydrogen phosphate (anhydrous), crospovidone type A, ascorbic acid (E300), sodium stearyl fumarate and riboflavin (E101). KUVAN® 100 mg powder for oral solution. Each sachet contains 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin) + excipients (mannitol (E421), potassium citrate (E332), sucralose (E955) and ascorbic acid (E300). KUVAN® 500 mg powder for oral solution. Each sachet contains 500 mg of sapropterin dihydrochloride (equivalent to 384 mg of sapropterin) + excipients (mannitol (E421), potassium citrate (E332), sucralose (E955) and ascorbic acid (E300). **Therapeutic indications:** Treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. KUVAN® is also indicated for the treatment of HPA in adults and paediatric patients of all ages with tetrahydrobiopterin (BH_4) deficiency who have been shown to be responsive to such treatment. **Dosage:** The calculated daily dose should be rounded to the nearest multiple of 100. The starting dose in adult and paediatric patients with PKU is 10 mg/kg once daily. The dose can be adjusted between 5 and 20 mg/kg/day. The starting dose in adult and paediatric patients with BH_4 deficiency is 2 to 5 mg/kg total daily dose. Doses may be adjusted up to a total of 20 mg/kg/day. **Determination of response:** Response to treatment is determined by a decrease in blood phenylalanine (Phe) following treatment with KUVAN®. Blood Phe levels are checked before treatment and after 1 week of treatment with KUVAN® at the recommended starting dose. If an unsatisfactory response is observed, the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of Phe levels up to 1 month. The dietary Phe should be kept constant during this period. A satisfactory response is defined as a ≥30 percent reduction in blood Phe level or attainment of the therapeutic blood Phe goals defined by the treating physician. Patients treated with KUVAN® must continue a restricted Phe diet and undergo regular clinical assessments. **Administration:** KUVAN® is administered with a meal. For patients with PKU, KUVAN® should be administered as a single daily dose, and at the same time each day preferably in the morning. For patients with BH_4 deficiency, divide the total daily dose into 2 or 3 administrations, distributed over the day. Patients above 20 kg body weight: Tablets should be placed in a cup of water with 120 to 240 ml of water and stirred until dissolved; the content of the sachet(s) should be placed in 120 to 240 ml water and stirred until dissolved. Please consult the SmPC for instructions for the administration of KUVAN® in children up to 20 kg body weight. **Dose adjustment:** The patient's adherence to treatment and diet should be reviewed before considering a dose adjustment. Blood Phe and tyrosine (Tyr) levels should be tested 1–2 weeks after each dose adjustment and monitored frequently thereafter. Discontinuation of KUVAN® should only be done under a physician's supervision. **Special populations:** Safety and efficacy of KUVAN® in patients above 65 years of age and in patients with renal or hepatic impairment have not been established. Caution must be exercised when prescribing to these populations. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** Sustained or recurrent dysfunction in the Phe-Tyr- dihydroxy-L-phenylalanine (DOPA) metabolic pathway can result in deficient body protein and neurotransmitter synthesis. Prolonged exposure to low blood Phe and Tyr levels during infancy has been associated with impaired neurodevelopmental outcome. Active management of dietary Phe and overall protein intake while taking KUVAN® is required to ensure adequate control of blood Phe and Tyr levels and nutritional balance. Consultation with a physician is recommended during illness as blood Phe levels may increase. An increase in Phe above pre-treatment levels may occur upon cessation of treatment (rebound). There are limited data regarding the long-term use of KUVAN®. KUVAN® contains <1 mmol (23 mg) sodium per tablet (essentially "sodium free"). **Interaction with other medicinal products:** Inhibitors of dihydrofolate reductase (methotrexate, trimethoprim) may interfere with BH_4 metabolism. BH_4 is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use with all medicinal products that cause vasodilation. Caution should be also exercised when prescribing KUVAN® to patients receiving levodopa: convulsion, exacerbation of convulsion, increased excitability and irritability have been observed during co-administration in BH_4-deficient patients. **Fertility, pregnancy and lactation:** There are limited data from the use of KUVAN® in pregnant women. Uncontrolled Phe levels above 600 µmol/L are associated with a very high incidence of neurological, cardiac, facial dysmorphism, and growth anomalies. Maternal blood Phe levels must therefore be strictly controlled before and during pregnancy. KUVAN® should only be considered if dietary management does not adequately reduce blood Phe levels and should not be used during breastfeeding. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. **Overdose:** Headache and dizziness have been reported after the administration of KUVAN® above the recommended maximum dose of 20 mg/kg/day. Treatment of overdose should be directed to symptoms. A shortening of the QT interval was observed in a study with a single supra-therapeutic dose of 100 mg/kg; this should be taken into consideration in managing patients who have a pre-existing shortened QT interval. **Summary of the safety profile:** Approximately 35% of the 579 patients aged 4 years and over who received treatment with KUVAN® (5 to 20 mg/kg/day) in the clinical trials for KUVAN® experienced adverse reactions. The most commonly reported adverse reactions are headache and rhinorrhoea. In a further clinical trial, approximately 30% of the 27 children aged below 4 years who received treatment with sapropterin dihydrochloride (10 or 20 mg/kg/day) experienced adverse reactions. The most commonly reported adverse reactions are "amino acid level decreased" (hypophenylalaninaemia), vomiting and rhinitis. In the pivotal clinical trials and in the post-marketing experience for KUVAN®, the following adverse reactions have been identified – within each frequency grouping, adverse reactions are presented in order of decreasing seriousness – *Immune system disorders*: Not known: Hypersensitivity reactions (including serious allergic reactions) and rash. *Metabolism and nutrition disorders*: Common: Hypophenylalaninaemia. *Nervous system disorders*: Very common: Headache. *Respiratory, thoracic and mediastinal disorders*: Very common: Rhinorrhoea. Common: Pharyngolaryngeal pain, nasal congestion, coughs. *Gastrointestinal disorders*: Common: Diarrhoea, vomiting, abdominal pain , dyspepsia, nausea. Not known: Gastritis, oesophagitis. *Paediatric population*: Frequency, type and severity of adverse reactions in children essentially the same as those in adults. **Legal category:** Prescription only medicine. **Marketing authorisation holder:** BioMarin International Limited. Shanbally, Ringaskiddy, County Cork, Ireland. **Marketing authorisation number(s):** EU/1/08/481/001, EU/1/08/481/002, EU/1/08/481/003. **Date of first authorisation:** 2 December 2008. **Date of revision of the text:** March 2019

Healthcare professionals should report adverse events in accordance with their local requirements.

Adverse events should also be reported to BioMarin on +1 415 506 6179 or drugsafety@bmrn.com