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News Release

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Merck KGaA, Darmstadt, Germany, Receives EU-Approval to Extend Kuvan Use to Children with PKU Below 4 Years of Age

- **European Commission decision confirms earlier CHMP recommendation for change to product information Bullet point B (short and to the point)**

Darmstadt, Germany, July 20, 2015 – Merck KGaA, Darmstadt, Germany, a leading company for innovative and top-quality high-tech products in healthcare, life science and performance materials today announced that the European Commission (EC) has authorized a change to the European marketing authorization for its product Kuvan® (sapropterin dihydrochloride), to allow its use in children with phenylketonuria (PKU) below 4 years of age who have been shown to be responsive to such treatment. The EC decision follows the positive recommendation from the Committee for Medicinal Products for Human Use (CHMP) in May 2015, which was based on a review of data from SPARK*, a Phase IIIb clinical study. The EC decision is applicable to all 28 EU member states and the basis for corresponding decisions issued by Norway, Iceland and Liechtenstein.

“PKU is a rare disease with significant consequences – but if managed appropriately, it doesn’t have to impair child development or quality of life for children and adults. We are committed to helping patients with PKU, both at adult age and during childhood. The positive EC decision allows physicians to use Kuvan also in children right from diagnosis, who have shown to be responsive to the medication”, said Luciano Rossetti, Head of Global Research & Development at the biopharmaceuticals business of Merck KGaA, Darmstadt, Germany.

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Commenting on the news, Professor Dr. Ania Carolina Muntau of the University Hospital Hamburg-Eppendorf, Hospital for Children and Youth Medicine, lead investigator of the SPARK* study said, “Today’s news is a very positive development for children with PKU under the age of 4 who are suitable for the therapy. Managing PKU in young children through the maintenance of a phenylalanine-restricted diet alone is very challenging, and parents will welcome this approval, which could make the treatment easier. The evidence shows that Kuvan significantly improves tolerance to phenylalanine, allowing more flexibility in the management of the very restrictive diet in PKU patients”.

Detailed 26-week data from the SPARK study were presented at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium in September 2014. Results showed that the addition of Kuvan to a phenylalanine-restricted diet significantly increased phenylalanine tolerance by 30.5 mg/kg/day in children with PKU below 4 years of age and responsive to Kuvan, when compared with phenylalanine tolerance in children following a phenylalanine-restricted diet alone ($p<0.001$). In the group treated with phenylalanine-restricted diet plus Kuvan phenylalanine tolerance was increased from 37.1 mg/kg/day at baseline to 80.6 mg/kg/day after 26 weeks, and in the phenylalanine-restricted diet alone from 35.8 mg/kg/day at baseline to 50.1 mg/kg/day after 26 weeks, respectively.

PKU is an inborn metabolic disorder that causes the toxic accumulation of phenylalanine, an essential amino acid contained in all protein-rich foods, in the brain and blood.[1,2] Untreated, PKU can lead to intellectual disability, seizures and other serious medical problems.[1,2] In many countries, implementation of national newborn screening programs has allowed identification of children with PKU at birth, enabling the management of the disease to begin as early as possible in order to prevent potentially severe neurological damage.[3] However, in Europe there has not been, to date, a licensed medication for the treatment of PKU in children who are below 4 years of age.

Following EC approval, the Summary of Product Characteristics (SmPC) will be updated to include details about the use of Kuvan in this younger population. It affects approximately 1/10,000 newborns in Europe.

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The original European marketing authorization for Kuvan was granted in 2008. In Europe, Kuvan was the first, and remains the only medication in combination with phenylalanine-restricted diet designed to reduce the concentration of phenylalanine in the blood and brain in those patients who are responsive to Kuvan to prevent the debilitating effects of PKU.[4] Kuvan is already indicated in patients of all ages with tetrahydrobiopterin (BH4) deficiency, and in those aged 4 years and above with PKU (due to phenylalanine hydroxylase enzyme deficiency) who are responsive to Kuvan.

Kuvan is marketed by the biopharmaceuticals business of Merck KGaA, Darmstadt, Germany, outside the USA, Canada and Japan, by BioMarin in the USA and Canada, and under the name Biopten® by Asubio Pharma in Japan. In the USA and Europe, Kuvan received orphan drug designation.

*SPARK: **S**afety **P**ediatric Effic**A**cy Pha**R**macokinetic with **K**uvan (sapropterin dihydrochloride)

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About phenylketonuria (PKU)

PKU is an autosomal recessive genetic disorder caused by a defect or a deficiency of the enzyme phenylalanine hydroxylase (PAH) or its cofactor tetrahydrobiopterin (BH4). PAH is required for the metabolism of phenylalanine, an essential amino acid found in all protein-containing foods. It affects approximately 1/10,000 newborns in Europe. If PKU patients are not treated with a phenylalanine-restricted diet, phenylalanine will accumulate in the blood and brain to abnormally high levels, thereby resulting in a variety of complications including mental retardation and brain damage, mental illness, seizures and tremors, and clinically significant cognitive problems. Universal systematic newborn screening programs were developed in the 1960s and early 1970s to enable diagnosis of all patients with PKU patients at birth.

About tetrahydrobiopterin (BH4) deficiency

BH4 deficiency is a very rare inborn error of metabolism, and is estimated to account for 1–2 % of cases of hyperphenylalaninemia (HPA). BH4 deficiency is an autosomal recessive genetic condition and can result from deficiencies of any of the five different enzymes involved in BH4 synthesis and regeneration. BH4 is a necessary co-factor for PAH. Therefore, BH4 deficiency impairs PAH activity leading to a biochemical situation similar to PKU, with HPA resulting from deficient conversion of phenylalanine to tyrosine. In addition, since BH4 is also a necessary co-factor for both tyrosine hydroxylase and tryptophan hydroxylase, BH4 deficiency causes deficiencies in the downstream neurotransmitter products of these amino acids including catecholamines and serotonin. Dietary limitation of whole protein or phenylalanine intake is often not necessary with BH4 treatment. However, since BH4 does not cross the blood brain barrier, concomitant

therapy with neurotransmitter precursors, i.e. levodopa and 5-hydroxytryptophan, may be necessary to boost central nervous system substrate levels for catecholamine and serotonin synthesis, respectively

About Kuvan
Kuvan® (sapropterin dihydrochloride) is the first oral therapy and approved in Europe for the treatment of hyperphenylalaninemia (HPA) due to a deficiency of the enzyme phenylalanine hydroxylase (PAH) or its cofactor tetrahydrobiopterin (BH4)) in patients of all age who have shown to be responsive to Kuvan. Kuvan was developed jointly by BioMarin Pharmaceutical Inc. and the biopharmaceuticals business of Merck KGaA, Darmstadt, Germany. In the US, Kuvan is marketed by BioMarin and is indicated for the treatment of HPA due to PKU without age restriction. Kuvan is to be used in conjunction with a phenylalanine-restricted diet.
Kuvan is the synthetic form of 6R-BH4, a naturally occurring co-factor that works in conjunction with the enzyme phenylalanine hydroxylase (PAH) to metabolize phenylalanine into tyrosine. Clinical data show that Kuvan produces significant reductions in blood phenylalanine concentration in a large subset of patients.
Most common adverse reactions reported with the use of Kuvan include headache, rhinorrhea, pharyngolaryngeal pain, nasal congestion, cough, diarrhea, vomiting, abdominal pain, and low levels of phenylalanine in the blood.
Kuvan is approved in 51 countries worldwide, including member states of the European Union and the USA. Under the terms of the agreement with BioMarin, The biopharmaceuticals business of Merck KGaA, Darmstadt, Germany,has exclusive rights to market Kuvan in all territories outside the USA, Canada and Japan.

About the SPARK study
SPARK is a Phase IIIb, multicenter, open-label, randomized, controlled study designed to assess the efficacy, safety, and population pharmacokinetics of Kuvan in patients younger than 4 years old with PKU who have been previously shown to be responsive to Kuvan in a response test. The study was requested by the European Medicines Agency (EMA) as a post-authorization measure and conducted under a Pediatric Investigational Plan. Patients were randomized to Kuvan (10 mg/kg/day) plus a phenylalanine-restricted diet, or to a phenylalanine-restricted diet alone, for 26 weeks. Correspondent to a patient's phenylalanine tolerance after approximately 4 weeks, the Kuvan dose could be increased in a single step to 20 mg/kg/day. The primary endpoint of the study was to compare phenylalanine tolerance achieved in both arms after 26 weeks of treatment. The group of patients receiving Kuvan had an adjusted mean phenylalanine tolerance of 80.6 mg/kg/day at the end of 26 weeks of treatment compared with that of 50.1 mg/kg/day in the group of patients receiving diet alone (Δ 30.5 mg/kg/day, $p<0.001$)). The mean phenylalanine tolerance in the group receiving Kuvan in addition to a phenylalanine-restricted diet (n=27) increased from a baseline of 37.1°mg/kg/day (standard deviation [SD] 17.3 mg/kg/day) to 80.6 mg/kg/day (SD 4.2 mg/kg/day) after 26 weeks. In the group following a phenylalanine-restricted diet alone (n=29), the increase was from 35.8 mg/kg/day (SD 20.9 mg/kg/day) to 50.1 mg/kg/day (SD 4.3 mg/kg/day).
Secondary study endpoints included change in levels of blood phenylalanine during the study period, change in dietary phenylalanine tolerance over time (from baseline to 26 weeks) in both groups, as well as assessment of neurodevelopmental function, growth parameters and safety.
Frequency, type and severity of adverse reactions in children who received treatment with sapropterin dihydrochloride were essentially similar to those in adults. The most common adverse reactions in the SPARK trial were reported as "amino acid level decreased" (hypophenylalaninemia), rhinitis and vomiting. The long-term efficacy and safety of Kuvan are being assessed in the ongoing study's 3-year extension period, in which all patients are offered to receive Kuvan in addition to the phenylalanine-restricted diet.

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Merck KGaA of Darmstadt, Germany, is a leading company for innovative and top-quality high-tech products in healthcare, life science and performance materials. The company has six businesses – Biopharmaceuticals, Consumer Health, Allergopharma, Biosimilars, Life Science and Performance Materials – and generated sales of € 11.3 billion in 2014. Around 39,000 employees work in 66 countries to improve the quality of life for patients, to foster the success of customers and to help meet global challenges. Merck KGaA, Darmstadt, Germany, is the world's oldest pharmaceutical and chemical company – since 1668, the company has stood for innovation, business success and responsible entrepreneurship. Holding an approximately 70% interest, the founding family remains the majority owner of the company to this day. Merck KGaA, Darmstadt, Germany holds the global rights to the Merck name and brand. The only exceptions are Canada and the United States, where the company operates as EMD Serono, EMD Millipore and EMD Performance Materials.