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Sapropterin dihydrochloride use in pregnant women with phenylketonuria: An interim report of the PKU MOMS sub-registry

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ABSTRACT

For pregnant women with phenylketonuria (PKU), maintaining blood phenylalanine (Phe) < 360 μmol/L is critical due to the toxicity of elevated Phe to the fetus. Sapropterin dihydrochloride (sapropterin) lowers blood Phe in tetrahydrobiopterin (BH_4) responsive patients with PKU, in conjunction with a Phe-restricted diet, but clinical evidence supporting its use during pregnancy is limited. As of June 3, 2013, the Maternal Phenylketonuria Observational Program (PKU MOMS) sub-registry contained data from 21 pregnancies — in women with PKU who were treated with sapropterin either before (N = 5) or during (N = 16) pregnancy. Excluding data for spontaneous abortions (N = 4), the data show that the mean of median blood Phe [204.7 ± 126.6 μmol/L (n = 14)] for women exposed to sapropterin during pregnancy was 23% lower, and had a 58% smaller standard deviation, compared to blood Phe [267.4 ± 300.7 μmol/L (n = 3)] for women exposed to sapropterin prior to pregnancy. Women on sapropterin during pregnancy experienced fewer blood Phe values above the recommended 360 μmol/L threshold. When median blood Phe concentration was <360 μmol/L throughout pregnancy, 75% (12/16) of pregnancy outcomes were normal compared to 40% (2/5) when median blood Phe was >360 μmol/L. Severe adverse events identified by the investigators as possibly related to sapropterin use were premature labor (N = 1) and spontaneous abortion (N = 1) for the women and hypophagia for the offspring [premature birth (35w4d), N = 1]. One congenital malformation (cleft palate) of unknown etiology was reported as unrelated to sapropterin. Although there is limited information regarding the use of sapropterin during pregnancy, these sub-registry data show that sapropterin was generally well-tolerated and its use during pregnancy was associated with lower mean blood Phe. Because the teratogenicity of elevated maternal blood Phe is without question, sapropterin should be considered as a treatment option in pregnant women with PKU who cannot achieve recommended ranges of blood Phe with dietary therapy alone.

1. Introduction

Maternal phenylketonuria (PKU) syndrome refers to the teratogenic effects of elevated maternal blood phenylalanine (Phe) during pregnancy [1]. The risk of congenital abnormalities increases with increasing maternal blood Phe concentration [2]. In addition to elevated maternal blood Phe concentrations, evidence of harm has also been shown for blood Phe concentrations <120 μmol/L during pregnancy [3]. Therefore, for pregnant women with PKU, maintaining clinically recommended

Abbreviations: AE, adverse event; Apgar, Appearance, Pulse, Grimace, Activity, Respiration; BH_4, tetrahydrobiopterin; BMI, Body Mass Index; CDC, Centers for Disease Control and Prevention; ID, identification; LMP, last menstrual period; OFC, occipitofrontal circumference; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU MOMS, Maternal Phenylketonuria Observational Program; MedDRA, Medical Dictionary for Regulatory Activities; PKU, phenylketonuria; PKUDOS, Phenylketonuria Demographics Outcomes and Safety; SAE, serious adverse event; WHO, World Health Organization.

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blood Phe concentrations is critical [4]. However, achieving tight metabolic control through dietary therapy alone can be problematic due to poor social support, impairments in cognitive, psychiatric and executive function, lack of insurance and financial resources, and other issues [5,6]. Therefore, patients with PKU are often non-adherent [7]. In addition, >50% of patients with PKU ages 0–45 years and >75% of patients with PKU ages 24–45 years are reportedly lost to follow-up by metabolic clinics [5].

Sapropterin dihydrochloride (sapropterin; KUVAN®, BioMarin Pharmaceutical, Inc., Novato CA USA), a synthetically-prepared salt of naturally occurring tetrahydrobiopterin (BH_4), a co-factor for the phenylalanine hydroxylase enzyme, was proposed as adjunct therapy to lower blood Phe over 14 years ago [8]. Sapropterin is indicated to lower blood Phe in tetrahydrobiopterin (BH_4) responsive PKU in conjunction with a Phe-restricted diet. A 6-week, multicenter, double-blind, placebo-controlled trial of 88 known responder patients with PKU showed that 18/41 (44%) patients on sapropterin 10 mg/kg/day had a ≥30% reduction in blood Phe from baseline compared to 4/47 (9%) of controls [9–11]. In an 8-day, multicenter study of 90 children with PKU (ages 4 to 12 years) who were administered 20 mg/kg/day sapropterin, 50 children (56%) had a ≥30% decrease in blood Phe [11]. In a 22-week, multicenter, open-label extension study, a dose-dependent reduction of plasma Phe concentration was observed during a forced dose-titration phase (i.e., 5, 20, and 10 mg/kg/day of sapropterin consecutively for 2-weeks each) [12].

The use of sapropterin in pregnant women has not been studied in clinical trials and, because animal reproduction studies have shown an adverse effect on the fetus but potential benefits may warrant use of the drug in pregnant women despite potential risks, sapropterin is labeled in the United States as a pregnancy 'Category C' drug [13]. Teratogenicity studies with sapropterin have been conducted in rats at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose of 20 mg/kg/day, based on body surface area) and in rabbits at oral doses of up to 600 mg/kg/day (about 10 times the maximum recommended human dose, based on body surface area). No clear evidence of teratogenic activity was found in either species; however, in the rabbit teratogenicity study, there was an increase (not statistically significant) in the incidence of holoprosencephaly at the 600 mg/kg/day dose compared to controls [11]. In 2005, Koch et al. reported on the successful use of sapropterin in human pregnancy [14]. Since then, only a few other case reports have been published. The PKU and Pregnancy Working Group at the NIH 2012 PKU Scientific Review Conference stated that while preliminary data in the literature are encouraging, they are insufficient to recommend sapropterin use during pregnancy [15].

This publication is an interim analysis of the Maternal Phenylketonuria Observational Program (PKU MOMS) sub-registry. The PKU MOMS sub-registry is designed to collect data on pregnancy and lactation in all sapropterin-treated women who are following the standard of care for pregnant women with PKU. This sub-registry collects safety and efficacy data on pregnant women who are treated with sapropterin during, or prior to, pregnancy as well as safety and outcome data for their offspring.

2. Methods

2.1. PKUDOS registry

The Phenylketonuria Demographics Outcomes and Safety (PKUDOS) registry is a phase 4 observational study designed to provide up to 15 years of data on patients with PKU who are or have been treated with sapropterin. The registry started in September 2008 and, as of June 7, 2013, it contained information on 1224 enrolled patients with a diagnosis of PKU from 52 participating PKUDOS sites in the United States. All registry patients were on sapropterin therapy, planned to receive the drug within 90 days, or had previously received sapropterin. All patients were required to consent to provide health information at a PKUDOS participating center.

2.2. PKU MOMS (Maternal Phenylketonuria Observational Program) sub-registry

As of June 3, 2013, PKU MOMS sub-registry contained maternal and offspring information for 23 pregnant women with PKU and 17 live births from 13 clinical sites located in the United States. The data presented extends from the beginning of the PKU MOMS sub-registry in 2008 to June 3, 2013. This includes women exposed to sapropterin prior to conception and continued on drug during pregnancy (N = 17), one woman who started on drug during pregnancy (N = 1), and women who were exposed to sapropterin prior to, but not during, pregnancy (N = 5). A separate consent form was signed before entry into PKU MOMS authorizing the mother and her baby to undergo assessments and laboratory tests.

Inclusion criteria:

- Willing to enroll in (or are already enrolled in) PKUDOS registry.
- Agree to follow the standard of care for pregnant women with PKU in the United States (NIH, 2000, NIH Consensus Statement [16]) during the study.
- Agree to be followed by a hospital or PKU clinic offering the standard of care for maternal PKU.
- Are within 10 weeks of their last menstrual period.

Exclusion criteria:

- Patients who have not adhered to the standard of care for pregnant women with PKU in the United States.

2.3. Clinical assessments

Clinical assessments were performed per the standard of care, or per current medical practice, at each participating medical center and were conducted from detection of pregnancy up to 6 months post-partum (i.e., offspring visit). The data, if available, were entered into the sub-registry by study coordinators or designated personnel at the clinical sites on a quarterly to annual basis. A clinical research associate from the study sponsor conducted monitoring visits at clinical sites every ~12–18 months to perform maternal and offspring source document verification. Queries were generated for discrepant or missing data to confirm and verify information. At the time of this data analysis, several open queries may have been unresolved and these data points may not be included in this analysis. Recommended assessments are shown in Table 1 of the supplement.

The seriousness and relatedness of adverse events (AEs) were assessed by the investigators. These events were coded using the current Medical Dictionary for Regulatory Activities (MedDRA 16.1). The women that participated in the sub-registry have AEs collected outside their pregnancy in PKUDOS; however this analysis includes AEs that occurred during pregnancy and those with missing dates (i.e., unknown relationship to pregnancy). Concomitant medications were classified using World Health Organization (WHO) Drug Information [17].

Per protocol, sites followed the standard of care for pregnant women with PKU in the United States during the study [16]. The sub-registry did not capture information on what each clinic considers a "clinical response" to sapropterin or their assessment of responder vs. non-responder.

2.4. Pregnancies

Data are shown for 21 completed pregnancies from 18 women (3 women had multiple pregnancies), which include the pregnancies that culminated in a live birth (N = 17) and those that ended in