

Tetrahydrobiopterin as a Novel Therapeutic Intervention for Autism

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Summary: Tetrahydrobiopterin (BH₄) is an essential cofactor for several critical metabolic pathways that have been reported to be abnormal in autism spectrum disorder (ASD). In addition, the cerebrospinal fluid concentration of BH₄ is reported to be depressed in children with ASD. Over the past 25 years, several clinical trials have suggested that treatment with BH₄ improves ASD symptomatology in some individuals. Two ongoing clinical protocols may help further define the efficacy of BH₄ treatment in children with ASD. First, children with ASD who had low concentrations of cerebrospinal fluid or urine pterins were treated in an open-label manner with 20 mg/kg per day of BH₄. The majority of children (63%) responded positively to treatment, with minimal adverse events (AEs). Second, a double-blind placebo-controlled

study examining the efficacy of 20 mg/kg per day of BH₄ treatment in children with ASD is currently underway. Safety studies from the commercially available forms of BH₄ document the low incidence of AEs, particularly serious AEs. Studies have also documented the ability of BH₄ to cross the blood-brain barrier. Based on the importance of BH₄ in neurodevelopmental metabolic pathways, the safety of BH₄ treatment, and the evidence for a therapeutic benefit of BH₄ treatment in children with ASD, we conclude that BH₄ represents a novel therapy for ASD, one that may gain wider use after further clinical studies have established efficacy and treatment guidelines. **Key Words:** Tetrahydrobiopterin, autism spectrum disorder, monoamine neurotransmitters, nitric oxide, treatment.

INTRODUCTION

Although many studies have clearly linked autism spectrum disorder (ASD) to CNS and systemic biological abnormalities, most autism treatment research has focused on behavioral interventions.¹ Behavioral treatments are costly and labor-intensive, and may progress slowly.¹ In addition, current biologically based treatments do not appear to alter the course of the disorder.^{2,3} Most studies of biological interventions have focused on symptom reduction, targeting the behaviors associated with ASD (e.g., self-injurious behavior, aggression, hyperactivity, and obsessive-compulsive behavior) rather than the core features of the disorder.^{3,4}

Tetrahydrobiopterin, or BH₄, is a naturally occurring substance that is an essential cofactor for several critical metabolic pathways, including those responsible for the production of monoamine neurotransmitters, the breakdown of phenylalanine, and the production of nitric ox-

ide. Abnormalities in several of these metabolic pathways or the products of these pathways for which BH₄ is essential have been noted in individuals with ASD. In addition, abnormalities in CNS concentrations of BH₄ have been reported in individuals with ASD. Over the past 25 years, a limited number of clinical trials have reported encouraging results with BH₄ treatment for children with ASD. Here, we review the evidence in support of the idea that children with ASD may have a BH₄ deficiency and that treatment with BH₄ may be beneficial in children with ASD. In addition, we review the evidence that systemically administered BH₄ actually enters the CNS, and also discuss the safety of the commercially available BH₄ products that have regulatory approval.

GENERAL ROLE OF BH₄ IN METABOLIC SYSTEMS

BH₄ is part of the pteridine family of naturally occurring compounds with a heterocyclic pteridine structure. Pterins are pteridine derivatives with a 2-amino-4-oxo base. The pterins include BH₄, biopterin, and neopterin, but only BH₄ is biologically active.

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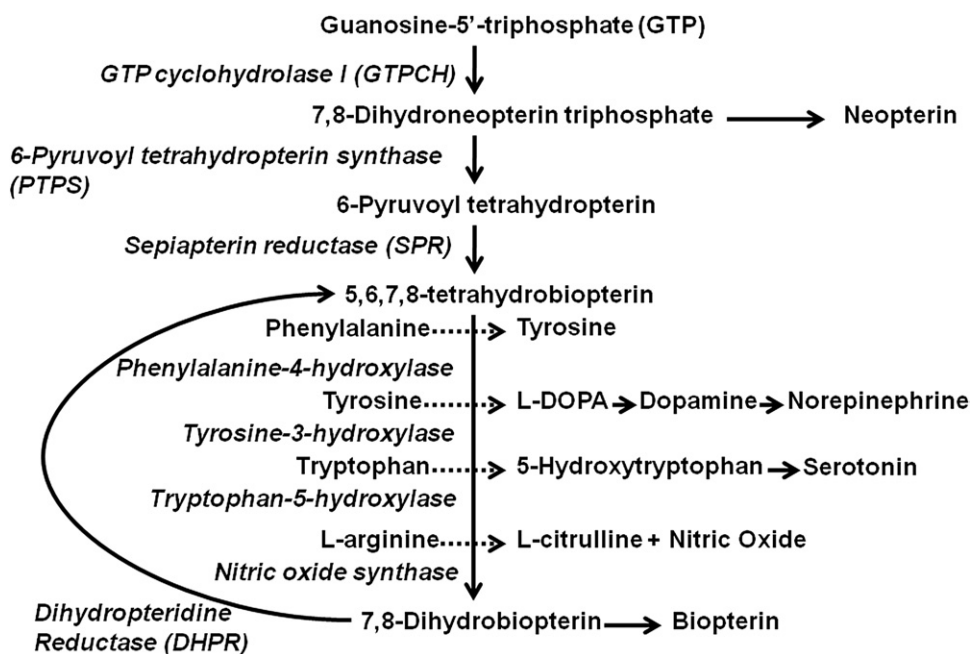


FIG. 1. Simplified pathway for the production and recycling of tetrahydrobiopterin (BH_4). Included are major enzymes, intermediates, and metabolites in this pathway. Dashed lines represent the enzymatic reactions that use BH_4 to produce neurotransmitters and nitric oxide; names of enzymes are italicized.

BH_4 is synthesized *de novo* from GTP, a purine nucleotide, by three enzymatic reactions (GTP cyclohydrolase, 6-pyruvoyltetrahydropterin synthase, and sepiapterin reductase) (FIG. 1).⁵ Once BH_4 is synthesized, it is used as a cofactor by three aromatic amino acid hydroxylases (phenylalanine-4-hydroxylase, tyrosine-3-hydroxylase, and tryptophan-5-hydroxylase) to catalyze the conversion of phenylalanine, tyrosine, and tryptophan to tyrosine, L-dopa, and 5-hydroxytryptophan, respectively (FIG. 1). In this process, BH_4 is converted into 7,8-dihydrobiopterin, which can be recycled to remake BH_4 through a salvage pathway catalyzed by dihydropteridine reductase. Some of these products of the hydroxylase enzymes are further converted into neurotransmitters: L-dopa is converted into dopamine, which is further converted into norepinephrine, and 5-hydroxytryptophan is converted into serotonin. Additionally, BH_4 is essential in the production of nitric oxide, an important second messenger molecule used primarily for communication in vascular and neural tissues. In this reaction, nitric oxide synthase converts L-arginine and oxygen to L-citrulline and nitric oxide (FIG. 1).

A deficiency in BH_4 synthesis or recycling can result in neurological disorders. Hyperphenylalaninemia, specifically phenylketonuria (PKU) type IV, presents at birth with elevated phenylalanine in the blood and represents approximately 1–2% of PKU cases. Severe mental retardation develops if phenylalanine levels are not controlled early in life. BH_4 deficiency can also result in dopamine-responsive dystonia, a neurological disorder that demonstrates a wide range of symptoms and ages of

presentations. Patients with dopamine-responsive dystonia invariably demonstrate dystonia with diurnal variation.⁶

EVIDENCE FOR BH_4 DEPLETION IN ASD

The role of BH_4 in neurodevelopmental disorders, including ASD, is not well understood. The CSF concentration of BH_4 has been reported to be 42% lower in children with ASD than in neurotypical children.⁷ Further analysis of the ASD children identified younger and older subgroups. When the subgroups were compared with the control group, only the ASD children younger than 7 years old demonstrated significantly lower BH_4 concentrations. This younger group also demonstrated a reduction in total pterins and biopterin, essentially indicating that the deficit in BH_4 was not due to a synthesis or recycling deficit but reflected a problem with the general availability of pterins.

Although the reason for reduction of CSF BH_4 in ASD is not known, there is evidence that metabolic pathways that consume and recycle BH_4 are dysfunctional in children with ASD. Several lines of evidence suggest that children with ASD manifest excessive inflammation and overactivation of the immune system.^{8–10} As already noted, nitric oxide, a key mediator of inflammation and immune response, is produced by a BH_4 -dependent reaction. Thus, it is possible that BH_4 in ASD could be depleted by the overactivation of the immune system and inflammatory processes during an excessive production of nitric oxide. Children with ASD might also have an

underlying reduction in BH₄ recycling. Folate is necessary for an alternative BH₄ salvage pathway that uses the enzyme dihydrofolate reductase. Available folate might be reduced in children with ASD, given that folate supports oxidative stress pathways and that the oxidative stress pathways seem to be overactive in children with ASD.¹¹⁻¹⁴ Lastly, because BH₄ can act as a superoxide radical scavenger, it may be depleted in the setting of high oxidative stress states.^{15,16}

Children with ASD have symptoms not inconsistent with a CNS BH₄ deficiency. Such deficiency can result in low production of monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine. Many children with ASD have clinical symptoms, such as obsessive-compulsive disorder and anxiety, that are seen in other disorders in which serotonin deficiency has been implicated,¹⁷ and dysfunction in the serotonin system in ASD has been documented.¹³ Across studies, however, response of children with ASD to selective-serotonin reuptake inhibitors has been mixed,¹⁸⁻²⁰ and research suggests that at least a subgroup of children with ASD have elevations in serotonin levels.²¹ Children with ASD have a high rate of executive function problems, inattention, and hyperactivity, all symptoms suggesting dopamine and norepinephrine deficits.²²⁻²⁴ In some children with ASD, such behaviors are mitigated by psychopharmaceuticals designed to increase levels of dopamine and norepinephrine.^{25,26} This provides indirect evidence that some children with ASD may have deficits in the production or utilization of monoamine neurotransmitters. However, because ASD is a very heterogeneous disorder, further research will be needed to clarify the potential role of monoamine neurotransmitter deficits in ASD.

PREVIOUS CLINICAL TRIALS OF BH₄ FOR ASD

In 1984, Japanese researchers reported the first case studies of BH₄ treatment in children with ASD.²⁷ Two boys with ASD, ages 7 and 5 years, were treated with 1–2.5 mg/kg per day of BH₄.²⁸ The 7-year-old showed marked improvement in hyperactivity, mood lability, and stereotypic behaviors; both boys showed moderate improvement in general autistic symptoms. This initial evidence led to further clinical studies on BH₄ as a treatment for autistic symptomatology, the majority of which were conducted in Japan. Over a 6-year period, from 1985 to 1990, four Japanese researchers studied more than 300 mildly to severely affected autistic children in five open-label studies and one double-blind placebo-controlled study.²⁷⁻³⁵ Response was measured as the percentage of children who demonstrated moderate or marked global improvement. Treatment with oral BH₄ at a dose of 1–3 mg/kg per day over 4–24 weeks resulted in a response rate of 41% to 64% (Table 1). Two additional clinical studies, one double-blind placebo-controlled crossover and one open-label, were conducted by Swedish researchers using an oral BH₄ dose of 3–6 mg/kg per day.^{36,37} These studies demonstrated limited general improvement in autistic symptoms with BH₄ treatment.

Several studies have pointed to improvement in specific autistic symptoms with BH₄ treatment. Nakane et al.³⁴ noted that, within the autistic symptoms cluster of the Rating Scale for Abnormal Behavior in Children (RSABC), the greatest improvement was found in communication, cognitive ability, adaptability, and verbal expression. Fernell et al.³⁷ found specific improvements

Table 1. Clinical Trials Evaluating Tetrahydrobiopterin (BH₄) in Autism

References	Tetrahydrobiopterin Treatment	Participants, no.		Response Rate, %	
		BH ₄	Placebo	BH ₄	Placebo
Controlled Clinical Trials					
Naruse et al. ³² (1990)	1–3 mg/kg per day × 12 wk (Biopten granules)*	41	42	53	31
Danfors et al. ³⁶ (2005)	Double-blind placebo-controlled				
	6 mg/kg per day × 26 wk (R-BH ₄). [†]	12	0	—	—
	Double-blind crossover				
	Subtotal	53	42	53	31
Open-Label Clinical Trials					
Naruse et al. ²⁸ (1984)	1–2.5 mg/kg per day (Biopten granules)*	2	0	100	—
Naruse et al. ³¹ (1990)	1–2 mg/kg per day × 4–8 wk (Biopten granules)*	17	0	64	—
Takesada et al. ³⁵ (1990)	1–3 mg/kg per day × 12–96 wk (Biopten granules)*	97	0	54	—
Nakane et al. ³⁴ (1990)	1–3 mg/kg per day × 12–105 wk (Biopten granules)*	24	0	42	—
Nagahata et al. ³³ (1990)	1–3 mg/kg per day × 12–24 wk (Biopten granules)*	136	0	48	—
Fernell et al. ³⁷ (1997)	3 mg/kg per day × 3 months (R-BH ₄). [†]	6	0	—	—
	Subtotal	280	0	—	—
	Grand total	333	42	51	31

*Supplied by Daiichi Asubio Pharma (Tokyo, Japan). [†]Supplied by Suntory, Ltd. (Pharmaceutical Division, Tokyo, Japan).

in social responsiveness (primarily in eye contact and social interactions), communication, and cognitive abilities using the Parental Satisfaction Survey (PASS). Danfors et al.³⁶ demonstrated specific improvement in social interactions using the Childhood Autism Rating Scale (CARS).

Several studies have suggested that specific patient characteristics may be associated with better response to treatment with BH₄. In an open-label study, Naruse et al.³⁰ noted that younger children with ASD (<5 years of age) were more likely than older children with ASD (>10 years of age) to respond to BH₄ treatment. In a double-blind placebo-controlled study, Naruse et al.³² noted that patients under the age of 5 years had a more robust response to BH₄, compared with placebo, than did those over the age of 5 years. In a double-blind placebo-controlled crossover trial, Danfors et al.³⁶ noted that improvement in social interactions on the CARS was positively correlated with the intellectual quotient as measured by the Griffith Developmental Scales.

Although these Japanese studies treated children without knowledge of the CSF BH₄ concentration, the two Swedish studies measured CSF BH₄ concentration. Fernell et al.³⁷ and Danfors et al.³⁶ treated children with CSF BH₄ concentrations of less than 12 and 30 nmol/L, respectively. Danfors et al.³⁶ found a borderline significant correlation ($r^2 = 0.25$, $p = 0.10$) between CSF BH₄ concentration before treatment and improvement in social interactions on the CARS with BH₄ treatment. Although Fernell et al.³⁷ demonstrated that CSF BH₄ concentration increased by an average of 63% with treatment, the study did not correlate initial or final CSF BH₄ concentration with behavioral variables.

Only Fernell et al.³⁷ examined functional CNS changes with treatment. With positron emission tomography, BH₄ treatment was shown to decrease the baseline elevation in D₂ receptor binding found in children with ASD. The authors suggested that BH₄ treatment resulted in a normalization of dopamine metabolism in children with ASD.

Although the clinical trials performed to date suggest some therapeutic effect of BH₄ treatment on autism symptoms, these studies are limited in several respects. First, most of the studies are open-label, leading to potential biases from the nonblinded clinicians and parents. Only two double-blind placebo-controlled studies have been performed, and one of those was limited in sample size. Larger double-blind placebo-controlled studies are needed to assess efficacy. Second, most studies have examined only behavioral markers of ASD. This may be due, in part, to the fact that the mechanism of action of BH₄ in the treatment of ASD is poorly understood. It will be important to understand and measure the biological effects of BH₄ treatment and understand how these effects correlate with autism symptoms. The development

of such biological markers will allow clinical studies to more objectively measure the therapeutic effects of BH₄ and could help improve the understanding of the biological underpinnings of ASD. Lastly, the dose of BH₄ varies across studies, potentially affecting the CNS availability of BH₄ in the various studies. A standard treatment protocol needs to be defined, in order to compare and combine information across trials.

CURRENT TREATMENT OF ASD WITH BH₄

Currently, there are only two protocols available for the treatment of ASD with BH₄. Both protocols provide BH₄ in a single daily dose of 20 mg/kg per day. One of the authors (R.E.F.) is targeting children with both ASD and evidence of pterin deficiency, and the other authors (G.R.E., L.C.H.) are conducting a double-blind placebo-controlled trial examining treatment efficacy.

Open-label treatment in children with ASD and pterin deficiency

Given the importance of BH₄ in critical metabolic pathways and the potential therapeutic role of BH₄ in autism, patients seen in the medically based autism clinic at University of Texas Health Science Center at Houston who were diagnosed with pervasive developmental or autism disorder were screened for abnormally low pterin levels. Screening occurred after exclusion of any medical disorders that might result in neurodevelopmental disabilities, including mitochondrial, metabolic, epileptiform and genetic disorders. The CSF BH₄ levels were examined if available; otherwise, a fasting urine neopterin level was measured.

Patients received BH₄ as sapropterin dihydrochloride (Kuvan; BioMarin, Novato, CA). Eight patients met criteria for treatment, agreed to Kuvan treatment after the benefits and risks were explained, had no contraindications for treatment with Kuvan, and provided informed consent for the examination of their clinical information for research purposes. All patients were treated with 20 mg/kg per day of Kuvan to be taken with a meal once per day. Response to Kuvan was assessed at a clinical follow-up visit that occurred, on average, 3 months after starting Kuvan. The severity, improvement and efficacy subscales of the Clinical Global Impression Scale (CGI) were completed by the treating physician at follow-up. Severity was rated on a seven-point scale ranging from 1, for normal, to 7, for the most severely ill patients. Improvement was rated on a seven-point scale ranging from 1 for very much improved to 7 for very much worse. The efficacy index represented clinical response *versus* adverse events (AEs) and ranges from 0.25 (unchanged or worsening of disease with AEs that outweigh the therapeutic effect) to 4.00 (marked improvement with no AEs).

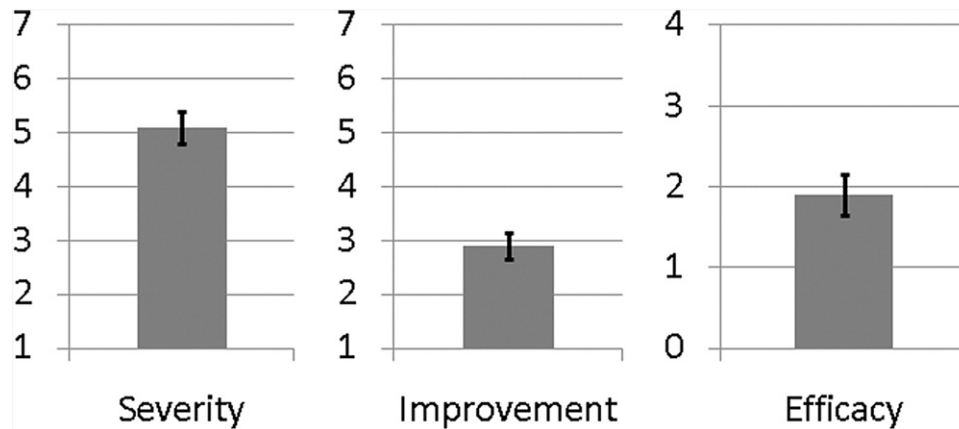


FIG. 2. The average Clinical Global Impression subscale values for eight patients with autism spectrum disorder after 3 months of oral tetrahydrobiopterin therapy at 20 mg/kg per day. On average, patients were minimally improved to much improved and had efficacy index scores representing minimal to moderate improvement with mild to no adverse events. Error bars represent standard error.

At the start of treatment, CGI severity scale scores indicated that the patients were markedly ill. Overall, five of the eight patients (63%) responded positively to Kuvan with improvement in social interactions and either verbal or nonverbal communication. FIG. 2 presents the mean and standard error across all eight patients for the three CGI scales, as measured after Kuvan treatment. At follow-up, on average, the patients were minimally improved to much improved, with efficacy index scores representing minimal to moderate improvement and mild to no AEs.

The parents and teacher of one patient completed several behavioral questionnaires before and after BH₄ supplementation. This patient demonstrated improvements in many cognitive and behavioral areas, including improvements in social awareness, communication, cognition, motivation, and autistic mannerisms on the parent and teacher Social Responsiveness Scale; lethargy and stereotypy on the parent and teacher Aberrant Behavior Checklist; and adaptive skills, depression, somatization, attention, social skills, functional communication, and activities of daily living on the parent and teacher Behavioral Assessment System for Children scale.

Five of the eight patients (63%) demonstrated some AEs. Parents of four of the eight patients (50%) reported mild irritability. Two of these four patients responded positively to Kuvan. In these patients, the irritability was not significant enough to discontinue or decrease the dose of Kuvan. The other two patients with irritability did not respond positively to Kuvan, and the treatment was discontinued in these patients. Notably, at 6 and 8 years of age these latter two patients were older than most of the others. One child demonstrated sleep disturbance. Decrease of the Kuvan dose to 10 mg/kg per day resulted in resolution of the sleep disturbance with continuation of the previously noted positive effects.

Double-blind placebo-controlled trial with open-label extension

At the Children's Health Council in Palo Alto, California, a phase II double-blind, placebo-controlled study randomized control trial (RCT) of sapropterin began in early 2009. Study participants are aged 3 to 6 years old, with a confirmed diagnosis of autistic disorder, and without significant cognitive delay. The primary objective of this study is to evaluate the efficacy of sapropterin (20 mg/kg per day) *versus* placebo to demonstrate measurable improvements on the core symptoms of autism measured by the CGI after 16 weeks of treatment. The secondary objectives of the study are to evaluate the efficacy of sapropterin on changes in core behavioral domains and co-occurring problems such as hyperactivity, attention, and impulsiveness as indicated by direct and observational measures. In addition, the safety of sapropterin at the proposed dose in this population is being assessed, with monitoring of treatment-emergent AEs.

At the end of the 16-week randomized double-blind study, families are offered the choice of entering an open-label protocol. In this protocol, an open-label extension option is provided to subjects who completed that randomized study; those subjects are eligible for commercially formulated sapropterin (Kuvan) at 20 mg/kg per day and they are assessed for efficacy and safety for 16 additional weeks of treatment. As in the RCT, the primary outcome measure is the CGI, collected before, during, and after 16 weeks of treatment. Because one half of the subjects will have been exposed to placebo in the RCT study, exposing all subjects to active drug in the extension study creates the potential to see improvement in children not previously exposed to active treatment. Although this part of the study is open-label, finding improvement primarily in children not previously exposed to sapropterin will add evidence of its

benefits. As of writing, the study is ongoing and participant assignment (treatment *vs* placebo) was still unknown to the investigators, so the effect of treatment could not be assessed.

BH₄: ABILITY TO ENTER THE CENTRAL NERVOUS SYSTEM

Several animal studies have documented the ability of BH₄ to cross the blood–brain barrier into the CNS. Five rhesus monkeys were administered 15–20 mg/kg of a BH₄ diastereoisomer intravenously. The CSF BH₄ concentration increased 20- to 700-fold above baseline within 90 min of administration with peak CSF concentration occurring at 90–180 min after BH₄ administration; the BH₄ concentration gradually returned to baseline over 15 hours.³⁸ Intraperitoneal administration of approximately 24 mg/kg of racemic BH₄ in 12 rats increased CNS BH₄ concentration twofold after 90 minutes.³⁹ Mice administered BH₄ at 100 μmol/kg subcutaneously demonstrated significant increases in CNS BH₄ within 1–2 hours, with a significant increase in CNS BH₄ sustained for up to 8 hours.^{40,41} Oral administration of BH₄ in mice has also been shown to result in an increase in the CNS activity of tyrosine hydroxylase, a BH₄-dependent enzyme.⁴²

Several case studies have examined CSF concentrations of BH₄ or BH₂ with oral administration of BH₄ in humans. CSF BH₄ concentrations increased 16- to 21-fold after six doses of racemic BH₄ given at 10 mg/kg per dose every 12 hours in a 10 year-old boy with hyperphenylalaninemia.⁴³ CSF BH₂ concentration increased following 20 mg/kg of BH₄ in two patients with 6-pyruvoyltetrahydropterin synthase deficiency.^{44,45} Fernell et al.³⁷ demonstrated that CSF BH₄ concentration increased by an average of 63% 24 hours after the last administration of 3 months of oral treatment with 3 mg/kg per day of BH₄ divided into two daily doses. These studies provide evidence that BH₄ readily crosses into the CNS in humans.

SYNTHETIC BH₄

Daiichi Asubio Pharma (now Asubio Pharma in Japan, Asubio Pharmaceuticals in the USA) was the first to study the clinical use of BH₄. Biopten granules 2.5% (sapropterin), a synthetic form of BH₄ developed by Daiichi Asubio Pharma, was approved in Japan to treat BH₄ deficiency in 1992. Kuvan brand sapropterin dihydrochloride is a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (6R-BH₄ or BH₄) manufactured by BioMarin (Novato, CA). Kuvan has the same active ingredient as Biopten (i.e., sapropterin). Kuvan is approved by the U.S. Food and Drug Administration for BH₄-responsive PKU.

Clinical safety of synthetic BH₄

More than a decade of market experience with Biopten in Japan has established that it is generally safe.⁴⁶ Clinical trials conducted by Daiichi Asubio Pharma and BioMarin exposed more than 1100 human participants to sapropterin formulations at various dosages. These studies indicate that sapropterin has a favorable safety profile.⁴⁶ BioMarin has studied sapropterin with a dose ranging from 5 to 20 mg/kg per day. The clinical safety of Kuvan has been evaluated in several BioMarin-sponsored studies. A total of 72 healthy volunteers participated in two phase I pharmacokinetic studies, 579 subjects with PKU were treated with Kuvan in four phase II or phase III studies, and 116 poorly controlled systemic hypertension patients participated in a placebo-controlled phase II study.⁴⁶

An overall analysis of the available safety data indicates that Kuvan is well tolerated and has a favorable safety profile in healthy volunteers, in subjects with PKU, and in subjects with hypertension. No deaths were reported in any of the BioMarin-sponsored studies. Adverse events reported in all studies were generally graded mild; severe AEs were infrequent. Incidence and frequency of AEs had little or no correlation with study drug dose. In placebo-controlled studies, the incidence and frequency of AEs reported for participants treated with placebo were generally comparable to those reported for subjects treated with Kuvan. The most frequently reported (>4%) AEs were headache, diarrhea, abdominal pain, upper respiratory tract infection, pharyngolaryngeal pain, vomiting, and nausea.

In ongoing studies in children with PKU or BH₄ deficiency, one serious adverse event, gastroesophageal reflux, was assessed by an investigator as drug-related. The participant was concomitantly taking ibuprofen, a medication known for its association with gastrointestinal disorders, and ibuprofen was reported as a second suspect medication. The physicochemical properties of 6R-BH₄ include low pH and high solubility; combined, these properties could potentially increase the likelihood of developing gastrointestinal disorders, especially with the concurrent use of ibuprofen. After the event, Kuvan was reintroduced without further gastrointestinal symptoms.

In a 10-year post-marketing safety surveillance program of sapropterin, three patients with underlying neurologic disorders experienced convulsions, exacerbation of convulsions, overstimulation, or irritability during co-administration of L-dopa and sapropterin.

Forty-three nonclinical toxicology studies have been conducted for sapropterin.⁴⁶ Most of these studies were conducted in mice, rats, dogs, and marmosets at doses ranging from 20 to 4000 mg/kg using intravenous and oral administration routes. In a 52-week marmoset toxicology study, the 'no observable adverse event' level was 320 mg/kg per day. The only observed AEs were

salivation and vomiting, both possibly caused by the low pH of the dosing solution; no laboratory or histopathologic abnormalities were found. In a similar 52-week rat toxicology study, the no observable AE level was 40 mg/kg per day; animals treated with 400 mg/kg per day for 52 weeks demonstrated a low incidence of mild basophilic infiltrates in the renal collecting tubules; this was not associated with changes in clinical chemistry or urinalysis results. No renal tubular changes were found in a subsequent rat carcinogenicity study, in which rats were exposed to doses up to 250 mg/kg per day of sapropterin for 104 weeks. The safety of Kuvan is supported by these data and by other nonclinical pharmacology, pharmacokinetic, and toxicology studies.

Clinical safety of synthetic BH₄ safety in autism

Daiichi Asubio Pharma conducted seven studies in which 451 patients with autism were treated for 5–105 weeks with sapropterin at doses of 1–5 mg/kg per day. Of the 451 patients treated, 97 (21.5%) experienced 149 AEs for which a causal relationship with study drug could not be excluded. The most frequently reported AEs were behavioral (sleep disorders, excitement, hyperkinesias), urinary symptoms (increased frequency, enuresis, polyuria), and loose stools. There were no significant differences in the incidence of AEs between patients treated with sapropterin in all seven studies and the 115 patients treated with placebo in the two placebo-treated studies. No deaths were reported.

Four participants developed AEs severe enough to discontinue sapropterin. These AEs included hyperkinesias, panic, and tics; transient mild syncope attacks were noted in one patient with a prior history of epilepsy. For some patients, symptoms persisted for several weeks after discontinuation of sapropterin, but AEs eventually resolved in all participants. Adverse events were also reported in the Swedish clinical trials. Fernell et al.³⁷ reported sleep disruption and increased anger and aggression in three of the six patients studied, but these symptoms were not severe enough to discontinue treatment with BH₄. In the study by Danfors et al.,³⁶ 10 of the 12 patients developed sleep disruption or increased aggression or both, but these AEs were just as frequent during the treatment and placebo arm of the trial. As already noted, AEs of sleep disruption and aggression were also observed in the recent series of children treated with Kuvan at University of Texas Health Science Center at Houston, but did not necessitate discontinuation of Kuvan in the children who gained benefit from the treatment.

POTENTIAL FOR BH₄ AS A NOVEL THERAPY IN AUTISM

Clinical studies provide both direct and indirect evidence that the concentration of CNS BH₄ is depressed in

children with ASD. Clinical trials suggest that treatment with BH₄ results in improvement in autism symptomatology in some children with ASD. These clinical studies are mostly open-label, however, and use potentially subjective behavioral dependent measures. Two double-blind studies have been completed, but with a limited number of participants. Further double-blind placebo-controlled studies will be needed to document further the efficacy of BH₄ treatment in children with ASD. One such clinical trial currently underway should shortly provide additional information regarding the efficacy of BH₄ treatment in children with ASD.

A particularly important positive characteristic of BH₄ is the safety profile. BH₄ has a low incidence of serious AEs and appears generally safe. In clinical trials, it has been well tolerated, and very few patients who benefit from BH₄ treatment have discontinued treatment because of AEs. It is not known whether AEs are dose dependent. The treatment dose has varied widely throughout clinical studies. Further investigations may provide better insight into the optimal therapeutic dose that maximizes development and minimizes the incidence of AEs.

The importance of BH₄ in ASD and other neurodevelopmental disorders should not be understated. Low CNS BH₄ levels can result in devastating neurodevelopmental consequences. First, BH₄ is necessary for the production of nitric oxide, a soluble molecule that is important for signaling cell proliferation, neuronal motility, and synaptic maturation during development⁴⁷ and for communication between neurons and both neuronal and non-neuronal cells.⁴⁸ Second, BH₄ has been associated with growth factors, including nerve growth factors, in animal models.⁴⁹ Third, BH₄ has been shown to be a superoxide radical scavenger.^{15,16} Fourth, reduced levels of monoamine neurotransmitters could result in dysfunction of important neural pathways, leading to underdevelopment of such important pathways. Fifth, BH₄ is an enhancer of the synaptic release of a wide range of neurotransmitters, including the catecholamines serotonin, acetylcholine, glutamate, and GABA.^{50,51} Thus, BH₄ is involved in several metabolic and neurotransmitter pathways critical for CNS function and development. Low BH₄ levels during development could have devastating consequences to the CNS, leading to or potentiating the neuropathology underlying ASD. The central role of BH₄ in a wide variety of CNS and non-CNS metabolic pathways that are known to be dysfunctional in ASD makes BH₄ a potentially important factor in ASD, and one that may have a therapeutic role.

Disclosures

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