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Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Kuvan (sapropterin dihydrochloride) in pediatric patients. This review was triggered by the expanded pediatric indication to include patients 1 month to 4 years of age.

Sapropterin 100 mg tablets, NDA 022181, was first approved on December 13, 2007 to reduce blood phenylalanine (Phe) levels in patients 4 years of age and older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU) in conjunction with a Phe-restricted diet. On April 23, 2014, sapropterin was approved for use in patients 1 month to 4 years of age to reduce blood Phe levels with HPA due to BH4-responsive PKU.



For the purpose of this review, we searched the FAERS database for all reports of adverse events with sapropterin received from January 1, 2013 through July 31, 2016. The review of the FAERS pediatric reports resulted in the identification of 47 pediatric cases of serious, unlabeled events, including 4 death cases. Overall, the majority of the cases had other plausible explanations to account for the adverse events (such as PKU, history of seizures, infection). Several cases lacked clinical information for proper assessment. There were three non-fatal cases of unlabeled events (epistaxis and insomnia) that we could not exclude the role of sapropterin. However, epistaxis and insomnia are common background events in children. Therefore, it is difficult to attribute the events of epistaxis or insomnia solely to sapropterin.

The pediatric safety profile described in the majority of the FAERS cases is consistent with the known safety profile and the current sapropterin label. We did not identify any new safety concerns that warrant labeling update at this time. DPV-I plans to continue postmarketing surveillance of all adverse events with the use of sapropterin in pediatric patients.

1 INTRODUCTION

This review evaluates postmarketing adverse event reports with a serious outcome and drug utilization data for Kuvan (sapropterin dihydrochloride). This review was triggered by the expanded pediatric indication to reduce blood phenylalanine (Phe) levels in patients 1 month to 4 years of age with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU).

1.1 PEDIATRIC REGULATORY HISTORY

Sapropterin 100 mg tablets, NDA 022181, was first approved on December 13, 2007 to reduce blood Phe levels in patients 4 years of age and older with HPA due to BH4-responsive PKU in conjunction with a Phe-restricted diet. On December 19, 2013, sapropterin 100 mg powder for oral solution, NDA 205065, was approved with the same indication. On April 23, 2014, sapropterin was approved for use in patients 1 month to 4 years of age to reduce blood Phe levels with HPA due to BH4-responsive PKU. This latter supplemental indication is the basis for this review and the clinical studies leading to its approval is summarized below.

Clinical Studies

The following regulatory history was summarized from Dr. Carla Epp's (medical officer in the Division of Gastroenterology and Inborn Errors Products (DGIEP)) clinical review of the pediatric supplement to extend the indication to patients 1 month to 4 years of age for sapropterin.[1]

> On September 10, 2013, the sponsor submitted Efficacy Supplement 13 to NDA 022181for sapropterin tablets to support an expanded pediatric indication to reduce blood Phe levels in patients 1 month to 4 years of age with HPA due to BH4-responsive PKU. The supplement included the results of a population pharmacokinetic (PK) study (Sub-study 2) and a 6-month safety and efficacy trial (Sub-study 1) conducted as part of an ongoing 7-year study (PKU-015) to evaluate the safety of sapropterin on neurocognitive functioning in pediatric 6 years of age or younger. The studies were conducted to fulfill a postmarketing commitment and in response to a Pediatric Written Request (PWR) issued on October 31, 2011.
>
> Sub-study 1 was a 6-month, open-label, one-arm trial to evaluate safety, efficacy, and baseline neurocognitive function in patients with PKU ages 0 to 6 years. The PWR stipulated that a minimum of 60 BH4-responsive patients must be enrolled for the 6-month safety and efficacy study; however, only 57 patients met the protocol definition of a Phe responder. The efficacy data for PKU-015 Sub-study1 indicated that there was a

reduction in blood Phe levels following treatment with sapropterin for 4 weeks in pediatric patients ages 0-6 years who were maintained on a stable Phe diet. There was insufficient data to support long-term efficacy because the trial did not control for dietary Phe intake for the remainder of the 6-month treatment period. The observed safety profile of sapropterin in the trial data and postmarketing data provided by the applicant was consistent with the labeling for sapropterin. Sapropterin labeling includes a precaution to monitor blood Phe levels during treatment to prevent prolonged elevations in blood Phe levels or prolonged levels of blood Phe that are too low. Sixteen patients in Sub-study 1 experienced blood Phe levels below the age-based reference range; the majority of these events occurred during the first four weeks of treatment.

Sub-study 2 was a 4-week open-label PK study in patients 6 years of age and younger. Participants received sapropterin 20 mg/kg/day as a single dose for 4 weeks. Of the 94 enrolled patients, 93 patients completed the sub-study; 80 patients were included in the population PK analysis. Fifty-seven patients who met the protocol criterion for sapropterin responder were enrolled in the 6-month safety and efficacy sub-study. The data from the PK sub-study supports the short term (4 week) efficacy of sapropterin in BH4-responsive patients age 0 to 6 years. The exposure-response relationship supported the increased efficacy of the 20 mg/kg dose. Safety concerns about a higher incidence of hypophenylalaninemia were noted in patients dosed with 20 mg/kg (also seen in clinical trial PKU-008), especially in the younger age groups, led to the decision to recommend the 10 mg/kg starting dose for children less than 7-years-old and a starting dose range of 10-20 mg/kg for patients older than 7 years of age.

1.2 SUMMARY OF RELEVANT PREVIOUS FDA SAFETY REVIEWS

On August 13, 2010, the Division of Pharmacovigilance (DPV) performed a FDAAA Section 915 New Molecular Entity Safety Summary Analysis in patients treated with sapropterin. At the time of the analysis, sapropterin had been used by < 10,000 patients. A search of the Adverse Event Reporting System database from the initiation of marketing (December 13, 2007) to August 13, 2010 yielded 267 reports. No unlabeled or unexpected serious adverse events were identified.[2]

As discussed in section 1.1 above, DGIEP conducted a clinical review of Efficacy Supplement 13 for NDA 022181. In the Efficacy Supplement, the sponsor submitted an assessment of all adverse events reported from December 2007 to December 2012. The clinical reviewer also conducted an independent review of the reports (for which clinical data were available) of serious adverse events (SAEs). It was determined by the clinical reviewer that most cases were unrelated to treatment with sapropterin or represented events already identified in the sapropterin labeling.[1]

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES[3]

----------**WARNINGS AND PRECAUTIONS**----------

- Hypersensitivity reactions including anaphylaxis have occurred (5.1).
- Gastritis was reported in clinical trials. Monitor patients for signs of gastritis (5.2).
- Children younger than 7 years treated with Kuvan doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years of age and older (5.3).
- Monitor blood Phe levels during treatment to ensure adequate blood Phe control (5.4).
- Identify non-responders to Kuvan treatment: not all patients with PKU respond to treatment with Kuvan (5.5).
- Treat all patients with a Phe-restricted diet: the initiation of Kuvan therapy does not eliminate the need for ongoing dietary management (5.6).
- Monitor liver function tests in patients with liver impairment who are receiving Kuvan (5.7).
- Monitor patients when co-administering Kuvan with medications known to inhibit folate metabolism, or with levodopa. Monitor patients for hypotension when co-administering Kuvan with medications known to affect nitric oxide-mediated vasorelaxation (5.8, 5.9, 5.10).
- There have been postmarketing reports of hyperactivity with administration of Kuvan. Monitor patients for hyperactivity (5.11).

----------**ADVERSE REACTIONS**----------

- The most common adverse reactions (incidence $\geq$ 4 %) in patients treated with Kuvan are headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion (6.1).

----------**USE IN SPECIFIC POPULATIONS**----------

- The efficacy and safety of Kuvan have not been established in neonates. The safety of Kuvan has been established in children younger than 4 years in trials of 6 months duration and in children 4 years and older in trials of up to 3 years in length. In children aged 1 month and older, the efficacy of Kuvan has been demonstrated in trials of 6 weeks or less in duration.

(b) (4)

(b) (4)

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

[a] IMS Health, IMS National Sales Perspectives™. APR2014 -JULY 2016. Extracted SEPT 2016. NSP 2016-1672 Kuvan channels 9-30-16.xls

[b] DARRTS:SDN 592; Accessed OCT 2016; link: \\CDSESUB1\evsprod\NDA022181\022181.enx

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy	
Date of Search	August 15, 2016
Time Period of Search	January 1, 2013[*] - July 31, 2016
Search Type	Quick Query
Product Name	Active Ingredient: Sapropterin dihydrochloride
Search Parameters	All ages, all outcomes, worldwide

[*] DGIEP reviewed postmarketing adverse events from December 2007 – December 2012 as part of the approval of Efficacy Supplement 13.

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports* from January 1, 2013 to July 31, 2016 with sapropterin

	All reports (US)	**Serious[†] (US)**	**Death (US)**
Adults (≥ 17 years)	467 (450)	99 (82)	6 (4)
Pediatrics (0 - <17 years)	549 (526)	**100[‡] (76)**	**6[§]** (6)

***** May include duplicates and transplacental exposures, and have not been assessed for causality

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

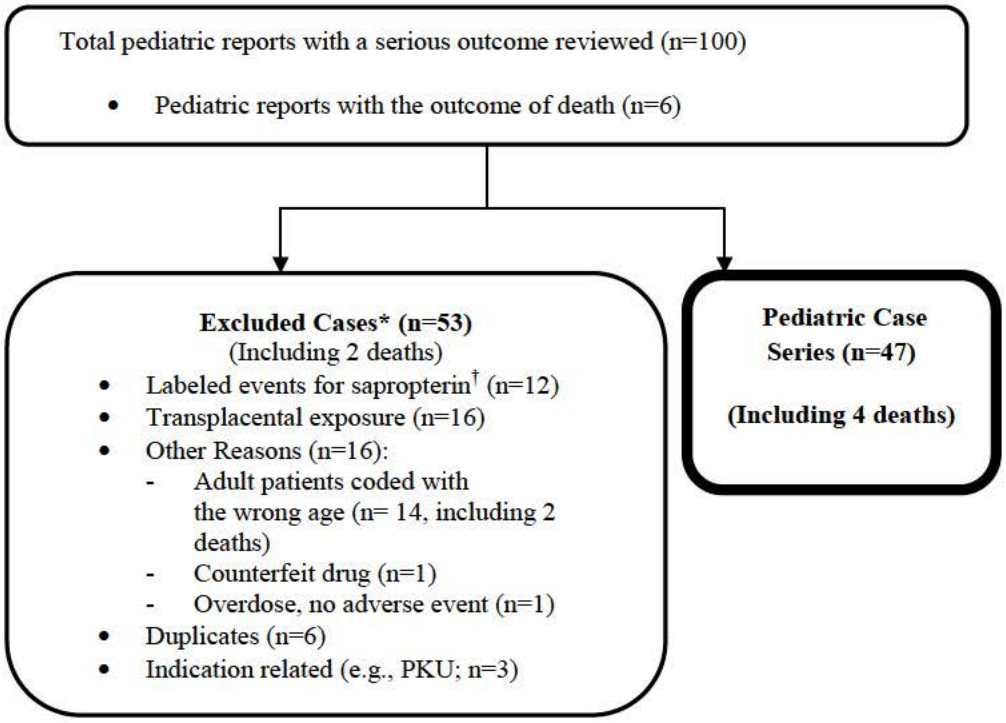
‡ See Figure 3.2.2. Fourteen of the 100 reports were adult patients and coded with the wrong age.

§ Two of the six death cases were adult patients and coded with the wrong age.

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 100 pediatric reports with a serious outcome for sapropterin from January 1, 2013 to July 31, 2016; however, 14 reports involved adults and were coded with the wrong age. See **Figure 3.2.2** below for the specific selection of serious pediatric cases with sapropterin in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Sapropterin



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above
† The labeled events/PTs[c] were: abdominal pain (n=4), rash (n=3), headache/migraine (n=2), pharyngitis (n=2), dizziness (n=2), gastrointestinal bleed (n=2), vomiting (n=2), cough (n=1), diarrhea (n=1), gastritis (n=1), nausea (n=1), dyspnea (n=1), hypersensitivity (n=1), peripheral edema (n=1). They did not appear to occur at an increased frequency or severity.

3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control Numbers for the Pediatric Case Series.

Table 3.2.3 Characteristics of FAERS Pediatric Reports of Unlabeled Events that had a Serious Outcome with Sapropterin (N=47)

Age (n=46*)	0 - < 1 month	1
	1 month - <2 years	6
	2- < 6 years	13
	6- <12 years	19
	12- < 17 years	7
Sex	Male	25
	Female	21
	Unknown	1

[c] Events are not mutually exclusive

Table 3.2.3 Characteristics of FAERS Pediatric Reports of Unlabeled Events that had a Serious Outcome with Sapropterin (N=47)		
Country	United States	35
	Foreign	12
Reported Reason for Use	Phenylketonuria	38
	Atypical phenylketonuria	3
	Tetrahydrobiopterin deficiency	2
	Unknown	4
Serious Outcome[†]	Death	4
	Life-threatening	0
	Hospitalized	17
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	31

[*] One pediatric case reported that the patient was an "infant" but did not report an age.

[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=4)

A total of four cases reported an outcome of death. The mean reported age[d] was 3 years and ranged from 10 months to 7 years (N=3). Two of the four death cases contained limited information and did not report a cause of death. In the third death case, it was reported that a 7-year-old male with a history of PKU and seizures passed away in the middle of the night after a seizure. It was also reported that the patient had profound motor and cognitive disease, multi-system disease, and a questionable diagnosis of tetrahydrobiopterin deficiency. The patient had been on sapropterin for 3 years at the time of death. The seizure and death was most likely attributable to the patient's underlying condition. The remaining death case that involved a sapropterin overdose in the setting of off-label use is described below.

Case 11914936, 2016, USA: A 15-month-old female with a history of PKU experienced "apneic events" minutes after receiving a dose of sapropterin. The patient started treatment with sapropterin 600 mg orally once daily (65 mg/kg/day; weight 9.3 kg) approximately one month prior to the events. Concomitant medications included baclofen, gabapentin, glycopyrronium bromide, levodopa/carbidopa, lansoprazole, and vitamins. The event was reported as severe and

[d] One pediatric death case reported that the patient was an "infant" but did not report an exact age.

the patient's parents decided on a 'do not resuscitate' (DNR) status. The patient expired two days after the events. The reporter assessed the event of apnea as likely related to underlying cerebral leukodystrophy and not to treatment with sapropterin.

Reviewer comment: Sapropterin was used off-label. The patient likely has atypical PKU/biopterin deficiency because she was on levodopa/carbidopa, which is commonly prescribed in these types of disorders.[4] The patient was also receiving more than the recommended amount of sapropterin (65 mg/kg/day); the recommended starting dose for patients 1 month to 6 years is 10 mg/kg/day. The dose can be increased to 20 mg/kg/day in non-responders after one month. Although the patient experienced "apneic events" minutes after receiving a dose of sapropterin, she had been on the drug for one month prior to the events. It is likely the apneic events were attributable to underlying diseases. Other possible causes include concomitant drug therapy[e,f] and an overdose of sapropterin in the setting of off-label use.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS UNLABELED ADVERSE EVENT CASES (N=43)

We reviewed 43 reports that described serious non-fatal unlabeled events. Of the 43 reports, 26 had alternative plausible explanations for the events (such as PKU, history of seizures, infection). Twelve cases lacked clinical information for proper assessment and two lacked a temporal relationship. The remaining three cases that we cannot exclude the role of sapropterin are described below.

***Epistaxis* (n=2)**

There were two cases of the unlabeled event of epistaxis identified.

Case 9799371, US, 2014: A 2-year-old female initiated sapropterin 100 mg orally daily for PKU. The patient had a history of convulsions, which started weeks before starting sapropterin treatment. The patient had no prior history of nose bleeds. The patient was not taking concomitant medication. It was reported that the patient experienced seizures and epistaxis on a daily basis since starting sapropterin. At the time of the report, the events of epistaxis and seizures were ongoing. The patient experienced her latest nose bleed five days after starting sapropterin and experienced her latest seizure six days after starting sapropterin. No treatment was provided for the event. No other information was provided.

Reviewer's comment: The patient's adverse events were temporally associated with initiation of sapropterin. The patient had a history of seizures prior to sapropterin treatment, but no prior

[e] Gabapentin is labeled for apnea in the Adverse Reactions – Other Adverse Events Observed During All Clinical Trials.

[f] Baclofen is labeled for dyspnea and respiratory depression in the W/P section and apnea in the Adverse Reactions – Clinical Studies section.

history of nosebleeds. Although epistaxis has been reported to occur rarely during seizures[5]*, we cannot exclude the role of sapropterin in the development of epistaxis in this patient.*

Case 10727802, US, 2015: A 9-year-old male initiated sapropterin 500 mg orally daily (20 mg/kg) for PKU. The patient experienced heavy nose bleeds and some blood clots from his left nostril approximately 1 year after starting sapropterin. It was reported that the patient had been experiencing this event at least once a week. No other clinical details were reported.

***Insomnia* (n=1)**

There was one case of the unlabeled event of insomnia identified.

Case 12642535, US, 2016: A 13-year-old male initiated treatment with sapropterin for an unknown indication. The patient developed insomnia, agitation, and psychomotor hyperactivity. Treatment with sapropterin was held due to the event and dechallenge was reported as positive. The event was reported as resolved on an unspecified date.

Reviewer's comment: Hyperactivity and agitation are labeled events. Although the case lacked detailed clinical information and patients with PKU often have behavioral problems, hyperactivity, and anxiety,[1] *we cannot exclude the role of sapropterin because of a positive dechallenge.*

3.4.1 Off-label Use (n=5)

Sapropterin is approved in other countries for non-PKU indications. Adverse events reported with sapropterin in the setting of off-label use are of interest to DGIEP. In four of the 43 non-fatal reports, sapropterin was used for atypical PKU (n=2) and tetrahydrobiopterin deficiency (n=2). The adverse events in these cases were gastroenteritis (n=1), pyrexia (n=1), acute pancreatitis (n=1), and seizure (n=1); they were either labeled events or related to the patient's underlying condition. The remaining off-label use case was described in section 3.3.

4 DISCUSSION

(b) (4)

The review of the FAERS pediatric cases resulted in the identification of 47 pediatric cases of serious, unlabeled events, including 4 death cases. The majority of the cases had other plausible explanations to account for the adverse events (such as PKU, history of seizures, infection). Several cases lacked clinical information for proper assessment. There were three non-fatal cases of unlabeled events of epistaxis and insomnia that we could not exclude the role of

sapropterin. To identify the total number of reports of epistaxis and insomnia with sapropterin, we performed an additional FAERS search beyond our search time period specified in table 3.1.1. The FAERS search identified one additional case of epistaxis with a serious outcome (see Appendix D). Overall, there were a small number of FAERS cases with a serious outcome, a lack of rechallenge information to strengthen the association, and the patient's underlying disease confounded many of the cases. Epistaxis and insomnia are common background events in children.[6,7] These adverse events are commonly reported in pediatric clinical trials in both active drug and placebo groups. In addition, we are not aware of any pharmacological mechanisms of sapropterin that would suggest that epistaxis or insomnia is related to sapropterin. Therefore, it is difficult to attribute the events of epistaxis or insomnia solely to sapropterin.

Of note, product labeling for sapropterin in Canada includes epistaxis and insomnia in the Adverse Reaction – Less Common Clinical Trial Adverse Events (< 2 %) section.[8]

5 CONCLUSION

The Office of Surveillance and Epidemiology analyzed: (b) (4) and (2) the pediatric postmarketing adverse event reports for sapropterin products received in FAERS from January 1, 2013 to July 31, 2016. The pediatric safety profile described in the majority of reports is consistent with the known safety profile and the current sapropterin label. We did not identify any new safety concerns that warrant labeling update at this time.

6 RECOMMENDATIONS

DPV-I plans to continue postmarketing surveillance of all adverse events with the use of sapropterin in pediatric patients.

7 APPENDICES

(b) (4)



7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=47)

FAERS Case Number	Version Number	Manufacturer Control Number	FAERS Case Number	Version Number	Manufacturer Control Number
11914936	1	US-BIOMARINAP-US-2016-108589	10678580	1	US-BIOMARINAP-US-2014-105074
11138142	1	US-BIOMARINAP-US-2015-106446	11656304	5	US-BIOMARINAP-US-2015-107803
10144379	2	JP-BIOMARINAP-JP-2014-103078	9772721	2	US-BIOMARINAP-US-2013-100603
11310322	1	IT-BIOMARINAP-IT-2015-106922	10508167	2	TR-BIOMARINAP-TR-2014-104298
12568330	1	US-BIOMARINAP-US-2016-110352	11740991	1	US-BIOMARINAP-US-2015-107819
9458544	2	US-BIOMARINAP-US-2013-101256	9123504	1	US-BIOMARINAP-US-2013-100373
11744761	1	US-BIOMARINAP-US-2015-108088	10253768	6	US-BIOMARINAP-US-2014-103471
12574501	1	US-BIOMARINAP-US-2016-110489	9714934	1	IT-BIOMARINAP-IT-2013-101952
12279915	1	US-BIOMARINAP-US-2016-109530	9161530	2	FR-BIOMARINAP-FR-2013-100440
11660541	4	US-BIOMARINAP-US-2015-107749	12193044	2	US-BIOMARINAP-US-2016-109252
10725133	2	US-BIOMARINAP-US-2015-105266	9799371	1	US-BIOMARINAP-US-2013-102169
11281479	1	US-BIOMARINAP-US-2015-106853	11310544	1	IT-BIOMARINAP-IT-2015-106924
11807993	2	TR-BIOMARINAP-TR-2015-108292	11050100	1	US-BIOMARINAP-US-2015-106110

FAERS Case Number	Version Number	Manufacturer Control Number	FAERS Case Number	Version Number	Manufacturer Control Number
10949838	2	US-BIOMARINAP-US-2015-105841	9732651	1	US-BIOMARINAP-US-2013-101964
9987957	3	CA-BIOMARINAP-CA-2014-102696	10727802	1	US-BIOMARINAP-US-2015-105275
12224029	1	US-BIOMARINAP-US-2016-109346	10608203	1	US-BIOMARINAP-US-2014-104775
10542223	2	US-BIOMARINAP-US-2014-104389	9017596	1	CA-BIOMARINP-002928
10737549	1	US-BIOMARINAP-US-2015-105281	12642535	1	US-BIOMARINAP-US-2016-110686
10608183	1	US-BIOMARINAP-US-2014-104745	10608202	2	US-BIOMARINAP-US-2014-104728
9912100	2	US-BIOMARINAP-US-2014-102529	10192572	1	US-BIOMARINAP-US-2014-103262
10170532	1	US-BIOMARINAP-US-2014-103182	9287103	1	US-BIOMARINAP-US-2013-100771
9926147	1	US-BIOMARINAP-US-2014-102605	10369394	2	CA-BIOMARINAP-CA-2014-103800
9064362	1	US-BIOMARINAP-US-2013-100232	11917352	1	CA-BIOMARINAP-CA-2016-108622
9349848	1	JP-BIOMARINAP-JP-2013-100901			

7.4 Appendix D. Line Listing of Additional Epistaxis (N=4) and Insomnia (N=11) FAERS Cases

To identify the total number of reports of epistaxis and insomnia with sapropterin, we performed an additional FAERS search beyond our initial search time period (Section 3). We searched for reports of epistaxis or insomnia in all patients with a serious and non-serious outcome for the time period of December 13, 2007 (U.S. approval date) to our initial search start date (January 1, 2013).

FAERS Case #	Country	Outcome	Summary of Case Narrative
12297312	USA	Non-serious	A 13-year-old male with a history of PKU and new onset aggressive behavior. Concomitant medications included risperidone and imipramine. The patient started Kuvan 800 mg orally daily (23 mg/kg). One year later, the patient developed recurring **nose bleeds**. It was reported that the patient was also vomiting every morning at school. No laboratory or diagnostic tests were reported. The outcome of the event was reported as not resolved. No other information was provided.
7213576	USA	Non-serious	A 4-year-old female started Kuvan 300 mg orally daily (16 mg/kg) for PKU. It was reported that within the past 18 months, the patient experienced **nose bleeds** once every two months. One **nose bleed** was related to trauma.
10635493	USA	Non-serious	A 4-year-old female started on Kuvan 20 mg/kg/day for PKU. The patient was not receiving concomitant medication at the time of the event. One day after initiating Kuvan, the patient experienced moderate **nose bleeds**. The patient's parent described the **nose bleeds** as "dripping down the patient's face, occurring several times during the day for the duration of three days". It was reported that the patient never had **nose bleeds** before and was otherwise not sick. No action was taken with Kuvan due to the event. The outcome of the event was reported as resolved three days later.
8273100	France	Hospitalization	A 16-year-old female with a past medical history of nightmares, day sleeping, dystonic crisis, and GTP hydrolase deficiency started Kuvan 100 mg orally daily (2.2 mg/kg). Concomitant medications included levodopa/carbidopa and oxitriptan. Concurrent conditions included viral rhinitis. Three months after starting Kuvan, the patient presented to the hospital with hematemesis. Gastrointestinal investigation and coagulation was normal. **Epistaxis** was the final diagnosis. Kuvan treatment

FAERS Case #	Country	Outcome	Summary of Case Narrative
			continued. The patient recovered from the events four days later.
11816341	USA	Non-serious	A 2-year-old male started Kuvan for an unknown indication. On an unspecified date, reported as since starting Kuvan, the patient **had not slept through the night**. The reporter stated that, before starting Kuvan, the patient would wake up once or twice a night every once in a while but otherwise slept throughout the night. He now gets up every two hours. The patient reportedly had more energy now and "letting him run it all out does not help." The mother tried skipping the patient's afternoon nap but that did not help. No laboratory or diagnostic tests were reported. The outcome of the event was reported as not resolved. No other information was provided.
7172947	USA	Non-serious	A 2-year-old male started on Kuvan 14 mg/day for PKU. While on Kuvan the patient experienced poor appetite, **poor sleeping patterns**, teeth grinding, and cough. Kuvan was discontinued one week after initiation. The events resolved after Kuvan was discontinued.
10635481	USA	Non-serious	A 4-year-old female with a history of PKU started on Kuvan 700 mg orally daily (20 mg/kg). Concomitant medication included "Periflex Junior". Two weeks after starting Kuvan, the patient experienced a **sleep disorder**, began to exhibit increasingly naughty behaviors, and had increased energy. The patient also experienced psychomotor activity and four previous episodes of nocturia. It was reported that the patient had poor public behavior. On an unspecified date, phenylalanine levels were drawn which showed no improvement and actually rose (levels not provided). Kuvan was discontinued due to the event. Approximately 2 ½ weeks after discontinuing Kuvan, the grandmother reported that the patient returned to pre-trial baseline with regard to behavior and energy. The reporter assessed the event of **sleep disorder** as related to treatment with Kuvan.
7383601	USA	Non-serious	A 6-year-old female with PKU started on Kuvan for PKU. Approximately 2 weeks after starting Kuvan, the patient was **staying up later and not going to sleep** and was over stimulated easily. The patient would go to school and was busy all day. It was reported that the patient should have been tired but wasn't. No concomitant medications were taken. Kuvan was discontinued and the events

FAERS Case #	Country	Outcome	Summary of Case Narrative
			resolved 2 days later.
7837541	USA	Non-serious	An 8-year-old male with PKU started on Kuvan 500 mg orally daily (22 mg/kg). The patient also had a history of attention-deficit/hyperactivity disorder (ADHD) and behavioral problems. Approximately 1-2 weeks prior to starting Kuvan, amphetamine and dextroamphetamine were discontinued. The same month as starting Kuvan, the patient experienced increased hyperactivity, back, arm and leg pain, and **inability to sleep**. Kuvan therapy continued and all events remained ongoing.
10635557	USA	Non-serious	An 8-year-old male with PKU started on Kuvan 20 mg/kg orally daily. One day after starting Kuvan, the patient experienced moderate increased hyperactivity, which included **trouble sleeping**, behavior issues at school, loose stools, and gagging/vomiting. According to the patient's mother, these events started approximately 24 hours after initial administration with Kuvan and lasted for approximately 5 days. The mother reported difficulty in giving Kuvan to the patient, both in his formula and juice. Kuvan was discontinued 5 days later due to the event. The outcome of the event was reported as resolved. The mother reported that the patient experienced constipation and did not have a bowel movement until 2-3 days after stopping Kuvan.
10635475	USA	Non-serious	A 9-year-old male patient with anxiety and PKU started on Kuvan 1000 mg orally daily (19 mg/kg). After starting Kuvan, the patient experienced bed wetting, significant anxiety, **sleep disturbance**, sadness, vomiting, diarrhea, **poor sleep qu**ality, and hyperventilation. All of these symptoms coincided with the patient's start at a new school. Treatment included venlafaxine and melatonin. The patient's phenylalanine levels were between 0.9 mg/dL and 4.5 mg/dL since starting Kuvan. The reporter noted that none of the patient's phenylalanine levels were above the target range. Three months after starting Kuvan, the patient no longer experienced vomiting and all other symptoms were reported to be a little better. The family declined any change in Kuvan treatment.
6970997	USA	Non-serious	A 10-year-old male started on Kuvan 1200 mg orally daily (20 mg/kg) for PKU. Within days of starting Kuvan, the patient had **trouble sleeping** and became worse as treatment with Kuvan

FAERS Case #	Country	Outcome	Summary of Case Narrative
			continued. Within 2-3 weeks of taking Kuvan, it was reported that the sleeping problem was "serious". Initially, the patient would have **trouble falling asleep, would wake up 2-3 times in the middle of the night, and was unable to fall back asleep**. The patient's mother would wake up and find him starring at the wall. Since receiving treatment with melatonin there were no further complaints about not being able to sleep. Treatment with Kuvan was continued. The **insomnia** resolved 4 months after starting Kuvan.
12462024	USA	Non-serious	A 41-year-old female started on Kuvan for PKU. On an unknown date, the patient experienced **insomnia**, anxiety, heart racing, and a lot of energy. Four days after taking Kuvan, the events began to resolve.
7319262	USA	Non-serious	A 37-year-old female started on Kuvan for PKU. A few weeks after starting Kuvan, the patient was "extremely moody" and had **insomnia**. No other information was provided.
7840633	USA	Non-serious	A 30-year-old female started Kuvan 20 mg/kg for PKU. Past medical history included supraventricular tachycardia, irritable bowel syndrome, reflux, and "low blood sugar feeling". Concomitant medications included unspecified contraceptives and multivitamins. One week after starting Kuvan, the patient experienced an increase in frequency of "a low blood sugar feeling", which included feeling weak, cold, sweaty, and "just strange". Phenylalanine level was 0.6 (unknown units). Eating would improve the symptoms for approximately 15 to 20 minutes. Eleven days after starting Kuvan, the patient had **trouble sleep**ing, finding it hard to focus, and was feeling hungry all the time. Phenylalanine level was 1.4 (unknown units). The Kuvan dose was decreased to 10 mg/kg to give the patient relief from her symptoms. The following day, the patient began to feel better and two days later she reported feeling back to normal. Phenylalanine level was 2.2 (unknown units).

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