Pediatric-Focused Safety Review:
Kuvan (sapropterin dihydrochloride)
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Outline

- Background Information
- Relevant Safety Labeling
- Pediatric Studies
- Pediatric Labeling Changes
- Adverse Events
- Summary

Background Information: Kuvan (sapropterin diHCL)

- **Drug:** Kuvan (sapropterin diHCL)
- **Drug Class:** Phenylalanine hydroxylase activator (PAH)
- **Indication:** To reduce blood Phe levels in conjunction with a Phe-restricted diet in patients with HPA due to BH4-responsive PKU
- **Initial Dose:** Age 1 month - 6 years: 10mg/kg once daily
  Age ≥ 7 years: 10-20 mg/kg once daily
- **Formulation:** Oral tablet (100 mg)
  Powder for oral solution (100 mg, 500 mg)
- **Sponsor:** BioMarin Pharmaceutical

Phe: phenylalanine
BH4: tetrahydrobiopterin
HPA: hyperphenylalaninemia
PKU: Phenylketonuria
diHCL: dihydrochloride

Background Information: Kuvan (sapropterin diHCl)

U.S. Approval History

NDA #	Formulation	Approval	Indication
022181	Sapropterin 100 mg tablet	12/13/2007	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.
205065	Sapropterin powder (100 mg and 500 mg unit dose packets) for oral solution	12/19/2013	"Same indication as above"
022181 s13	Sapropterin 100 mg tablet	04/23/2014*	To reduce blood Phe levels in patients 1 month – 4 years of age with HPA due to BH4- PKU in conjunction with a Phe-restricted diet

* Initiator for the current review and presentation

Relevant Safety Labeling: Kuvan (sapropterin diHCl)

Section 5 Warnings and Precautions

5.1 Hypersensitivity Reactions including anaphylaxis

5.2 Gastritis

5.3 Hypophenylalaninemia

5.4 Monitor blood phenylalanine levels during treatment

5.5 Identify non-responders to Kuvan treatment

5.6 Treat all patients with a Phe-restricted diet

Relevant Safety Labeling: Kuvan (sapropterin diHCL)

Section 5 Warnings and Precautions

5.7 Monitor patients with hepatic impairment

5.8 Monitor patients when co-administering Kuvan and medications known to inhibit folate metabolism

5.9 Monitor patients for hypotension when co-administering Kuvan and drugs known to affect nitric oxide-mediated vaso-relaxation

5.10 Monitor patients when co-administering Kuvan and levodopa

5.11 Monitor Patients for Hyperactivity

Pediatric Studies: Kuvan (sapropterin diHCL)

- 4-week open-label, population pharmacokinetic (PK) study in 94 BH4-responsive patients 0 to < 6 years of age who received 20 mg/kg/dose
  - Exposure-response relationship supported short-term, increased efficacy of 20 mg/kg dose

- 6-month open-label, one-arm safety and efficacy study conducted as part of an ongoing 7-year study to evaluate safety of sapropterin on neurocognitive functioning in 57 patients age 0 to 6 years
  - Reduction in blood Phe levels after 4 weeks of sapropterin diHCL treatment in patients maintained on a stable Phe diet
  - Insufficient data to support long-term efficacy because study did not control for dietary Phe intake for treatment period beyond 4 weeks

Pediatric Studies: Kuvan (sapropterin diHCL)

- Higher incidence of hypophenylalaninemia noted in population PK study, especially in the younger age groups, and led to age-specific recommendations for starting dose
  - 10 mg/kg for age less than 7 years
  - 10-20 mg/kg for age 7 years and older
- Observed safety profile of sapropterin in 6 month open-label study was consistent with sapropterin labeling
  - Low blood Phe levels below age-based reference range noted in 16 patients and occurred in most during first 4 weeks of treatment

Pediatric Labeling Changes Kuvan (sapropterin diHCl)

8.4 Pediatric Use

- Efficacy and safety of Kuvan have not been established in neonates

- In children ages 1 month to 16 years, the efficacy of Kuvan has been demonstrated in trials of 6 weeks or less in duration

Pediatric Labeling Changes Kuvan (sapropterin)

8.4 Pediatric Use

- The effectiveness of Kuvan alone on reduction of blood Phe levels beyond 4 weeks could not be determined due to concurrent changes in dietary Phe intake during a multicenter, open-label, single arm study in 57 patients ages 1 month to 6 years who were defined as Kuvan responders after 4 weeks of Kuvan treatment and Phe dietary restriction were treated for 6 months with Kuvan at 20 mg/kg per day.

- 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

Adverse Events
Kuvan (sapropterin HCL)

Total pediatric reports with a serious outcome reviewed (N=100)

Pediatric reports with the outcome of death (N=6)

Excluded cases* (N=53)
(Including 2 deaths)
Labeled events for sapropterin (N=12)
Transplacental exposure (N=16)
Other reasons (N=16)
-Adult patients coded with wrong age (N=14, including 2 deaths)
-Counterfeit drug (N=1)
-Overdose, no adverse event (N=1)
Duplicates (N=6)
Indication related (e.g., PKU, N=3)

Pediatric Case Series (N=47)
Including 4 deaths

*Reports reviewed and excluded for the reasons listed.

Adverse Events
Kuvan (sapropterin diHCl)
Summary of Fatal Cases (n=4)

- Age provided (n=3), range: 10 months to 7 years
  - Two fatal cases contained insufficient clinical information

- ***A 7 year-old boy*** with a history of atypical PKU & seizures died in the middle of the night after having a seizure. He had profound motor and cognitive disease and had been on sapropterin for 3 years at time of death. The seizure and death were attributed to his underlying condition.

- ***A 15-month-old female*** with a history of atypical PKU who had been receiving sapropterin 600 mg orally once daily (65 mg/kg/day; weight 9.3 kg) for approximately 1 month, experienced "apneic events" minutes after receiving a dose of sapropterin. Concomitant meds: baclofen gabapentin, bromide, carbidopa/levodopa, and glycopyrronium. The event was reported as severe and the patient died two days after the reported "apneic events". Note: patient status was 'do-not-resuscitate'.

Adverse Events
Kuvan (sapropterin)

Summary of Non-Fatal Serious Unlabeled Cases (N=43)

- 26 cases with alternative plausible explanations for reported events (e.g. PKU, history of seizures, infection)
- 12 cases lacked clinical information for proper assessment
- 2 cases lacked a temporal relationship to sapropterin diHCl use
- 3 cases could not exclude role of sapropterin diHCl

Adverse Events
Kuvan (sapropterin diHCl)
3 Non-Fatal Serious Unlabeled Cases*

- **2 reports of nosebleeds/epistaxis**

- A 2-year-old girl with PKU and a history of seizures developed daily epistaxis after starting sapropterin diHCl 100 mg orally daily for PKU. No concomitant medications were reported. Seizure frequency upon starting sapropterin was reported as daily. Events were ongoing at the time of the report.

- A 9-year-old boy experienced heavy nosebleeds and some blood clots from his left nostril approximately 1 year after starting sapropterin 500 mg orally daily (20 mg/kg) for PKU. The events occurred approximately weekly. No other clinical details were reported.

* Unlabeled events are underlined.

Adverse Events
Kuvan (sapropterin)

3 Non-Fatal Serious Unlabeled Cases

- **1 report of insomnia**

- A 13-year-old boy developed insomnia, agitation, and psychomotor hyperactivity an unknown time after starting unknown dose of sapropterin diHCl for an unknown indication. The event was reported as resolved on an unspecified date.

* Unlabeled events are underlined.

Summary
Kuvan (sapropterin diHCl)

- No new pediatric safety signals identified.
- Plan to monitor for epistaxis and insomnia in all patient populations.
- FDA recommends continued pharmacovigilance monitoring.
- Does the Committee agree?

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