CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215910Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	November 15, 2022
Reviewer:	Danielle Abraham, PhD, MPH Division of Epidemiology I
Team Leader:	Kira Leishear White, PhD, MS Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name:	SEZABY (phenobarbital sodium)
Application Type/Number:	NDA 215910
Applicant/sponsor:	Sun Pharma Advanced Research Company, Ltd.
OSE RCM #:	2022-897

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

SEZABY (phenobarbital sodium) for injection, for intravenous use, is a barbiturate.[1] The proposed indication for this new drug application (NDA) is for the treatment of neonatal seizures in term and preterm infants.[2] Phenobarbital is thought to inhibit seizures through potentiation of synaptic inhibition through an action on the $GABA_A$ receptor.[3]

The incidence of neonatal seizure is between 1 and 5 per 1,000 live births.[4] There are multiple etiologies of neonatal seizure including hypoxic ischemic encephalopathy (HIE), ischemic stroke, intracranial hemorrhage, central nervous system infection, cortical malformation, acute or inborn errors of metabolism, and genetic etiologies, with HIE being the most common.[5] Neonatal seizures are associated with adverse outcomes including mortality (up to 20%), epilepsy (13-33%), global developmental delay (up to 55%), cerebral palsy (up to 43%), and intellectual disability (up to 40%).[6] Seizures themselves and their underlying etiology may have negative impacts on neurodevelopment (1).[7]

Currently, there are no FDA approved treatments for neonatal seizures. Phenobarbital is unapproved by the FDA; however, it has been marketed since 1912 (Luminal, F Bayer and Co.), which is prior to implementation of the Federal Food, Drug, and Cosmetic Act of 1938.[8] Phenobarbital is currently available in oral and injectable formulations.[9] Despite being unapproved, phenobarbital is typically a first-line treatment for neonatal seizures (2, 3). Several other off-label therapies may be used for neonatal seizure management.[10] For example, levetiracetam and phenytoin/fosphenytoin may be used as first-line or second-line treatment (2, 3). There are no guidelines on duration of treatment for neonatal seizures.[11] Infants may continue antiseizure medications after hospital discharge (4). Practice patterns for drug selection and treatment protocols, including duration of treatment, differ by hospitals/neonatal intensive care units (NICUs) (4-6). In neonates, phenobarbital is also used off-label for the treatment of neonatal abstinence syndrome (7).

In neonates, the lyophilized powder is reconstituted and administered as an initial intravenous loading dose with, if clinically indicated, a second loading dose followed by maintenance dosing.[12] The elimination half-life of the drug is approximately one week in neonates.[13] The proposed labeling for SEZABY as of November 14, 2022, includes a boxed warning for risks

[1] Draft SEZABY labeling dated November 14, 2022.
[2] Ibid.
[3] Ibid.
[4] Kao A. NDA 215910 Sezaby (phenobarbital sodium). Draft Clinical Review dated October 24, 2022. U.S. Food and Drug Administration.
[5] Ibid.
[6] Ibid.
[7] Ibid.
[8] Ibid.
[9] DailyMed. National Library of Medicine. Available from https://dailymed.nlm.nih.gov/dailymed/. Accessed October 28, 2022.
[10] See footnote 4.
[11] Ibid.
[12] See footnote 1.
[13] Ibid.

from concomitant use with opioids; dependence and withdrawal reactions after use of SEZABY for a longer duration than recommended; and abuse, misuse, and addiction with unapproved use in adolescents and adults. Additional warnings and precautions for SEZABY include respiratory depression or insufficiency; serious dermatologic reactions; drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity; hypersensitivity reactions; exacerbation of porphyria; infusion site reactions; QT prolongation; embryofetal toxicity with unapproved use in adolescents and adults; neonatal adverse reactions from unapproved maternal phenobarbital use; sedation, respiratory depression, and withdrawal in neonates exposed to phenobarbital through breast milk; and suicidal behavior and ideation with unapproved use in adolescents and adults. The most common adverse reactions (incidence >5% patients overall) are abnormal respiration, sedation, feeding disorder, and hypotension.[14]

1.2. Describe the Safety Concern

In the clinical review, the Division of Neurology 2 (DN2) noted that there were no long-term safety data collected in the pivotal trial submitted to this NDA (NCT-01720667, NEOLEV2); the pivotal trial compared the efficacy of levetiracetam to phenobarbital over a five-day trial period.[15] However, DN2 was concerned about nonclinical findings of neuronal apoptosis in rodents as well as prior publications that demonstrated decreased intelligence quotient (IQ) in children previously treated with phenobarbital and lower verbal and intelligence scale scores in adult males who had been exposed to phenobarbital in utero.[16]

Phenobarbital, along with some other antiepileptic drugs (AEDs), causes neuronal apoptosis in rodents (8). In rodents, exposure to phenobarbital in the postnatal period negatively impacts excitatory and inhibitory synaptic development (9) and leads to long-term impacts on social, emotional, and cognitive function (10).

Both observational and randomized controlled clinical studies have assessed the impact of phenobarbital on neurodevelopmental outcomes. These studies have examined neurodevelopmental outcomes related to in utero phenobarbital exposure, long-term phenobarbital exposure, neonatal exposure to phenobarbital for seizure prevention, and neonatal seizure treatment with phenobarbital.

Two studies examined adult males born between 1959 and 1961 who were part of the Danish Perinatal Cohort (11). Both studies, using independent samples, compared those with phenobarbital exposure in utero to those without phenobarbital exposure in utero. In the first study, those with phenobarbital exposure in utero had significantly worse than predicted verbal IQ (mean difference [MD]= -7.17, one-sided p-value=0.04) but not performance IQ (MD= -4.92, one-sided p-value=0.13) or full scale IQ (MD= -6.61, one-sided p-value=0.06), based on the Wechsler Adult Intelligence Scale. In the second study, those with phenobarbital exposure in utero had significantly worse than predicted intelligence scores (MD= -4.77, one-sided p-value=0.002), as measured by the Danish Military Draft Board Intelligence Test.

[14] See footnote 1.
[15] See footnote 4.
[16] Ibid.

In a randomized controlled trial that compared phenobarbital to placebo for the treatment of febrile seizures in children 8 to 36 months of age (n=217), the phenobarbital group had significantly lower IQ, assessed by the Stanford-Binet Scales of Intelligence, after two years of treatment (-7.03, p=0.0068) and six months after treatment discontinuation (-4.29, p=0.092) (12, 13). After school entry (range=6 years 8 months to 10 years 1 month of age), IQ was still lower in the phenobarbital group, but the difference was attenuated and no longer statistically significant (-3.71, p=0.087) (14). The phenobarbital group had significantly worse Wide Range Achievement Test reading standard scores but not arithmetic and spelling scores (14). A second randomized controlled trial of phenobarbital compared to placebo for the treatment of febrile seizures restricted to children 6 months to 3 years of age (n=65) (15). After eight to twelve months of treatment, there were no significant differences in IQ, assessed by the Bayley Scales of Infant Development or the Stanford-Binet Intelligence Scale, between the groups (15). The Bayley Scales of Infant and Toddler Development assess cognitive, language, motor, adaptive behavior, and socio-emotional development (16).

In neonates, two randomized, controlled studies examined whether phenobarbital, compared to placebo, reduced the risk of seizures in infants with HIE. In Hall et al. (1998), 40 infants were randomized, and neurodevelopment was assessed at 6, 12, 24, and 36 months with Gessel, Bayley Scales, or Stanford-Binet assessments (17). At 36 months, among the 31 infants who completed their assigned treatment, infants in the treatment arm were significantly (p=0.003) less likely to have died or survived with moderate or severe neurologic impairment (4/15 versus 13/16) (17). In Singh et al. (2005), 60 infants were randomized and, after exclusions, 25 assigned to receive phenobarbital and 20 assigned to receive no drug (control group) (18). Based on the Amiel-Tison neurological assessment at three months, there was no statistically significant difference in the proportion of infants discharged alive who were neurologically abnormal at three months (3/20 [15%] in the phenobarbital group, 7/17 [41%] in the control group (relative risk [RR]=0.36 [95% CI: 0.11, 1.20]) (18).

Several randomized controlled trials (19, 20) and observational studies (21-24) examined long-term neurodevelopmental outcomes among infants with neonatal seizure comparing those treated with phenobarbital to an active comparator group. These studies used levetiracetam or fosphenytoin as an active comparator. However, nonclinical data suggest that levetiracetam may be neuroprotective (25). The Bayley Scale was the most used outcome assessment. In these studies, assessments typically occurred within 24 months of follow-up. Two of these studies demonstrated negative impacts of phenobarbital. Initial treatment with phenobarbital was associated with significantly worse neurodevelopmental outcomes (neuromotor, intellectual disability) at 12 months, compared to initial treatment with levetiracetam (20), and significantly more developmental delay at 18-24 months, compared to initial treatment with fosphenytoin (21). Maitre et al. (2013) examined cumulative dosage of both phenobarbital and levetiracetam (oral and intravenous formulations) prior to discharge (24). Out of the 280 infants in the study, 141 received both phenobarbital and levetiracetam. After adjustment, increasing exposure to levetiracetam (per 300 mg/kg) was associated with significant declines in Bayley cognitive scores (-2.2, p=0.001), motor scores (-2.6, p=0.001), and language scores (-2.3, p=0.001). The dose-response relationship was more pronounced with phenobarbital exposure; after adjustment, increasing exposure to phenobarbital (per 100 mg/kg) was associated with significant declines in Bayley cognitive scores (-8, p=0.01), declines in motor scores (-9, p=0.023), and increases in cerebral palsy diagnosis. At an earlier time point (12 months), using the Developmental Assessment of Young Children (in lieu of the Bayley), significant dose-response findings were noted for both medications but only noted for motor domains.

Although non-specific to phenobarbital, one recent study found that 64% of neonates continued antiseizure medications after discharge (68% phenobarbital monotherapy, 13% levetiracetam monotherapy, 20% polytherapy). The study assessed outcomes related to duration of treatment. Discontinuing antiseizure medications at hospital discharge was not statistically inferior to maintaining medications at discharge in neurodevelopment at 24 months (6). There was also no difference in postneonatal epilepsy or motor function outcomes at 24 months (6).

Overall, evidence suggests a potential risk for adverse impacts of SEZABY on long-term neurodevelopment. Nonclinical studies demonstrate that phenobarbital impacts rodent neurodevelopment. Clinical evidence that phenobarbital has negative impacts on neurodevelopment stems from studies of multiple indications and findings are mixed. Although adverse neurodevelopmental outcomes are serious and have long-term implications, it is difficult to parse out the contribution of neonatal seizure treatment, neonatal seizures, and underlying etiologies of neonatal seizure on neurodevelopmental outcomes. Long-term neurodevelopmental outcome data in neonates treated with phenobarbital is mostly limited to data from infants 24 months of age or less at follow-up. In neonates, there is also limited quantification of thresholds of exposure by duration or dose.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

The signal has already been detected in the literature; however, data from longer follow-up and additional understanding and characterization of the signal is needed, especially in the context of the neurologic risk posed by the underlying indication.

1.4. Statement of Purpose

DN2 requested that the Division of Epidemiology I (DEPI-I) conduct an assessment to determine whether Active Risk Identification and Analysis (ARIA) in the Sentinel Distributed Database (SDD) would be sufficient to assess the long-term impact of phenobarbital on neurodevelopment. The study will have a regulatory goal of signal refinement, with a need for a moderate level of statistical precision and certainty, with study findings possibly informing SEZABY labeling.

1.5. Effect Size of Interest or Estimated Sample Size Desired

To be determined.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The population of interest is infants with neonatal seizure. The definitive, clinical diagnosis of neonatal seizure is made by electroencephalogram (EEG) (26). Relying on clinical signs alone may result in missed seizures or inaccurate diagnosis of seizures (27). There are International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) codes for neonatal seizure as well as Current Procedural Terminology® (CPT) codes for EEG.

2.2 Is ARIA sufficient to assess the intended population?

Yes, ARIA is sufficient to identify infants with evidence of neonatal seizure. Studies differ in their use of claims-based codes or algorithms to identify neonatal seizure (28-30). Validation studies of codes or algorithms for neonatal seizure in administrative, claims databases are limited. EEG results are not available for most patients in SDD. Oh et al. (2019) used an algorithm-based approach, which included EEG claims, to identify infants with neonatal seizure in a U.S. administrative claims database (30). The validity of this approach was not determined; however, the proportion of infants with neonatal seizure treated with AEDs in the study cohort of infants with neonatal seizures was only 29.6% (30), which is much lower than expected (3, 5). However, Bateman et al. (2015) conducted a validation as part of a large, 2000-2007, Medicaid claims study that examined the relationship between in utero calcium channel blocker exposure and neonatal seizures (28). Neonatal seizure was identified with ICD-9 claims (779.0x) within 90 days of birth. The validation was conducted through chart review by one co-author who validated 50 cases from a single, academic medical center (28). Charts were examined for clinical documentation of seizure activity, phenobarbital treatment, and/or EEG results (28) This ICD-9 code was found to have a positive predictive value (PPV) of 0.86, suggesting claims in ARIA would be sufficient to identify neonatal seizure.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is any inpatient, intravenous treatment with SEZABY, including initial treatment with SEZABY.

3.2 Comparator Exposure(s)

To control for the neurodevelopmental impacts of the underlying indication, an active comparator(s) is necessary for the study. Plausible comparators include other off-label treatments for neonatal seizure (e.g., levetiracetam, fosphenytoin).

Comparisons may also be conducted within those exposed to SEZABY, comparing neurodevelopmental outcomes by cumulative dosage and duration of exposure to phenobarbital. Such studies could address whether there is a dose-response relationship or certain thresholds of exposure that are important for understanding risks of adverse neurodevelopmental outcomes.

3.3 Is ARIA sufficient to identify the exposure of interest?

No, ARIA would not be sufficient to capture full utilization of SEZABY and possible active comparator medications. Healthcare Common Procedure Coding System (HCPCS) codes would capture information on the administration of injectable medications, like SEZABY. However, the consolidation of inpatient codes to the admission date (as is done for data formatted in the Sentinel Common Data Model) would limit the ability to identify dates of exposure, which is necessary to identify initial treatment and capture duration of exposure. Some infants may receive oral formulations of antiseizure medications during hospitalization and/or after discharge (21, 24). Pharmacy claims would adequately capture outpatient prescriptions, including date and dosage information, for antiseizure medications. The bundling of inpatient payments would limit the capture of inpatient, oral antiseizure medications.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcome of interest is long-term neurodevelopmental outcomes. Major neurodevelopmental disability can be reliably captured around 18-24 months of age (31). Neurodevelopmental domains of interest include motor skills, cognition, language, and behavior. Neurodevelopmental domains like cognitive function and neuromotor function are more optimally assessed at older, school ages (e.g., 5 years of age) (31). Consequently, infants treated with SEZABY should be followed for a minimum of five years.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient to assess long-term neurodevelopmental outcomes due to a lack of necessary outcome assessments and insufficient follow-up time.

Results of validated, age-appropriate instruments that assess neurodevelopment, such as the Bayley, are not available in ARIA. There are validated ICD-9 algorithms to capture neurodevelopmental disorders in children (32). These algorithms demonstrate adequate validity, based on PPVs ≥0.80, for autism spectrum disorder/pervasive developmental disorder, attention deficit disorder/hyperkinetic syndrome of childhood, learning difficulty, developmental speech or language disorder, intellectual disability, and behavioral disorder but not developmental coordination disorder (PPV=0.38) (32). Additionally, only 5% of diagnoses in this validation study were from those <3 years of age and the sensitivity of these algorithms are not known (32). These claims could be used to identify long-term neurodevelopmental disorders, but they are insufficient to identify less pronounced functional effects.

To adequately assess neurodevelopmental effects for some domains, follow-up of infants is needed for a minimum of five years. Only 26% of those captured in SDD have at least five years of follow-up,[17] so assessing outcomes at school-age (e.g., ~5 years) would not be feasible in ARIA.

[17] Sentinel. Key Database Statistics. U.S. Food and Drug Administration. Available from https://www.sentinelinitiative.org/about/key-database-statistics. Accessed October 24, 2022.

5 COVARIATES

5.1 Covariates of Interest

Multiple covariates are of interest for this study including:

- Infant demographics: sex, race/ethnicity
- Delivery/birth characteristics: complications, delivery type, prematurity
- Maternal socio-demographics: education, socio-economic status
- Seizure characteristics: etiology, severity, neuroimaging results
- Site of care: specific hospital
- Clinical characteristics: hepatic/renal dysfunction, co-morbidities, Apgar score
- Co-treatments: therapeutic hypothermia, other antiseizure medications
- Other non-seizure medications

5.2 Is ARIA sufficient to assess the covariates of interest?

Several of these covariates would be available through claims data (e.g., infant sex, co-morbidities, injection co-treatments), although some information may need to be derived from maternal claims information. From the above list, key covariates include prematurity, maternal education, and etiology. Claims-based ICD-9-CM codes for gestational age do not have sufficient validity to identify preterm infants and implementation of an algorithm with possible mother-infant linkage would be required (33). However, ARIA has algorithm/linkage capabilities, and ICD-10-CM codes provide more detailed gestational age information (34). Maternal education is not available in the SDD. Although census-based proxies of socio-demographics are available in the SDD, these may not sufficiently control for confounding (35). ARIA does not have the ability to capture seizure severity and neuroimaging results. Overall, ARIA would not be sufficient to capture several covariates of interest, including the key covariate of maternal education.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The prospective study would need to conduct covariate adjusted estimates of risk.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, ARIA would be sufficient. There are analytic tools in ARIA available to adjust for multiple covariates. Stratification is also possible.

7 NEXT STEPS

Based on a DEPI-I assessment and Signal Assessment Meeting (SAM) deliberations, DEPI-I has determined that ARIA is insufficient to assess the long-term impact of SEZABY on neurodevelopment. Insufficiency was found in three domains, and thus the following PMR for a prospective study to assess the long-term neurodevelopmental effects of SEZABY in patients with neonatal seizures will be issued:

Conduct a prospective study with appropriate comparator(s) to assess long-term neurodevelopmental effects of Sezaby in patients with neonatal seizures. Ensure capture of and adjustment for potential confounders. Assess neurodevelopmental effects using validated, age-appropriate developmental assessments of motor skills, cognition, language, and behavior. Follow patients for a minimum of 5 years.

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/s/

DANIELLE S ABRAHAM
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KIRA N LEISHEAR WHITE
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JUDITH W ZANDER
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GERALD J DALPAN
11/15/2022 03:57:06 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/08/2022

To: Amy Kao, Clinical Reviewer, M.D.
Division of Neurology Products (DN II)

Josephine Little, Regulatory Project Manager, (DN II)

Tracy Peter, Associate Director for Labeling, (DN I/II)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Sezaby (phenobarbital sodium) for injection, for intravenous use, CIV

NDA: 215910

In response to DN II consult request dated March 2, 2022, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for Sezaby (phenobarbital sodium) for injection, for intravenous use, CIV.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II on October 27, 2022, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 11, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAMUEL A FASANMI
11/08/2022 03:35:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 11/4/2022 **Date consulted:** 3/4/2022

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health (DPMH)

To: Division of Neurology 2 (DN2)

Drug: SEZABY (phenobarbital injection)

NDA : 215910

Applicant: Sun Pharmaceutical Industries (SUN), the US agent for Sun Pharma Advanced Research Company, Ltd. (SPARC)

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of neonatal seizures

Materials Reviewed:

- Applicant's submission package for NDA 215910, February 17, 2022.
- DPMH Consult Request, dated March 4, 2022. DARRTS Reference ID 4947508

Consult Question: "Request DPMH to review PLLR labeling."

INTRODUCTION AND BACKGROUND

On February 17, 2022, Sun Pharma (SPARC) submitted a 505(b)(2) New Drug Application (NDA) for SEZABY (phenobarbital injection) for the treatment of neonatal seizures. DN2 consulted DPMH on March 4, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- SEZABY (phenobarbital injection) NDA 215910 is a 505(b)(2) application that references safety and efficacy data from IND 109622 and bioequivalence data from IND 132342. This NDA submission is considered a Type 3 submission – New Formulation.
- Phenobarbital is currently marketed in the US by West-Ward Pharmaceuticals in both tablet and injection (IM or IV) formulations. The unapproved IV injectable formulation contains benzyl alcohol.
- SEZABY (phenobarbital injection) NDA 215910 was granted Orphan Drug Designation for the indication of the treatment of neonatal seizures on October 2, 2019.
- SEZABY (phenobarbital injection) NDA 215910 was granted Fast Track designation on August 24, 2021, and Rare Pediatric Disease designation on August 26, 2021.

Phenobarbital Drug Characteristics[1]

- Drug Class: Anticonvulsant
- Mechanism of Action: The mechanism by which phenobarbital inhibits seizures likely involves potential of synaptic inhibition through action on the $GABA_A$ receptor.
- Molecular Weight: 254.22 Daltons
- Half-life: In adults, the elimination half-life is 106 hours after a single dose. In infants, the elimination half-life is about 1 week.
- % Protein Bound: 35-60%
- Dosage: Loading dose: 20mg/kg administered by intravenous infusion over 15 minutes. If clinically indicated, a second loading dose may be administered over the subsequent 15 minutes. The recommended maintenance dose of SEZABY if 4.5 mg/kg/day given in 2 or 3 divided doses administered intravenously over at least 15 minutes for 5 days.

Current State of Labeling[2]

*Note: Phenobarbital has not been approved by FDA. The information that follows is labeling for an unapproved phenobarbital product.

- **DOSAGE AND ADMINISTRATION**: For anticonvulsant use- In pediatric patients and infants, phenobarbital at a loading dose of 15 to 20 mg/kg produces blood levels of about 20 mcg/mL shortly after administration. In pediatric patients, phenobarbital at a maintenance dose is typically dosed at 3 to 6 mg/kg/day.

  Reviewer comment: Despite phenobarbital being used since 1912, there is no clear consensus on the optimal phenobarbital therapeutic levels to be attained;

[1] Proposed package insert, SEZABY (phenobarbital injection) NDA 215910
[2] Phenobarbital unapproved labeling. DailyMed. Accessed 10/17/2022. DailyMed - PHENOBARBITAL elixir (nih.gov)

however, phenobarbital levels between 10 and 40 mg/L most likely represent favorable drug exposure.[3]

- Serious adverse reactions: sedation, respiratory depression
- Labeling is not in the Physician Labeling Rule or the Pregnancy and Lactation Labeling Rule Format.
- There is no boxed warning for embryofetal toxicity.
- There is no contraindication for pregnancy or lactation.
- **WARNINGS**
  Usage in Pregnancy–Pregnancy Category D. Barbiturates can cause fetal damage when administered to a pregnant woman. Retrospective, case-controlled studies have suggested a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. Barbiturates readily cross the placental barrier and are distributed throughout fetal tissues; the highest concentrations are found in the placenta, fetal liver, and brain. Fetal blood levels approach maternal blood levels following parenteral administration.

  Withdrawal symptoms occur in infants born to women who receive barbiturates throughout the last trimester of pregnancy. If phenobarbital is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

  Nonteratogenic Effects–Reports of infants suffering from long-term barbiturate exposure in utero included the acute withdrawal syndrome of seizures and hyperirritability from birth to a delayed onset of up to 14 days
- **Nursing Mothers**
  Caution should be exercised when phenobarbital is administered to a nursing woman, because small amounts of barbiturates are excreted in the milk.
- There are no existing pregnancy testing/contraception recommendation.
- There are no known drug-drug interactions with hormonal contraceptives.

REVIEW

PREGNANCY

The proposed indication for this product is neonatal seizures; however, discussions with the Division of Neurology 2 (DN2) indicate there could be a potential for off-label use in females of reproductive potential.

Epilepsy and Pregnancy[4,5]

Epilepsy affects approximately 1% of the U.S. population, including over a million women of reproductive potential. Data on the effects of untreated epilepsy on pregnancy are limited, but uncontrolled seizures during pregnancy have been associated with adverse effects on both the

[3] Sima, M et al. What is the Best Predictor of Phenobarbital Pharmacokinetics to Use for Initial Dosing in Neonates. Pharmaceutics. 2021. 13 (301).
[4] O'Connor SE, Zupanc ML. Women and epilepsy. J Pediatr Pharmacol Ther. 2009;14(4):212-220.
[5] Voinescu PE, Pannell PB. Management of epilepsy during pregnancy. Expert Rev Neurother. 2015;15(10):1171-1187.

mother and fetus, including miscarriage, abruptio placentae, preterm birth, stillbirth, and maternal death. Because of the risk of adverse effects of seizures on the mother and fetus, epilepsy requires continuous treatment during pregnancy.

Nonclinical Experience

In animal studies reported in the literature, administration of phenobarbital during pregnancy resulted in adverse developmental effects including increased incidences of fetal malformations, growth deficits, and neurobehavioral and reproductive functional abnormalities.

For additional information, the reader is referred to the Pharmacology/Toxicology review by Edward Fisher, Pharm D.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature from 1956 through 2022 using the PubMed database and the following search terms, "phenobarbital," and "pregnancy," or "teratogenicity." Publications located in the Applicant's search are included in the DPMH literature review.

DPMH Review of Literature

DPMH performed a search of the literature from using PubMed and Embase using the search terms "phenobarbital" and "pregnancy," "stillbirth," "miscarriage," "congenital malformations," and "pregnancy outcomes." The DPMH search of the published literature focused on the past 10 years (January 1, 2012, through August 31, 2022), because the earlier literature has been summarized in reviews by Reprotox[6], Briggs[7] and Cochrane systematic reviews.[8]

Reprotox[9] states, "Phenobarbital use during pregnancy was associated with a 6-20% incidence of birth defects in the offspring. Seizure control during pregnancy is an important goal. Supplementation with folic acid and near-term treatment of pregnant women with vitamin K have been recommended, although the evidence for vitamin K is limited."

In Drugs in Pregnancy and Lactation,[10] Briggs rates phenobarbital use during pregnancy as, "Human data suggest risk." In the pregnancy risk summary, Briggs states:

> "Phenobarbital therapy in the epileptic pregnant woman presents a risk to the fetus in terms of major and minor congenital defects, hemorrhage at birth, and addiction. Adverse effects on neurobehavioral development have also been reported. The risk to the mother, however, is greater if the drug is withheld and seizure control is lost. The risk: benefit ratio, in this case, favors continued use of the drug during pregnancy at the lowest possible level to control seizures. Use of the drug in nonepileptic patients does not seem

[6] 2022 Reproductive Toxicology Center

[7] Briggs GG, Towers CV, Forinash AB. Briggs *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk.* 12th edition. [Philadelphia, PA., Lippincott Williams and Wilkins, 2022], 1039-1043.

[8] Weston J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child (review). Cochrane Database of Systematic Reviews. 2016;11.

[9] 2022 Reproductive Toxicology Center

[10] Briggs GG, Towers CV, Forinash AB. Briggs *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk.* 12th edition. [Philadelphia, PA., Lippincott Williams and Wilkins, 2022], 1039-1043.

to pose a significant risk for structural defects, but neurodevelopment, hemorrhage, and addiction in the newborn are still of concern."

A Cochrane systematic review[11] of monotherapy treatment of epilepsy reviewed prospective controlled trials, cohort studies, pregnancy registries, and randomized controlled-trials published through September 2015. Twenty-three of the studies examined the prevalence of major congenital malformations (MCMs) in children exposed to phenobarbital monotherapy *in utero*. The following observations were described:

- Children exposed to phenobarbital were at a higher risk of malformations than children born to women without epilepsy (5 studies examined, RR 2.84, 95% CI 1.57-5.13), but not those born to women with untreated epilepsy (13 studies examined, RR 1.95, 95% CI 0.97-3.93).
- Children exposed to phenobarbital were at a higher risk of MCMs than children exposed to gabapentin (RR 8.33, 95%CI 1.04-50.00), levetiracetam (RR 2.33, 95%CI 1.04-5.00) or lamotrigine (RR 3.13, 95%CI 1.64-5.88).
- The review also stated that phenobarbital was associated with an increased risk of cardiac defects compared to carbamazepine, lamotrigine, phenytoin, or oxcarbazepine with the increased risk falling between 2-3%.

In 2017, Veroniki, et al.[12] performed a systematic review and meta-analysis of 96 studies of antiepileptic drug (AED) exposures in pregnancy and found an increased risk of MCMs with phenobarbital monotherapy (OR 1.83, 95% CI 1.35-2.47).

Additional studies located in the DPMH literature search include the following (details of the studies can be found in Appendix A):

- Blotiere, et al.[13] found an increased risk of ventricular septal defects with phenobarbital exposure[14]
- Vajda, et al.[15] found an increased rate of MCMs in AED-exposed pregnancies compared to unexposed pregnancies (7.1% vs 2.8%), there was no specific association with phenobarbitone exposure, but only 8 of the 1972 AED-exposed pregnancies had exposures to phenobarbitone.
- Tomson, et al. found an MCM prevalence rate of 6.5% with phenobarbital exposure, with a dose-dependent increased risk of malformations.[16]

[11] Weston J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child (review). Cochrane Database of Systematic Reviews. 2016;11.
[12] Veroniki AA, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and meta-analysis of congenital malformations and prenatal outcomes. BMC Medicine. 2017;15:95
[13] Blotiere PO, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019;93(2):e167-e180.
[14] Blotiere PO, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019;93(2):e167-e180.
[15] Vajda FJE, et. al. Antiepileptic drugs and foetal malformation: analysis of 20 years of data in a pregnancy register. Seizure 2019;65:6-11.
[16] Tomson T, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018;17:530-38

Recent studies have also examined the effects of prenatal exposure to phenobarbital and overall intelligence (as measured by standard intelligence testing, such as the Wechsler Intelligence Scale for Children), motor delay and autism spectrum disorders. Several studies report an association between prenatal phenobarbital exposure and developmental delay;[17,18,19] however, not all studies reported this association.[20]

As noted in the studies reviewed by Briggs[21] and Reprotox[22] referenced earlier in this section, there are reports of an increased risk of bleeding complications with infants exposed to phenobarbital prenatally. The DPMH literature search located one paper that addressed the risk of bleeding complications with AEDs.

- Using the Medicaid Analytic eXtract database, Panchaud[23] and colleagues studied 3,594,268 total pregnancies, 11,752 of these had an AED prescription overlapping with delivery and found no difference in the risk for either postpartum hemorrhage (RR 0.74, 95% CI 0.06-0.91) or neonatal bleeding complications (RR 0.87, 95% CI 0.71-1.06). A separate analysis of phenobarbital was not performed.

The 2022 annual update for the North American Antiepileptic Drug (NAAED) Pregnancy Registry notes that 200 patients have been exposed to phenobarbital monotherapy during the first trimester of pregnancy. The prevalence of major congenital malformations is reported to be 6% (95% CI 3.3 to 10.5%). The prevalence of major congenital malformations in infants unexposed to AEDs is 1.7%.

Reviewer comment:
Based on nonclinical and epidemiologic studies, phenobarbital may increase the overall risk for major congenital malformations (MCMs) in infants exposed in utero; however, studies comparing phenobarbital-exposed pregnancies compared to pregnancies of unexposed women with epilepsy are less likely to demonstrate an increased risk of MCMs, raising the possibility of confounding by indication. There are reports of neonatal withdrawal and sedation in infants exposed to phenobarbital later in pregnancy and during labor. In addition, as noted in Briggs and Reprotox, there are reports of increased risk of bleeding in infants exposed to phenobarbital in utero. Several studies also report adverse effects on intellectual and motor development, although the data are not consistent. Additionally, there is the potential for sedation and withdrawal in the neonate exposed to phenobarbital in utero.

[17] Adams J, et al. Neuropsychological effects in children exposed to anticonvulsant monotherapy during gestation: phenobarbital, carbamazepine, and phenytoin. Epilepsy Behav. 2022;127:108533.
[18] Thomas SV, et al. Differential impact of antenatal exposure to antiseizure medications on motor and mental development in infants of women with epilepsy. Epileptic Disord. 2022;24(3):531-540.:PMID 35770752
[19] Gopinath N, et al. Children (10-12 years of age) of women with epilepsy have lower intelligence, attention and memory: observations from a prospective cohort case-control study. Epilepsy Research. 117:58-62.
[20] [20] Bjork MH, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. 2022;79(7):672-681.
[21] Briggs GG, Towers CV, Forinash AB. Briggs *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk.* 12th edition. [Philadelphia, PA., Lippincott Williams and Wilkins, 2022], 1039-1043.
[22] 2022 Reproductive Toxicology Center
[23] Panchaud A, et al. Anticonvulsants and the risk of perinatal bleeding complications: a pregnancy cohort study. Neurology 2018;91:e533-e542.

Since SEZABY is indicated for use in neonates, the Labeling Policy Team, DN2 and DPMH agreed that subsection 8.1, Pregnancy, is not applicable to the indicated population and will be omitted. However, since there is the potential for off-label use, this safety-related information is important and will be included in labeling under subsection 5.11, Embryofetal Toxicity with Unapproved Use in Adolescents and Adults and subsection 5.12, Neonatal Adverse Reactions from Unapproved Maternal Phenobarbital Use.

LACTATION

Nonclinical Experience

Phenobarbital is present in rat milk.[24]

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature from 1956 through 2022 using the PubMed and LactMed databases and the following search terms, "phenobarbital," and "lactation". Publications located in the Applicant's search are included in the DPMH literature review.

DPMH's Review of the Literature

DPMH performed a search of the literature using PubMed and Embase using the search terms "phenobarbital," and "lactation," or "breastfeeding."

The American Academy of Pediatrics classified phenobarbital as one that should be administered to nursing mothers with caution.[25]

Briggs[26] rates phenobarbital use during lactation as, "Limited human data- potential toxicity."

Hale's Medications and Mother's Milk rates phenobarbital as, "L4- limited data-possibly hazardous." Hale reports the following:

> "Phenobarbital is a long half-life barbiturate frequently used as an anticonvulsant in adults and during the neonatal period. Its long half-life in infants may lead to significant accumulation and blood levels higher than mother although this is infrequent. During the first 3-4 weeks of life, phenobarbital is poorly absorbed by the neonatal gastrointestinal tract. However, protein binding by neonatal albumin is also poor, 36-43%, as compared to the adult, 51%. Thus, the volume of distribution is higher in neonates and the tissue concentrations of phenobarbital may be significantly higher. The half-life in premature infants can be extremely long (100-500 hours).

[24] Masahiro M, et al. Determination of plasma phenobarbital concentration by high performance liquid chromatography in rat offspring. J Chromatography B Biomedical Science and Applications. 1999;723: No1-2, pg 301.

[25] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776-789.

[26] Briggs GG, Towers CV, Forinash AB. Briggs *Drugs in Pregnancy and Lactation: A reference guide to fetal and neonatal risk.* 12th edition. [Philadelphia, PA., Lippincott Williams and Wilkins, 2022], 1039-1043.

Although varied, milk/plasma ratios vary from 0.46 to 0.6.[27,28,29] In one study, following a dose of 30 mg four times daily, the milk concentration of phenobarbital averaged 2.74 mg/L sixteen hours after the last dose.[30] The dose an infant would receive was estimated at 2 -4 mg/day.[31] Phenobarbital should be administered with caution and close observation of the infant is required, including plasma drug levels. One should generally expect the infant's plasma level to be approximately 30-40% of the maternal level. In some reported cases, the infant plasma levels have reached twice that of the maternal plasma levels 2.5 hours after the maternal dose.[32] In general, the infant will receive 1/3rd of mother's dose. Possibility of withdrawal symptoms such as jitteriness, irritability, crying, sweating may be expected when drug withdrawn."

LactMed[33] states, "Inter- and intra-patient variability in excretion of phenobarbital into breastmilk is extensive. Phenobarbital in breastmilk apparently can decrease withdrawal symptoms in infants who were exposed in utero, but it can also cause drowsiness in some infants, especially when used with other sedating drugs. Monitor the infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of psychotropic drugs. Sometimes breastfeeding might have to be limited or discontinued because of excessive drowsiness and poor weight gain. If there is concern, measurement of the infant's serum phenobarbital concentration might help rule out toxicity."

In addition, LactMed provides a summary of the published literature, which is provided below.

Drug Levels

Maternal Levels

- In a lactation study (Westernik et al. 1965),[34] eight women took phenobarbital for 3 days. The average milk levels at 23 hours after the last dose were as follows:
  - 0.85 mg/L (range 0.8 to 1 mg/L) in 4 women taking 90 mg daily
  - 1.25 mg/L (range 1 to 1.5 mg/L) in 2 women taking 150 mg daily
  - 5.2 mg/L (range 2.7 to 5 mg/L) in 2 women taking 225 mg daily

  The same paper reported on two women taking phenobarbital 125 mg 3 times daily along with phenytoin.

[27] Tyson RM, Sharder EA, Perlman HH. Drugs transmitted through breast milk. II Barbiturates. J Pediatr 1938:14:86-90.
[28] Kaneko S, Sato T, Suzuki K. The levels of anticonvulsants in breast milk. Br. J Clin Pharmacol. 1979;7(6):624-627.
[29] Nau H, et al. Anticonvulsants during pregnancy and lactation: transplacental, maternal and neonatal pharmacokinetics. Clin Pharmacokinet 1982;7(6):508-543.
[30] Nau H, et al. Anticonvulsants during pregnancy and lactation: transplacental, maternal and neonatal pharmacokinetics. Clin Pharmacokinet 1982;7(6):508-543.
[31] Horning MG. Identification and quantification of drugs and drug metabolites in human milk using GC-MS-COM methods. Mod Probl Pediatr. 1975;15:73-79.
[32] Pote M, Kulkarni R, Agarwal M. Phenobarbital toxic levels in a nursing neonate. Indian Pediatr. 2004;41:963-964.
[33] Drugs and Lactation Database (LactMed), National Library of Medicine, NCBI Bookshelf https://www.ncbi.nlm.nih.gov/books/NBK501272/, accessed 5/10/2022
[34] Westerink D, Glerum JH. Pharm Weekbl. 1965;100:577–83. [Separation and micro-determination of phenobarbital and phenytoin in human milk].

    - In one woman, milk phenobarbital levels were fairly constant during the day, averaging from 5.6 to 6 mg/L at 6 am, 10 am and 8 pm between days 3 and 7 postpartum.
    - In the other woman, milk levels averaged 7.3, 7.8 and 8.8 mg/L at 6 am, 10 am and 8 pm, respectively, between days 5 and 11 postpartum.
- In a case report (Horning et al. 1975),[35] the breastmilk phenobarbital level was 2.7 mg/L 16 hours after the last dose of phenobarbital in a patient taking phenobarbital 30 mg 4 times daily for 3.5 days at 6 days postpartum.
- In a lactation study (Kaneko et al. 1979),[36] an unstated number of women took phenobarbital and other anticonvulsants in unstated dosages. Eight phenobarbital breastmilk levels were measured between days 3 and 32 postpartum at unstated times after dosing of phenobarbital and other anticonvulsants. Phenobarbital milk levels averaged 10.4 mg/L (range 0.5 to 33 mg/L), while maternal serum levels of phenobarbital averaged 19.3 mg/L.
- In a lactation study (Gomita et al. 1995),[37] phenobarbital breastmilk concentrations were determined in a group of 26 mothers with epilepsy who were taking phenobarbital alone or in combination with other anticonvulsants. The extent of breastfeeding was not reported. Breastmilk was collected at four different time intervals after delivery: within 5 days postpartum, 6 to 10 days postpartum, 1 to 2 months postpartum and 3 to 5 months postpartum. Breastmilk samples were obtained 2 to 3 hours after the last dose of the day. Between 13 and 18 mothers provided samples in each time-period. For each mg/kg of phenobarbital that the mothers took, their breastmilk concentrations increased by about 1 to 2 mg/L with monotherapy and 1.25 to 2.5 mg/L with combination therapy. The difference between monotherapy and combination therapy was statistically significant only during the first 5 days postpartum. Additionally, between 14 and 18 infants provided serum samples in each time-period. For each mg/kg of phenobarbital that the mothers took, their infants' serum concentrations increased by about 2 to 5 mg/L with monotherapy and combination therapy, except during the first 5 days postpartum when an increase in serum phenobarbital concentration was about 10 mg/L for each mg/kg of the mothers' dose. This greater serum concentration in the early days postpartum probably reflects transplacental passage to some extent.[40]
- In a lactation study (Shimoyama et al., 2000),[38] six breastmilk samples and eight plasma samples were obtained during the first week postpartum from four patients who were taking phenobarbital. Phenobarbital dosages ranged from 30 to 150 mg daily in 3 divided doses. Milk samples were obtained 2 to 3 hours after a dose. The levels of phenobarbital in breast milk and plasma were 6.05 ± 1.2 µg /mL

[35] Horning MG, Stillwell WG, Nowlin J, et al. Identification and quantification of drugs and drug metabolites in human breast milk using GC-MS-COM methods. Mod Probl Paediatr. 1975;15:73–9.
[36] Kaneko S, Sato T, Suzuki K. The levels of anticonvulsants in breast milk. Br J Clin Pharmacol 1979;7:624-7. Letter. PMID: 465285
[37] Gomita Y, Furuno K, Araki Y, et al. Phenobarbital in sera of epileptic mothers and their infants. Am J Ther. Ther.1995;2:968–71.
[38] Shimoyama R, Ohkubo T, Sugawara K. Characteristics of interaction between barbiturate derivatives and various sorbents on liquid chromatography and determination of phenobarbital in Japanese human breast milk. J Liq Chromatogr Relat Technol. 2000;23:587–99.

(mean ± S.D., range of 4.5 - 7.6 µg /mL) and 14.0 - 9.0 µg /mL (mean ± S.D., range of 4.3 - 29.6 µg /mL), respectively. The milk versus plasma concentration ratios (M / P ratio) of phenobarbital were 0.35 - 0.1 (mean ± S.D., range of 0.23 ± 0.44). The level of phenobarbital in breast milk was lower than in the maternal plasma. Using the values presented in the Shimoyama et al study, LactMed calculated the average weight-adjusted infant dosage to be 72.5% (range 39 to 135%) of the maternal dosage.

Infant Levels

- In a case report (Granström ML et al. 1982),[39] an infant whose epileptic mother was taking phenobarbital 100 mg, primidone 625 mg, phenytoin 200 mg and sulthiame 200 mg daily during pregnancy and postpartum was partially breastfed. At 17 days of age, the phenobarbital serum level was 2 mg/L. The proportion of breastfeeding was increased, and at 1 month of age, the infant's serum phenobarbital level was 12.7 mg/L. Breastfeeding continued, but by 2 months of age, the infant's serum phenobarbital concentration was 1 mg/L.

  Reviewer comment: The metabolism of phenobarbital is mainly hepatic. The long half-life of phenobarbital in the pediatric population (20-133 hours in infants and up to 500 hours in neonates) and the lower plasma protein binding in neonates compared to adults (43% versus 51%) could explain why blood levels of phenobarbital are higher in newborns than in their mothers. Phenobarbital may cause sedation, and the risk is sedation is higher in breastfed infants whose mothers use other drugs to treat seizures and other conditions.[40]

- In a case report (Pote, et al. 2004),[41] a breastfed infant (extent not stated) of a mother who was taking phenobarbital 90 mg daily during pregnancy and postpartum had phenobarbital plasma levels measured on day 6 and 19 postpartum. On day 6, the plasma levels were 12.1 and 28.3 mg/L before and 2.5 hours after the mother's dose, respectively. On day 19, infant plasma levels had increased to 15.4 and 54.7 mg/L before and 2.5 hours after the mother's dose, respectively. To avoid cumulative dose effect of phenobarbital, the authors noted that breastfeeding was gradually withdrawn, and the infant was monitored for withdrawal reactions. There were no reports of any adverse effects in the infant.

<u>Effects in Breastfed Infants</u>

- In a case series (Tyson et al. 1938),[42] 41 infants of breastfeeding mothers taking phenobarbital were observed. Of the 41 infants, there were two 1-week-old infants whose mothers had been receiving phenobarbital 100 mg at bedtime for 3

[39] Granström ML, Bardy AH, Hiilesmaa VK. Prolonged feeding difficulties of infants of primidone mothers during neonatal period: preliminary results from the Helsinki study. In, Janz D et al, eds Epilepsy, pregnancy and the child 1982;New York. Raven Press:357-8.
[40] Davanzo R. et al. Antiepileptic drugs and breastfeeding. Italian Journal of Pediatrics. 2013. 39 (50).
[41] Pote M, Kulkarni R, Agarwal M. Phenobarbital toxic levels in a nursing neonate. Indian Pediatr 2004;41:963-4. Letter.
[42] Tyson RM, Shrader EA, Perlman HH. Drugs transmitted through breast milk, II: Barbiturates. J Pediatr. 1938;13:86–90.

to 5 nights who exhibited deep slumber with difficulty in awakening that was possibly caused by phenobarbital in breastmilk.

- In a case report (Finch E and Lorber J, 1954),[43] a mother was taking phenobarbital 390 mg daily and phenytoin 400 mg daily during pregnancy and postpartum. Her infant was drowsy at birth, refused to suck and was given partial formula feeding. At 5 days of age, her infant was admitted to the hospital pale and collapsed with bruising, bleeding, and a decreased hemoglobin, thought to be due to methemoglobinemia. Breastfeeding was discontinued, and the infant was given a transfusion which rapidly improved her condition. On day 10, the mother resumed breastfeeding the infant. Within 24 hours the infant was extremely sedated and refused to suck and was fed breastmilk with a spoon. The sedation persisted for 2 days until breastmilk was discontinued permanently because of a return of methemoglobinemia. The extreme sedation was probably due to phenobarbital in the milk. The authors believed that the methemoglobinemia was probably caused by the phenytoin.
- In a case report (Juul S. Ugeskr Laeger, 1969),[44] an infant death occurred from overlying and suffocation by a parent during sleep. Sedation from phenobarbital, primidone, and phenytoin in breastmilk was possibly a contributing factor. Phenobarbital was found in the infant's serum (8 mg/L) and liver (16 mcg/g) on autopsy.

  Reviewer comment: As noted above, phenobarbital is metabolized in the liver and has a very long half-life in the pediatric population and lower plasma protein binding in neonates compared to adults (43% versus 51%), which explains why blood levels of phenobarbital are higher in newborns than in their mothers. Phenobarbital may cause sedation.

- In a case report (Gopfert-Geyer I et al., 1982),[45] probable drug withdrawal symptoms, manifested as spontaneous tremors, occurred in a breastfed infant in the third month of life when her mother who was taking phenobarbital (dose not stated) during pregnancy and breastfeeding, abruptly discontinued nursing.
- In a case report (Knott et al. 1987), a breastfed infant whose mother was taking phenobarbital 90 mg, primidone 375 mg, and carbamazepine 800 mg daily did well despite a phenobarbital saliva level of 3.4 mg/L. At 7 months of age, after the mother abruptly stop nursing, the infant had several "startle reactions" and infantile seizures occurred which were confirmed by an abnormal electroencephalogram. Continued phenobarbital administration to the infant for 15 months controlled the seizures and no more occurred up to 5 years of age.[46]

[43] Finch E, Lorber J. Methemoglobinemia in the newborn. Probably due to phenytoin excreted in human milk. J Obstet Gynaecol Br Emp. 1954;61:833–4.
[44] Juul S. Ugeskr Laeger. 1969;131:2257–8. [Barbiturate poisoning via breast milk?]. PubMed PMID: 5372729.
[45] Gopfert-Geyer I, Koch S, Rating D, et al. Delivery, gestation, data at birth, and neonatal period in children of epileptic mothers. In Janz D,Bossi L, Dam M et al., eds. Epilepsy, pregnancy, and the child. New York Raven Press 1982:179-87.
[46] Knott C, Reynolds F, Clayden G. Infantile spasms on weaning from breast milk containing anticonvulsants. Lancet 1987;330:272-3. Letter. PMID: 2886736

In addition to the cases referenced in LactMed, a search of the published literature located an additional a systematic review[47] on anticonvulsants and lactation. The cases reviewed in this systemic review were the same as those cited in LactMed.

Reviewer comment:
Published case reports and case series indicate that phenobarbital can accumulate in breast milk. The published reports indicate a milk/plasma ratio (<1), and a relative infant dose (RID) between 20 to 50% the weight-adjusted maternal dose.[48] Infants that are treated with phenobarbital are typically given maintenance doses of 3 to 6 mg/kg/day, and infant serum phenobarbital levels typically range between 10 and 40 mg/L. Published studies that included information about infant serum levels of phenobarbital in breastfed infants exposed to mothers taking phenobarbital reported levels ranging between 2mg/L to 54.7 mg/L, which suggests that phenobarbital may be present at clinically significant levels in breastfed infants. DPMH discussed the published lactation studies[49,50] with the FDA Clinical Pharmacology team. They noted several limitations in the studies including lack of data that could confirm that the assay used to quantify phenobarbital in breast milk was adequately validated, and a lack of AUC comparisons to make a determination of drug excretion in breast milk. Given the limitations of the lactation studies, only qualitative data will be included in labeling.

Adverse effects in breastfed infants have been reported including symptoms of sedation, respiratory depression and withdrawal. There are also reports that breastfeeding can reduce withdrawal in neonates exposed to phenobarbital prenatally.[51] Since SEZABY is indicated for use in neonates, the Labeling Policy Team, DN2 and DPMH agreed that subsection 8.2, Lactation, is not applicable to the indicated population and will be omitted. However, since there is the potential for off-label use, this safety-related information is important and will be included in labeling under section 5.13, Sedation, Respiratory Depression, and Withdrawal in Neonates Exposed to Phenobarbital Through Breast Milk.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There was no indication of adverse effects on fertility in rats at a dose of 60 mg/kg/day. Phenobarbital has been shown to cause chromosomal damage to germ cells in male mice and insignificant lethal effects in female mice (decreased implantations). Neonatal exposure in rodents leads to permanent alteration in female reproductive function and permanent decreases in testosterone and increased sexual dysfunction in males.

The reader is referred to the Pharmacology/Toxicology review by Edward Fisher, PharmD for additional information.

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[47] Shawahna R, Zaid L. Concentrations of antiseizure medications in breast milk of lactating women with epilepsy: a systematic review with qualitative synthesis. Seizure. 2022;98:57-70.
[48] Verstegen RHJ, Anderson PO, Ito S. Infant drug exposure via breast milk. BJCP. 2020;1-17.
[49] Gomita Y, Furuno K, Araki Y, et al. Phenobarbital in sera of epileptic mothers and their infants. Am J Ther. Ther.1995;2:968–71.
[50] Westerink D, Glerum JH. Pharm Weekbl. 1965;100:577–83. [Separation and micro-determination of phenobarbital and phenytoin in human milk].
[51] Drugs and Lactation Database (LactMed), National Library of Medicine, NCBI Bookshelf https://www.ncbi.nlm.nih.gov/books/NBK501272/, accessed 5/10/2022

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature from 1956 through 2022 using the PubMed database and the following search terms, "phenobarbital," and "pregnancy," or "fertility."

Male Fertility

The applicant reports that there were no indications of direct adverse effects on male fertility in the published literature but cited reports of aspects of male sexual development and functioning that might affect fertility.

- Hong, et al.[52] found in vitro inhibition of sperm motility with chlorpromazine, but not phenobarbital
- Verrotti, et al.[53] found that liver-enzyme-inducing antiepileptic drugs increased serum sex hormone-binding globulin (SHBG) concentrations, leading to diminished bioactivity of testosterone.

Female Fertility

- Sukumaran, et al.[54] followed a sample of 375 women with epilepsy who were of reproductive age for 10 years. 7.1% (1/14) of those not on antiepileptic drugs (AEDs) had infertility; 31% (67/211) exposed to one AED, 40.7% (35/86) of those on 2 AEDs, and 60.3% (35/58) exposed to 3 or more AEDs had infertility. Women exposed to phenobarbital (n=19) were more likely to have infertility than those exposed to other AED monotherapies (n=225), OR 1.1517 (95% CI 0.937-2.455), p=0.028.

DPMH Review of Literature

DPMH performed a search of the literature using PubMed and Embase using the search terms "phenobarbital" and "fertility," "infertility," and "hormonal contraceptives."

A search of the published literature did not reveal additional cases related to phenobarbital and human infertility.

Data from the published literature indicates that phenobarbital increases the activity of the cytochrome 450 3A4 (CYP3A4) enzyme system, which is also the primary enzyme system metabolizing estrogens and progesterone.[55] This can lead to reduced circulating levels or hormonal contraceptives, increasing the risk of contraceptive failure.[56, 57] In addition, phenobarbital has been shown to increase levels of sex-hormone binding globulin (SHBG),

[52] Hong CY, et al. Effects of chlorpromazine and other drugs acting on the central nervous system on human sperm motility. Euro J Clin Pharmacol. 1982;22(5):413-6.
[53] Verrotti A, et al. Hormonal and reproductive disturbances in epileptic males patients: emerging issues. Reprod Toxicol. 2011;31(4):519-27
[54] Sukumaran SC, et al. Polytherapy increased the risk of infertility in women with epilepsy. Neurology. 2010;75(15): 1351-5.
[55] Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010;3(2):183-192.
[56] Crawford P. Interactions between antiepileptic drugs and hormonal contraception. CNS Drugs. 2002;16:263-272
[57] Perrucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2005;61:246-255.

which decreases the unbound, biologically active portions of circulating estrogens and progesterone, which can also contribute to reduced contraceptive effectiveness.[58]

Reviewer comment: (b) (4) (b) (4) *Since this drug will be indicated for use in neonates, subsection 8.3, Infertility is inapplicable to the indicated population and will be deleted.*

The published literature also indicates an adverse effect of phenobarbital on the effectiveness of hormonal contraception. Since SEZABY is indicated for use in neonates, the Labeling Policy Team, DN2 and DPMH agreed that information regarding use of non-hormonal contraception is not relevant to the indicated population and should not be included in SEZABY labeling.

DISCUSSION AND CONCLUSIONS

Pregnancy

Based on nonclinical and epidemiologic studies, phenobarbital may increase the overall risk for major congenital malformations (MCMs) in infants exposed *in utero*. There are reports of neonatal withdrawal and sedation in infants exposed to phenobarbital late in pregnancy and during labor. In addition, there are reports of increased risk of bleeding in infants exposed to phenobarbital prenatally. Several studies also report adverse effects on intellectual and motor development, although the data are not consistent. Additionally, use of SEZABY late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying and feeding difficulties) in the neonate.

Although SEZABY is indicated to treat neonatal seizures, there is a potential for off-label use. After discussion between the Labeling Policy Team, DN2 and DPMH, the teams decided that information regarding the risk for major congenital malformations, bleeding, and sedation and withdrawal in infants exposed to phenobarbital prenatally is important safety information, and this information will be included in subsection 5.11, Embryofetal Toxicity with Unapproved Use in Adolescents and Adults and subsection 5.12 Neonatal Adverse Reactions from Unapproved Maternal Phenobarbital Use. Subsection 8.1, Pregnancy, will be omitted since this labeling subsection is not applicable to the indicated population.

Lactation

Phenobarbital is present in breast milk. The published reports indicate a milk/plasma ratio (<1), and a relative infant dose (RID) between 20-50% the weight-adjusted maternal dose.[59] Infants that are treated with phenobarbital are typically given maintenance doses of 3 to 6 mg/kg/day, and infant serum phenobarbital levels typically range between 10 and 40 mg/L. Published studies that included information about infant serum levels of phenobarbital in breastfed infants exposed to mothers taking phenobarbital reported levels ranging between 2mg/L to 54.7 mg/L, which suggests that phenobarbital may be present at clinically significant

[58] Wilbur K. Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. Clin Pharmacokint. 2000;38:355-365

[59] Verstegen RHJ, Anderson PO, Ito S. Infant drug exposure via breast milk. BJCP. 2020;1-17.

levels in breastfed infants. As noted in the review, however, there are limitations in the methodology in the published reports, including lack of data that could confirm that the assay used to quantify phenobarbital in breast milk was adequately validated, and a lack of AUC comparisons to make a determination of drug excretion in breast milk. Therefore, only qualitative information from these studies will be included in labeling. Adverse effects on the breastfed infant have been reported including sedation, respiratory depression, and withdrawal symptoms (when breastfeeding is stopped).

After discussion between the Labeling Policy Team, DN2 and DPMH, the teams decided that information regarding the risk for sedation, respiratory depression and withdrawal in infants exposed to phenobarbital through breastfeeding will be included in subsection 5.13, Sedation, Respiratory Depression, and Withdrawal in Neonates Exposed to Phenobarbital Through Breast Milk. Subsection 8.2, Lactation, will be omitted since this labeling subsection is not applicable to the indicated population.

Females and Males of Reproductive Potential

Data on the effects of phenobarbital on human fertility are limited and are not sufficient to determine any adverse effect on fertility. In discussions with the Nonclinical team, the team determined that animal fertility data were not relevant to humans and that this information should remain in section 13.

Additionally, published data indicate reduced efficacy when hormonal contraceptives are administered concomitantly with phenobarbital.

After discussion between the Labeling Policy Team, DN2 and DPMH, the teams decided that information regarding the use of non-hormonal contraceptives was not relevant to the indicated population, therefore, language about contraception will not be included in SEZABY labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 5.11, 5.12 and 5.13 of labeling for compliance with the PLLR. Since this drug is indicated for neonates, subsections 8.1, 8.2 and 8.3 will be omitted from labeling since these subsections are not applicable (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.11 Embryofetal Toxicity with Unapproved Use in Adolescents and Adults

SEZABY is not approved for use in adolescents or adults. Based on findings from prospective controlled trials, cohort studies, pregnancy registries, and randomized controlled-trials, phenobarbital can cause fetal harm when administered during pregnancy. Data from observational studies suggest an increased risk of major congenital malformations in infants of mothers who received phenobarbital during pregnancy.

5.12 Neonatal Adverse Reactions from Unapproved Maternal Phenobarbital Use

SEZABY is not approved for use in adolescents or adults. Phenobarbital crosses the placenta and may produce respiratory depression, hypotonia, and sedation in neonates of mothers who received phenobarbital during pregnancy. The use of SEZABY late in pregnancy can result in the following adverse reactions in neonates:

- Sedation (respiratory depression, lethargy, hypotonia) and/or
- Withdrawal reactions (hyperreflexia, irritability, restlessness, tremors, inconsolable crying and feeding difficulties) .

Neonatal coagulation defects have been reported within the first 24 hours in neonates exposed to phenobarbital during pregnancy. Administration of vitamin K to the mother before obstetric delivery and to the neonate at birth has been shown to prevent or correct these defects.

5.13 Sedation, Respiratory Depression and Withdrawal in Neonates Exposed to Phenobarbital Through Breast Milk

SEZABY is not approved for use in adolescents or adults. Phenobarbital is present in breast milk and may accumulate in breastmilk. Phenobarbital has been detected in some infants exposed to breast milk from phenobarbital-treated mothers. There are reports of sedation, respiratory depression and withdrawal in infants exposed to phenobarbital through breast milk.

APPENDIX A: Phenobarbital and Pregnancy Outcomes.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
Thomas SV, et al.[60] 2022 India	Prospective pregnancy registry (Kerala Registry of Epilepsy and Pregnancy)	1,485 Infants between ages 12-24 months (mean age 15.3 months) exposed *in utero* to AEDs (Phenobarbitone exposed n=83)	Mothers enrolled pre-pregnancy or first trimester; exposure from first trimester	18.1% of infants exposed to phenobarbitone were considered as having motor developmental delay; 25.3% of those exposed to phenobarbitone were considered as having delayed mental development. There was a dose-response, with higher doses associated with greater motor and developmental delay.	Developmental assessment by Developmental Assessment Scale for Indian Infants (a modified Bayley Scale, Version 1); confounders controlled for include mother's age, seizure type, epilepsy classification, and infants birth weight, and malformation status.
Bjork MH, et al. 2022 Denmark, Finland, Iceland, Norway, and Sweden	Retrospective cohort study using the Nordic register-based antiepileptic drugs in pregnancy (SCAN-AED, 1996-2017)	4,494,926 children, 24,825 were exposed to AEDs *in utero* (45 children of women with epilepsy exposed to phenobarbital, 175 exposed to phenobarbital [all indications]) Median age at follow-up was 8 years old (range 4.0-12.1 years)	Exposure to AEDs from last menstrual period to birth	The risk of developing autism spectrum disorder (ASD) after exposure to phenobarbital *in utero* was not significant: Hazard Ratio (HR), full adjustment= 1.40 (95% CI 0.58-3.37). Exposure to topiramate and valproate were associated with increased risk of ASD. Topiramate HR (adj)= 1.40 (95%CI 1.50-4.65) Valproate (HR (adj)=3.44 (95%CI 2.77-4.28)	Adjusted for maternal age, education, marital status, parity, use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalizations the year before the last menstrual period.

[60] Thomas SV, et al. Differential impact of antenatal exposure to antiseizure medications on motor and mental development in infants of women with epilepsy. Epileptic Disord. 2022;24(3):531-540.:PMID 35770752

Adams J, et al.[61] 2022 USA	Case-control study recruited from a surveillance study conducted between 1983-1993 in 5 maternity units in Boston	Exposure at any time during pregnancy Mean age at testing 9.4 months of age	3 groups exposed to AED monotherapy Carbamazepine n=41 Phenobarbital n=34 Phenytoin n=40 Each group was matched to an unexposed group of mothers according to educational and socioeconomic characteristics and the children were matched by sex and age at testing	Children exposed to AEDs in utero had lower performance on verbal (F [df3, 109=4.34, p=0.006) and full-scale IQ (F[df3], 109] =4.07, p=0.009. (Analysis was performed using a mixed model analysis of variance. The F = factor, df=degrees of freedom) Children exposed to phenobarbital had lower performance compared with controls on verbal (p=0.009) and full-scale IQ scores (p=0.04) Children exposed to phenobarbital also performed worse than children exposed to phenytoin on verbal (p=0.02) and full-scale IQ (p=0.07) There was no significant difference in children exposed to phenobarbital and those exposed to carbamazepine.	Children were assessed by a dysmorphologist, parents had IQ testing, and all were within normal range, exclusions included exposure to other teratogens, premature birth, multiple birth, auditory impairment, or first language other than English. IQ testing performed using the Wechsler Intelligence Scale for Children, version III
Vajda FJE, et al[62] 2019 Australia	Prospective pregnancy registry	2148 pregnancies of women with epilepsy (1972 exposed, 176 unexposed) Phenobarbitone-exposed n=2 (monotherapy), n=6 (as part of combination therapy)	Exposure during at least the first half of pregnancy	The rate of malformations in AED-exposed pregnancies was 7.1% compared to the 2.8% rate in unexposed pregnancies. For individual AED monotherapy, only valproate was associated with a statistically significant increase in malformations- at valproate 700 mg/day Hazard ration=3.11, 95%CI 1.30-10.22)	Follow-up through phone contact, information confirmed through medical record examination

[6161] Adams J, et al. Neuropsychological effects in children exposed to anticonvulsant monotherapy during gestation: phenobarbital, carbamazepine, and phenytoin. Epilepsy Behav. 2022;127:108533.
[62] Vajda FJE, et. al. Antiepileptic drugs and foetal malformation: analysis of 20 years of data in a pregnancy register. Seizure 2019;65:6-11.

Tomson T, et al.[63] 42 countries 2018	Prospective pregnancy registry (June 20, 1999-May 20, 2016)	7355 exposed to antiepileptic drug monotherapy (Phenobarbital-exposed n=294 [4%])	First trimester	Prevalence of MCMs with phenobarbital exposure 6.5% There was a dose-dependent increased risk of malformations with phenobarbital Phenobarbital > 130 mg/day vs 80 mg/day OR 2.36 (95% CI 0.81-6.86) Risk of MCMs compared to reference (Lamotrigine 325 mg/day) OR 2.46 (95% CI 1.16-5.23)	Risk of teratogenicity compared among the antiepileptic drugs. Pregnancies with exposures to known teratogens or other diseases known to increase adverse pregnancy outcomes were not included in the sample. Data collected included demographics, type of epilepsy, seizure frequency, family history of MCMs, "other risk factors". Data collected after each trimester, at birth and one year after birth. Limitations- no unexposed control group, not a random sample
Blotiere PO, et al.[64] France 2019	Retrospective cohort study (French National Health Insurance claims information system, January 2011 – March 2015)	1,886,825 pregnancies (Phenobarbital-exposed n=80)	Prescription dispensed between 1 month before and two months after conception	Phenobarbital was associated with increased risk for ventricular septal defect (VSD) (OR 10.5, 95% CI 1.31-39.3)	Covariates included maternal age at birth, year of start of pregnancy, preconception folic acid supplementation, pregestational diabetes. Women exposed to AEDs were older than unexposed women, were more likely to be lower income, and more likely to have pregestational diabetes Authors note caution in interpreting the findings related to phenobarbital and VSD due to the low number of phenobarbital exposures.
Veroniki AA, et al.[65] Canada 2017	Systematic review and meta-analysis	96 studies (n=58,461 pregnancies) (Phenobarbital monotherapy n=1709)	Exposure *in utero*	Phenobarbital exposure was associated with MCMs compared with unexposed controls (OR 1.83, 95% CI 1.35-2.47)	

[63] Tomson T, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018;17:530-38.
[64] Blotiere PO, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. Neurology. 2019;93(2):e167-e180.
[65] Veroniki AA, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and meta-analysis of congenital malformations and prenatal outcomes. BMC Medicine. 2017;15:95

Veroniki AA, et al.[66] Canada 2017	Systematic review and meta-analysis	29 observational cohort studies (n=5100 infants/children) Number of exposures to phenobarbital not provided	Exposure *in utero* or via breastfeeding	Phenobarbital monotherapy was not associated with and increased risk of cognitive developmental delay or autism. The combination of carbamazepine+phenobarbital+valproate was associated with greater odds of psychomotor delay compared with controls (OR 19.12 95%CI 1.49-337.50) The Bayesian random-effects network meta-analysis (NMA) for cognitive delay (11 cohort studies, 933 children) found only Valproate associated with cognitive developmental delay compared to unexposed controls (OR 7.40, 95%CI 3.00-18.46.	Number of exposures to any of the individual drugs was not described in the paper or supplementary materials, making interpretation difficult. Different studies used different methods of assessing cognitive development.
Panchaud A, et al.[67] USA 2018	Medicaid Analytic eXtract Database (2000-2010)	3,594,268 total pregnancies; 11,752 with an anticonvulsant prescription overlapping with delivery (Phenobarbital n=666)	Prescriptions dispensed that overlapped with the date of delivery (month before delivery)	Anticonvulsant that induces cytochrome P450 enzymes (phenobarbital, primidone, phenytoin, oxcarbazepine, carbamazepine) and may impair vitamin K metabolism were compared to anticonvulsants that do not induce cytochrome P450 enzymes regarding the risk for postpartum hemorrhage and neonatal bleeding complications.	The authors concluded that there was no increased risk of bleeding complications with the use of anticonvulsants that induce cytochrome P450. Covariates included maternal demographics, indication for anticonvulsant medication, medical comorbidities and obstetric complications, medications that are risk factors for bleeding or proxies for conditions that might increase bleeding.

[66] Veroniki AA, et al. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breastfeeding: a systematic review and meta-analysis. BMJ Open. 2017;7(7):e017248

[67] Panchaud A, et al. Anticonvulsants and the risk of perinatal bleeding complications: a pregnancy cohort study. Neurology. 2018;91:e533-e542.

				The prevalence of postpartum hemorrhage (PPH) in the anticonvulsant inducer group compared to non-inducer group was RR 0.74 (95% CI 0.60-0.91); the RR of neonatal bleeding complications was 0.87 (95% CI 0.71-1.06) Separate analysis of phenobarbital was not reported.	
Tomson T, et al.[68] EURAP Study Group 2015	Prospective observational cohort study (Data from study initiation in 1999 through May 24, 2013)	7055 pregnancies exposed to AED monotherapy with lamotrigine (n=1910), carbamazepine (n=1713), (valproic acid n=1171), levetiracetam (n=324), oxcarbazepine (n=2662) or phenobarbital (n=260) and to polytherapy (n=1415)	At the time of conception	7.7% of phenobarbital pregnancies ended with a spontaneous abortion; 0.8% ended with stillbirth	Risk for intrauterine deaths were greater in women with a history of MCMs, a history of previous intrauterine deaths, and AED polytherapy.
Barroso FV, et al.[69] 2015 Brazil	Retrospective case-control longitudinal	Pregnant women exposed to AEDs n=82, 32 exposed to phenobarbital	Exposure anytime during pregnancy	No statistical difference in MCMs; stillbirths, neonatal deaths, or low birth weight. Increased risk for hemorrhagic	No separate analysis by individual drug, no untreated disease comparator group, small sample size

[68] Tomson T, et al. Antiepileptic drugs and intrauterine death: a prospective observational study from EURAP. Neurology. 2015;85:580-588.
[69] Barroso FV, et al. Perinatal outcomes from the use of antiepileptic drugs during pregnancy: a case-control study. J Matern Fetal Neonatal Med. 2015;28(12):1445-50.

	study (10-year follow-up)	monotherapy/25 phenobarbital as part of polytherapy) compared to unexposed pregnant women (n=316		complications in women taking AEDs (6.2% vs 0.09%, p=0.011)	
Gopinath N, et al.[70] 2015 India	Prospective registry of epilepsy and pregnancy	Children of mothers with epilepsy 16 children were unexposed in utero, 112 were exposed to AED monotherapy and 61 exposed to polytherapy Phenobarbital monotherapy exposed n=22	Mother's enrolled preconception or during the first trimester of pregnancy	Full Scale IQ of children born to women with epilepsy was 8.5 points lower than unexposed matched controls. Full scale IQ for children exposed to was significantly lower (p=0.01) compared to unexposed controls.	Infants screened for malformations by clinical at birth and again at 3 months. Mental and motor development assessed at 1 year of age. Intelligence and language assessed at age 6, then again at ages 10-12 (which are discussed in this paper) IQ assessed though the Wechsler Intelligence Scale for Children 4th edition (WISC_IV); visual memory assessed by Wechsler Memory Scale Visual Representation and Rey Auditory verbal learning test (RAVLT) Attention was assessed using the Trail Making Test The authors note that the dosage used for phenobarbital was high compared to valproate and propose this as a factor in its effect on intelligence.
Tica OS, et al.[71] 2013 Romania	Case report	37-week stillborn fetus	Exposed to phenobarbital 0.1 gm/day and carbamazepine 0.4 mg/day for the first 4 months of gestation, then	Stillborn fetus presented with sirenomelia type II with oligohydramnios, absence of a bladder, kidney, rectum, uterus, and a single umbilical artery	

[70] Gopinath N, et al. Children (10-12 years of age) of women with epilepsy have lower intelligence, attention and memory: observations from a prospective cohort case-control study. Epilepsy Research. 117:58-62.
[71] Tica OS, et al. Sirenomelia after phenobarbital and carbamazepine therapy in pregnancy. Birth Defects Res A Clin Mol Teratol. 2013;97(6):425-8.

			phenobarbital 0.1mg/day until the end of pregnancy		
Hernandez-Diaz S, et al.[72] US 2012	Prospective cohort study (North American AED Pregnancy Registry) 1997-2011.	5,667 AED monotherapy-exposed pregnant women (phenobarbital n= 199) 442 AED unexposed pregnant women without epilepsy	First trimester	There were 11 (5.5%) MCMs in the phenobarbital-exposed group. The RR was 5.1 (95% CI 1.8-14.9) compared to unexposed comparator, and RR 2.9 (95% CI 1.4-5.8) compared to lamotrigine-exposed Phenobarbital was associated with a higher risk for cardiac malformations and oral clefts compared to unexposed.	Confounders included in the analysis included maternal age, race, education, alcohol use, smoking, folic acid supplementation, illicit drug use, chronic diseases, and calendar year.
Zuppa AA, et. al.[73] 2011 Italy	Retrospective cohort study	23 infants born to mothers exposed to phenobarbital during gestation	Exposed to phenobarbital at time of delivery	11 infants (47.8%) had symptoms of either sedation or withdrawal, one full-term SGA infant had severe cardiorespiratory depression at birth requiring intubation and ventilation. None of the infants had severe neonatal abstinence syndrome. All infants had serum levels of phenobarbital in the therapeutic range at birth.	Study examined infants born at a single university hospital during a 7-year time-period.
Tomson T, et al.[74] EURAP 2011	Prospective cohort study (EURAP) from	4540 pregnancies exposed to AED monotherapy	First trimester	In the phenobarbital <150 mg/day there were 157 normal infants and 9 with malformations (2 cardiac, 1	Confounders included in the analysis were maternal age, parental history of MCMs,

[72] Hernandez-Diaz S, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012;78:1692-1699.
[73] Zuppa AA, et al. Infants born to mothers under phenobarbital treatment: correlation between serum levels and clinical features in neonates. Eur J Obstet Gynecol Reprod Biol. 2011;159(1):53-6.
[74] Tomson T, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of date from the EURAP epilepsy and pregnancy registry. Lancet Neurology. 2011;10-609-617.

	initiation in 1999 through June 9, 2010.	carbamazepine (n=1402), lamotrigine (n=1280), valproic acid (n=1010), or phenobarbital (n=217)		hypospadias, 1 neural tube defect, 1 polydactyly, 1 renal and 3 "other") In the phenobarbital exposed group ≥ 150 mg there were 44 normal infants, and 7 with malformations (4 cardiac, 1 oro-facial cleft, 1 polydactyly, and 1 "other") Compared to lamotrigine < 300 mg/day, phenobarbital was associated with a greater risk of MCMs OR 2.5 (95% CI 1.11-5.85) and this risk increased with phenobarbital doses greater than 150 mg/day OR 8.2 (95% CI 3.16-21.53)	geographic region, parity, type of epilepsy, education, folic acid use, and sex of the child
Timmerman G, et al.[75] Hungary 2009	Retrospective observational study of infant pregnant women who overdosed on phenobarbital (1960-1993) compared to their unexposed siblings	Children of 1044 self-poisoned women (phenobarbital-exposed n=88; 34 during the first trimester)	34 first trimester exposures	There were 3 MCMs in children exposed to phenobarbital during the first trimester (1 diaphragmatic defect, 1 undescended testes and 1 with multiple defects) The risk of MCMs was not greater in the phenobarbital-exposed group compared to unexposed siblings OR 1.4, 95% CI 0.6-3.5)	These were acute, one-time exposures for most pregnancies; only one woman who overdosed was being treated for epilepsy.

[75] Timmerman G, et al. Congenital abnormalities of 88 children born to mothers who attempted suicide with phenobarbital during pregnancy: the use of a disaster epidemiological model for the evaluation of drug teratogenicity. Pharmacoepidemiology and Drug Safety. 2009;18:815-825.

Table 2. Major malformation percentages in various pregnancy registries.

-	Hernandez-Diaz, 2012 (NAAPR)[a]	Campbell, 2014 (UKEPR)[b]	Tomson, 2018 (EURAP)[c]	Blotière 2019 (French National Health Insurance Claims Data)[d]	Vajda 2019 (Australian Pregnancy Register (APR))[e]
Phenytoin (PHT)	2.9% (95% CI 1.5–5.0) n=12/416	NA	6.4% (95% CI 2.8–12.2) n=8/125	NA	2.3% n=1/44
Phenobarbital (PB)	5.5% (95% CI 2.8–9.7) n=11/199	NA	6.5% (95% CI 4.2–9.9) n=19/294	2.5% n=2/80	NA
Carbamazepine (CBZ)	3.0% (95% CI 2.1–4.2) n= 31/1033	2.6% (95% CI 1.9%-3.5%) n=43/1657	5.5% (95% CI 4.5–6.6) n=107/1957	1.2% n=6/512	5.9% n=24/409
Valproate (VPA)	9.3% (95% CI 6.4–13.0) n=30/323	6.7% (95% CI 5.5%-8.3%) n=82/1220	10.3% (95% CI 8.8–12.0) n=142/1381	6.0% n=55/913	14.8% n=43/290
Lamotrigine (LTG)	2.0% (95% CI 1.4–2.8) n=31/1562	2.3% (95% CI 1.8%-3.1%) n=49/2098	2.9% (95% CI 2.3–3.7) n=74/2514	1.5% n=44/2997	4.9% n=20/406
Levetiracetam (LEV)	2.4% (95% CI 1.2–4.3) n=11/450	NA	2.8% (95% CI 1.7–4.5) n=17/599	1.2% n=7/579	3.6% n=5/139

[a,b,c] All data were given as percentage, 95% confidence interval of prevalence, and the number of malformations among pregnancies exposed to the particular AED.
[d, e] All data were given as percentage, and the number of malformations among pregnancies exposed to the particular AED.
[d] Percentages were calculated from the raw data in the article.
[d,e] 95% Confidence interval (CI) was not reported.

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CATHERINE A ROCA
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LYNNE P YAO
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	October 26, 2022
Reviewer:	Karen Long, PharmD, Safety Evaluator Division of Pharmacovigilance I (DPV I)
Team Leader:	Allen Brinker, MD, MS DPV I
Division Director:	Cindy Kortepeter, PharmD DPV I
Product Name:	Sezaby (phenobarbital injection)
Subject:	Serious hypersensitivity reactions, infusion-site or injection-site reactions, laryngospasm, hypotension, and hypertension
Application Type/Number:	NDA 215910
Applicant/Sponsor:	Sun Pharmaceutical Industries, Inc.
TTT Record ID:	2022-1765, 2022-1975

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for an association between phenobarbital and serious hypersensitivity reactions, infusion-site or injection-site reactions, laryngospasm, hypotension, and hypertension. For purposes of this review, serious hypersensitivity reactions included drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), and anaphylaxis; infusion-site or injection-site reactions included tissue necrosis/gangrene, thrombosis, or thrombophlebitis. Division of Neurology 2 (DN2) requested this review to assist with proposed labeling for NDA 215910, Sezaby (phenobarbital injection). Only cases reporting phenobarbital injection were included for analysis of infusion-site or injection-site reactions, hypotension, and hypertension. Although this review was prompted by pending regulatory action for an injectable product, cases associated with oral phenobarbital were added for the analysis of serious hypersensitivity reactions as these adverse events may take more time to develop.

DPV identified a total of 71 FAERS and medical literature cases with reasonable evidence of a causal association to phenobarbital reporting the following adverse events: DRESS (28), SJS/TEN (30), administration site necrosis/gangrene (4), administration site thrombophlebitis (2), anaphylaxis (3), infusion-related hypotension (4), and infusion-related hypertension (1); one case reported overlapping DRESS and SJS/TEN and is included in both case series. All 28 cases of DRESS were assessed with a probable causal association with phenobarbital. The median time to onset was 18 days (mean 20.2, range 5-60). Most cases of SJS/TEN (22 of 30) were assessed with a probable causal association with phenobarbital; the cases assessed with possible causal association did not provide sufficient information regarding time to onset or event resolution. The median time to onset was 14 days (mean 13.6, range 1-30).

Two of the four cases of necrosis were assessed with a probable causal association with phenobarbital; the other two cases (one intramuscular and one intravenous) were assessed with a possible causal association because they reported administration of phenobarbital with other concomitant medications at the site. One of the two cases of thrombophlebitis was assessed with a probable causal association with phenobarbital; the other case did not provide sufficient information regarding event resolution. The three cases of anaphylaxis and four cases of infusion-related hypotension occurred on the same day as phenobarbital administration. One case of anaphylaxis and two cases of hypotension were assessed with a probable causal association with phenobarbital; the cases assessed with possible causal association reported possible concomitant suspect products or did not provide sufficient information regarding event resolution. The one case of infusion-related hypertension was assessed with a possible causal association with phenobarbital; the case did not report details on the adverse event or information on treatment.

Most cases (66/71) reported a serious regulatory outcome, including death (9), life-threatening (10), hospitalization (59), disability (4), required intervention (6), and other serious outcomes (11); a case can have more than one serious outcome. Four of the 28 cases of DRESS reported death; two occurred secondary to respiratory failure, one from hepatic failure, and one from multiorgan failure (including hepatic failure). Most cases (27 of 28) reported other organ

involvement, primarily liver. Four of the 30 cases of SJS/TEN reported death; two occurred secondary to hepatic failure, one from complications of TEN including infection, and one from sepsis and gastrointestinal hemorrhage. Approximately half of the cases (16 of 30) reported extensive injury with body surface area >30%. All four cases of necrosis reported serious outcomes; three required amputation and one required skin grafting. DPV identified two non-serious cases of thrombophlebitis from intravenous administration not requiring interventions. All three cases of anaphylaxis reported serious outcomes and reported treatment interventions. Three of the four cases of infusion-related hypotension reported serious outcomes. One case of hypotension reported death and did not report additional details on the adverse event, administration of concomitant medications, or information on treatment.

Administration site necrosis/gangrene or thrombophlebitis and hypotension with intravenous administration are known adverse events associated with the use of barbiturate therapy. In addition, there is likely under-reporting of adverse events with phenobarbital in spontaneous reporting systems, including FAERS, because of its long history of use on the market and known adverse events in labeling for unapproved phenobarbital injection.

Because of the severity of the events and need for prompt intervention to mitigate the adverse event, DPV recommends the addition of DRESS, SJS/TEN, infusion-site and injection-site reactions (tissue necrosis/gangrene, thrombophlebitis), anaphylaxis, and infusion-related hypotension to the WARNINGS AND PRECAUTIONS section of the labeling. Given the severity of these events and the importance of prescriber awareness and patient counseling, we also recommend changes to the (b) (4) labeling and MEDICATION GUIDE to reflect the potential risk of DRESS and SJS/TEN with phenobarbital.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for an association between phenobarbital and serious hypersensitivity reactions, infusion-site or injection-site reactions, laryngospasm, hypotension, and hypertension. For purposes of this review, serious hypersensitivity reactions included drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), and anaphylaxis; infusion-site or injection-site reactions included tissue necrosis/gangrene, thrombosis, or thrombophlebitis. Division of Neurology 2 (DN2) requested this review to assist with proposed labeling for NDA 215910, Sezaby (phenobarbital injection). Only cases reporting phenobarbital injection were included for analysis of infusion-site or injection-site reactions, hypotension, and hypertension. Although this review was prompted by pending regulatory action for an injectable product, cases associated with oral phenobarbital were added for the analysis of serious hypersensitivity reactions as these adverse events may take more time to develop.

1.1 BACKGROUND AND REGULATORY HISTORY

Phenobarbital is a long-acting barbiturate that is an unapproved prescription drug product; it was first used as a sedative hypnotic and antiepileptic drug (AED) in 1912.[1] FDA permits some unapproved prescription drugs to be marketed if the drug is subject to an open drug efficacy study implementation (DESI) program proceeding, health care professionals rely on the drug to treat serious medical conditions when there is no FDA-approved drug to treat the condition, or there is insufficient supply of an FDA-approved drug.[2]

Phenobarbital injection and oral tablets/solution are currently marketed in the United States as unapproved prescription drug products by several manufacturers. The injection is available as 65 mg/mL and 130 mg/mL vials, containing alcohol, propylene glycol, and benzyl alcohol in water for injection. Phenobarbital injection in its current formulation with the preservative benzyl alcohol is not recommended for use in neonates because of the risk for fatal "gasping syndrome" characterized by a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse. Phenobarbital tablets are available in various doses (15, 16.2, 30, 32.4, 60, 64.8, 97.2, and 100 mg) and oral solution is available as 20 mg/5ml.[3,4,5,6]

In February 2022, Sun Pharmaceutical Industries, Inc. submitted NDA 215910 under rare pediatric disease priority review for a preservative-free phenobarbital injection solution 100 mg per vial for the treatment of neonatal seizures. The product is a lyophilized powder for reconstitution with sodium chloride, free of benzyl alcohol and propylene glycol, and is a highly alkaline solution (pH range 9.2-10). DN2 consulted the Division of Pharmacovigilance (DPV) to review FAERS and the medical literature for cases of phenobarbital with serious hypersensitivity reactions, infusion-site or injection-site reactions, laryngospasm, hypotension, and hypertension to inform the proposed labeling. For purposes of this review, serious hypersensitivity reactions included DRESS, SJS/TEN, and anaphylaxis; infusion-site or injection-site reactions included tissue necrosis/gangrene, thrombosis, or thrombophlebitis. Only cases reporting phenobarbital injection were included for analysis of infusion-site or injection-site reactions, hypotension, and hypertension.

1.2 RELEVANT PRODUCT LABELING

Unapproved phenobarbital injection currently has the following excerpted information regarding hypersensitivity reactions and intravenous administration:[3]

WARNINGS
Dermatologic Reactions
Exfoliative dermatitis and Stevens-Johnson syndrome, possibly fatal, are rare hypersensitivity reactions to phenobarbital. Physicians should be alert to signs which may precede the onset of barbiturate-induced cutaneous lesions, and the drug should be discontinued whenever dermatological reactions occur.

Intravenous Administration
Too rapid administration may cause severe respiratory depression, apnea, laryngospasm, hypertension or vasodilation with fall in blood pressure.

PRECAUTIONS
Parenteral solutions of barbiturates are highly alkaline. Therefore, extreme care should be taken to avoid perivascular extravasation or intraarterial injection. Extravascular injection may cause local tissue damage with subsequent necrosis; consequences of intraarterial injection may vary from transient pain to gangrene of the limb. Any complaint of pain in the limb warrants stopping the injection.

DOSAGE AND ADMINISTRATION
Intravenous Administration
Intravenous injection is restricted to conditions in which other routes are not feasible, either because the patient is unconscious (as in cerebral hemorrhage, eclampsia or status epilepticus), or because the patient resists (as in delirium) or because prompt action is imperative. Slow IV injection is essential, and patients should be carefully observed during administration. This requires that blood pressure, respiration and cardiac function be maintained, vital signs be recorded and equipment for resuscitation and artificial ventilation be available. The rate of intravenous injection for adults should not exceed 60 mg/min for phenobarbital sodium.

When given intravenously, do not use small veins, such as those on the dorsum of the hand or wrist. Preference should be given to a larger vein to minimize the risk of irritation with the possibility of resultant thrombosis. Avoid administration into varicose veins because circulation there is retarded. Inadvertent injection into or adjacent to an artery has resulted in gangrene requiring amputation of an extremity or a portion thereof. Careful technique, including aspiration, is necessary to avoid inadvertent intraarterial injection.

Treatment of Adverse Effects Due to Inadvertent Error in Administration
Extravasation into subcutaneous tissues causes tissue irritation. This may vary from slight tenderness and redness to necrosis. Recommended treatment includes the application of moist heat and the injection of 0.5% procaine solution into the affected area.

Intraarterial injection of any barbiturate must be avoided. The accidental intraarterial injection of a small amount of the solution may cause spasm and severe pain along the course of the artery. The injection should be terminated if the patient complains of pain or if other indications of accidental intraarterial injection occur, such as a white hand with cyanosed skin or patches of discolored skin and delayed onset of hypnosis.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

DPV used the case definition criteria in **Table 1** to develop the case series for this analysis.

Table 1. Case Definition Criteria

Adverse Event	Inclusion Criteria (Any of the Following)	Exclusion Criteria*
DRESS†	• HCP reported diagnosis of DRESS • HCP reported diagnosis of anticonvulsant hypersensitivity syndrome with clinical manifestations compatible with DRESS[7,8] (see **Appendix A**)	• Cases reporting toxic drug-induced exanthema or differential diagnosis of other serious skin reaction
SJS/TEN†	• HCP reported diagnosis of SJS/TEN • Non-HCP reported diagnosis of SJS/TEN requiring hospitalization and describing clinical manifestations compatible with SJS/TEN[9] (see **Appendix B**)	• Cases reporting a diagnosis of any of the following: staphylococcal scalded skin syndrome (SSSS), linear IgA dermatosis, pemphigus (any type), acute graft-versus-host disease, pemphigoid, acute generalized exanthematous pustulosis (AGEP), toxic shock syndrome, Kawasaki syndrome, and generalized bullous fixed drug eruption.
Infusion site or injection site reactions‡	• HCP reported infusion site or injection site reactions including necrosis, gangrene, thrombosis, or thrombophlebitis	• Cases reporting thrombosis or necrosis not localized to administration site (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism, hepatic necrosis, etc.)
Anaphylaxis†	• HCP reported anaphylactic reaction • Cases describing clinical manifestations consistent with World Allergy Organization criteria[10] (see **Appendix C**)	• Cases reporting "shock" not referring to cardiovascular related adverse events
Laryngospasm†	• HCP reported laryngospasm	
Hypotension‡	• HCP reported infusion-related decrease in blood pressure, hypotension, or cardiovascular shock	• Cases reporting use of oral phenobarbital administration or transplacental phenobarbital exposure
Hypertension‡	• HCP reported infusion-related increase in blood pressure or hypertension	• Cases reporting use of oral phenobarbital administration or transplacental phenobarbital exposure

* Note: Patients receiving phenobarbital as part of an outpatient regimen or as part of a multi-drug oral intentional overdosage were assumed to receive oral phenobarbital
† Included cases reporting phenobarbital injection and oral administration
‡ Included cases reporting phenobarbital injection only
Abbreviations: HCP=healthcare professional

2.2 CAUSALITY CRITERIA

We assessed all cases meeting the case definition described in Section 2.1 for a causal association with phenobarbital using elements from the guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*.[11] We categorized the cases as probable, possible, unlikely, or unassessable based on the strength of the evidence for a causal association as described in **Table 2**. We excluded cases we assessed as unlikely or unassessable from further analysis.

Table 2. Causality Classification and Criteria

Category	Assessment Criteria
Probable	• Event with plausible temporal sequence to drug intake • Absence of factors with a potential contributory or confounding role; may have factors with an incidental role • Response to drug withdrawal is clinically reasonable (positive dechallenge)
Possible	• Event with plausible or reasonable yet less plausible temporal sequence to drug intake • Presence of factors with a potential contributory role • Information on drug disposition may be lacking or unclear • Information on medical history or concomitant medications may be lacking or unclear
Unlikely	• Event with improbable temporal sequence to drug intake • Presence of factors with a confounding role
Unassessable	• Causality cannot be assessed because information is insufficient or contradictory

We adapted the following definitions and assessment criteria from the World Health Organization (WHO) – Uppsala Monitoring Centre (UMC) Causality Categories[12] and Antoniri and colleagues[13] to assess causality:

- Plausible temporal sequence to drug intake
  - A positive argument in support of the view that the drug is causally involved, pharmacologically or pathologically (i.e., the temporal sequence plausibility is based on the known safety profile and effects of the drug)
- Incidental role of factors other than the suspect drug
  - Having no or an insignificant effect on the adverse event reported and on the assessment of the causal role of the suspect drug
- Contributory role of factors other than the suspect drug
  - Having some potential effect on the adverse event reported while allowing the assessment of the causal role of the suspect drug
- Confounding role of factors other than the suspect drug
  - Having a potentially significant effect on the adverse event reported precluding the assessment of the causal role of the suspect drug
- Positive dechallenge
  - A response (i.e., resolution of events) after suspect drug withdrawal (discontinuation or dose reduction) that is clinically reasonable, with or without treatment; this may occur in the setting of co-suspect or concomitant drug withdrawal

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 3**.

Table 3. FAERS Search Strategy*	
Date of search	September 30, 2022
Time period of search	All reports through September 29, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: PHENOBARBITAL, PHENOBARBITAL CALCIUM, PHENOBARBITAL DIETHYLAMINE, PHENOBARBITAL SODIUM
MedDRA search terms (Version 25.0)	**Search #1**† **PTs:** *Laryngospasm, Hypotension, Neonatal hypotension, Blood pressure decreased* **HLTs:** *Angioedemas* **SMQs:** *Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ) Narrow search, Severe cutaneous adverse reactions (SMQ) Narrow search, Anaphylactic reaction (SMQ) Narrow search, Anaphylactic/anaphylactoid shock conditions (SMQ) Narrow search,*
	Search #2 **HLTs:** *Skin ischaemic conditions, Necrosis NEC* **HLGT:** *Administration site reactions* **SMQs:** *Thrombophlebitis (SMQ) Broad search, Embolic and thrombotic events (SMQ) Narrow search*
	Search #3 **SMQ:** *Hypertension (SMQ) Narrow search*
* See **Appendix D** for a description of the FAERS database. † FAERS search restricted to U.S. reports only. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, HLGT=High Level Group Term, HLT=High Level Term, PT=Preferred Term	

2.4 LITERATURE SEARCH STRATEGY

DPV searched the medical literature for case reports with the strategy described in **Table 4**.

Table 4. Literature Search Strategy	
Date of search	October 6, 2022
Database	1. Embase 2. PubMed

Table 4. Literature Search Strategy	
Search terms	1. ('phenobarbital'/exp/mj OR 'phenobarbital'/mj) AND ('severe cutaneous adverse reaction'/exp/mj OR 'severe cutaneous adverse reaction'/mj OR 'dress syndrome'/exp/mj OR 'dress syndrome'/mj OR 'anaphylaxis'/exp OR 'anaphylaxis' OR 'angioneurotic edema'/exp OR 'angioneurotic edema' OR 'hypotension'/exp/mj OR 'hypotension'/mj OR 'shock'/exp/mj OR 'shock'/mj OR 'larynx spasm'/exp OR 'larynx spasm' OR 'larynx disorder' OR 'thromboembolism'/exp OR 'thromboembolism' OR 'thrombophlebitis'/exp OR 'thrombophlebitis' OR 'thrombosis'/exp OR 'thrombosis' OR 'extravasation'/exp OR 'extravasation' OR 'necrosis'/exp OR 'necrosis' OR 'infusion reaction'/exp OR 'infusion reaction' OR 'infusion site extravasation'/exp OR 'infusion site extravasation' OR 'infusion site reaction'/exp OR 'infusion site reaction' OR 'gangrene' OR 'intraarterial drug administration'/exp OR 'intraarterial drug administration' OR 'hypertension'/exp/mj OR 'hypertension'/mj) 2. (phenobarbital) AND ((stevens johnson syndrome) OR (toxic epidermal necrolysis) OR (DRESS) OR (drug reaction with eosinophilia and systemic symptoms) OR (anticonvulsant hypersensitivity) OR (anaphylaxis) OR (angioedema) OR (laryngospasm) OR (hypotension) OR (shock) OR (thrombosis) OR (thrombophlebitis) OR (thromboembolism) OR (extravasation) OR (necrosis) OR (gangrene) OR (injection site reaction) OR (infusion site reaction) OR (intra-arterial) OR (hypertension)
Years included in search	All years through 2022
Other criteria	Limits: Human, English

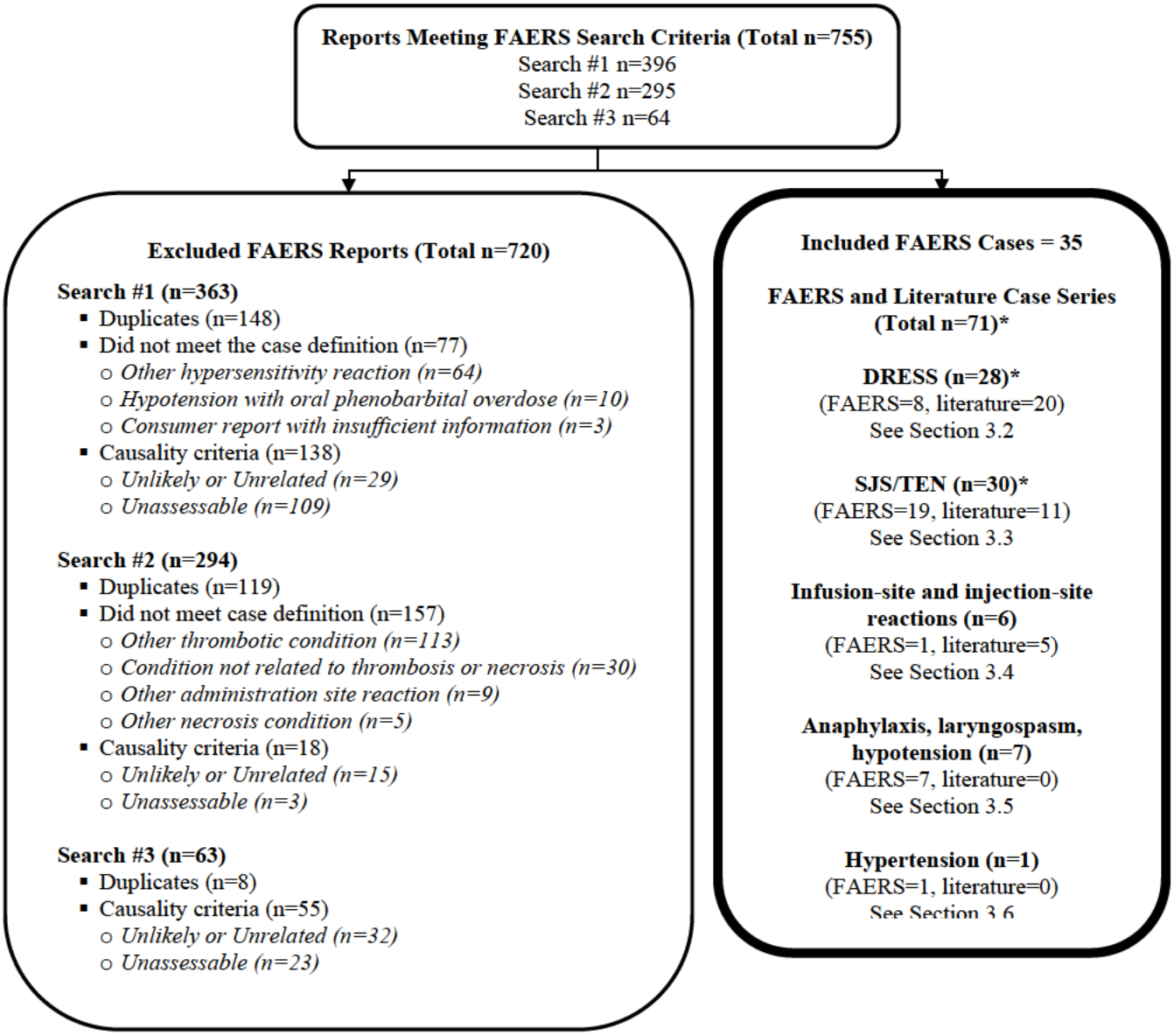
3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

The FAERS search retrieved 755 reports. DPV developed the FAERS case series as shown in **Figure 1** after applying the case definitions in Section 2.1, the causality criteria in Section 2.2, accounting for duplicate reports, and reviewing the medical literature for additional case reports not retrieved from the FAERS search. The cases are further discussed in Sections 3.2-3.6 below.

Appendix E contains a line listing of the 71 cases in this case series.

Figure 1. FAERS and Literature Case Selection



* Literature case reports were identified from the search strategy outlined in Section 2.4. FAERS includes any case identified in either FAERS alone or in both FAERS and the literature. Literature includes cases only identified in the literature. One FAERS case reported overlapping DRESS and SJS/TEN and is included in both case series.

3.2 Drug Reaction with Eosinophilia and Systemic Symptoms (n=28)

DPV identified 28 cases reporting DRESS (FAERS=8, literature=20) with reasonable evidence of a causal association to phenobarbital use; one case reported overlapping DRESS and SJS/TEN and is included in both case series. All 28 cases were assessed with a probable causal association with phenobarbital. All 28 cases reported serious outcomes and treatment interventions. Four cases reported death; two occurred secondary to respiratory failure, one from hepatic failure, and one from multiorgan failure (including hepatic failure).

Table 5 summarizes the 28 FAERS and medical literature cases of DRESS reported with phenobarbital for this case series.

Table 5. Descriptive Characteristics of DRESS With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA Through September 29, 2022 or Published Through October 6, 2022 (N=28)		
Case source[*] and FAERS report type	**FAERS**	**8**
	15-Day	5
	Direct	3
	Literature	**20**
Year received by FDA or published[*]	FAERS	2011 (3), 2015 (4), 2017 (1)
	Literature	1971 (1), 1986 (1), 1989 (1), 1992 (1), 1997 (1), 2003 (2), 2005 (1), 2007 (1), 2008 (1), 2009 (1), 2011 (1), 2013 (3), 2014 (1), 2017 (1), 2018 (1), 2021 (1), 2022 (1)
Country derived	USA	10
	Foreign	18
Age (years)	Mean	15.4
	Median	5.25
	Range	10 months – 84 years
Sex	Female	18
	Male	10
Serious outcome(s)[†]	Death	4
	Life-threatening	2
	Hospitalization	28
	Other serious	4
Reported reason for use (n=27)	Seizure/epilepsy	17
	Febrile seizures	4
	Seizure prophylaxis	3
	Neonatal seizure	1
	Icter	1
	Cerebral metastasis	1
Total daily dose (mg) (n=16)	Mean	86.7
	Median	100
	Range	15-194.4
	Other:	4 mg/kg/day (2), 5 mg/kg/day (1)
Route of administration (n=24)	Oral	22
	Intravenous, then oral	2
Time to onset (days)	Mean	20.2
	Median	18
	Range	5-60

Table 5. Descriptive Characteristics of DRESS With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA Through September 29, 2022 or Published Through October 6, 2022 (N=28)			
Reported signs and symptoms‡	Rash	28	
	Fever	26	
	Eosinophilia	23	
	Lymphadenopathy	17	
	Atypical lymphocytes	6	
	Leukocytosis	4	
	Thrombocytopenia	4	
	Other hematological	3	
Other organ involvement‡ (n=27)	Liver	26	
	Liver failure	4	
	Lung	6	
	Heart	2	
	Kidney	1	
	Pancreas	1	
	CNS§	1	
Therapeutic interventions‡	Hospitalization treatment NOS		25
	Intensive care treatment NOS		3
	Corticosteroids		22
	IVIG		9
	Antipyretics		8
	Antimicrobials		7
	Antihistamines		3
	Intubation		2
	Wound care/dressing		1
Drug disposition	Discontinued	28	
Event resolution	Resolved with treatment	24	
	Progressed to death	4	
Time to event resolution (days) (n=19)	Mean	69.8	
	Median	37.5	
	Range	5 days – 1 year	
	Other:	unspecified “weeks” later (3)	
Causality assessment	Probable	28	

* FAERS - Includes any case identified in either FAERS alone or in both FAERS and the literature
Literature - Includes cases only identified in the literature

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. Literature cases were assigned an outcome of death or hospitalization if this information was reported in the case.

‡ A case can have more than one characteristic.

§ One case reported limbic encephalitis and syndrome of inappropriate antidiuretic hormone secretion

Abbreviations: NOS=not otherwise specified, IVIG=intravenous immunoglobulin

Three example cases of DRESS with phenobarbital are described below. The cases provide reasonable evidence of a causal association with phenobarbital, with a plausible temporal relationship and absence of factors with a potential contributory or confounding role. The first case reports death from DRESS progression and multiorgan failure. The latter two cases report a clinically reasonable response to drug withdrawal after receiving treatment; the prolonged time to resolution of symptoms even with treatment in these cases is consistent with DRESS.

Literature article: Chen et al., TWN, 2003, Outcome: DE, HO

A literature article[14] reported a 3-month-old female experienced DRESS with multiorgan failure 2 weeks after receiving phenobarbital 4 mg/kg PO daily for new onset seizures, resulting in death. Two weeks after phenobarbital initiation, she developed fever and rash over both feet; she was admitted to the emergency department and diagnosed with viral exanthem and treated with acetaminophen and antihistamine and continued phenobarbital. Ten days later she was hospitalized for persistent fever and progressive rash. On hospital day 1 (24 days after phenobarbital initiation), she presented with hepatosplenomegaly, cervical lymphadenopathy, and generalized morbilliform eruptions without desquamation. Laboratory values showed elevated leukocyte count of 19.9 x 10^9/L (3% band forms, 52% neutrophils, 35% lymphocytes, 8% monocytes, 1% atypical lymphocytes) and elevated hepatic enzymes (ALT 159 U/L, AST 202 U/L). On day 2 phenobarbital was discontinued. One week after admission the patient developed hepatic failure, pleural effusions, and ascites. Laboratory values showed hypoalbuminemia (albumin 2.4 g/dL), conjugated hyperbilirubinemia (direct bilirubin 5.1 mg/dL), coagulopathy (prothrombin time >l00 s), hyperammonemia (ammonia 394 ug/dL), and elevated hepatic enzymes (ALT 330 U/L, AST 823 U/L). Virological investigations for cytomegalovirus, human herpes virus type 6, hepatitis B virus, and Epstein-Barr virus and urine and blood cultures were all negative. The patient received intravenous immunoglobulin 1 g/kg and methylprednisolone 2 mg/kg per day, but events progressed and she subsequently developed multiorgan failure and expired 2 weeks after hospitalization (38 days after phenobarbital initiation).

FAERS #8007638v1, MCN: 2011MA006387, USA, 2011, Outcomes: HO, OT

A literature article[15] reported a 2-year-old male experienced DRESS with hepatitis approximately 3 weeks after receiving phenobarbital 60 mg PO daily for febrile seizures. Medical history included frequent febrile seizures since 6 months of age. Concomitant medications at time of hospital admission included acetaminophen, ibuprofen, rectal diazepam as needed, loratadine, diphenhydramine, and multivitamin. After 2 weeks of phenobarbital initiation, the dose was titrated up to 60 mg daily. Soon thereafter, he developed a rash on his cheeks that quickly spread to his entire body, and during the week prior to hospital admission the rash progressed with fever and shaking episodes diagnosed as rigors. The patient was admitted to the hospital for presumed bronchiolitis with viral exanthem. He presented with a diffuse morbilliform rash on his cheeks and upper chest with mild desquamation of the cheeks and periorbital and perioral edema. Laboratory values showed elevated WBC count 20,100 cells/mm^3 with 31% atypical lymphocytes, and elevated liver enzymes (ALT 441 U/L, AST 328 U/L, with normal bilirubin and ALP). On day 1 of hospital admission (4 weeks after phenobarbital initiation), phenobarbital and ibuprofen were discontinued; he was transferred to the intensive care unit and received IV fluid resuscitation, supplemental oxygen, acetaminophen,

vancomycin, and ceftriaxone. On day 2, he received intravenous immunoglobulin 2 g/kg and prednisolone 1 mg/kg BID. On day 3, skin biopsy confirmed a hypersensitivity reaction. On day 7, liver function tests peaked (ALT 729 U/L, AST 851 U/L, ALP 531 U/L, total bilirubin 5.2 mg/dL); vitamin K was given for asymptomatic mild coagulopathy. His daily fevers were treated with ice packs and ibuprofen. His fever, rash, and hepatic enzymes improved and he was discharged on hospital day 12 with a 4-week steroid taper. A transient recurrence of rash occurred after the 4-week taper and the steroid taper was extended an additional 2 weeks with resolution of symptoms.

FAERS #11820098v1, MCN: 2015RIS00167, USA, 2015, Outcomes: HO, OT

A literature article[16] reported a 2-year-old female experienced DRESS with myocarditis, hepatitis, and acute kidney injury 1 month after receiving phenobarbital at an unknown dose and route for an unknown indication. On day 1 of hospital admission (6 weeks after phenobarbital initiation), the patient presented with fever, facial edema, bilateral cervical adenopathy, and a desquamating erythematous rash on the face, trunk, and extremities; symptoms started 1 month after initiating phenobarbital. Laboratory values showed elevated WBC count 25,000/uL (30% neutrophils, 50% lymphocytes, 5% monocytes, 14% eosinophils, 1% metamyelocytes), and elevated liver enzymes (ALT 456 U/L, AST 446 U/L, ALP 193 U/L). The patient was initially treated with intravenous immunoglobulin 2 g/kg for presumed Kawasaki disease at an outside hospital and was diagnosed with DRESS confirmed by skin biopsy when transferred to the secondary hospital. She then received methylprednisolone 0.5 mg/kg/dose q6h. A week into her hospitalization, she developed acute-onset hypotension, lactic acidosis, and acute kidney injury. An echocardiogram revealed global hypokinesis, left ventricular dilation, mild mitral and tricuspid valve regurgitation, and decreased contractility consistent with the diagnosis of myocarditis. After a 3-week hospitalization she was discharged with prednisone 2 mg/kg/day for 4 months followed by tapering. During her steroid taper she developed relapse of her rash and was treated with high dose IV methylprednisolone. After a duration of 7 months, she was admitted again for relapse after another attempted tapering and treated with intravenous immunoglobulin 2 g/kg and maintained on prednisone 0.5 mg/kg/day; echocardiogram showed normal cardiac function.

3.3 STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS (N=30)

DPV identified 30 cases reporting SJS/TEN (FAERS=19, literature=11) with reasonable evidence of a causal association to phenobarbital use; one case reported overlapping DRESS and SJS/TEN and is included in both case series. Most cases (22 of 30) were assessed with a probable causal association with phenobarbital; the cases assessed with possible causal association did not provide sufficient information regarding time to onset or event resolution. Most cases (28 of 30) reported serious outcomes and 29 cases reported treatment interventions (1 case did not report treatment information). Four cases reported death; two occurred secondary to hepatic failure, one from complications of TEN including infection, and one from sepsis and gastrointestinal hemorrhage.

Table 6 summarizes the 30 FAERS and medical literature cases of SJS/TEN reported with phenobarbital for this case series.

Table 6. Descriptive Characteristics of SJS/TEN With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA Through September 29, 2022 or Published Through October 6, 2022 (N=30)		
Case source[*] and FAERS report type	**FAERS**	**19**
	15-Day	3
	Direct	16
	Literature	**11**
Year received by FDA or published[*]	FAERS	1977 (1), 1978 (1), 1986 (1), 1989 (1), 1994 (1), 1995 (1), 1998 (2), 1999 (1), 2002 (1), 2003 (2), 2004 (2), 2005 (1), 2007 (1), 2009 (1), 2011 (1), 2012 (1)
	Literature	1973 (1), 2003 (1), 2005 (1), 2009 (4), 2012 (1), 2014 (1), 2021 (2)
Country derived	USA	10
	Foreign	20
Age (years)	Mean	12.1
	Median	4.5
	Range	2 months – 70 years
Sex	Female	16
	Male	14
Serious outcome(s)[†] (n=28)	Death	4
	Life-threatening	5
	Hospitalization	25
	Required intervention	5
	Disability	3
	Other serious	4
Reported reason for use	Seizure/epilepsy	21
	Febrile seizures	4
	Seizure prophylaxis	2
	Infantile seizure	1
	Post-traumatic epilepsy	1
	Trigeminal neuralgia	1
Total daily dose (mg) (n=20)	Mean	82.5
	Median	60
	Range	20-300
	Other:	5 mg/kg/day (2)
Route of administration (n=24)	Oral	23
	Intravenous, then oral	1
Time to onset (days) (n=25)	Mean	13.6
	Median	14
	Range	1-30[‡]

Table 6. Descriptive Characteristics of SJS/TEN With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA Through September 29, 2022 or Published Through October 6, 2022 (N=30)		
Reported signs and symptoms‡	Rash	30
	Mucus membrane involvement	22
	Fever	19
	BSA involvement >30%	16
	Ocular involvement	16
	Liver involvement	6
	Lung involvement	3
	Hematological	3
	Gastrointestinal involvement	2
Therapeutic interventions‡ (n=29)	Hospitalization treatment NOS	14
	Intensive care or burn unit NOS	14
	Corticosteroids	10
	Antimicrobials	7
	IVIG	5
	Wound care/dressing	5
	Surgical intervention	4
	Intubation	3
	Antihistamines	2
	Antipyretics	2
Drug disposition	Discontinued	30
Event resolution	Resolved with treatment	22
	Progressed to death	4
	Unknown	4
Time to event resolution (days) (n=13)	Mean	22
	Median	14
	Range	6-105
Causality assessment	Probable	22
	Possible	8

* FAERS - Includes any case identified in either FAERS alone or in both FAERS and the literature
Literature - Includes cases only identified in the literature
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. Literature cases were assigned an outcome of death or hospitalization if this information was reported in the case.
‡ One case reported previous TEN with primidone (primidone is metabolized to phenobarbital) and subsequent TEN a year later occurring 1 day after inadvertent phenobarbital exposure.
§ One case can have more than one characteristic.
Abbreviations: BSA=body surface area, NOS=not otherwise specified, IVIG=intravenous immunoglobulin

Three example cases of SJS/TEN with phenobarbital are described below. The cases provide reasonable evidence of a causal association with phenobarbital, with a plausible temporal relationship and absence of factors with a potential contributory or confounding role. The first case reports death from complications of TEN including infection. The latter two cases report a clinically reasonable response to drug withdrawal after receiving treatment.

FAERS #5914712v1, Direct Report, USA, 2005, Outcome: DE

A 13-month-old male experienced TEN 9 days after receiving phenobarbital 75 mg IV x 1 followed by 40 mg PO daily for febrile seizures, resulting in death. Medical history included bronchiectasis and eczema; no concomitant medications were reported. The patient was started on phenobarbital for febrile seizures that were increasing in frequency and associated with cyanosis and agonal breathing. On day 9 after phenobarbital initiation, the patient developed fever, diffuse erythema, and large cervical nodes; skin biopsy was consistent with TEN. On day 14, he received intravenous immunoglobulin therapy. On day 26, the patient died "from complications of TEN" including "Staph infections."

FAERS #3144054v1, Direct Report, USA, 1998, Outcomes: LT, HO

A 27-month-old male experienced SJS/TEN 19 days after receiving phenobarbital 30 mg PO BID for seizures. Medical history included seizure activity presumed secondary to fever; there were no concomitant medications. The patient developed bilateral rash on the ears and cheeks 19 days after phenobarbital initiation. He was hospitalized on day 24 with fever, upper respiratory symptoms, and worsened pustular rash that progressed to the entire body with open blisters; phenobarbital was discontinued. On day 25, he developed swelling around the lips and eyes. On day 29, he had significant areas of breakdown and sloughing over the entire body, including conjunctiva and oral mucosa. He was transferred to the burn unit and managed with aggressive wound care and nutritional support. On day 51, he was discharged with only a few remaining areas of skin breakdown.

Literature article: Kaputu-Kalala-Malu et al., COG, 2014, Outcome: Hospitalization

A literature article[17] reported a 2.5-year-old male experienced TEN 12 days after receiving phenobarbital 50 mg (3.8 mg/kg/dose) PO daily for generalized tonic-clonic epileptic seizures. The patient developed fever and widespread erythematous rash on day 12 after phenobarbital initiation. He was hospitalized on day 19 with fever and disseminated bullous mucocutaneous lesions affecting 35% of the body surface area. Dermatological evaluation revealed necrotic erosive lesions affecting the ocular and oral mucous membranes and cutaneous lesions on the head, face, neck, upper limbs, pelvic girdle, and lower limbs consisting of areas of bubbles with a confluent necrotic roof separated by areas of epidermal necrosis producing a typical "wet linen" detachment with Nikolsky's sign. Skin biopsy for pathological examination could not be performed for logistical reasons. He was admitted to the ICU for isolation and supportive management. He received saline swabs and miconazole gel for oral mucosal lesions, ophthalmic tetracycline and artificial tears, surgical debridement of skin lesions, wound dressings, topical silver sulfadiazine and fusidic acid, empiric antibiotics (ampicillin, gentamycin, cefotaxime, amoxicillin-clavulanic acid), acetaminophen, ibuprofen, and tramadol. By hospital day 25 (44 days after phenobarbital initiation), the patient had healing of lesions and regeneration of the epidermis with hypochromic scars.

3.4 INFUSION-SITE AND INJECTION-SITE REACTIONS (N=6)

DPV identified six cases reporting infusion-site or injection-site reactions (FAERS=1, literature=5) with reasonable evidence of a causal association to phenobarbital use, and a plausible temporal relationship. We identified four cases of necrosis reporting serious outcomes: one case of necrosis from intramuscular administration requiring lower limb amputation, one case of necrosis from intravenous extravasation requiring skin grafting, and two cases of necrosis from inadvertent intra-arterial administration requiring distal hand amputation. Two cases of necrosis were assessed with a probable causal association with phenobarbital; the other two cases (one intramuscular and one intravenous) were assessed with a possible causal association because they reported administration of phenobarbital with other concomitant medications at the site. We identified two non-serious cases of thrombophlebitis from intravenous administration not requiring interventions. One case of thrombophlebitis was assessed with a probable causal association with phenobarbital; the other case did not provide sufficient information regarding event resolution. The cases are summarized in **Table 7**.

Table 7. Summary of Infusion-Site or Injection-Site Reactions Reported in This FAERS and Medical Literature Case Series, Received by FDA Through September 29, 2022 or Published Through October 6, 2022

Case/Year	Age Sex	Reason for Use	Phenobarbital Dose/Route	Administration Site	Adverse Event Description	Treatment and Outcome
20774841v1, Goudjo et al. 2022[18]	14 d M	Neonatal infection	40 mg IM daily; Also received ceftazidime, betamethasone, gentamycin	IM injection of thigh	Nicolau syndrome; ischemic necrosis of foot extending to upper third of right leg	Resuscitation, analgesics, antibiotics; required trans tibial amputation of right lower limb
Schafer et al. 2005[19]	14 d M	Subclinical status epilepticus	20 mg/kg IV x1 dose	IV in dorsum of right foot	Extravasation and tissue necrosis of dorsum of right foot, full-thickness skin necrosis	Cleaning, topical antibiotics, debridement; required skin grafting
Bulic et al. 2018[20]	13 w M	Broncho-pulmonary dysplasia, intracerebral bleeding	Unk dose daily; given intra-arterial; Also received methylprednisolone, fentanyl	IV in radial/ volar side of right wrist	Vascular compromise, necrosis and dry gangrene of all digits and distal palm	Heparin, acetylsalicylic acid, dextran, heparin soaked gauze; required amputation of all digits and distal palm
Polster et al. 2006[21]	7 y U	Status epilepticus	12 mg/kg x 1 dose; given intra-arterial	IV in volar site of wrist	Distal phalanx necrosis D III-V	Hyperbaric oxygen therapy; required amputation of distal phalanges
DeNicola et al. 1981[22]	14 y M	Reye's syndrome	20 mg/kg x 1 loading dose, 5 mg/kg maintenance therapy IV	IV in left hand and leg	Thrombophlebitis with soreness, tenderness, palpable cord from left radial wrist to antecubital fossa and from dorsum of foot to knee; confirmed by vascular surgeon	No treatment reported; vascular discomfort and ataxia subsided over the next 3 months
DeNicola et al. 1982[23]	20 y F	Reye's syndrome	10 mg/kg IV x 1	IV in right hand	Thrombophlebitis with palpable cord in right hand 1 month after discharge	No treatment or outcome reported

Abbreviations: d=day, w=week, y=year, M=male, F=female, IM=intramuscular, IV=intravenous

3.5 ANAPHYLAXIS, LARYNGOSPASM, OR INFUSION-RELATED HYPOTENSION (N=7)

DPV identified seven FAERS cases reporting anaphylaxis (2), anaphylaxis with laryngospasm (1), or infusion-related hypotension (4) with reasonable evidence of a causal association to phenobarbital use. Only cases reporting phenobarbital injection were included for analysis of hypotension. All seven cases reported a plausible temporal relationship and occurred on the same day as phenobarbital administration. One case of anaphylaxis and two cases of hypotension were assessed with a probable causal association with phenobarbital; the cases assessed with possible causal association reported possible concomitant suspect products or did not provide sufficient information regarding event resolution. All three cases of anaphylaxis reported serious outcomes and reported treatment interventions. Three of the four hypotension cases reported serious outcomes. One case of reported death and did not report additional details on the adverse event, administration of concomitant medications, or information on treatment. One case reported treatment interventions, and two cases were closely observed and monitored.

Table 8 summarizes the seven FAERS cases of anaphylaxis, laryngospasm, or infusion-related hypotension reported with phenobarbital for this case series.

Table 8. Descriptive Characteristics of Anaphylaxis, Laryngospasm or Infusion-Related Hypotension With Phenobarbital in This FAERS Case Series, Received by FDA Through September 29, 2022 (N=7)

	Anaphylaxis (n=3)	**Hypotension (n=4)**
Report type		
Periodic	0	1
Direct	3	3
Initial FDA received year	1993 (1), 2000 (1), 2016 (1)	1972 (1), 1990 (1), 1993 (1), 1999 (1)
Country derived – USA	3	4
Age (years)		
Mean	30.4	55.25
Median	34	54.5
Range	1.21-56	35-77
Sex		
Female	1	1
Male	2	3
Serious outcome(s)*	(n=3)	(n=3)
Death	0	1
Life-threatening	2	1
Hospitalization	1	1
Required intervention	1	0
Other	2	1
Reported reason for use	Seizure 1 Abnormal EEG 1 Drug detoxification 1	Status epilepticus 2 Seizure 1 Acute anxiety 1
Dose (mg)		
Mean	90	956.25
Median	90	1162.5
Range	30-150	100-1400
Route of administration	PO 2 IV 1	IV 3 IM 1

Table 8. Descriptive Characteristics of Anaphylaxis, Laryngospasm or Infusion-Related Hypotension With Phenobarbital in This FAERS Case Series, Received by FDA Through September 29, 2022 (N=7)		
	Anaphylaxis (n=3)	**Hypotension (n=4)**
Reported signs and symptoms	Neck swelling, dyspnea, hemoptysis, cardiopulmonary arrest (1)[†] Facial flushing, laryngospasm, apnea (1) Pruritis, total body rash, dyspnea (1)	Hypotension, respiratory compromise (2) Hypotension, cardiac arrhythmia, "electrocerebral silence" (1) Mild hypotension (1)[‡]
Therapeutic interventions	Steroids, nebulizers, intubation, CPR (1)[†] Epinephrine, steroids, antihistamines, nebulizers, intubation (1) Ambulance transfer to hospital (1)	Monitoring/observation (3) Dopamine, intubation (1)
Event resolution	Resolved with treatment (1) Unknown (2)	Progressed to death (1) Resolved with treatment (1) Unknown (2)
Causality assessment		
Probable	1	2
Possible	2	2

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

† One case reported events approximately 1 hour after administration of phenobarbital 30 mg PO and flu vaccine IM

‡ Mild drop in blood pressure from 120/85 to 110/70 mmHg

Abbreviations: EEG=electroencephalogram, PO=oral, IV=intravenous, IM=intramuscular, CPR=cardiopulmonary resuscitation

3.5.1 Anaphylaxis, laryngospasm

Two cases of anaphylaxis (one with laryngospasm) with phenobarbital are described below.

FAERS #3555977v1, Direct Report, USA, 2000, Outcomes: RI, LT

A 15-month-old male experienced an anaphylactic reaction after receiving phenobarbital 150 mg per gastrostomy tube x1 followed by 25 mg BID for an abnormal EEG. Medical history included mental retardation, multiple congenital problems, and repair of coarctation of the aorta. Concomitant medications included propranolol, fluticasone, nebulizers, and acetaminophen. "Several hours later" after starting phenobarbital, the patient "developed itchiness, followed by a total body rash and increased work of breathing, culminating to anaphylaxis." The patient was intubated and received epinephrine, dexamethasone, diphenhydramine, and albuterol/racemic epinephrine nebulizers. The events were reported as resolved, but the patient "eventually died due to underlying heart condition."

> ***Reviewer comments:*** *This case provides reasonable evidence of a probable causal association with phenobarbital, with a plausible temporal relationship, absence of factors with a potential contributory or confounding role, and clinically reasonable response to drug withdrawal after receiving treatment.*

FAERS #4996317v1, Direct Report, USA, 1993, Outcomes: OT

A 34-year-old female experienced an anaphylactic reaction after receiving phenobarbital 90 mg PO x 1 for polydrug dependence and detoxification. Medical history included drug abuse and allergy to morphine. The patient was not receiving any concomitant medications. On the same

day after starting phenobarbital, the patient experienced facial flushing and laryngospasm advancing to difficulty breathing and anaphylactic reaction. Respirations were reported as "shallow and slow rate advancing to cessation of breathing." Treatment included "IV started and assistance with breathing until ambulance came to take to medical hospital." No further information was provided.

> ***Reviewer comments:*** *This case provides reasonable evidence of a possible causal association with phenobarbital, with a plausible temporal relationship and absence of factors with a potential contributory or confounding role. However, the case did not report information on event resolution or treatment.*

3.5.2 Infusion-Related Hypotension

Two cases of infusion-related hypotension with phenobarbital are described below.

FAERS #3357988v1, Direct Report, USA, 1999, Outcomes: HO, LT
A 35-year-old male experienced hypotension after receiving phenobarbital 1400 mg (11 mg/kg) IV x 1 for refractory seizures. Patient had allergies to penicillin and erythromycin and no significant medical history was reported. Concomitant medications included lorazepam, phenytoin, carbamazepine, and acyclovir. Phenobarbital was added for refractory seizures and administered via a syringe "65 mg/cc x 21 cc to infuse over 30 min at no faster than 60 mg/min." "Shortly after infusion" the patient experienced "significant drop in BP (dec to 80/40 [mmHg])." The patient required intubation and dopamine infusion titrated up to 20 mcg/kg/min to maintain blood pressures at 100/60s and was transferred to the intensive care unit. The next day, blood pressures stabilized and the patient was transferred back to the floor and started on phenobarbital 260 mg q12h (route unknown); no further seizures or hypotension were reported.

> ***Reviewer comments:*** *This case provides reasonable evidence of a probable causal association with phenobarbital, with a plausible temporal relationship, absence of factors with a potential contributory or confounding role, and clinically reasonable response to drug withdrawal after receiving treatment.*

FAERS #5016696v1, Direct Report, USA, 1993, Outcomes: DE
A 73-year-old male experienced hypotension, cardiac arrhythmia, and "electrocerebral silence" after receiving phenobarbital 1125 mg IV x1 for status epilepticus. Medical history included status epilepticus, intracerebral hemorrhage, meningitis, hypertension, diabetes mellitus, pulmonary embolism, myocardial infarction, and renal insufficiency. Concomitant medications included phenytoin, nifedipine, metaproterenol, acyclovir, ampicillin, ceftazidime, and clindamycin. The patient died from unknown causes; no further information was reported.

> ***Reviewer comments:*** *This case provides reasonable evidence of a possible causal association with phenobarbital, with a plausible temporal relationship. However, the case did not report additional details on the adverse event, administration of concomitant medications, or information on treatment.*

3.6 INFUSION-RELATED HYPERTENSION (N=1)

DPV identified one FAERS case reporting infusion-related hypertension with phenobarbital use, summarized below.

FAERS #3260153v1, Direct Report, USA, 1999, Outcomes: HO

A 77-year-old male experienced increased blood pressure after receiving phenobarbital 60 mg IV q6h approximately for 1 day for seizures. Medical history included seizure and atrial fibrillation. Concomitant medication included nafcillin. The patient presented to the emergency department with mental status changes, atrial fibrillation, atrial flutter, and "went into grand mal seizures." The patient received midazolam and fosphenytoin and underwent left temporal lobe tumor removal. The patient was transferred to the ICU and started on phenytoin and nafcillin and developed a maculopapular rash all over the body; phenytoin and nafcillin were discontinued and IV methylprednisolone and diphenhydramine were given. The patient was then started on phenobarbital IV and developed a reaction of "increased HR [heart rate]/RR [respiratory rate]/BP [blood pressure]" – no further details were provided on the reaction. Phenobarbital was discontinued and the event was reported as resolved.

> ***Reviewer comments:*** *This case provides reasonable evidence of a possible causal association with phenobarbital, with a plausible temporal relationship and positive dechallenge. However, the case did not report additional details on the adverse event or information on treatment.*

4 DISCUSSION

DPV identified a total of 71 FAERS and medical literature cases with reasonable evidence of a causal association to phenobarbital reporting the following adverse events: DRESS (28), SJS/TEN (30), administration site necrosis/gangrene (4), administration site thrombophlebitis (2), anaphylaxis (3), infusion-related hypotension (4), and infusion-related hypertension (1); one case reported overlapping DRESS and SJS/TEN and is included in both case series. Most cases (66/71) reported a serious regulatory outcome, including death (9), life-threatening (10), hospitalization (59), disability (4), required intervention (6), and other serious outcomes (11); a case can have more than one serious outcome.

Of the 28 cases reporting DRESS (FAERS=8, literature=20), all 28 cases reported serious outcomes and treatment interventions. Four cases reported death; two occurred secondary to respiratory failure, one from hepatic failure, and one from multiorgan failure (including hepatic failure). All 28 cases were assessed with a probable causal association with phenobarbital. The median time to onset was 18 days (mean 20.2, range 5-60). Most cases (27 of 28) reported other organ involvement, primarily liver.

Of the 30 cases reporting SJS/TEN (FAERS=19, literature=11), most cases (28 of 30) reported serious outcomes and 29 cases reported treatment interventions (1 case did not report treatment information). Four cases reported death; two occurred secondary to hepatic failure, one from complications of TEN including infection, and one from sepsis and gastrointestinal hemorrhage. Most cases (22 of 30) were assessed with a probable causal association with phenobarbital; the

cases assessed with possible causal association did not provide sufficient information regarding time to onset or event resolution. The median time to onset was 14 days (mean 13.6, range 1-30). Approximately half of the cases (16 of 30) reported extensive injury with body surface area >30%.

DPV identified four cases of necrosis reporting serious outcomes: one case of necrosis from intramuscular administration requiring lower limb amputation, one case of necrosis from intravenous extravasation requiring skin grafting, and two cases of necrosis from inadvertent intra-arterial administration requiring distal hand amputation. Two cases of necrosis were assessed with a probable causal association with phenobarbital; the other two cases (one intramuscular and one intravenous) were assessed with a possible causal association because they reported administration of phenobarbital with other concomitant medications at the site. DPV identified two non-serious cases of thrombophlebitis from intravenous administration not requiring interventions. One case of thrombophlebitis was assessed with a probable causal association with phenobarbital; the other case did not provide sufficient information regarding event resolution.

DPV identified seven FAERS cases reporting anaphylaxis (3) or infusion-related hypotension (4). All seven cases reported a plausible temporal relationship and occurred on the same day as phenobarbital administration. One case of anaphylaxis and two cases of hypotension were assessed with a probable causal association with phenobarbital; the cases assessed with possible causal association reported possible concomitant suspect products or did not provide sufficient information regarding event resolution. All three cases of anaphylaxis reported serious outcomes and reported treatment interventions. Three of the four hypotension cases reported serious outcomes. One case reported death and did not provide additional details on the adverse event, administration of concomitant medications, or information on treatment. One case reported treatment interventions, and two cases were closely observed and monitored.

Administration site necrosis/gangrene or thrombophlebitis and hypotension with intravenous administration are known adverse events associated with the use of barbiturate therapy. Some proposed mechanisms for administration site injuries with barbiturates include arterial spasm, arterial damage and thromboses, crystal microemboli, intravascular thromboses, and direct cytotoxicity, which may occur from the highly alkaline solution or the barbiturate molecule itself.[3,24,25,26] Several medical literature case series have reported hypotension in patients treated with intravenous phenobarbital, especially with higher dosing.[27,28,29]

DPV identified one FAERS case reporting infusion-related hypertension with phenobarbital; no additional literature cases were identified. The case reported a plausible temporal relationship and positive dechallenge, but did not report details on the adverse event or information on treatment; therefore, a probable causal association could not be established.

There is likely under-reporting of adverse events with phenobarbital in spontaneous reporting systems, including FAERS, because of its long history of use on the market. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed. Phenobarbital has been on the market since 1912 and the MedWatch reporting system for FAERS was first implemented in the 1960s. Generally, according to the Weber Effect, adverse

event reporting trends tend to increase in the first 2 years after introduction of a new agent to the market or approval of a new indication, and the number of reports decreases over time.[30] In addition, because labeling for unapproved phenobarbital injection includes known adverse events with intravenous administration such as hypotension and infusion-site and injection-site reaction (thrombosis, gangrene, irritation), manufacturers or distributors of unapproved phenobarbital may not report these adverse events as they are required to report to FDA all serious and *unexpected* adverse drug experiences associated with the use of their drug products.[31]

Because of the severity of the events and need for prompt intervention to mitigate the adverse event, DPV recommends the addition of DRESS, SJS/TEN, infusion-site and injection-site reactions (tissue necrosis/gangrene, thrombophlebitis), anaphylaxis, and infusion-related hypotension to the WARNINGS AND PRECAUTIONS section of the labeling. Given the severity of these events and the importance of prescriber awareness and patient counseling, we also recommend changes to the (b) (4) labeling and MEDICATION GUIDE to reflect the potential risk of DRESS and SJS/TEN with phenobarbital.

5 CONCLUSION

In conclusion, we identified cases from FAERS and the medical literature that support a causal association between phenobarbital and the adverse events of DRESS, SJS/TEN, infusion-site and injection-site reactions (tissue necrosis/gangrene, thrombophlebitis), anaphylaxis, and infusion-related hypotension. Most cases reported serious outcomes and required therapeutic interventions to mitigate the adverse events. Labeling of these adverse events is warranted to facilitate prompt identification of the adverse events and discontinuation of therapy to prevent serious outcomes.

6 RECOMMENDATIONS

DPV recommends adding language to the WARNINGS AND PRECAUTIONS section of phenobarbital labeling to reflect the potential risks of:

- Drug reaction with eosinophilia and systemic symptoms
- Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
- Infusion-site and injection-site reactions: tissue necrosis/gangrene, thrombophlebitis
- Anaphylaxis
- Infusion-related hypotension

DPV also recommends adding language to the (b) (4) (b) (4) labeling and MEDICATION GUIDE to reflect the potential risk of DRESS and SJS/TEN with phenobarbital.

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20. Bulic K, Antabak A, Lorencin M. Near-Complete Hand Loss Following an Unintentional, Intra-arterial Medicine Injection in an Infant. J Pediatr Intensive Care. 2018 Mar;7(1):43-45.
21. Polster T, Weltzien A, Barthel M, Otte J. Distal phalanx necrosis after intra-arterial injection of phenobarbital during treatment of subtle generalized convulsive status epilepticus. Neuropediatrics. 2006 Dec;37(06):P63.
22. DeNicola LK, Hays DP. Phlebothrombosis as a complication of barbiturate-induced coma for neuroresuscitation. Drug Intell Clin Pharm. 1981 Jul-Aug;15(7-8):601-2.
23. DeNicola LK, Hays DP. Thrombophlebosis due to high-dose barbiturates. Drug Intell Clin Pharm. 1982 Nov;16(11):880.
24. Goldberg I, Bahar A, Yosipovitch Z. Gangrene of the upper extremity following intra-arterial injection of drugs. A case report and review of the literature. Clin Orthop Relat Res. 1984 Sep;(188):223-9.
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26. Ellertson DG, Lazarus HM, Auerbach R. Patterns of acute vascular injury after intra-arterial barbiturate injection. Am J Surg. 1973 Dec;126(6):813-7.
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29. Hocker S, Clark S, Britton J. Parenteral phenobarbital in status epilepticus revisited: Mayo Clinic experience. Epilepsia. 2018 Oct;59 Suppl 2:193-197.
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31. 21 CFR 310.305. Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications. Available from https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-310/subpart-D/section-310.305. Accessed October 20, 2022.

8 APPENDICES

8.1 APPENDIX A. CLASSIFICATION OF DRESS

RegisCAR Scoring System for Classifying DRESS Cases as Definite, Probable, Possible, or no Case[a]

Score	−1	0	1	2	Min.	Max.
Fever ≥ 38·5 °C	No/U	Yes			−1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			$0{\cdot}7–1{\cdot}499 \times 10^9\ L^{-1}$	$\geq 1{\cdot}5 \times 10^9\ L^{-1}$		
Eosinophils, if leucocytes $< 4{\cdot}0 \times 10^9\ L^{-1}$			10–19·9%	≥ 20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					−2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement[a]					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			−1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					−4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. [a]After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

[a] Adapted from Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007 Mar;156(3):609-11.

8.2 APPENDIX B. CLASSIFICATION OF SJS/TEN

Cutaneous findings in Stevens-Johnson syndrome/toxic epidermal necrolysis[b]

Condition	Extent of skin detachment (% of BSA)	Distribution pattern	Types of skin lesions	Mucosal erosions
SJS	<10%	Widespread	Macules with blisters or flat atypical targets	Yes
Overlap SJS/TEN	10-30%	Widespread	Macules with blisters or flat atypical targets	Yes
TEN with spots	>30%	Widespread	Macules with blisters or flat atypical targets	Yes
TEN without spots	>10%	Trunk to widespread	Blisters on confluent erythema	Yes
BSA=body surface area, SJS=Stevens-Johnson Syndrome, TEN=toxic epidermal necrolysis				

[b] Adapted from Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993 Jan;129(1):92-6.

8.3 APPENDIX C. CRITERIA FOR ANAPHYLAXIS

World Allergy Organization Criteria for Anaphylaxis[c]

Anaphylaxis is highly likely when either one of the following two criteria is fulfilled:
Criterion 1 – Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following: • Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia). • Circulatory compromise: Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia, collapse, syncope, incontinence). • Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens.
Criterion 2 – Acute onset of hypotension* or bronchospasm† or laryngeal involvement (e.g., stridor, vocal changes, odynophagia) after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.
* Hypotension is defined as a decrease in systolic BP >30 percent from that person's baseline. For adults and children older than 10 years, hypotension may also be defined as systolic BP <90 mmHg. In infants and children younger than 10 years, hypotension is defined as: - Less than 70 mmHg from 1 month to 1 year - Less than (70 mmHg + [2 x age]) from 1 to 10 years - Less than 90 mmHg from 11 to 17 years † Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.

[c] Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472.

8.4 APPENDIX D. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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.

8.5 APPENDIX E. FAERS LINE LISTING OF PHENOBARBITAL CASE SERIES (N=71)

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
DRESS									
1	14-FEB-2017	13230689	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-17-00338	15-DAY	0.833	M	USA	HO
2	24-NOV-2015	11771901	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-15-02006	15-DAY	2	F	USA	HO,LT
3	09-DEC-2015 30-NOV-2015	11820098 11785912	1 1	2015RIS00167 US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-15-02049	15-DAY	2	F	USA	OT,HO
4	09-JUN-2011 11-AUG-2010	8007638 7536145	1 2	2011MA006387 US-RANBAXY-2010US-36614	15-DAY	2	M	USA	HO,OT
5	10-NOV-2015	11721914	1	623173	DIRECT	2.55	F	USA	HO
6	11-JUL-2011 20-DEC-2010	8049607 7722180	1 2	2011MA008032 US-RANBAXY-2010US-40246	15-DAY	3.5	F	USA	HO,OT
7	30-AUG-2011	8744463	1	US-FDA-7717632	DIRECT	7.64	F	USA	HO,LT
8	24-JUL-2015	11312229	1	607015	DIRECT	39	F	USA	HO
9	1992	Nagata et al.		Nagata T, Kawamura N, Motoyama T, Miyake M, Yoden A, Yoshikawa K, Oguni T, Yamasiro K, Mino M. A case of hypersensitivity syndrome resembling Langerhans cell histiocytosis during phenobarbital prophylaxis for convulsion. Jpn J Clin Oncol. 1992 Dec;22(6):421-7.	LIT	2	F	JPN	HO
10	2007	Giordano et al.		Giordano N, Amendola A, Papakostas P, Cipolli F, Rollo F, Martini G, Ciacci G, Nuti R. A clinical case of drug hypersensivity syndrome with phenobarbital administration: drug-induced rash with eosinophilia and systemic symptoms or lupus-like syndrome? Clin Exp Rheumatol. 2007 Mar-Apr;25(2):339.	LIT	84	F	ITA	HO
11	2009	Huang et al.		Huang YL, Hsieh MY, Hsiao PF, Sheen JM, Yu HR, Kuo HC, Chen ST, Huang JL, Yang KD, Lee WI. Alopecia areata universalis after phenobarbital-induced anti-convulsant hypersensitivity syndrome. Immunol Invest. 2009;38(5):383-97.	LIT	3	M	TWN	HO
12	2013	Armin et al.		Armin S, Ramezani K, Chavoshzadeh Z, Mansouri M. Drug Rash With Eosinophilia and Systemic Symptoms Syndrome in Infancy: A Report of Two Rare Cases. Journal of Comprehensive Pediatrics. 2013 November; 4(4): 200-2.	LIT	0.125	M	IRN	HO

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
13	2013	Armin et al.		Armin S, Ramezani K, Chavoshzadeh Z, Mansouri M. Drug Rash With Eosinophilia and Systemic Symptoms Syndrome in Infancy: A Report of Two Rare Cases. Journal of Comprehensive Pediatrics. 2013 November; 4(4): 200-2.	LIT	0.132	F	IRN	HO
14	2022	Douilly et al.		Douilly C, Lepoix E, Azzouz B, Morel A, Trenque T. DRESS syndrome sous phénobarbital : une réaction d'hypersensibilité aux médicaments, connue mais oubliée des prescripteurs–à propos d'un cas [DRESS syndrome to phenobarbital: A hypersensitivity reaction to drugs known but forgotten by prescribers-A case report]. Therapie. 2022 Jul-Aug;77(4):493-495.	LIT	25	F	FRA	HO
15	2011	Giri et al.		Giri PP, Roy S, Bhattyacharya S, Pal P, Dhar S. Dress syndrome with sepsis, acute respiratory distress syndrome and pneumomediastinum. Indian J Dermatol. 2011 Nov;56(6):763-5.	LIT	10	F	IND	DE,HO
16	2003	Baruzzi et al.		Baruzzi A, Contin M, Barbara G, Cremon C, De Giorgio R, Patrizi A, Albani F, Corinaldesi R. Drug rash with eosinophilia and systemic symptoms secondary to phenobarbitone. Clin Neuropharmacol. 2003 Jul-Aug;26(4):177-8.	LIT	31	F	ITA	HO
17	2003	Chen et al.		Chen CJ, Huang YC, Wang CY, Lin TY. Fatal anticonvulsant hypersensitivity syndrome in an infant. Eur J Pediatr. 2003 Dec;162(12):893-4.	LIT	0.25	F	TWN	DE,HO
18	2005	Li et al.		Li AM, Nelson EA, Hon EK, Cheng FW, Chan DF, Sin NC, Ma KC, Cheung KL, Fok TF. Hepatic failure in a child with anti-epileptic hypersensitivity syndrome. J Paediatr Child Health. 2005 Apr;41(4):218-20.	LIT	11	M	HKG	HO
19	1997	Descamps et al.		Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, Descamps D, Saraux JL, Grange MJ, Grossin M, Navratil E, Crickx B, Belaich S. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. Br J Dermatol. 1997 Oct;137(4):605-8.	LIT	25	F	FRA	HO
20	2013	Zeng et al.		Zeng Q, Wu Y, Zhan Y, Tang L, Zhou Y, Yin J, Fan F, Zhang G, Lu Q, Xiao R. Leukemoid reaction secondary to hypersensitivity syndrome to phenobarbital: a case report. Int J Clin Exp Pathol. 2013;6(1):100-4. Epub 2012 Nov 20.	LIT	27	F	CHN	HO
21	1989	Mockli et al.		Mockli G, Crowley M, Stern R, Warnock ML. Massive hepatic necrosis in a child after administration of phenobarbital. Am J Gastroenterol. 1989 Jul;84(7):820-2.	LIT	2	M	USA	DE,HO

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
22	1986	Savich et al.		Savich RD, Traisman HS. Phenobarbital hypersensitivity reaction. IMJ Ill Med J. 1986 Apr;169(4):232-4.	LIT	7	M	USA	HO
23	2014	Chaabane et al.		Chaabane A, Ben Fadhel N, Chadli Z, Ben Fredj N, Boughattas NA, Aouam K. Phenobarbital-induced DRESS: a lichenoïd picture. Iran J Allergy Asthma Immunol. 2014 Dec;13(6):453-5.	LIT	49	M	TUN	DE,HO
24	2018	Ladhari et al.		Ladhari C, Aouinti I, Zgolli F, Lakhoua G, Zayani H, Zaiem A, El Aidli S., Daghfous R, Kastalli S. Phenobarbital induced DRESS syndrome: an atypical presentation. Fundamental and Clinical Pharmacology 2018 32 (87) Supplement 1	LIT	19	F	TUN	HO,OT
25	2017	Suthar et al.		Suthar R, Sankhyan N, Shree H, Singhi P. Reversible Vegetative State in a Child Due to Drug Reaction with Eosinophilia and Systemic Symptoms. Indian J Pediatr. 2017 Mar;84(3):249-250.	LIT	1.25	F	IND	HO
26	2021	Osada et al.		Osada A, Arimitsu T, Nakazaki H, Kin T, Kaburagi S, Morita K, Nakajima Y, Kitahara H, Takahashi H, Hida M. Severe drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms in a 1-month-old infant with trisomy 21. J Dermatol. 2021 Oct;48(10):E496-E497.	LIT	0.083	M	JPN	HO
27	2008	Sakuma et al.		Sakuma K, Kano Y, Fukuhara M, Shiohara T. Syndrome of inappropriate secretion of antidiuretic hormone associated with limbic encephalitis in a patient with drug-induced hypersensitivity syndrome. Clin Exp Dermatol. 2008 May;33(3):287-90.	LIT	68	M	JPN	HO
28	1971	Bakshi et al.		Bakshi S, Bhakoo ON. Unusual phenobarbitone sensitivity. Indian J Pediatr. 1971 Sep;38(284):372-4.	LIT	8	F	IND	HO
SJS/TEN									
1	16-MAR-2012	8462648	1	US-FDA-8214507	DIRECT	0.167	M	USA	OT
2	03-DEC-2003	4039317	1	207367	DIRECT	0.25	F	USA	RI,HO
3	01-FEB-1978	4322536	1		DIRECT	0.75	F	USA	
4	26-AUG-2002	3833444	1	174979	DIRECT	0.916	F	USA	RI,LT,HO,DS
5	26-DEC-1995	5338292	1		DIRECT	1	F	USA	HO
6	26-OCT-2005	5914712	1	261494	DIRECT	1.083	M	USA	DE
7	08-JUL-1986	4494567	1		DIRECT	2	F	USA	HO
8	27-OCT-1989	4681316	1		DIRECT	2	M	USA	DE

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
9	01-SEP-1998	3144054	1		DIRECT	2	M	USA	LT,HO
10	13-JUL-2004	4172984	1	222668	DIRECT	2.4	F	USA	OT,HO
11	11-JUL-2011 20-DEC-2010	8049607 7722180	1 2	2011MA008032 US-RANBAXY-2010US-40246	15-DAY	3.5	F	USA	HO,OT
12	09-DEC-2004	5698785	1	234020	DIRECT	4	F	USA	RI,HO
13	03-APR-2007	6288437	1	299512	DIRECT	4	M	USA	RI,HO,LT
14	01-JUL-1977	4317424	1		DIRECT	9	F	USA	
15	10-MAR-1994	5093740	1		DIRECT	9	F	USA	HO,LT
16	27-MAR-2003	3927861	2	USA030330729	15-DAY	21	F	USA	DS,HO
17	18-FEB-1999	3210902	1		DIRECT	25	F	USA	HO,LT
18	27-OCT-2009 06-NOV-2009	7159034 7184056	1 1	US-MYLANLABS-2009S1018074 WWISSUE-366	15-DAY	41	M	USA	DS,HO,OT
19	08-APR-1998	3132692	1		DIRECT	42	M	USA	RI,HO
20	2003	Uzüm et al.		Uzüm K, Caksen H, Gündüz Z, Ustünbaş HB, Kandemir O. A fatal case of toxic epidermal necrolysis associated with liver cirrhosis. J Emerg Med. 2003 Jan;24(1):92-3.	LIT	6	F	TUR	DE,HO
21	2005	Kobayashi et al.		Kobayashi A, Yoshita T, Sugiyama K, Miyashita K, Niida Y, Koizumi S, Tseng SC. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. Ophthalmology. 2006 Jan;113(1):126-32.	LIT	6	M	JPN	HO
22	2012	Gaur et al.		Gaur S, Agnihotri R. Phenobarbital induced Stevens-Johnson syndrome in a child. Indian J Pharmacol. 2012 Jul-Aug;44(4):531-2.	LIT	12	M	IND	HO
23	2009	Mamishi et al.		Mamishi S, Fattahi F, Pourpak Z, Aghaee FM, Moinfar Z, Mohammadi M, Ashrafi M, Moin M. Severe cutaneous reactions caused by barbiturates in seven Iranian children. Int J Dermatol. 2009 Nov;48(11):1254-61.	LIT	5	M	IRN	HO
24	2009	Mamishi et al.		Mamishi S, Fattahi F, Pourpak Z, Aghaee FM, Moinfar Z, Mohammadi M, Ashrafi M, Moin M. Severe cutaneous reactions caused by barbiturates in seven Iranian children. Int J Dermatol. 2009 Nov;48(11):1254-61.	LIT	6	F	IRN	HO

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
25	2009	Mamishi et al.		Mamishi S, Fattahi F, Pourpak Z, Aghaee FM, Moinfar Z, Mohammadi M, Ashrafi M, Moin M. Severe cutaneous reactions caused by barbiturates in seven Iranian children. Int J Dermatol. 2009 Nov;48(11):1254-61.	LIT	2	M	IRN	HO
26	2021	Ayele et al.		Ayele BA, Ali K, Mulatu E. Toxic epidermal necrosis associated with phenobarbitone: a case report and brief review of the literatures. Allergy Asthma Clin Immunol. 2021 Sep 8;17(1):88.	LIT	14	M	ETH	HO
27	2014	Kaputu-Kalala-Malu et al.		Kaputu-Kalala-Malu C, Ntumba-Tshitenge O, Misson JP. Nécrolyse épidermique toxique induite par le phénobarbital chez un enfant Rwandais: à propos d'uncas [Toxic epidermal necrolysis induced by phenobarbital in a Rwandan child: report of a case]. Pan Afr Med J. 2014 Mar 14;17:202.	LIT	2.5	M	CON	HO
28	1973	Stüttgen et al.		Stüttgen G. Toxic epidermal necrolysis provoked by barbiturates. Br J Dermatol. 1973 Mar;88(3):291-3.	LIT	70	F	DEU	DE,HO
29	2009	Gubinelli et al.		Gubinelli E, Canzona F, Tonanzi T, Raskovic D, Didona B. Toxic epidermal necrolysis successfully treated with etanercept. J Dermatol. 2009 Mar;36(3):150-3.	LIT	59	F	ITA	HO
30	2021	Holtz et al.		Holtz M, Grimstad F, Higgins J, Denny G, Strickland J, Dowlut-McElroy T. Vulvovaginal Involvement in Pediatric Stevens-Johnson Syndrome: A Case Series. J Pediatr Adolesc Gynecol. 2021 Oct;34(5):745-748.	LIT	9	M	USA	HO
Infusion-Site and Injection-Site Reactions									
1	02-MAY-2022 13-APR-2022 13-MAY-2022 11-MAY-2022	20774841 20703365 20826017 20812052	1 1 1 1	TG-LUPIN PHARMACEUTICALS INC.-2022-06354 TG-ORGANON-O2204TGO000686 TG-BAUSCH-BL-2022-011175 TG-MLV Pharma LLC-2128656	15-DAY	0.038	M	TGO	HO,DS,OT
2	2005	Schafer et al.		Schäfer T, Kukies S, Stokes TH, Levin LS, Donatucci CF, Erdmann D. The prepuce as a donor site for reconstruction of an extravasation injury to the foot in a newborn. Ann Plast Surg. 2005 Jun;54(6):664-6.	LIT	0.038	M	USA	HO
3	2018	Bulic et al.		Bulic K, Antabak A, Lorencin M. Near-Complete Hand Loss Following an Unintentional, Intra-arterial Medicine Injection in an Infant. J Pediatr Intensive Care. 2018 Mar;7(1):43-45.	LIT	0.25	M	CRO	HO
4	2006	Polster et al.		Polster T, Weltzien A, Barthel M, Otte J. Distal phalanx necrosis after intra-arterial injection of phenobarbital during treatment of subtle generalized convulsive status epilepticus. Neuropediatrics. 2006 Dec;37(06):P63.	LIT	7	U	DEU	HO

	Initial FDA Received Date or Year Published	FAERS Case #	Version #	Manufacturer Control # or Literature Citation	Case Type	Age (yr)	Sex	Country Derived	Serious Outcome(s)*
5	1981	DeNicola et al.		DeNicola LK, Hays DP. Phlebothrombosis as a complication of barbiturate-induced coma for neuroresuscitation. Drug Intell Clin Pharm. 1981 Jul-Aug;15(7-8):601-2.	LIT	14	M	USA	
6	1982	DeNicola et al.		DeNicola LK, Hays DP. Thrombophlebosis due to high-dose barbiturates. Drug Intell Clin Pharm. 1982 Nov;16(11):880.	LIT	20	F	USA	
Anaphylaxis, Laryngospasm, or Infusion-Related Hypotension									
1	18-OCT-2000	3555977	1		DIRECT	1.21	M	USA	RI,LT
2	17-MAY-1993	4996317	1		DIRECT	34	F	USA	OT
3	30-SEP-1999	3357988	1		DIRECT	35	M	USA	HO,LT
4	01-MAR-1972	4269918	1		PERIODIC	36	M	USA	
5	20-OCT-2016	12870482	1	FDA-CDER-CTU-8827	DIRECT	56	M	USA	LT,HO,OT
6	21-JUL-1993	5016696	1		DIRECT	73	M	USA	DE
7	24-DEC-1990	4768112	1		DIRECT	77	F	USA	OT
Infusion-Related Hypertension									
1	29-APR-1999	3260153	1		DIRECT	77.31	M	USA	HO

* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome. Literature cases were assigned an outcome of death or hospitalization if this information was reported in the case.

Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, DS= disability, RI=required intervention, OT=other medically significant, LIT=literature, yr=years, M=male, F=female, U=unknown

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN M LONG
10/26/2022 09:40:40 AM

ALLEN D BRINKER
10/26/2022 09:46:05 AM

CINDY M KORTEPETER
10/26/2022 11:35:27 AM

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 25, 2022

To: Nick Kozauer, M.D., Director
Division of Neurology II
Office of Neuroscience

Through: Dominic Chiapperino, Ph.D., Director
Joshua Lloyd, M.D., Medical Officer Team Leader
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Emily Deng, M.D., M.P.H., Medical Officer
Neil Varshneya, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **Drug:** Phenobarbital sodium
NDA Number: 215910
Indication: Treatment of Neonatal Seizures
Dosage form: Phenobarbital sodium for injection, 100 mg/vial
Applicant: Sun Pharma Advanced Research Company, Ltd. (SPARC)
PDUFA Goal Date: Nov 17, 2022
Materials Reviewed: New NDA submission, received on Feb 17, 2022 (Supporting Document 1), and subsequent amendments

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Neurology II (DN2) to evaluate phenobarbital 100 mg injection for any Controlled Substance Staff (CSS) comments and input regarding the submission and proposed labeling. Sun Pharma Advanced Research Company, Ltd. (SPARC) has developed a benzyl alcohol-free phenobarbital injection for intravenous injection for the treatment of neonatal seizures. The proposed product is intended to provide a safety advantage compared to current, unapproved marketed phenobarbital products containing benzyl alcohol, which poses potential toxicity concerns for neonates.

The Applicant submitted this NDA through the 505(b)(2) regulatory pathway by referencing published literature to support the safety. The Applicant submitted data from an investigator-sponsored study (NEOLEV2, CSR submitted under IND 109622) to support the safety and efficacy of phenobarbital for the proposed indication. Additionally, the Sponsor conducted a relative bioavailability study (PHEN-20-01) under IND 132342 to establish bioequivalence between the proposed product and an unapproved marketed phenobarbital formulation manufactured by West-Ward, which was used in the investigator-sponsored study (NEOLEV2).

Phenobarbital is a barbiturate drug that has been listed in schedule IV of the Controlled Substances Act (CSA) based on legislation enacted in 1970, however, phenobarbital has never been evaluated and approved under an NDA. Unapproved formulations of phenobarbital sodium injection have been used as a sedative, hypnotic, pre-anesthetic, and anticonvulsant for adults and pediatric populations.

In a Type C guidance meeting dated July 1, 2021, under IND 132342, CSS advised the Applicant to provide or reference appropriate data related to abuse and dependence associated with phenobarbital such that the drug product, if approved, can be appropriately labeled in Section 9 and other relevant sections of the prescribing information. Specifically, the Applicant was advised to submit a proposal for scheduling and a summary of what is known about the abuse

potential and dependence liability of phenobarbital to support the scheduling proposal and labeling for phenobarbital.

2. Conclusions

- Phenobarbital is a sedative with known potential for abuse and development of dependence and is listed in schedule IV of the Controlled Substances Act (CSA) [21 CFR 1308.14 (c) (45)] based on legislation enacted in 1970.
- The available abuse-related data (i.e., submitted in this NDA and generated in the Office of Surveillance and Epidemiology review) are consistent with the Applicant's proposal that phenobarbital sodium remain controlled under schedule IV of the CSA for the following reasons:
    - Phenobarbital is a central nervous system depressant and is classified as a long-acting barbiturate with a 6-hour duration of action and a half-life of approximately 100 hours. Phenobarbital produces CNS-depressant effects by increasing the duration of chloride ion channel opening at the $GABA_A$ receptor and blocking the excitatory α-amino-3-hydroxy-5-methylisozazole-4-propionic acid (AMPA) and kainite receptors.
    - Nonclinical data demonstrate the reinforcing effects and ability of phenobarbital to produce dependence and withdrawal, consistent with a schedule IV level of control under the CSA.
        - In self-administration studies in rats, consumption of phenobarbital was comparable to saline and lower than other CNS depressants. In baboons, rates of phenobarbital self-administration exceeded vehicle.
        - In drug discrimination studies, phenobarbital generally substituted for other barbiturates and produced full generalization.
        - In physical dependence studies in rats and monkeys, phenobarbital produced withdrawal signs following repeated administration.
    - The results of Study PHEN-20-01 demonstrated that phenobarbital sodium intravenous injection over 15 minutes at a dose of 2 mg/kg in healthy volunteers resulted in abuse-related adverse events, such as somnolence, euphoric mood, and dizziness.
    - Data from human abuse potential studies with phenobarbital are limited. A systematic review by Fraser et al., (Fraser & Jasinski, 1977) indicated that phenobarbital is subject to misuse and abuse because of its ability to relax anxious feelings and remove inhibition. Phenobarbital intramuscular injection in healthy volunteers at 557.1 mg/70 kg resulted in clinically significant intoxication as measured by post-rotatory nystagmus and subjective effects as measured by drug-liking scores comparing to placebo. However, the dose required to produce reinforcing effects for phenobarbital are much higher than that of schedule II comparators such as pentobarbital, secobarbital.

- Although the Applicant did not identify any human physical dependence studies for phenobarbital in the published literature, the development of tolerance and a well-defined acute withdrawal syndrome have been well-documented in the clinical setting. Additionally, tolerance to the sedative effects of phenobarbital and the development of physical dependence have been demonstrated in animal models. The dose and treatment duration required to produce physical dependence for phenobarbital is unknown; however, prolonged usage of phenobarbital may result in physical dependence and a sedative/hypnotic drug class-specific withdrawal syndrome after abrupt cessation or rapid dose reduction. Withdrawal symptoms associated with phenobarbital discontinuation are similar to alcohol or benzodiazepine withdrawal and include increased psychomotor activity, agitation, muscular weakness, tremulousness, hyperpyrexia, diaphoresis, delirium, convulsions, elevated blood pressure, pulse and temperature, tremor of eyelids, tongue and hands (Miller & Gold, 1998).
- According to the epidemiological data review conducted by the Office of Surveillance and Epidemiology, oral phenobarbital is the most commonly used oral barbiturate in the outpatient setting, but oral phenobarbital utilization has declined and has been consistently lower than benzodiazepines from 2013 to 2021. However, the utilization of injectable phenobarbital doubled from 2016 to 2021. Injectable phenobarbital is the most commonly used barbiturate in the hospital setting.
- The current abuse pattern of phenobarbital is similar to that of the benzodiazepine drug class. Phenobarbital continues to be abused for sedation, relaxation, or mitigation of side effects from the use of other substances. Epidemiological data suggest that phenobarbital is generally not a primary drug of abuse and is typically abused with other substances (i.e., polysubstance use). Both nonfatal adverse events and fatal overdose deaths associated with phenobarbital occur primarily in the context of polysubstance use. Although utilization-adjusted rates of abuse of phenobarbital are lower than that of benzodiazepines, utilization-adjusted rates of overdose deaths involving barbiturates including phenobarbital were higher than benzodiazepines in the years 2014 to 2018.

- **Comments to the Division of Neurology II**
  - Neonates will receive an initial loading dose of phenobarbital, followed by a maintenance dose of phenobarbital for up to 5 days. We defer to DN2 if the proposed dosing frequency and treatment duration for phenobarbital may pose a risk of developing physical dependence, and its clinical consequences, in neonates, as the Applicant did not provide information related to the development of withdrawal and rebound seizure upon drug discontinuation in this patient population.

3. Recommendations

Based on our findings in the Conclusions section, we recommend the following:

1. The Controlled Substance Staff has not identified any issues or concerns that would preclude approval of this NDA.
2. Phenobarbital should remain controlled under schedule IV of the Controlled Substances Act based on the evidence summarized above.
3. Although the proposed product is indicated for the treatment of neonatal seizures, it will be the first approved injectable phenobarbital product (other available phenobarbital injectable products remain unapproved, marketed products) and has the potential for significant off-label use for other indications (e.g., alcohol or benzodiazepine withdrawal, seizure in other patient populations). Phenobarbital carries similar risks of misuse, abuse, physical dependence and withdrawal to that of benzodiazepines, which are also controlled under schedule IV, and phenobarbital has a narrower safety margin with higher utilization-adjusted rates of overdose deaths, as compared to benzodiazepines. Therefore, the phenobarbital labeling should adequately inform patients and health care providers about the serious risks of concomitant use with opioids or alcohol or other CNS depressants and the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions in the Boxed Warning, Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections of labeling, similar to what has been done for the benzodiazepine drug class[1]. Additionally, the abuse and dependence labeling for phenobarbital should also be consistent with other drugs in the barbiturate class, where appropriate (i.e., with regard to general, non-product specific information).
4. Labeling is currently under negotiation with the Applicant at this time. For the final agreed upon labeling, refer to the approved labeling, if this NDA is approved.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

The chemical structure of phenobarbital sodium is shown in Figure 1. Phenobarbital sodium has a molecular formula of $C_{12}H_{11}N_2NaO_3$ and a molecular weight of 254.22 g/mol. The IUPAC name for phenobarbital sodium is sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate. The chemical properties and structural identifiers of phenobarbital sodium including the IUPAC Name, PubChem ID, CASRN, Molecular Formula, Molecular Weight, Canonical SMILES, InChI, and InChIKey are shown in Table 1.

[1] Benzodiazepine Drug Class: Drug Safety Communication - Boxed Warning Updated to Improve Safe Use, Sep 23,2020

Figure 1. Chemical Structure of Phenobarbital Sodium.

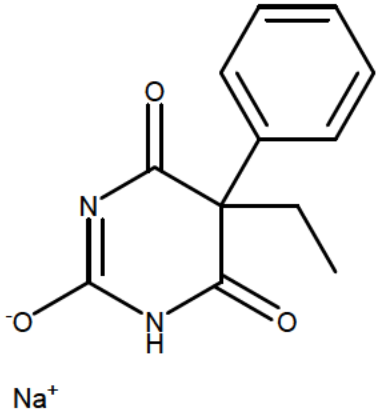


Table1: Chemical Properties and Structural Identifiers of Phenobarbital Sodium

Property or Identifier	Value
Common Name	Phenobarbital sodium
IUPAC Name	Sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate
CASRN	57-30-7
PubChem ID	23674889
Molecular Formula	$C_{12}H_{11}N_2NaO_3$
Molecular Weight	254.22 g/mol
Canonical SMILES	CCC1(C(=O)NC(=NC1=O)[O-])C2=CC=CC=C2.[Na+]
InChI	InChI=1S/C12H12N2O3.Na/c1-2-12(8-6-4-3-5-7-8)9(15)13-11(17)14-10(12)16;/h3-7H,2H2,1H3,(H2,13,14,15,16,17);/q;+1/p-1
InChIKey	WRLGYAWRGXKSKG-UHFFFAOYSA-M
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number SMILES = Simplified Molecular-Input Line-Entry System InChI = International Chemical Identifier InChIKey = InChIKey is a hashed version of the full InChI (using the SHA-256 algorithm)	

Phenobarbital was evaluated for its similarity in chemical structure to other drugs already controlled under the CSA using chemical informatics analyses. The Tanimoto coefficient (Tc), a measurement of chemical structure similarity, for phenobarbital and each substance in a CSA drug schedule was computed with the RDK7 molecular fingerprint (O'Boyle and Sayle, 2016) using open-source cheminformatics software (RDKit). A Tc value for molecular fingerprints ranges from '0' to '1', where '0' results from fingerprints with no similarities and '1' results from identical fingerprints. Phenobarbital is a schedule IV substance and is substantially similar in chemical structure to other drugs already controlled in schedule IV of the CSA, including mephobarbital (PubChem ID: 8271; Tc = 0.87).

1.2. Drug Product

The proposed product, phenobarbital sodium injectable, 100 mg/vial is intended to be administered as an intravenous infusion after being reconstituted with 10 ml of 0.9% sodium chloride. The qualitative and quantitative composition of the proposed product is summarized in Table 2:

Table 2: Qualitative and Quantitative Composition of the Proposed Drug Product

Component	Quality Standard	Unit Quantity						Function
		Bulk solution[2]		(b) (4)		After reconstitution[3]		
		mg/mL	%w/v	mg/vial	% w/w	mg/mL	%w/v	
Phenobarbital sodium[1]	USP	(b) (4)		100.0	100.0	10.0	1.0	Active
(b) (4)								
0.9% Sodium chloride injection	USP	-	-	-	-	(b) (4)		Reconstitution solvent
[1] Actual quantity of Phenobarbital sodium to be calculated according to its potency.								
(b) (4)								
[3] (b) (4) titution.								

Source: NDA 215910 submission, Module 2.3.P.1

Please refer to the CMC review for a complete discussion of their findings and approvability of this Application.

2. Nonclinical Pharmacology

2.1 Receptor Activity

Barbiturates, including phenobarbital, are central nervous system (CNS) depressants that modulate gamma-aminobutyric acid (GABA) receptors (heteropentameric ligand-gated ion channels) via an allosteric site that is distinct from the benzodiazepine class (Brunton and Knollman, 2022). Barbiturates, such as phenobarbital, enhance GABA binding, resulting in chloride channel opening and an influx of chloride ions, resulting in neuronal hyperpolarization

and decreased electrical transmission (Czapiński, 2005, Rogawski, 2004, Galanopoulou, 2008, Olsen and Betz, 2006). At high concentrations, barbiturates can directly activate Cl^- channels in the absence of endogenous GABA (Nestler, 2020). Barbiturates also show some inhibition of voltage-gated Ca^+ channels and a direct blockade of excitatory glutamate signaling. These properties may contribute to phenobarbital's hypnotic and anticonvulsant effects (Mihic, 2018).

2.2 Safety Pharmacology and Toxicology Studies

The acute effects of phenobarbital using the skeletal muscular grip-strength test in mice were assessed by Zadronzniak et al. (2009). Adult male Swiss mice were dosed with a single intraperitoneal (IP) injection of phenobarbital at doses from 80 to 180 mg/kg and forepaw grip-strength response was plotted versus dose. Phenobarbital reduced grip strength, and a linear regression analysis yielded a 50% response value at 128.7 mg/kg dose. These data are aligned with phenobarbital's hypnotic effects.

2.3 Animal Behavioral Studies

Phenobarbital was evaluated for abuse potential and dependence in nonclinical studies, including drug discrimination tests, self-administration tests, and physical dependence tests. Summaries of these animal behavioral studies are provided in Sections 2.3.1 through 2.3.3. Overall, the results from these studies are supportive of the current schedule of control for phenobarbital (schedule IV).

2.3.1 Drug Discrimination Studies

Phenobarbital was evaluated for its discriminative stimulus properties in animal subjects. In operant drug discrimination tests, phenobarbital generally substituted for other barbiturates and produced full generalization. For example, in rats trained to discriminate pentobarbital (PB) (10 mg/kg, IP) from saline, phenobarbital produced full substitution at the highest dose tested (40 mg/kg, IP) (Kalinina, Garibova, & Voronina, 1999). Similarly, in rhesus monkeys trained to discriminate intragastrically administered pentobarbital (10 mg/kg) from saline using a signaled shock-avoidance trail procedure, phenobarbital produced full substitution for the pentobarbital cue as did several benzodiazepines (de la Garza & Johanson, 1987). In rhesus monkeys trained to discriminate pentobarbital (10 or 19 mg/kg, IM) from saline, phenobarbital (32 mg/kg, IM) produced full substitution (Winger & Herling, 1982). The same authors produced similar results in pigeons (i.e., phenobarbital produced full substitution in pentobarbital trained animals) (Herling, Valentino, & Winger, 1980). Similarly, in pigeons trained to discriminate midazolam (1.0 or 3.0 mg/kg, IM) from saline under a fixed-ratio 30 schedule of food delivery, phenobarbital substituted for midazolam in 75% (i.e., 3 of 4) pigeons (Evans & Johanson, 1989) Finally, in baboons trained to discriminate 1.8 mg/kg oral lorazepam from placebo, phenobarbital and other barbiturates (amobarbital, hexobarbital, methohexital, pentobarbital, and secobarbital) did not generalize to the lorazepam stimulus cue (Ator & Griffiths, 1997). Collectively, these data suggest similarity in the stimulus effects of the barbiturate class and indicate a degree of similarity across GABAergic drugs (e.g., benzodiazepines).

2.3.2 Self-Administration Studies

Phenobarbital was also evaluated for its reinforcing effects in animal subjects. In operant self-administration tests where at least two subjects were studied, the reinforcing efficacy of

phenobarbital was mixed. For example, consumption of phenobarbital (0.1–3.2 mg/kg/injection, IV) in Sprague-Dawley rats was comparable to saline control and lower than other CNS depressants tested (Collins et al., 1984), and in baboons (Papio cynocephalus) rates of phenobarbital (0.1–32.0 mg/kg/injection, IV) consumption slightly exceeded vehicle (Griffiths et al., 1991). These studies suggest that phenobarbital has a low level of reinforcing efficacy.
In the Collins 1984 study, the reinforcing effects of 31 psychoactive compounds were examined in 788 rats. Drug-naïve female rats were individually housed and fitted with a saddle that was connected to a cannula through which they self-administered doses of test drugs via intravenous injection upon pressing a lever. Drugs were administered by a motor-driven syringe and each dose was followed by a 3 second "time out" during which further lever responses were not reinforced. In the phenobarbital groups, rats were offered a selected dose for 5 days after which the dose was reduced by 1 log unit (to 0.1 times the original dose) for 4 days. The reinforcing efficacy of the test drugs was scored based on injection rates observed during the last 3 days of dosing at each dosage level compared to the same time periods for saline controls. Subjects were considered reinforced if their injection rates were outside of the upper bound of the 90% confidence interval of injection rates that was established by the saline control groups. Subjects were also given a score on a scale of 0-3 based on the number of dose levels under which they were reinforced. A score of 0 indicated injection rates equal to saline control at both dose levels, a score of 1 indicated increased injection rates only at the high dose, a score of 2 indicated increased injection rates at both drug doses, and a score of 3 indicated response to only the reduced dose; this was interpreted as the highest level of reinforcement, as the high dose was sufficiently large that relatively few injections were needed to maintain response.

In rats, phenobarbital sodium was dissolved in saline (0.5 mol sodium carbonate per mol of phenobarbital) and was dosed at initial levels of 1 mg/kg (n = 7) and 3.2 mg/kg (n = 6) for 5 days. Doses were reduced by a factor of 10 (to 0.1 mg/kg and 0.32 mg/kg) for the second dosing period. Results of this study showed that only one rat in the 1 mg/kg group self-administered the compound at rates higher than saline control; reinforcement was only seen at the initial high dose. No subjects showed reinforcement in the 3.2 mg/kg group at either initial or reduced doses. Scores for reinforcement were, therefore, lower than scores seen in other CNS depressants studied such as diazepam, ethanol, flurazepam, methohexital, and pentobarbital. Total injections per group in the 1 mg/kg group were significantly ($p < 0.05$, Hotelling's T2-statistic) greater than in saline control groups. This difference was not seen in the 3.2 mg/kg group.

In the Griffiths 1991 study, the reinforcing effects of 12 sedative-anxiolytics were examined in 26 baboons. Drug experienced (n=17; 3 to 46 months) and drug-naïve (n=9) male baboons were individually housed and implanted with a jugular, femoral, or axillary venous silastic catheter through which they self-administered doses of test drugs. Drug administration was controlled via a valve system and always followed by a 3-hour "time out" period during which additional responses were not reinforced. Self-injection performance was established first with cocaine, then, after three days of six or more cocaine injections, test drugs or vehicle were substituted for cocaine for a period of approximately 15 days. This process was repeated multiple times for each animal with each repetition featuring administration a different dose or drug/vehicle. Three animals received phenobarbital at doses ranging from 0.1 to 32 mg/kg/injection. Rates of self-injection in these animals varied between approximately 1–3 injections per day of phenobarbital, only marginally greater than the 0–2 injections per day of vehicle. These same animals self-

injected cocaine at rates of between 7–8 injections per day, similar to the 6–8 injections per day of the short-acting barbiturates tested in other groups of animals. Depending on dose, the benzodiazepines showed higher levels of self-administration, intermediate between vehicle and control. The authors concluded that phenobarbital has a low potential for abuse and hypothesized that the low reinforcing effects of phenobarbital may be a result of its slow onset and elimination rate. Further, unlike the other barbiturates studied, brief periods of anesthesia were not noted after phenobarbital (or the benzodiazepines).

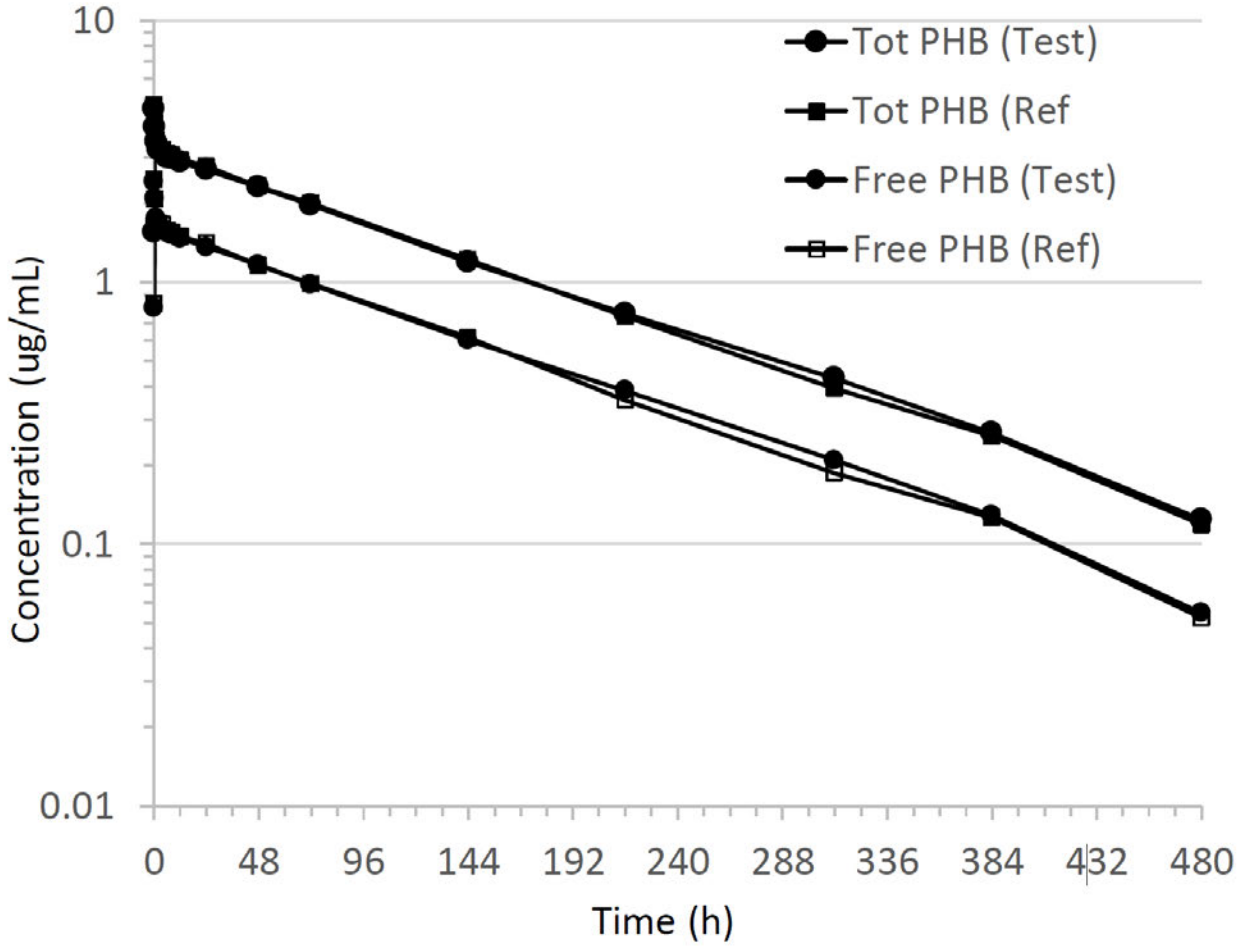
2.3.3 Physical Dependence

As a class, the barbiturates are known to produce physical dependence and withdrawal (Santos, Olmedo, & Kim, 2017) and there appears to be some cross-dependence with other CNS depressants (Tagashira, Urano, Hiramori, & Yanaura, 1983). In animals, changes in $GABA_A$ receptor density have been observed in both phenobarbital dependent, and withdrawn rats (Tanaka, Aoki, Satoh, Yoshida, & Kuroiwa, 1991) suggesting a $GABA_A$-based mechanism for phenobarbital dependence and withdrawal. In behavioral observations in animal subjects, phenobarbital was evaluated for its ability to produce signs of physical dependence following repeated administration. In one study, grand mal convulsions and delirium were noted within 48 and 72 hours of abstinence in Monkeys (Rhesus macaque) after discontinuation of repeated phenobarbital administration (50–100 mg/kg/day, IM or PO for 6 to 8 weeks) (Yanagita et al., 1970). In a study administering drug-adulterated food to male mice, phenobarbital at 2.5 mg/g for five days followed by 3.0 mg/g for two days produced significant signs of withdrawal after drug discontinuation as evidenced by decreases in body weight and food consumption. Withdrawal signs appeared to exhibit a biphasic development peaking ~20 and 32 hrs after phenobarbital discontinuation (Yutrzenka & Kosse, 1989) In another study, abstinence signs and withdrawal convulsions were present following repeated phenobarbital administration (140 mg/kg/day, PO) with severity varying as a function of exposure duration (10 days vs 35 days) (Gay et al., 1983).

3. Clinical Pharmacology

SPARC conducted a single-dose crossover study in healthy adults to evaluate the pharmacokinetics (PK) of total and unbound phenobarbital with the proposed phenobarbital sodium for injection formulation compared to a marketed, unapproved phenobarbital sodium intravenous formulation containing benzyl alcohol (manufactured by West-Ward) (Study PHEN-20-01). The purpose of the study is to bridge to the investigator study NEOLEV2 that was used to support the safety and efficacy for the proposed indication. The study was a two-sequence, two-period, single-dose crossover study where phenobarbital sodium for injection was given over 15 minutes at a dose of 2 mg/kg. As indicated in the figure and table below, the study results showed that the mean plasma concentration profiles of unbound and total phenobarbital were similar between the two formulations. Following the end of the infusion, plasma concentrations of unbound and total phenobarbital exhibited a biphasic decline for both treatments. The study also demonstrated that mean values for PK parameters, and half-life were comparable between the two intravenous formulations. In summary, the results from Study PHEN-20-01 established the scientific bridge between these two products. Please refer to the Clinical Pharmacology review for details regarding the study results and conclusions.

Figure 2: Mean Total and Unbound Phenobarbital Plasma Concentrations in Healthy Adult Subjects Administered a Single 2 mg/kg IV Dose of the Applicant's Proposed Phenobarbital for Injection Product Compared to the West Ward Formulation, Study PHEN-20-01



Source: NDA 215910 submission, Module 5.3.1.2

Table 4: Mean (CV%) Pharmacokinetic Parameters for Total and Unbound Phenobarbital by Treatment, Study PHEN-20-01

PK Parameter	**SPARC (N = 23)**		**West Ward (N = 23)**	
	Total	**Unbound**	**Total**	**Unbound**
Cmax (ug/mL)	4.72 (26.1)	2.48 (25.5)	4.80 (27.0)	2.53 (28.3)
AUC0- (h*ug/mL)	492 (18.6)	246 (19.7)	496 (17.5)	247 (19.6)
CL (L/h)	312 (31.0)	628 (31.9)	300 31.4)	604 (32.9)
PK Parameter	**SPARC (N = 23)**		**West Ward (N = 23)**	
	Total	**Unbound**	**Total**	**Unbound**
V (L)	46.3 (21.2)	92.1 (20.8)	43.6 (20.9)	87.2 (20.8)
Half-life (h)	107 (20.0)	106 (20.0)	104 (19.3)	105 (20.0)
Source: Table 11-3 and 11-4 of PHEN-20-01 CSR				

Source: NDA 215910 submission, Module 5.3.1.2

4. Clinical Studies

4.1 Summary of Abuse-Related Adverse Events Profiles in Clinical Studies

Two clinical studies were included in the NDA. Study design and abuse related adverse events are summarized below.

The Applicant conducted a Phase I single-dose, crossover study in healthy adults to demonstrate bioequivalence on the pharmacokinetics (PK) of total and unbound phenobarbital between SPARC's phenobarbital sodium injection formulation and West-Ward's phenobarbital sodium injection formulation (Study PHEN-20-01). The purpose of this study is to bridge to investigator-sponsored study (Study NEOLEV2) to demonstrate the safety and efficacy of phenobarbital for the treatment of neonatal seizures, in which West-Ward's phenobarbital sodium injection formulation were used. Safety results from these two studies in combination with a review of the published literature are used to support the safety of the proposed product.

Study PHEN-20-01
The study was an open-label, two-period, two-sequence, two-way crossover, single-dose bioavailability (BA) and bioequivalence (BE) study comparing single doses of 2 mg/kg of SPARC's proposed phenobarbital sodium for injection product (Test drug) with the currently marketed unapproved product by West-Ward Pharmaceuticals (Reference drug) in healthy adults. There was a 5-week wash out period between treatments. Safety evaluations were performed on all 24 subjects who received at least one dose of drug. No deaths or serious adverse events were reported in this study.

Frequency of treatment-emergent adverse events (TEAEs) by system organ class (SOC) and preferred term (PT) is summarized in the table below. Abuse-related adverse events reported in this study included somnolence, euphoric mood, and dizziness with similar rates reported between the test drug and reference drug groups. Assessments for drug accountability, withdrawal, and rebound events are not applicable, as this was a single-dose, inpatient study conducted in healthy volunteers.

Table 5: Study PHEN-20-01: Incidence of Treatment Emergent Adverse Events (TEAEs) by SOC and Preferred Term (Safety Population)

System Organ Class Preferred Term	Phenobarbital SPARC (N = 24) N(%)	Phenobarbital West-Ward (N = 25) N(%)	Total (N = 25) n (%)
Subjects having at least one TEAE	10 (41.7)	12 (48.0)	16 (64.0)
Nervous system disorders	8 (33.3)	8 (32.0)	12 (48.0)
Dizziness	2 (8.3)	2 (8.0)	3 (12.0)
Somnolence	6 (25.0)	7 (28.0)	10 (40.0)
Psychiatric disorders	1 (4.2)	2 (8.0)	3 (12.0)

Euphoric mood	1 (4.2)	1 (4.0)	2 (8.0)
Note 1: System organ class and preferred terms are coded using the MedDRA dictionary Version 23.1. Note 2: Percentages are based on number of subjects in respective treatment group in safety population. Program Name: T_14_3_1_2.sas Source: ADaM.ADAE; listing 16.2.7.1 Creation Date and Time: 30AUG2021:16:16 Source: Table 12-3 of the CSR for PHEN-20-01 study			

Source: NDA 215910 Submission, Module 2.3.P.1

Study NEOLEV2

The study was a randomized, double-blinded, active-controlled study to evaluate the safety and efficacy of levetiracetam (LEV) compared to phenobarbital (PB) in the first-line treatment of neonatal seizures. A total of 106 neonates were randomized to treatment with PB (42 patients) or LEV (64 patients). Subjects received an initial loading dose of study treatment, followed by a maintenance dose for up to 5 days. The specific treatment protocol is summarized below:

> As noted in module 2.7.4, "subjects randomized to receive LEV at the onset of electrographically confirmed seizure activity received an intravenous loading dose of LEV of 40 mg/kg given over 15 minutes. If electrographic seizures were confirmed to persist or recur more than 15 minutes after the first infusion was completed, a further 20 mg/kg load of LEV was administered IV over 15 minutes. Maintenance of LEV at 10 mg/kg/dose was given IV every 8 hours (q8) and continued for at least 5 days. If seizures persisted or recurred more than 15 minutes after the second LEV infusion was completed, a PB loading dose of 20 mg/kg was administered IV over 15 minutes. If seizures persisted or recurred more than 15 minutes after the first loading dose of PB was completed, a second 20 mg/kg dose was administered IV over 15 minutes. This resulted in PB being started within 1 hour of the onset of seizures if and when loading with LEV was ineffective. Subjects given any PB loading doses were started on maintenance PB with 1.5 mg/kg/dose given IV q8 hours and continued at least until the end of the study. Subjects randomized to the control group received an IV loading dose of 20 mg/kg PB given over 15 minutes at the onset of electrographically confirmed seizure activity. If electrographic seizures were confirmed to persist or recur more than 15 minutes after the first infusion was completed, a further 20 mg/kg load of PB was administered IV over 15 minutes. Maintenance PB at 1.5 mg/kg/dose was given IV q8 hours and continued for at least 5 days. If seizures persisted or recurred more than 15 minutes following the second PB infusion, a 40 mg/kg load of LEV was administered IV over 15 minutes. If seizures persisted or recurred more than 15 minutes after the first loading dose of LEV was completed, the second load of 20 mg/kg of LEV was administered IV over 15 minutes. Subjects given an LEV loading dose were started on maintenance LEV with 10 mg/kg/dose given IV q8 hours and continued at least until the end of the study."

An evaluation of abuse-related adverse events is not applicable for the studied patient population (i.e., neonates); however, sedation, which can be associated with drugs with abuse potential, was reported in approximately 16% of neonates treated with phenobarbital, as noted in the table

below. The Applicant did not provide data to inform the potential for withdrawal symptoms and/or rebound seizures upon drug discontinuation for this study.

Table 6: Study NEOLEV2: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population)

System Organ Class Preferred Term	Phenobarbital (N = 32) n (%)	Phenobarbital+ Levetiracetam (N = 55) n (%)	Levetiracetam (N = 19) n (%)	Overall (N = 106) n (%)
Nervous system disorders	5 (15.6)	9 (16.4)	1 (5.3)	15 (14.2)
Sedation	5 (15.6)	9 (16.4)	1 (5.3)	15 (14.2)

TEAE: Treatment-Emergent Adverse Event; N = Total number of subjects in each treatment group under the stated population; n = Number of subjects with non-missing data.
Notes: Percentages are based on N.
Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.
If any event for a subject in the final AE designation page from Day 1 to Day 5 and after Study Completion is marked as an AE, then all the events from both Final AE designation and Symptoms/Findings pages for that subject are considered as Adverse Events.
Reference: Listing 16.2.7.1, 16.2.7.2 NEOV2 Clinical Study Report
Program Name: slev_t14_3_1_2_2.sas. Dataset Used: ADAE Runtime ID: 30NOV2021 18:27

Source: NDA 215910 Submission, Module 1.14.1.3

4.2 Review of the Published Literature Informing Human Abuse Potential

Phenobarbital has been used in clinical practice as a sedative, hypnotic, pre-anesthetic, and anticonvulsant for more than 100 years. It is well known that barbiturates are generally abused to reduce anxiety, decrease inhibitions, and treat unwanted effects of illicit drugs (DEA,2020). The Applicant did not conduct a human abuse potential study in support of this NDA, however, they conducted a review of the published literature regarding the abuse potential and potential for development of physical dependence associated with phenobarbital, and the barbiturate drug class in general, in humans.

There are limited published reports of human abuse potential studies for the barbiturate drug class. Fraser et al. conducted a systematic review of the assessment of the abuse potential of sedative/hypnotics (depressants) (Fraser & Jasinski, 1977). In this review, the authors cited an unpublished human abuse potential study that compared the effects of pentobarbital 50, 120, and 288 mg/70 kg; secobarbital 75, 180, and 432 mg/70 kg; and phenobarbital 140, 360, and 557.1 mg/70 kg. All drugs were administered intramuscularly in10 healthy volunteers under double-blind conditions. Note both pentobarbital and secobarbital are listed as schedule II controlled substances under the Controlled Substance Act (CSA).

The study results showed that subjects identified all three drugs as having barbiturate-like subjective effects. As indicated in the figures below, pentobarbital, secobarbital, and phenobarbital produced dose-related increases in symptom and sign scores, subjects' and

observers' "liking" scores, and Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale scores as well as dose-related increases in postrotatory nystagmus. According to the authors, the PCAG scale is a specific measurement of the subjective effects for the sedative-hypnotic drug class and was used to differentiate these three drugs from other drugs such as morphine, amphetamine, LSD, and pyrahexyl, as well as placebo. The subjective effect assessment described in this study differs from abuse potential assessments from modern human abuse potential studies in that VAS measures on Drug Liking, Take Drug Again, High, and Overall Drug Liking are used to assess the subjective reinforcing effects in the modern human abuse potential study (Assessment of Abuse Potential of Drugs Guidance for Industry, 2017).

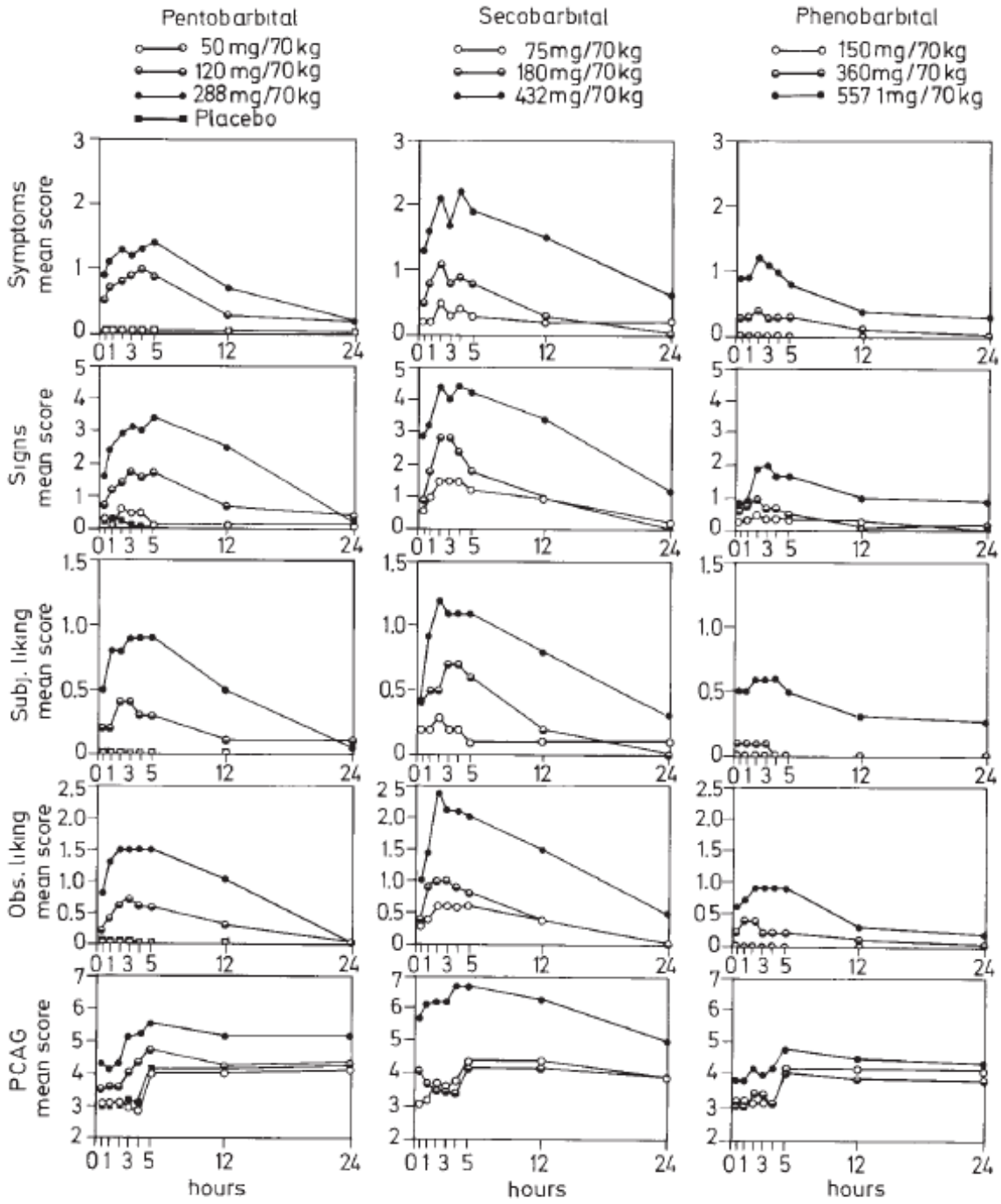


Fig. 2. Time-action curves for responses to intramuscularly administered pentobarbital, secobarbital, phenobarbital, and placebo as measured by PCAG scale scores, symptom and "liking" scale scores from subjects' single dose opiate questionnaire, and sign scores and observers' "liking" scores from observers' single dose opiate questionnaire

Sources: Fraser, H., & Jasinski, D. (1977). The assessment of the abuse potentiality of sedative/hypnotics (depressants)(Methods used in animals and man).

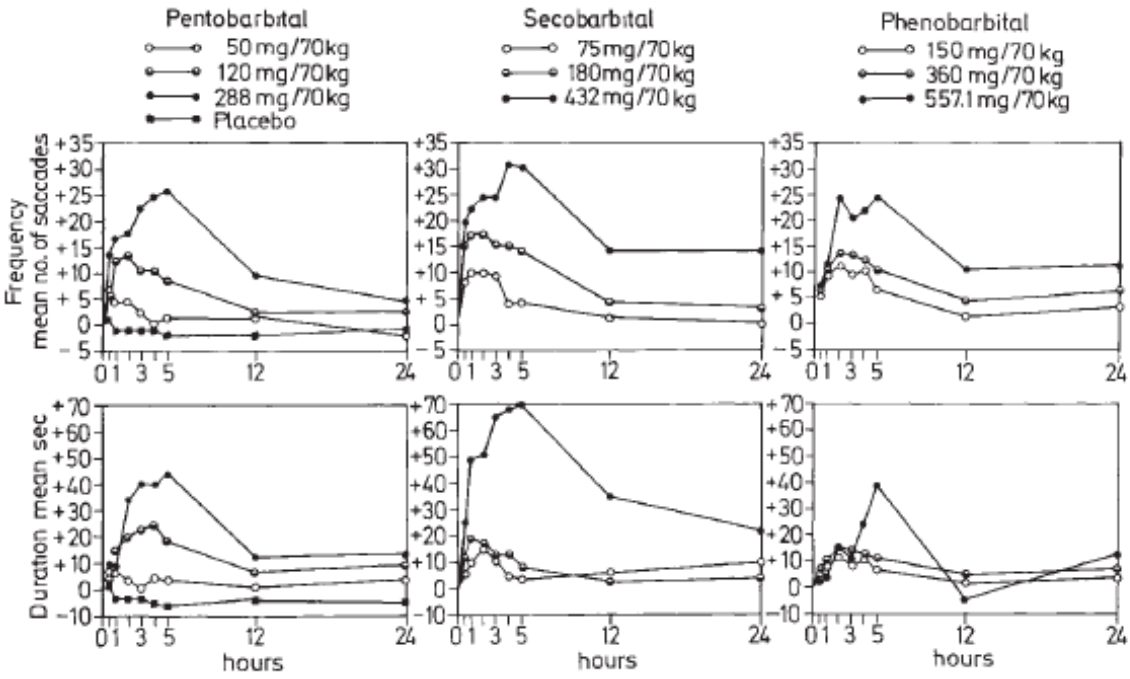


Fig. 3. Time-action curves for facilitation of duration and frequency of postrotatory nystagmus by pentobarbital, secobarbital, phenobarbital, and placebo. Each point represents mean change in frequency or duration from mean of two predrug controls. Nystagmus was recorded with a polygraph. Data were obtained in a crossover study employing 10 subjects

Source:Fraser, H., & Jasinski, D. (1977). The assessment of the abuse potentiality of sedative/hypnotics (depressants) (Methods used in animals and man).

The study results suggest that phenobarbital at the 557.1 mg dose produced the reinforcing effects as measured by drug liking scores and PACG scores. However, the dose required to produce reinforcing effects for phenobarbital are much higher than that of schedule II comparators such as pentobarbital and secobarbital.

4.3 Review of the Published Literature Informing the Potential for Development of Tolerance and Physical Dependence in Humans

For the purposes of this review, the following definitions of tolerance and physical dependence are based on FDA guidance on the assessment of abuse potential (Assessment of Abuse Potential of Drugs Guidance for Industry, 2017)

- Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.
- Tolerance is a state that develops as a result of physiological adaptation characterized by a reduced response to a specific dose of drug after repeated administration of the drug (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Tolerance to the sedative effects of phenobarbital and development of physical dependence with phenobarbital have been well demonstrated in animal models. Please refer to Section 2 of this review for additional details.

The Applicant did not identify any human physical dependence or tolerance studies specifically for phenobarbital in the published literature. The Applicant identified one systematic review of twenty studies reported that phenobarbital produced a higher rate of “adverse drug reaction related withdrawal” (ADR-related withdraw), compared to carbamazepine, valproic acid, and phenytoin (Zhang, Zeng, & Li, 2011). Additionally, physical dependence and tolerance with barbiturates have been well described in standard textbooks for clinical medicine (ASAM Principles of Addiction Medicine., Miller & Gold, 1998). Withdrawal symptoms associated with barbiturate including phenobarbital discontinuation are similar to alcohol or benzodiazepine withdrawal and include increased psychomotor activity, agitation, muscular weakness, tremulousness, hyperpyrexia, diaphoresis, delirium, convulsions, elevated blood pressure, pulse and temperature, tremor of eyelids, tongue and hands (Sellers,1988., Miller & Gold, 1998).

An acute withdrawal syndrome may appear upon discontinuation of barbiturates after prolonged use and may include symptoms of apprehension, muscular weakness, tremors, postural hypotension, anorexia, muscular twitches, and, in severe cases, psychosis and seizure (Smith and Wesson, 1970). However, barbiturates that produce more significant withdrawal symptoms generally have a short or intermediate half-life of approximately 10-50 hours and phenobarbital with a longer half-life is less prone to more significant withdrawal symptoms (Sellers, 1988). The most severe withdrawal reactions include seizures and delirium, which have an onset between 24 to 115 hours after stopping drug. In addition, patients may experience symptoms resembling alcohol delirium tremens, including disorientation and hallucinations. Smith and Wesson summarized addicting doses of common sedative-hypnotics. For example, some studies demonstrated that secobarbital sodium or pentobarbital sodium, 600 to 800 mg given daily for 35 to 57 days is sufficient to produce "major" signs of physical dependence (Smith & Wesson, 1970). However, the dosage and treatment duration required to produce "major" signs of withdrawal are not well established for phenobarbital.

Addicting Doses of Common Sedative-Hypnotics*

Drug	Dependence Producing Dosage (mg Daily)	Time Necessary to Produce Dependence (Days)	Reference No.	Drug Dosage Equivalent to 30 mg of Phenobarbital (mg)
Secobarbital Pentobarbital	800-2,200	35-57	1	100
Diazepam	80-120	42	3	10
Chlordiazepoxide hydrochloride	300-600	60-180	4	25
Meprobamate	2,400	270	5	400

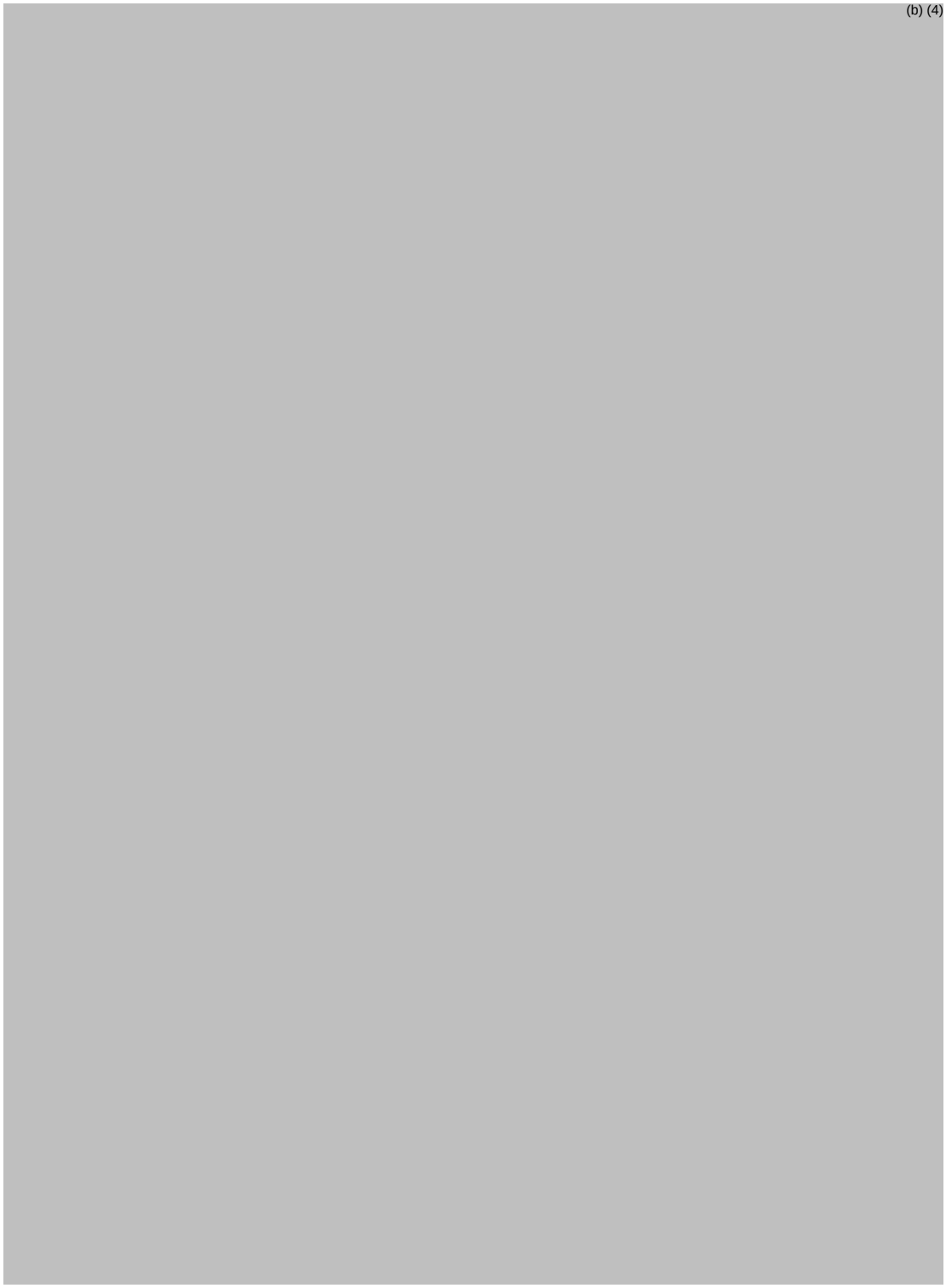
*Dosages sufficient to produce "major" withdrawal signs in humans.

Source: Smith, D. E., & Wesson, D. R. (1970). A new method for treatment of barbiturate dependence.

5. Regulatory Issues and Assessment

The Applicant submitted the following proposed draft labeling for **Section 9 Drug Abuse and Dependence**, as follows:

(b) (4)



6. Other Relevant Information

Consult review conducted by the Office of Surveillance and Epidemiology (OSE)

CSS consulted the Office of Surveillance and Epidemiology (OSE) for an evaluation of current epidemiological evidence of misuse, abuse, and misuse- and abuse-related adverse events, including overdose, for phenobarbital based on available epidemiology data, published data, international data sources, and postmarketing experience and Periodic Safety Update Reports (PSUR) as compared to other sedative/hypnotic drugs, including schedule IV benzodiazepines and schedule II and III barbiturates.

In their review, OSE analyzed patterns of use, abuse (or nonmedical use), associated morbidity, and overdose deaths for phenobarbital on an absolute scale (i.e., case counts) to examine the scope of, and public health burden associated with, nonmedical use of phenobarbital and the selected comparator drugs. OSE also calculated rates adjusted for utilization (i.e., the number of prescriptions dispensed for human drug products from outpatient pharmacies) to better understand the relative levels of abuse and harms associated with phenobarbital relative to the selected comparator drugs, considering different levels of "prescribed availability" in the community. Based on their review, OSE concluded the following:

- *The utilization of oral barbiturates in outpatient pharmacies decreased by (b) (4) from 2013 through 2021 and remained consistently lower than the utilization of non-injectable benzodiazepines in retail pharmacies from 2014 through 2018.*
- *In 2021, oral phenobarbital accounted for (b) (4)) of a total of (b) (4) oral barbiturate prescriptions dispensed in outpatient pharmacies, followed by oral butalbital at (b) (4)); oral butabarbital and secobarbital had minimal use.*
- *In non-federal hospitals, the utilization of injectable phenobarbital doubled from 2016 to 2021. Injectable phenobarbital accounted for (b) (4)) of a total of (b) (4) patients receiving any injectable barbiturates in 2021, followed*

by injectable methohexital at (b) (4)) and injectable pentobarbital at (b) (4)).

- *When epidemiology data analysis was restricted, the utilization-adjusted analyses for phenobarbital, butalbital, and benzodiazepines, using aggregate data for the five-year period, 2014 to 2018, OSE concluded that after adjusting for utilization, phenobarbital had a slightly higher five-year rate of abuse cases (b) (4) prescriptions dispensed than butalbital's rate but lower than benzodiazepines' rate (benzodiazepines were 2.4 times higher).*
- *Data from exposure calls to Poison Control Centers suggest that nonfatal adverse events associated with abuse involving phenobarbital occur primarily in the context of polysubstance use.*
- *The annual number of overdose deaths involving barbiturates remained consistently lower than overdose deaths involving benzodiazepines during the ten-year period (2011 to 2020), approximately 20 to 30 times lower depending on the year. In contrast, utilization-adjusted rates of overdose deaths involving barbiturates were higher than for benzodiazepines during the study period examined (2014 to 2018, using available data on benzodiazepines).*
- *Poison Control Center (PCC) cases of abuse and misuse involving phenobarbital and all comparators declined over the study period, proportional to declines in utilization in outpatient pharmacies. In contrast, overdose deaths involving barbiturates and overdose deaths involving benzodiazepines increased during the study period, before and after adjusting for utilization. Specifically, the annual prescription-adjusted rates of overdose deaths involving barbiturates increased around 1.5 times, from (b) (4) in 2013 to (b) (4) in 2020. The annual rates of overdose deaths involving benzodiazepines also increased around 1.5 times from 2014 to 2018.*
- *In the PCC data, among single-substance abuse cases, the oral route was the most common route of abuse for phenobarbital (b) (4) and comparators (b) (4)). The inhalation or injection route was rare for phenobarbital single-substance abuse cases (b) (4)*

Additionally, Dr. Karen Long and Dr. Allen Brinker from OSE's Division of Pharmacovigilance I (DPV I) evaluated post-marketing data, such as FDA Adverse Event Reporting System (FAERS) data and provided a descriptive analysis of FAERS and medical literature cases of phenobarbital abuse, misuse, diversion, overdose, dependence, withdrawal, toxicity, or elevated levels. Below is the excerpt from their review:

> *DPV included 57 FAERS and medical literature cases for analysis from January 1, 2012 to April 30, 2022 describing 1) abuse, misuse, dependence, withdrawal, or overdose or 2) toxicity or elevated levels with phenobarbital; toxicity was defined as adverse events related to supratherapeutic doses/levels or central nervous system (CNS)-related adverse events that may suggest abuse potential at therapeutic doses/levels. Among the 57 cases, DPV identified 40 cases describing abuse (32), misuse (5), dependence (9), withdrawal (3), or overdose (32) with phenobarbital [one case can report more than one event] and 17 cases describing*

toxicity or elevated levels with phenobarbital. Most cases (56/57) reported a regulatory serious outcome, including death (18), life-threatening (3), hospitalization (33), disability (1), required intervention (1), and other serious (35).

Most cases (49/57) involved multiple drugs or substances and the mean number of concomitant drugs or substances was higher in the cases reporting abuse, misuse, dependence, withdrawal, or overdose (mean 5.1) compared to cases reporting toxicity or elevated levels (mean 2.4). The most frequently reported categories of concomitant drugs included opioids (24), antiepileptic drugs (23), benzodiazepines (22),muscle relaxants (12), and antidepressants (11). Phenobarbital in isolation was reported in one case of abuse, one case of misuse/overdose, two cases of dependence/ withdrawal, and four cases of toxicity or elevated levels. Most cases reported use of oral phenobarbital or did not report a route of administration, and we identified only one case of intravenous phenobarbital use. Most cases were reported in adults (n=37, pediatric n=9, unknown n=11) with a mean age of 36.1 years (median 37, range 3 months-88.6 years). Most cases (27/57) reported seizure as the reason for phenobarbital use. We identified higher doses and phenobarbital levels in cases reporting abuse, misuse, dependence, withdrawal, or overdose compared to cases reporting toxicity or elevated levels, which corresponded to a higher severity of reported adverse events. Most reported adverse events were related to injury/poisoning, nervous system disorders, psychiatric disorders, cardiovascular disorders, and respiratory disorders.

DPV identified two cases describing abuse, misuse, or overdose of veterinary phenobarbital (canine and equine) in humans; both cases presented with CNS depression, involved ingestion of other substances (opiates and alcohol), and required hospitalization for the events. DPV did not identify any cases of severe withdrawal resulting in seizures, delirium, or death. DPV also did not identify any cases of toxicity or overdose resulting from accidental ingestion of phenobarbital or medication errors related to confusion in dosing and administration.

Although phenobarbital labeling includes extensive information regarding phenobarbital tolerance, dependence, withdrawal, and overdose, additional labeling regarding abuse potential may be reasonable and help inform prescribers and patients of these risks, particularly when used in combination with other drugs/substances of abuse (e.g., opioids, benzodiazepines, alcohol, etc.).

Review of labeling language for approved and unapproved, marketed barbiturate class drug

CSS conducted a review of nonproduct specific labeling language for general information regarding drug abuse, tolerance, dependence, and withdraw. The following general information are included in the labels of approved and unapproved, marketed barbiturate class drugs:

"Symptoms of acute intoxication with barbiturates include unsteady gait, slurred speech, and sustained nystagmus. Mental signs of chronic intoxication include confusion, poor judgment, irritability, insomnia, and somatic complaints.

The symptoms of barbiturate withdrawal can be severe and may cause death. These symptoms usually appear in the following order: anxiety, muscle twitching, tremor of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia, and orthostatic hypotension. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days.

As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than twofold. As this occurs, the margin between intoxicating dosage and fatal dosage becomes smaller."

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Memorandum (Neonatal-Perinatal Medicine Consultation)

To: Amy Kao, M.D.
Clinical Reviewer, DN2/OND/CDER

From: An N. Massaro, M.D.
Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Through: Gerri Baer, M.D.
Supervisory Medical Officer, Office of Pediatric Therapeutics, OCPP/OC

Date: October 25, 2022

Subject: Neonatal-Perinatal Medicine Consultation – NDA 215910 Phenobarbital (SEZABY)

MATERIALS REVIEWED:

1. NDA 215910 – Phenobarbital (SEZABY) - Sections 2.4 Nonclinical Overview; 2.5 Clinical Overview; 2.7.2 Summary of Clinical Pharmacology Studies; 2.7.3 Summary of Clinical Efficacy; 2.7.4 Summary of Clinical Safety; Draft Labeling

Published Literature
The reference list is included at the end of the consultation, following the recommendations.

NEONATAL-PERINATAL MEDICINE CONSULTATION QUESTION(S):

From Consult Request: Sun Pharma has submitted New NDA 215910 (phenobarbital sodium injection 100mg/vial) under 505b2 for treatment of neonatal seizures. This submission references safety and efficacy data from IND 109622 and bioequivalence data from IND 132342. This product has Rare Pediatric Disease Designation, Orphan Drug Designation, and the applicant requests priority review. This NDA submission is a type 7 previously marketed without an approved NDA. Because this phenobarbital injection is preservative free and indicated to treat neonatal seizures and is the first phenobarbital NDA application, we request OPT/Neonatology to assign a reviewer and attend the milestone meetings.

Specific questions raised for OPT Neonatology input over the review cycle:

1. Does the clinical approach to phenobarbital administration differ in preterm compared to term babies? Is there concern about differences in metabolism/excretion/protein binding in premature infants that would impact dosing/administration or monitoring? Do you think that an assessment of phenobarbital PK or other outcomes in preterm infants would be a potential PMR?
2. Assist with developing a PMR regarding potential long-term impact of phenobarbital on neurodevelopment.
3. Review current draft labeling. Questions during labeling discussions:
    a. Comment on practice of following total phenobarbital levels, rather than free and total levels (i.e., is the understanding of proportionality of unbound/total phenobarbital important to guide dosing in a situation of low albumin or high protein-binding drugs?).
    b. In your NICU practice, is the potential for increased clearance of phenobarbital in the setting of alkalinizing drugs an issue which has come up or that you have considered?

c. Proposed label includes the statement: "Drug product is free of benzyl alcohol and propylene glycol." Does noting that this formulation is free of BA be helpful to the health care provider?

BACKGROUND:

Description of the Disease Process

Neonatal seizures occur in 1-5 per 1000 live births, with approximately 14,000 cases per year in the U.S.[1] The majority of neonatal seizures are acute provoked seizures (i.e., attributable to an acute illness or brain insult such as hypoxia-ischemia, infection, metabolic abnormalities, etc.), with fewer cases of genetic or idiopathic epilepsy syndromes presenting in the neonatal period.[2]

The most recent consensus definition of seizures in the neonate proposed by the International League Against Epilepsy (ILAE)[1] is described as *"an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. The duration is not defined but has to be sufficient to demonstrate evolution in frequency and morphology of the discharges and needs to be long enough to allow recognition of onset, evolution, and resolution of an abnormal discharge."* This electrographic-based definition highlights the importance of electroencephalogram (EEG) in the accurate diagnosis of seizures in the neonate. While historically neonatal seizures have been characterized as clinical only, electroclinical, or electrographic only, reliable clinical diagnosis of seizures in the neonate is difficult and paroxysmal clinical events without a definite EEG correlate are now widely considered "non-seizure episodes" given that the clinical significance of these events is unclear. It has been proposed that contemporary clinical trials evaluating safety and efficacy of anti-seizure medications (ASM) include EEG-based inclusion criteria and endpoints.[3]

Long-term outcomes in children with neonatal seizures vary by underlying etiology and severity of seizures in the neonatal period. In general, neonatal seizures are associated with increased risk for mortality, neurodevelopmental impairment, and later epilepsy.[4] While these adverse outcomes may be attributable to underlying etiology (i.e., acute brain injury, genetic disorders, brain malformations, etc.), there is evidence to support that prolonged seizures may exacerbate brain injury due to secondary metabolic and microstructural changes.[5] Pharmacologic treatment of seizures with the goal of rapid seizure cessation and overall reduction of seizure burden is the clinical standard of care for neonatal seizures in the neonatal intensive care unit.

Available Therapeutics

There are no drugs approved for treatment of neonatal seizures. Phenobarbital is the first-line ASM used for neonatal seizures in the U.S.[6-8] and internationally,[9] and marketed, unapproved formulations have been used for over 50 years. Phenobarbital is currently marketed in the U.S. as a benzyl alcohol-containing formulation by West-Ward Pharmaceuticals. Other ASMs including phenytoin/fosphenytoin, levetiracetam, and benzodiazepines are also used, with less frequent use of topiramate, carbamazepine/oxcarbazepine, lidocaine and lacosamide.[7, 8]

Product Description and Regulatory History

Phenobarbital exerts its anticonvulsant effect by facilitating γ-aminobutyric acid (GABA)-mediated neurotransmission, leading to neuronal hyperpolarization and decreased electrical transmission. The Sponsor has developed a preservative-free phenobarbital injection for intravenous administration for the treatment of neonatal seizures.

The Sponsor has had several FDA interactions since 2019 regarding the regulatory pathway for their product including a several Type C meetings, teleconferences and email/written responses regarding the plan to perform bioavailability/bioequivalence (BA/BE) studies and drug-drug interaction studies to establish a pharmacokinetic (PK) bridge between West-Ward's drug product and Sun Pharma Advanced Research Company (SPARC)'s new formulation in order to rely on safety and efficacy data from the NeoLEV2 study[10] (see full description below) and published literature. These interactions also focused on the need for final analysis reports and complete safety and efficacy datasets from the NeoLEV2 study for review and independent analysis by the agency. The Sponsor obtained right of reference to the NeoLEV2 study (IND 109622).

The Sponsor was granted Orphan Drug Designation for the neonatal seizure indication on October 2, 2019.

Proposed Indication for Use (IFU): Treatment of neonatal seizures.

Reviewer comments: *The indication should specify "treatment of neonatal seizures in term and preterm infants" (see discussion of dosing in preterm infants below).*

Brief Summary of Available Study Data

Nonclinical Studies

Non-clinical data to support registration of phenobarbital is largely literature based.

The Sponsor summarizes these data in (b) (4):

(b) (4)

Other non-clinical toxicity concerns include *"sedation, prolonged APTT, altered lipid, glucose, and electrolyte metabolism, increase in liver, kidney and thymus weight, centrilobular hepatocellular hypertrophy and thyroid follicular cell hypertrophy."*

The Sponsor conducted two (rat and rabbit) 14-day repeat-dose intravenous toxicity studies and 7-day dose range finding studies (up to 200 mg/kg/day) as required locally prior to initiating clinical studies in India. No new toxicity concerns were observed. Effects on sedation, body weight, aPTT, and liver toxicity were observed as known effects of phenobarbital.

Clinical Studies

The Sponsor intends to rely upon the NeoLEV2 study as an adequate and well-controlled trial to support the safety and efficacy of IV phenobarbital for treatment of neonatal seizures, with supportive non-clinical, clinical pharmacology and other clinical data from the literature. In addition, the Sponsor conducted a clinical BA/BE study in adults to establish a PK bridge between the investigational product and the marketed, unapproved West-Ward formulation that was used in the NeoLEV2 study. (NeoLEV2 was funded by the FDA Office Of Orphan Products Development's Orphan Drugs Clinical Trials Grants Program (1 RO1FD004147) to evaluate levetiracetam, with phenobarbital used for the active control/comparator arm).

Summary of NeoLEV2 Study[10]:

Study Design: NeoLEV2 was a multi-site investigator-initiated Phase II preliminary efficacy, dose-escalation and safety study of levetiracetam (LEV) compared to phenobarbital (PB) in the first-line treatment of neonatal seizures. NeoLEV2 was a randomized, double-blinded, controlled treatment study that enrolled term infants (GA 36 to 44 weeks; weight >2.2 kg) with suspected seizures or at risk for seizures. Infants were randomized if they had EEG-confirmed seizures of at least 10 seconds in duration in a 60 (LEV):40 (PB) allocation ratio by using a block randomization strategy and stratified by site. The study used EEG to define eligibility and efficacy, including systematic continuous video EEG monitoring with validation of seizure diagnosis and drug efficacy through review by 2 independent neurophysiologists. The U.S. sites (5 out of 6 sites) in NeoLEV2 used the commercially available West-Ward phenobarbital formulation in the trial. The trial enrolled n=280 neonates between March 2013 to October 2017 and randomized n=106 neonates with EEG-confirmed seizures. A total of n=83 patients completed the study and were included in the mITT analyses (n=53 LEV; n=30 PB).

Dosing regimens:

- LEV 40 mg/kg loading dose (LD), with 20 mg/kg second LD (if needed), followed by 10 mg/kg/dose q8hrs maintenance x 5 days once seizures were controlled
- PB 20 mg/kg LD, with 20 mg/kg LD (if needed), followed by 1.5 mg/kg/dose q8hrs maintenance x 5 days once seizures were controlled
- If EEG seizures persisted after 2nd LD, the neonate was treated with the alternate treatment regimen. If seizures persisted after treatment with both study drugs, the neonate exited the study and was treated according to institutional protocols.

Primary endpoint: rate of achieving and maintaining electrographic seizure freedom for 24 hours.

Secondary endpoints: seizure cessation for 48 hours, rate of achieving and maintaining seizure freedom for 1 hour, length of seizure freedom between the two treatment groups, and sub-analyses of the primary outcome measure for subjects with HIE who underwent therapeutic hypothermia (40% of the enrolled population)

Main Efficacy Findings: The study demonstrated higher efficacy of PB compared to LEV across primary and secondary efficacy endpoints (Table 1). The majority (37/53, 70%) of neonates allocated to LEV received PB after initial treatment failure, while 20% (6/30) allocated to PB received secondary treatment with LEV. Secondary efficacy of PB was 54% (20/37) compared to 17% for LEV (1/6).

Table 1. Prespecified Primary and Secondary Efficacy Outcomes (mITT population)

	Phenobarbital (20–40 mg/kg), *n* (Cessation %)	Levetiracetam (40–60 mg/kg), *n* (Cessation %)	Fisher's Exact *P*	Relative Risk (95% CI)
Primary outcome measure				
24-h seizure cessation rate (*N* = 83)	24 of 30 (80)	15 of 53 (28)	<0.001	0.35 (0.22–0.56)
Secondary outcome measures				
48-h Seizure cessation rate (*N* = 75)	18 of 28 (64)	8 of 47 (17)	<0.001	0.26 (0.13–0.53)
1-h Seizure cessation rate (*N* = 83)	28 of 30 (93)	26 of 53 (49)	<0.001	0.53 (0.39–0.7)
Subanalysis of patients with HIE treated with hypothermia				
24-h seizure cessation rate (*N* = 27)	9 of 10 (90)	6 of 17 (35)	0.014	0.39 (0.2–0.77)

Main Safety Findings: Overall, 89 AEs were recorded, 53 in the PB treatment group and 36 in the LEV treatment group (32 in PB treated subjects, 51 in PB+LEV treated subjects, and 6 in LEV treated subjects). A total of 17 (16.0%) subjects experienced study drug-related TEAEs overall, 8 (19.0%) subjects in the PB treatment group and 9 (14.1%) subjects in the LEV treatment group (6 in PB treated subjects, 8 in PB+LEV treated subjects, and 3 in LEV treated subjects). Overall, 9 (8.5%) subjects experienced SAEs (and TESAEs) on at least one study day, 6 (14.3%) subjects in the PB treatment group, and 3 (4.7%) subjects in the LEV treatment group (4 in PB treated subjects, 5 in PB+LEV treated subjects, and 0 in LEV-only treated subjects). Treatment-emergent deaths were seen in 6 (5.7%) subjects overall during the study; 1 (2.4%) subject in the PB treatment group and 5 (7.8%) subjects in the LEV treatment group (all 6 received PB+LEV).

The most common TEAEs by system organ class were seen in respiratory, thoracic, and mediastinal disorders in 20 (18.9%) subjects overall, 12 (28.6%) subjects in PB treatment group, and 8 (12.5%) subjects in LEV treatment group; followed by nervous system disorders, 15 (14.2%) subjects overall, 8 (19.0%) subjects in the PB treatment arm and 7(10.9%) in the LEV treatment arm and metabolism and nutrition disorders in 15 (14.2%) subjects overall, 9 (21.4%) subjects in PB treatment group and 6 (9.4%) subjects in LEV treatment group. The most common TEAEs were seen in respiration abnormal (18.9% overall; 28.6% PB, 12.5% LEV; 25% PB only, 20% PB+LEV, 5% LEV only), followed by sedation (14.2% overall; 19% PB, 10.9% LEV; 15.6% PB, 16.4% PB+LEV, 5.3% LEV only) feeding disorder (12.3% overall; 16.7% PB, 9.4% LEV; 15.6% PB only, 12.7% PB+LEV, 5.3% LEV only), and hypotension (9.4% overall; 16.7% PB, 4.7% LEV; 15.6% PB only, 9.1% PB+LEV, 0 LEV only).

PK findings: Only sparse PK sampling through 48 hours from n=30 patients was collected in the NeoLEV2 study. Therefore, the Sponsor selected population PK models from the literature (Table 2) and evaluated simulations with the dosing regimen used in NeoLEV2. Overall, the 3 models captured the observed data from the NeoLEV2 study, with the majority of data within the 95% prediction interval of simulated data.

Table 2. Predicted PK parameters in neonates following 20mg/kg LD

Model	Cmax (ug/mL)	AUC (h*ug/mL)	CL (L/h/kg)	Vc (L/kg)
Shellhass et al	21.6	21300	0.0026	0.927
Marsot et al	24.1	3470	0.0058	0.836
Voller et al	22.5	5870	0.0041	0.894

Reviewer comments: *Overall findings of the NeoLEV2 study support the efficacy of PB for treatment of neonatal seizures. AEs reported are consistent with the literature and known clinical safety concerns including most commonly sedation, respiratory depression, and hypotension. It is noted that the PB maintenance dosing regimen used in NeoLEV2 (1.5mg/kg q 8hrs) was selected for pragmatic trial reasons in order to maintain blinding (i.e., LEV is dosed q8hrs). This differs from the usual dosing regimen of 4-5mg/kg/day divided q12hr more commonly used in clinical practice. Given the long half-life and usual clinical practice of q12 hr dosing, clinical pharmacology was asked to evaluate an alternative dosing regimen of 4.5mg/kg/day divided q12 hrs. Modeling and simulation (M&S) results supported the acceptability of q12 hr dosing and we recommend incorporation of this dosing recommendation in labeling to avoid prescriber confusion.*

Although the NeoLEV2 study only included infants 36 to 44 weeks GA, clinical experience and literature-based data support approval to include preterm infants given that actual body weight (rather than GA) is the most established covariate for estimation of PB dosing.[11, 12] The clinical pharmacology review team was asked to evaluate dosing in preterm infants based on published PK models in preterm infants.[13] M&S results supported that recommended dosing for full term infants results in similar concentrations in preterm infants, although a reduced second LD of 10 mg/kg was also noted to be acceptable in preterm infants. We agree with labeling PB to include dosing in preterm infants.

The NeoLEV2 study did not include assessment of long-term neurodevelopmental outcomes. While the Sponsor discusses that the clinical significance of the non-clinical concerns for neurotoxicity is unknown, studies reporting the potential association of phenobarbital on long-term neurodevelopment have reported mixed results.[14-20] Data from the Neonatal Seizure Registry suggested that higher cumulative exposure associated with continuing phenobarbital after NICU discharge was not associated with worse neurodevelopmental outcomes or later epilepsy at 2 years in a contemporary cohort of infants with neonatal seizures.[21] While these data are reassuring, we agree that assessment of long-term neurodevelopmental safety is an important endpoint in evaluating the risk-benefit of ASMs and concur that a PMR to evaluate potential effects of PB on long-term neurodevelopment is appropriate.

Summary of Clinical Studies in the Literature: The Sponsor summarized clinical studies in the literature including PK/PD studies, and prior clinical studies which were largely open-label, non-randomized studies (see 2.5 Clinical Overview, Table 9) that described seizure cessation rates of 43-85%, although many of these studies included seizures assessed by clinical criteria without use of EEG confirmation.

Regarding safety, the Sponsor summarized data from the literature representing treatment of 640 neonates with phenobarbital, primarily as short IV infusions over 5 to 30 minutes, in doses of 7 mg/kg up to as high as 40 mg/kg, often followed by lower IV maintenance doses of approximately 1 to 5 mg/kg/day. The most frequently reported AEs were sedation/drowsiness (15-31%), respiratory (6-40%), and cardiovascular abnormalities (hypotension 10-15%, bradycardia 6-20%).

Adult BA/BE Study (PHEN-20-01): *The study was a two-sequence, two-period, single-dose crossover study of SPARC's phenobarbital sodium for injection and West Ward's phenobarbital formulations given over 15 minutes at a dose of 2 mg/kg. The two study periods were separated by at least 5 weeks to allow for adequate washout. Serial PK samples were collected out to 48 hours post-dose and were analyzed for total and unbound phenobarbital by validated liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry (LC/MS-MS) method.*

Data from n=23 subjects who completed both study periods was analyzed. The Sponsor concluded that "overall, the findings from the statistical comparisons of Cmax and AUC showed the 90% confidence intervals were within

80.00 to 125.00, indicating that the two formulations are bioequivalent for both total and unbound phenobarbital."

Reviewer comments: *We defer to the Division whether the results from PHEN-20-01 are adequate to support a PK bridge between the two formulations but note that we agree with the overall approach of leveraging data from the NeoLEV2 study and the published literature to support the safety and efficacy of the SPARC preservative-free formulation if BA/BE is supported.*

Proposed Labeling

Relevant sections from Sponsor draft prescribing information (OPT provided input on comments in **bold** font):

(b) (4)

Reviewer comments: *See discussion above regarding labeling for use in preterm infants and M&S-based dosing recommendations.*

(b) (4)

Reviewer comments: *We agree with removal of* (b) (4) *but recommena* (b) (4) *reference to specific examples* (b) (4) *given that concomitant use of these drugs is frequent in infants with neonatal seizures.*

(b) (4)

Reviewer comments: *We agree that* (b) (4) *section 13 of labeling is appropriate and, as discussed above, that a PMR study to evaluate the clinical relevance of these findings is warranted.*

ANALYSIS/RESPONSE:

General Comments: Neonatal seizures comprise the most common neurological emergency in the NICU and are associated with significant risk for mortality and long-term morbidity. Unapproved use of phenobarbital remains the first-line treatment for neonatal seizures, with a long history of clinical experience. The development of a preservative-free formulation can provide benefit by avoiding the known risks for benzyl alcohol-related toxicity in neonates. Availability of an approved PB formulation for treatment of neonatal seizures has other benefits including improved safety from regulatory oversight and availability of evidence-

based prescribing information. Data from the adequate, well-controlled NeoLEV2 study and the published literature support the safety and efficacy of PB for treatment of neonatal seizures in term and preterm infants.

Specific Responses to Questions Raised During the Review Cycle:

1. *Does the clinical approach to phenobarbital administration differ in preterm compared to term babies? Is there concern about differences in metabolism/excretion/protein binding in premature infants that would impact dosing/administration or monitoring? Do you think that an assessment of phenobarbital PK or other outcomes in preterm infants would be a potential PMR?*

Reviewer comments: *Generally, in clinical practice, dosing and administration of PB does not differ in preterm compared to term infants. Although providers may follow PB levels more closely in the preterm infant and adjust dosing accordingly, dosing is not necessarily empirically adjusted based on GA. Given that there is adequate data in the published literature to support a dosing recommendation in preterm infants, we agree that a PMR for further assessment of PB PK in preterm infants is not needed.*

2. *Assist with developing a PMR regarding potential long-term impact of phenobarbital on neurodevelopment.*

Reviewer comments: *We recommend use of broad language in the PMR given that the exact design of a feasible study that could adequately address this concern is unclear at this time. We suggest: "Conduct a prospective study with an appropriate comparator to assess long-term neurodevelopmental effects of Sezaby in patients with neonatal seizures. Assess neurodevelopmental effects using validated, age-appropriate neurodevelopmental assessments, including assessments of motor skills, cognition, language and behavior. Follow patients for a minimum of 5 years."*

3. *Review current draft labeling. Questions during labeling discussions:*
   a. (b) (4)

Reviewer comments: (b) (4) *We agree with removal of the discussion* (b) (4) (b) (4) (b) (4)

   b. (b) (4)

Reviewer comments: (b) (4) (b) (4) *We agree with moving* (b) (4)

   c. *Proposed label includes the statement: "Drug product is free of benzyl alcohol and propylene glycol." Does noting that this formulation is free of BA be helpful to the health care provider?*

Reviewer comments: *We agree with including the revised language "SEZABY is not made with benzyl alcohol or propylene glycol" as noting that the formulation is preservative-free may be helpful to the health care provider when considering potential for AEs related to the benzyl alcohol component in the West-Ward product.*

RECOMMENDATIONS:

We recommend approval of SEZABY for treatment of neonatal seizures in term and preterm infants with a PMR to assess long-term neurodevelopmental safety associated with SEZABY exposure.

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/s/

AN N MASSARO
10/25/2022 04:41:40 PM

GERRI R BAER
10/26/2022 08:20:41 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 29, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215910
Product Name and Strength:	Sezaby (phenobarbital) for injection, 100 mg/vial
Applicant/Sponsor Name:	Sun Pharma Advanced Research Co Ltd (SPARC)
OSE RCM #:	2022-398-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling and responses to recommendations that we made during a previous label and labeling review[a] received on August 19, 2022 for Sezaby. The Division of Neurology 2 (DN 2) requested that we review the responses and revised container label and carton labeling for Sezaby (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Weitzman, B. Label and Labeling Review for Sezaby (NDA 215910). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUL 29. RCM No.: 2022-398.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BEVERLY WEITZMAN
08/29/2022 09:33:21 AM

STEPHANIE L DEGRAW
08/29/2022 01:17:32 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Integrated Review of Epidemiology and Drug Utilization

Date:	August 12, 2022
Reviewers:	Saranrat Wittayanukorn, PhD, Epidemiology Reviewer Tracy Pham, PharmD, Drug Utilization Analyst *Division of Epidemiology II*
Team Leaders:	Rose Radin, PhD, MPH Modupeola Adereti, PharmD, BCPS, BCACP (Acting) *Division of Epidemiology II*
Tertiary Reviewers:	Tamra Meyer, PhD, MPH Associate Director for Nonmedical Drug Use Rajdeep Gill, PharmD Associate Director for Drug Use *Division of Epidemiology II*
Subject:	Review of Recent Data on Use, Misuse, Abuse, and Related Outcomes of Phenobarbital and Selected Comparators
Drug Name:	Phenobarbital injection solution 100 mg/vial
Application Type/Number:	NDA 215910
Applicant/sponsor:	Sun Pharmaceutical Industries, Inc
OSE RCM #:	2022-706

This document contains proprietary drug use data and surveillance-system data obtained by FDA under contract. The drug use data/information, as well as results of analyses of National Poison Data System **cannot be released to the public/non-FDA personnel without explicit approval by the data vendor.**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In April 2022, the Controlled Substances Staff (CSS) consulted the Division of Epidemiology II (DEPI II) of the Office of Pharmacovigilance and Epidemiology (OPE) to provide data on phenobarbital utilization and information on the epidemiology of phenobarbital-associated abuse[i] and misuse (*i.e.,* nonmedical use), diversion, and overdose. Currently, there are no approved New Drug Applications (NDA)s for phenobarbital because its marketing predates the Federal Food, Drug, and Cosmetic Act of 1938. This review is designed to inform CSS' recommendations for:

- Drug scheduling, as phenobarbital is currently a schedule IV-controlled substance under the Controlled Substances Act (CSA), while some of the barbiturates are in schedule II, III, or IV
- Safety labeling about drug abuse and misuse for the first potential phenobarbital NDA 215910 that is currently under rare pediatric disease priority review

The purpose of this integrated review is to:

- Describe the utilization patterns of phenobarbital and other barbiturates in schedules II to IV that are for human use but could be prescribed by veterinarians
- Describe the scope and patterns of adverse events associated with phenobarbital abuse and misuse, and of fatal overdoses involving barbiturates, and to compare them with events involving comparator drugs in schedules II, III, and IV
- Compare utilization-adjusted rates of adverse events associated with phenobarbital abuse, and rates of fatal overdose involving barbiturates, with rates involving comparator drugs in schedules II, III, and IV

Data Sources and Methods

In this comparative review, we analyzed patterns of use, abuse (or nonmedical use), associated morbidity, and overdose deaths of phenobarbital on an absolute scale (i.e., case counts) to examine the scope of and public health burden associated with nonmedical use of phenobarbital and comparator drugs. We also calculated rates adjusted for utilization (i.e., the number of prescriptions dispensed for human drug products from outpatient pharmacies) to better understand the relative levels of abuse and harms associated with phenobarbital and comparator drugs, taking into account different levels of "prescribed availability" in the community.
We examined utilization data from proprietary databases available to FDA as well as data from U.S. poison control center cases and death certificates. Also, we reviewed published study reports cited in section 2.7.4.3.6, Summary of Clinical Safety, of the NDA 215910 original submission, for evidence on the scope and patterns of outcomes of interest involving phenobarbital. In collaboration with CSS, we selected the schedule II amobarbital, pentobarbital, and secobarbital and schedule III butabarbital and butalbital as comparator drugs to provide a point of reference for schedules above the current schedule. Per CSS request, we provided both outpatient (retail and mail-order/specialty) and non-federal hospital utilization data for all scheduled barbiturate drugs, including schedule IV methohexital (injectable), to understand the overall utilization across settings of care where barbiturates were commonly used. We did not include methohexital as a comparator in the epidemiology analysis. Data are also provided for

[i] We, along with other organizations and agencies, recognize that some terms, including abuse, can be stigmatizing, and that reducing stigma is critical to addressing the nation's crisis of addiction and overdose. We are currently exploring ways to minimize the use of such language in FDA documents.

benzodiazepines to represent schedule IV drugs[ii]; however, we acknowledge that the substantially higher utilization of benzodiazepines may impact the comparison of utilization-adjusted rates of outcomes involving phenobarbital relative to benzodiazepines, as described in section 4.2.1.

Review Findings

Drug utilization

Outpatient pharmacy prescription utilization data

We examined utilization data for oral and injectable barbiturates that are for human use but could be prescribed by veterinarians; note that veterinary barbiturate products were not captured in the data sources used in these analyses. Based on aggregated manufacturer sales data, as a proxy for use, the majority of oral barbiturates were used in outpatient pharmacies while the majority of injectable barbiturates were used in non-federal hospitals. The utilization of oral barbiturates in outpatient pharmacies decreased by (b) (4) from 2013 through 2021 and remained consistently lower than the utilization of non-injectable benzodiazepines in retail pharmacies from 2014 through 2018. For context, an estimated (b) (4) oral barbiturate prescriptions and (b) (4) oral phenobarbital prescriptions were dispensed in 2018, compared to (b) (4) non-injectable benzodiazepine prescriptions dispensed in the same year. In 2021, oral phenobarbital accounted for (b) (4) of total (b) (4) oral barbiturate prescriptions dispensed in outpatient pharmacies, followed by oral butalbital at (b) (4); oral butabarbital and secobarbital had minimal use. From 2013 to 2021, overall utilization of oral phenobarbital and butalbital decreased by (b) (4) and (b) (4) respectively. Single-ingredient oral phenobarbital accounted for (b) (4)) of total oral phenobarbital prescriptions dispensed in 2021; of these, veterinarians accounted for (b) (4). In contrast, veterinarians accounted for a minimal proportion of prescriptions written for combination phenobarbital, butalbital, butabarbital, or secobarbital. Single-ingredient oral phenobarbital prescriptions written by non-veterinarians ((b) (4) were mostly dispensed to patients ages 40 to <65 years old (b) (4)), followed by 65 years or older ((b) (4) and 20 to <40 years old ((b) (4)

Hospital patient utilization data

In non-federal hospitals, the utilization of injectable phenobarbital doubled from 2016 to 2021. Injectable phenobarbital accounted for (b) (4)) of total (b) (4) patients receiving any injectable barbiturates in 2021, followed by injectable methohexital at (b) (4) and injectable pentobarbital at (b) (4) Moreover, injectable phenobarbital was mostly used among patients ages 40 to <65 years old (b) (4)), followed by 20 to <40 years old ((b) (4) and 65 years or older ((b) (4) in 2021. Patients younger than 2 years of age accounted for (b) (4) of the (b) (4) patients who received injectable phenobarbital in 2021 and phenobarbital utilization among this age group decreased by (b) (4) from 2016 to 2021. Notably, utilization of injectable barbiturates among pediatric patients may be underestimated in the hospital data because these data were based on a robust sample of non-federal hospitals, children's hospitals and other standalone specialty hospitals are not included in the data source.

[ii] Office of Surveillance and Epidemiology. Division of Epidemiology. *Comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances.* FDA Internal Document; December 7, 2020.

Epidemiologic data

Patterns in phenobarbital abuse, misuse, abuse-related morbidity

From 2012 to 2021, each year U.S. PCCs documented few abuse and misuse cases that involved phenobarbital and even fewer involving barbiturate comparators: there were (b) (4) total abuse cases involving phenobarbital. Phenobarbital had a lower proportion of abuse or misuse cases among total cases than that for barbiturate and benzodiazepine comparators. Due to the small number of cases and prescriptions dispensed for schedule II barbiturates and schedule III butabarbital, we restricted the utilization-adjusted analyses to phenobarbital, butalbital, and benzodiazepines, using aggregate data for the five-year period, 2014 to 2018. After adjusting for utilization, phenobarbital had a slightly higher five-year rate of abuse cases (b) (4) prescriptions dispensed than butalbital's rate but lower than benzodiazepines' rate (benzodiazepines were 2.4 times higher).

Overall, data from exposure calls to PCCs suggest that nonfatal adverse events associated with abuse involving phenobarbital occur primarily in the context of polysubstance use. Specifically, poison center data showed that approximately (b) (4) of abuse cases involving phenobarbital also involved other substances. Slightly more abuse cases were polysubstance for other barbiturate comparators (b) (4) and schedule IV benzodiazepines ((b) (4) Generally, the proportion of phenobarbital polysubstance abuse cases was similar to schedule III butalbital. It is important to note that PCC case data have been shown to undercount fatal adverse events.

Among PCC abuse cases involving phenobarbital that were admitted to a health care facility, admission to a noncritical care unit was the most common ((b) (4) followed by critical care unit and psychiatric facility. Among single-substance phenobarbital abuse cases with a related medical outcome, minor effect was the most common category of medical outcome, followed by moderate effect.

Patterns in overdose deaths documenting barbiturate involvement

The annual number of overdose deaths involving barbiturates remained consistently lower than overdose deaths involving benzodiazepines during the ten-year period (2011 to 2020), approximately 20 to 30 times lower depending on the year. In contrast, utilization-adjusted rates of overdose deaths involving barbiturates were higher than for benzodiazepines during the study period examined (2014 to 2018, using available data on benzodiazepines).

Time trends

PCC cases of abuse and misuse involving phenobarbital and all comparators declined over the study period, proportional to declines in utilization in outpatient pharmacies. In contrast, overdose deaths involving barbiturates and overdose deaths involving benzodiazepines increased during the study period, before and after adjusting for utilization. Specifically, the annual prescription-adjusted rates of overdose deaths involving barbiturates increased around 1.5 times, from (b) (4) in 2013 to (b) (4) in 2020. The annual rates of overdose deaths involving benzodiazepines also increased around 1.5 times from 2014 to 2018. However, factors such as increasing involvement of more dangerous illicit substances in polysubstance overdose deaths and better documentation of individual drugs on the death certificate may have contributed to the observed increasing trend in overdose deaths.

Route of abuse
In the PCC data, among single-substance abuse cases, the oral route was the most common route of abuse for phenobarbital ([(b) (4)] and comparators ([(b) (4)] The inhalation or injection route was rare for phenobarbital single-substance abuse cases ([(b) (4)]

Literature Review
We searched for references to published study reports submitted by the Applicant and reviewed for evidence on the scope and patterns of misuse and abuse of phenobarbital and comparators. These studies were poor quality and could not inform our review because of major methodological limitations.

Methodologic considerations
Each data source has strengths and limitations that may impact interpretation of the findings. In this review, we compare estimates of abuse and abuse-related outcomes qualitatively, not with formal statistical testing. We also encourage cautious interpretation of the comparative analyses of outcomes involving phenobarbital versus comparators due to the small number of cases and relatively low utilization for phenobarbital and barbiturate comparators, especially when compared with the commonly used benzodiazepine drug class.

Conclusions

From postmarketing data readily available to FDA and evaluable in the timeframe of a priority review, evidence suggests that phenobarbital is abused, primarily with other substances, and this abuse is associated with adverse outcomes, including overdose deaths. Specifically, in U.S. PCC data, there were more phenobarbital abuse cases and higher utilization-adjusted rates of abuse than for barbiturate comparators, but rates were lower than for schedule IV benzodiazepines during the study period examined (2012 to 2021). Cautious interpretation of these findings is warranted because outpatient drug utilization data also suggest that phenobarbital and barbiturate comparators have relatively low utilization compared with benzodiazepines, and the total number of prescriptions dispensed in outpatient pharmacies for barbiturates also declined over time. Among U.S. drug overdose deaths with documented involvement of either barbiturates or benzodiazepines, as a class, from 2011 to 2020, barbiturates had lower overdose-death involvement than benzodiazepines, but had higher utilization-adjusted rates of overdose deaths. These data may be helpful in conjunction with pre-clinical and clinical data to determine changes in CSA scheduling and labeling for NDA 215910.

Recommendations

These epidemiologic data support adding warnings about misuse, abuse, and overdose to the label, including potentially a boxed warning about these risks. Considering findings from other disciplines in conjunction with our findings will be important for recommending a boxed warning because the low utilization of phenobarbital and other barbiturates may have contributed to the relatively low levels of abuse observed.

1 INTRODUCTION

In April 2022, the Controlled Substances Staff (CSS) consulted the Division of Epidemiology II (DEPI II) of the Office of Pharmacovigilance and Epidemiology (OPE) to provide current information on phenobarbital utilization and on the epidemiology of phenobarbital-associated abuse[iii] and misuse (*i.e.,* nonmedical use), diversion, and overdose. There are currently no approved New Drug Applications (NDA)s for phenobarbital because its marketing predates the Federal Food, Drug, and Cosmetic Act of 1938. This review is designed to inform CSS' recommendations for:

- Drug scheduling, as phenobarbital is a schedule IV-controlled substance under the Controlled Substances Act (CSA), while some of the barbiturates are in schedule II, III, or IV
- Safety labeling about drug abuse and misuse for the first potential phenobarbital NDA 215910 that is currently under rare pediatric disease priority review

CSS met with DEPI to plan for descriptive and comparative analyses of utilization data as well as epidemiologic data on abuse and related outcomes involving phenobarbital, relative to selected comparator drugs that are schedule IV to schedule II, using available drug utilization and epidemiologic surveillance databases and epidemiology data submitted by the Applicant.

The purpose of this integrated review is to:

- Describe the utilization patterns of phenobarbital and other barbiturates in schedules II to IV that are for human use, but could be prescribed by veterinarians.
- Describe the scope and patterns of adverse events associated with phenobarbital abuse and misuse, and of fatal overdoses involving barbiturates, and to compare them with events involving comparator drugs in schedules II, III, and IV
- Compare utilization-adjusted rates of adverse events associated with phenobarbital abuse, and rates of fatal overdose involving barbiturates, with rates involving comparator drugs in schedules II, III, and IV

1.1 REGULATORY HISTORY

Phenobarbital, a long-acting barbiturate, has been marketed in the United States since 1912; because marketing predates the Federal Food, Drug, and Cosmetic Act of 1938, it is not approved by the U.S. Food and Drug Administration. Currently, WestWard Pharmaceuticals markets phenobarbital as a prescription sedative, hypnotic, preanesthetic, and anticonvulsant for adult and pediatric patients. In February 2022, Sun Pharmaceutical Industries, Inc. submitted NDA 215910 for a preservative-free phenobarbital injection solution 100 milligram per vial for the treatment of neonatal seizures. This application is under rare pediatric disease priority review. **Table 1.1.1** shows the scheduled barbiturates and their clinical uses.

[iii] We, along with other organizations and agencies, recognize that some terms, including abuse, can be stigmatizing, and that reducing stigma is critical to addressing the nation's crisis of addiction and overdose. We are currently exploring ways to minimize the use of such language in FDA documents.

Table 1.1.1 List of Scheduled Barbiturates

Active Ingredient	Formulation	Schedule	Clinical Use	FDA Regulatory Status
Amobarbital	Injectable	II	Sedative Hypnotic, for the short-term treatment of insomnia, since it appears to lose its effectiveness for sleep induction and sleep maintenance after 2 weeks. Preanesthetic	Unapproved
Butabarbital	Oral Tablet Oral Solution	II	Sedative or hypnotic	Discontinued 10/21/2020
Butalbital-aspirin Butalbital-aspirin-caffeine Butalbital-aspirin-caffeine-codeine Butalbital-codeine-caffeine Butalbital-codeine-caffeine-acetaminophen	Oral Tablet Oral Capsule	III	Migraine or tension headache	Prescription
Methohexital	Injectable	IV	Indicated as anesthetic agent for surgical procedures in neonates and adults, and also as a hypnotic agent in adults.	Prescription
Pentobarbital	Injectable	II	Sedative Hypnotic, for the short-term treatment of insomnia, since they appear to lose their effectiveness for sleep induction and sleep maintenance after 2 weeks. Preanesthetic Anticonvulsant, in anesthetic doses, in the emergency control of certain acute convulsive episodes, e.g., those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics.	Prescription
Phenobarbital†	Oral Tablet Oral Solution Injectable	IV	Oral formulations are indicated as a sedative or an anticonvulsant for the treatment of generalized and partial seizures. Injectable formulation is indicated for the control of generalized tonic-clonic and complex partial seizures.	Unapproved
Phenobarbital-Hyoscyamine-Atropine-Scopolamine (Belladona Alkaloids)	Oral Tablet Oral Elixir	Unscheduled but schedule IV for certain brands	Use as an adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis, and duodenal ulcer.	Unapproved
Secobarbital	Oral Capsule	II	Hypnotic, for the short-term treatment of insomnia, since it appears to lose its effectiveness for sleep induction and sleep maintenance after 2 weeks. Preanesthetic	Discontinued 10/21/2020

†We examined utilization data for human phenobarbital drug products that could be prescribed by veterinarians. U.S. commercially available veterinary drug products containing phenobarbital such as Nobatol® are not captured in the data sources used for drug utilization analyses.

2 REVIEW METHODS AND MATERIALS

To meet the timeline for this NDA's priority review and PDUFA goal date, we selected data sources that would support an efficient review of phenobarbital and comparator barbiturate utilization, adverse events associated with misuse and abuse, and overdose deaths involving barbiturates. We also included epidemiologic data from the 2020 OSE comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substance[iv], and reviewed references to published study reports submitted by the Applicant. The sections below provide more details regarding comparator drugs, as well as data sources and methods.

2.1 CASE DEFINITIONS

Table 2.1.1 provides the case definitions for drug abuse, misuse, and nonmedical use that were used in our analyses; the Office of Surveillance and Epidemiology (OSE) Case Definition Working Group formalized these definitions in 2019.

Table 2.1.1 Definitions of Drug Abuse and Misuse[v, vi, vii]

Case Type	Definition
Drug abuse	Intentional, nontherapeutic use of a drug product or substance even once, to achieve a desired psychological or physiological effect
Drug misuse	Intentional use, for therapeutic purposes, of a drug product in a way other than prescribed by a health care provider or for whom it was not prescribed.
Nonmedical use	A composite outcome that includes the above case types, drug abuse and drug misuse. Some data sources use this composite outcome, even if they do not label it nonmedical use. It is also useful for labeling cases in which the intent of the affected person in each situation may not be fully understood or may not fit precisely into the abuse vs. misuse categories.

[iv] Office of Surveillance and Epidemiology. Division of Epidemiology. Comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances. FDA Internal Document; December 7, 2020.

[v] *Assessment of Abuse Potential of Drugs*; Guidance for Industry is available on FDA.gov: https://www fda.gov/regulatory-information/search-fda-guidance-documents/drug-abuse-and-dependence-section-labeling-human-prescription-drug-and-biological-products-content. Accessed March 2021.

[vi] *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*; Guidance for Industry is available on FDA.gov: http://inside fda.gov:9003/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm492172.pdf. Accessed March 2021.

[vii] *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry*; Guidance for Industry is available on FDA.gov: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-abuse-and-dependence-section-labeling-human-prescription-drug-and-biological-products-content. Accessed March 2021.

2.2 COMPARATOR DRUGS

In collaboration with CSS, we selected several comparator drugs with central nervous system (CNS) depressant effects, some within the same schedule as phenobarbital (schedule IV) and others in higher schedules (schedule II, schedule III). Inclusion in the comparative analyses was contingent on adequate numbers of events and prescriptions to support reliable estimates. (Formulations of products marketed in the United States are noted in parentheses.)

- Schedule II barbiturates
    - Amobarbital (injectable), pentobarbital (injectable), secobarbital (oral; comparative analysis considered for the years when it was marketed since it was discontinued in 2020)
- Schedule III barbiturates
    - Butalbital combination products (oral) and butabarbital (oral; comparative analysis considered for the years when it was marketed since it was discontinued in 2020)
- Schedule IV benzodiazepines
    - All products in the drug class (all formulations, except for injections or injectable solution formulations)
    - Per discussion with CSS about DEPI's time constraints, we used the benzodiazepines data from the *2020 OSE comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances.*[viii] Thus, the phenobarbital-to-benzodiazepines comparative analysis included the study years from the 2020 OSE review, 2012 to 2018.

In the selection process we acknowledged that calculating a rate of events per million prescriptions of the drug of interest dispensed may not fully adjust for the substantial differences in utilization between benzodiazepines and phenobarbital products. CSS and DEPI agreed that performing this analysis was helpful as one component in CSS's deliberations on scheduling and labeling recommendations, although these comparisons between benzodiazepines and phenobarbital products should be made cautiously. For a full discussion of the limitations to this comparison, see section 4.2.

Specific methods for analyzing comparators included:

- We included all formulations (i.e., oral or injectable products) if formulation-level information was available in a data source, for phenobarbital and barbiturate comparators.
- For benzodiazepines, based on the 2020 OSE comparative review, we excluded injections or injectable solution formulations because we expected injectable formulations to be a minor or negligible contributor in the data sources.
- We included single-ingredient and combination products.

Of note, per CSS request, we also examined the patient utilization patterns for CII and CIV injectable barbiturates (amobarbital, methohexital, phenobarbital, pentobarbital) to better

[viii] Office of Surveillance and Epidemiology. Division of Epidemiology. *Comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances.* FDA Internal Document; December 7, 2020.

understand the use of barbiturates that are commonly dispensed in hospitals. We did not include methohexital as a comparator in the epidemiology analysis.

Comparisons of estimates of abuse-related outcomes
In this review, we compare estimates of abuse and abuse-related outcomes qualitatively, not with formal statistical testing. Thus, apparent differences in estimates may not be statistically significant. Section 4.2 of the discussion explains the rationale for this qualitative approach.

2.3 DRUG UTILIZATION ANALYSES

We conducted utilization analyses for single-ingredient and combination oral and injectable barbiturates in the United States using proprietary databases available to the FDA. See **Appendix 8.1.1** for full database descriptions and the limitations associated with these analyses.

We analyzed data from the IQVIA National Sales Perspectives™ (NSP) database to determine the primary setting of care based on the national estimated number of bottles/vials/ampules of oral and injectable barbiturates sold from manufacturers to various settings of care from 2017 through 2021, cumulative.

We analyzed the Symphony Health Metys database to obtain the national annual estimates of prescriptions dispensed for oral and injectable barbiturates from U.S. retail and mail-order/specialty pharmacies, stratified by patient age (<2, 2 to <6, 6 to <12, 12 to <20, 20 to <40, 40 to <65, and 65+ years), from 2013 through 2021. This analysis also includes prescriptions (for human drug products) written by veterinarians but does not capture prescriptions for veterinary drug products. While this analysis did not focus on utilization patterns by prescriber specialty, we examined barbiturates dispensing for all provider specialties and excluded prescriptions written by veterinarians in the analyses by patient age. Note that outpatient prescription data include certain brands of combination phenobarbital-containing oral products that are unscheduled. The availability of these scheduled and unscheduled products with similar molecule and product names hindered our ability to separate them.

We analyzed the IQVIA Hospital Visit Analyzer (HVA) database to obtain the national annual estimates of patients who had inpatient and/or outpatient discharge billings for injectable barbiturates, stratified by patient age (<2, 2 to <6, 6 to <12, 12 to <20, 20 to <40, 40 to <65, and 65+ years), from U.S. non-federal hospitals from 2016 through 2021. HVA's sample does not include children's hospitals or other standalone specialty hospitals; therefore, total pediatric utilization may be underestimated in HVA database. The time-period examined was based on data availability at the time of this review.

2.4 NATIONAL POISON DATA SYSTEM (NPDS)

The NPDS captures data on all calls to U.S. poison control centers (PCCs) on a near real-time basis. See **Appendix 8.2** for a description of the NPDS database. Using Micromedex® Solutions to identify product codes for phenobarbital, we extracted data for closed, human exposure cases involving phenobarbital using the strategy described in **Table 2.4.1.** In addition, we also analyzed cases involving the comparator drugs described in **Table 2.4.1**. Product codes are included in **Appendix 8.2, Table 8.2.1.** At the time of extraction, the American Association of Poison Control Centers (AAPCC) had completed its standard processes for outcome adjudication and quality control for all these data and had locked the data to ensure reliability.

Table 2.4.1 NPDS Search Parameters

Report name	Case Log (Product Code)
Month/year of query	4/2022
Date range for query: Phenobarbital Selected comparators • Schedule II barbiturates: amobarbital, pentobarbital, secobarbital • Schedule II barbiturates: butabarbital and butalbital Formulation: Phenobarbital and schedule II-III barbiturates: any formulations, both single-ingredient and combination products	 1/1/2012-12/31/2021 1/1/2012-12/31/2021
Case type	Exposure
Case status	Closed
Species	Human

We identified cases from structured case listing data in NPDS, which uses data collected from calls to U.S. PCCs. It is important to note that PCC specialists classified the intent of these exposures according to AAPCC definitions for exposure reason. AAPCC definitions of misuse and abuse are consistent with the regulatory definitions provided in Section 2.1; however, the intent of the affected person in each situation may not be fully understood or may not fit neatly into the abuse vs. misuse categories. Therefore, when discussing NPDS data, we may use the term nonmedical use to refer to misuse and abuse cases combined. AAPCC definitions are described in **Appendix 8.2.1.** Of note, NPDS search parameters for benzodiazepines are provided in **Appendix 8.2, Table 8.2.2.**

The analysis of NPDS included:

1. Overall numbers of exposure cases, abuse cases, single-substance abuse cases, misuse cases, and single-substance misuse cases, involving phenobarbital and comparators 1/1/2012 to 12/31/2021
2. Selected characteristics of abuse cases involving phenobarbital and abuse cases involving comparators, 1/1/2012 to 12/31/2021
    a. For *all* abuse cases
        i. Age and gender
    b. For *single-substance* abuse cases
        i. Route of abuse (see definition in **Appendix 8.2, Table 8.2.3**)
        ii. Severity of related medical outcomes
            1. We also tabulated the cases that did not have clinical effects deemed related to the exposure, as determined by PCC specialists. AAPCC medical outcome definitions, as well as clinical effect relatedness definition are included in **Appendix 8.2, Table 8.2.3**.
        iii. Admission to health care facility (see definition in **Appendix 8.2, Table 8.2.4**.)

We conducted descriptive statistical analyses using SAS version 9.4 (SAS Institute, Cary, NC). **QC Process:** A separate analyst performed an independent quality assurance/quality control check using the same criteria; results from the two independent analyses were consistent.

2.5 NATIONAL VITAL STATISTICS SYSTEM MORTALITY DATA

NVSS-M contains death certificate data available as both public use and restricted use data files. Each death certificate contained a single underlying cause of death, up to twenty multiple causes, and demographic data. The underlying cause of death indicated the injury intent (e.g., accident, suicide, undetermined) and whether the cause was drug-induced. Data were available for 2020 and previous years. Public use data are accessible though the CDC WONDER online database (wonder.cdc.gov)[1] and through the National Center for Health Statistics (NCHS) website.[2] For this review, we used the publicly accessible databases to analyze drug overdose deaths and population-adjusted rates.[3] Data available on CDC WONDER are based on death certificates for U.S. residents.

Data on overdose deaths involving barbiturates complemented the PCC case data because PCC cases generally undercount fatal adverse events.[4] We tabulated drug poisoning (overdose) deaths in which the death certifier noted barbiturates or benzodiazepines as a cause of death on the death certificate. Given the time constraints of the review, it was not feasible to analyze overdose deaths involving phenobarbital, as identified in the restricted-use dataset, NVSS-M Drug-Involved Mortality.

We identified cases with the following algorithm:

1. The underlying cause-of-death field was one of the following International Classification of Diseases, Tenth Revision (ICD-10) codes: X40–X44 (drug poisonings (overdose) unintentional), X60–X64 (drug poisonings (overdose) suicide), X85 (drug poisonings

(overdose) homicide), and Y10–Y14 (drug poisonings (overdose) undetermined intent). This method for identifying drug overdose deaths is consistent with previous literature.[5]
AND

2. The multiple-cause-of-death fields contained the ICD-10 code for either barbiturates (T42.3) or for benzodiazepines (T42.4), denoting involvement of a drug from that respective drug class in the overdose death. This was the most specific categorization available with the time constraints for this review (**Table 2.5.1)**.

Table 2.5.1 Algorithm for Identifying Cases from the National Vital Statistics System – Mortality

Variable	**ICD-10 code**
Underlying Cause of Death	
Drug Poisoning (overdose)[a]	
Unintentional	X40-X44
Intentional/ suicide	X60-X64
Homicide	X85
Undetermined	Y10-Y14
Multiple Cause of Death	
Barbiturates	T42.3
Benzodiazepines	T42.4

Source: CDC WONDER. Multiple Cause of Death (Detailed Mortality) www.wonder.cdc.gov
[a]Underlying cause of death, drug poisoning

2.6 EPIDEMIOLOGY DATA SUBMITTED BY THE APPLICANT

We searched for references to published study reports containing data on the epidemiology of abuse, misuse, addiction, diversion, or overdose involving phenobarbital in section 2.7.4.3.6, Drug Abuse, within the Summary of Clinical Safety of the NDA 215910 original submission. For any reference provided as a citation for a statement on the epidemiology of an outcome of interest involving phenobarbital or barbiturates in general, we screened the full-text article and selected for full review the articles that held information on the outcomes of interest involving phenobarbital specifically. Our full review evaluated the totality of the evidence submitted by the Applicant on the scope and patterns of misuse and abuse of phenobarbital and comparators. In critiquing these studies, we emphasized the validity of fundamental study-design elements such as the outcome definition, study population, and ascertainment of the outcome and phenobarbital's involvement.

2.7 UTILIZATION-ADJUSTED ANALYSES OF ABUSE OR OVERDOSE

We calculated utilization-adjusted rates using data from NPDS and NVSS-M as data from these databases are nationally representative. The methods for calculations of utilization-adjusted rates of abuse or overdose deaths are as follows:

- As described in Section 2.2, we selected commonly prescribed schedule II barbiturates (Amobarbital, pentobarbital, secobarbital) and schedule III barbiturates (butalbital and butabarbital) as comparators

- *Denominator data* (total prescription units dispensed) for phenobarbital, barbiturate comparators, and benzodiazepine comparator were obtained as described in Section 2.3. See **Appendix 8.1.2, Table 8.1.1** and **Table 8.1.4**
    - We included utilization data for all ages for phenobarbital and barbiturate comparators
    - We restricted to individuals ages 6 and older for benzodiazepine's utilization data.
- *Numerator data* were obtained from NPDS and NVSS-M as described in Sections 2.4. and 2.5.
- Availability of formulation-level information varied by dataset and is described earlier in Section 2.2.
    - In brief, we included all formulations for phenobarbital and barbiturate comparators. We excluded injectable formulations for benzodiazepine comparators.
- When applicable (i.e., estimates of prescriptions dispensed were available and of sufficient number), we calculated the utilization-adjusted rates by dividing the number of events (numerator) by the estimated total prescription units dispensed (denominator) for phenobarbital and comparators.
    - When molecule-level information was not available, we calculated the utilization-adjusted rates by using drug class (i.e., barbiturates and benzodiazepines).

In this review, we only calculated prescription-adjusted analyses of abuse or overdose. We did not calculate dosage unit-adjusted analyses because we included all formulations for phenobarbital and barbiturate comparators. Dosage units for injection and injectable products, as well as differences in formulations (e.g., oral vs injectable) are complicated to quantify, and would make dosage unit-adjusted analyses complicated to interpret.

3 RESULTS

3.1 UTILIZATION DATA

Based on the sales distribution data over the cumulative time from 2017 through 2021, approximately (b) (4) of oral barbiturate bottles were sold to outpatient pharmacies (retail and mail-order/specialty) while (b) (4) of injectable barbiturate vials/ampules were sold to non-federal hospitals.[ix] Therefore, we examined oral barbiturate utilization from retail and mail-order/specialty pharmacies, and injectable barbiturate utilization from non-federal hospitals.

3.1.1 Prescription Data from Outpatient Pharmacies

Table 8.1.1 and **Table 8.1.2** in **Appendix 8.1.2, and Figure 3.1** below provide the annual estimates of prescriptions dispensed for oral and injectable barbiturates that are for human use from U.S. retail and mail-order/specialty pharmacies from 2013 through 2021. Note that veterinary drug products are not captured in these analyses.

The total number of prescriptions dispensed for oral and injectable barbiturates decreased by (b) (4) from (b) (4) prescriptions in 2013 to (b) (4) prescriptions in 2021. Oral barbiturates accounted for the vast majority or (b) (4) of total barbiturate prescriptions dispensed throughout the study period while the utilization of injectable barbiturates was minimal.

Approximately (b) (4) oral phenobarbital prescriptions ((b) (4) of prescriptions dispensed for total oral barbiturates) were dispensed in 2021 compared to (b) (4) prescriptions dispensed in 2013 (a (b) (4)). Of the prescriptions dispensed in 2021, single-ingredient oral phenobarbital accounted for (b) (4)) compared to (b) (4)) for combination oral phenobarbital. Veterinarians wrote approximately (b) (4) dispensed for single-ingredient oral phenobarbital, and (b) (4) prescriptions ((b) (4) dispensed for combination oral phenobarbital; note that prescriptions were dispensed for human drug products only. In contrast, non-veterinarians (primarily family practice/general practice/internal medicine and neurology providers) wrote (b) (4) dispensed for single-ingredient oral phenobarbital, and (b) (4) dispensed for combination oral phenobarbital. From the data *excluding prescriptions written by veterinarians*, patients ages 40 to <65 years old accounted for (b) (4)) of prescriptions for single-ingredient oral phenobarbital in 2021, followed by patients ages 65 years and older at (b) (4)), 20 to <40 years old at (b) (4)), and 19 years old or younger at (b) (4)). Patients ages 65 years or older accounted for (b) (4)) of prescriptions for combination oral phenobarbital in 2021, followed by patients ages 40 to <65 years old at (b) (4)), 20 to <40 years old at (b) (4)), and 19 years old or younger at (b) (4)).

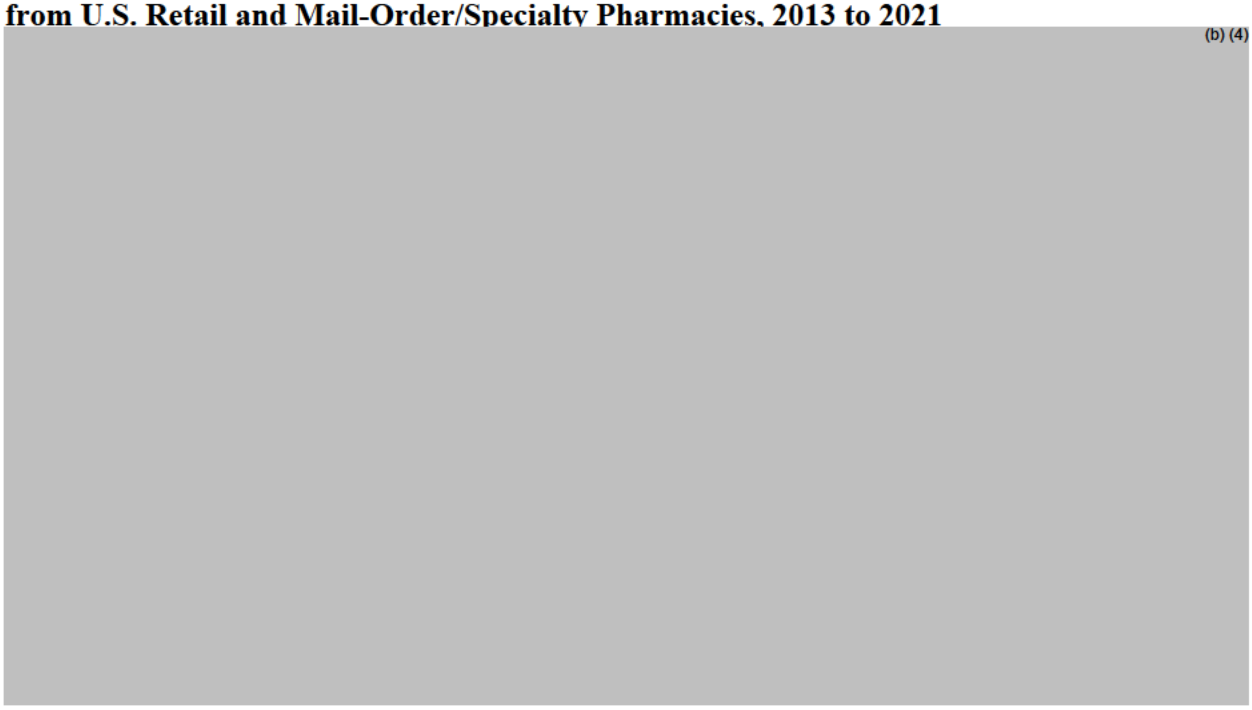
The vast majority of combination oral butalbital prescriptions were written by non-veterinarians. From these data, excluding prescriptions written by veterinarians, approximately (b) (4) combination oral butalbital prescriptions ((b) (4) of prescriptions dispensed for any oral

[ix] Source: IQVIA National Sales Perspectives™, 2017-2021. Data extracted April 2022.

barbiturates) were dispensed in 2021 compared to [redacted] prescriptions dispensed in 2013 (a [redacted] decrease). Patients aged 40 to <65 years old accounted for [redacted]) of prescriptions for combination oral butalbital in 2021, followed by patients ages 65 years and older at [redacted]), 20 to <40 years old at [redacted]), and 19 years old or younger at less than [redacted], data not shown).

There was little to no use of single-ingredient oral butabarbital and secobarbital products throughout the study period.

Figure 3.1 National Annual Estimates of Prescriptions* Dispensed for Oral Barbiturates from U.S. Retail and Mail-Order/Specialty Pharmacies, 2013 to 2021



Source: Symphony Health Metys™, 2013-2021. Data extracted April 2022.
*Data include human drug products, including those that were prescribed by veterinarians, and unscheduled combination oral phenobarbital. Veterinary drug products are not captured in this analysis. Prescriptions dispensed for oral butabarbital and secobarbital were minimal ([redacted]). Moreover, oral butabarbital and secobarbital were discontinued in October 2020.

3.1.2 Patient Data from Non-Federal Hospitals

Appendix 8.1.2, Table 8.1.3 and **Figure 3.2** below provide the national annual estimates of patients who had inpatient and/or outpatient discharge billings for single-ingredient injectable barbiturates from U.S. non-federal hospitals from 2016 through 2021. Phenobarbital and methohexital were the top commonly used injectable barbiturate products throughout the study period. In 2021, an estimated [redacted] total patients had inpatient and/or outpatient discharge billings for any injectable barbiturate; a [redacted] patients in 2016. Of these patients, an estimated [redacted] had inpatient and/or outpatient discharge billings for injectable phenobarbital or methohexital, respectively. The hospital utilization of injectable pentobarbital [redacted] was small.

The number of patients who had inpatient and/or outpatient discharge billings for injectable phenobarbital doubled from [redacted] patients in 2016 to [redacted] patients in 2021. Injectable phenobarbital utilization was mainly among patients ages 40 to <65 years old at [redacted] patients) in 2021, followed by patients ages 20 to <40 years old at [redacted]) and 65 years and older at [redacted]). An estimated [redacted] pediatric patients younger than 2 years of age [redacted]) had inpatient and/or outpatient discharge billings for injectable phenobarbital in 2021, compared to [redacted] patients in 2016 (a [redacted]).

From 2016 to 2021, the number of patients who had inpatient and/or outpatient discharge billings for injectable methohexital decreased by [redacted] from [redacted] patients to [redacted] patients, and for injectable pentobarbital decreased by [redacted] from [redacted] patients to [redacted] patients. Similar to phenobarbital, injectable methohexital utilization was mainly among patients ages 40 to <65 years old at [redacted]), followed by patients aged 65 years and older at [redacted] patients), and 20 to <40 years old at [redacted]) in 2021. In contrast, pentobarbital injectable utilization was mainly among patients younger than 2 years of age at [redacted] patients) and ages 2 to <6 years old at [redacted]) in 2021.

Figure 3.2 National Annual Estimates of Patients* Who Had Inpatient and/or Outpatient Discharge Billings for Injectable Barbiturates from U.S. Non-Federal Hospitals, 2016 to 2021

Source: IQVIA Hospital Visit Analyzer, 2016-2021. Data extracted April 2022.
*Summing patients is not advisable and will overestimate patient counts due to the possibility of double counting patients who may switch between treatment within a study period or over multiple periods in the study.

3.2 National Poison Data System (NPDS)

3.2.1 *Summary of Exposure Cases Involving Phenobarbital and Selected Comparators from 2012 to 2021*

Over a ten-year period (2012 to 2021), there were (b) (4) total exposure cases involving phenobarbital, and the most common reasons for exposure were unintentional therapeutic error, (b) (4) and intentional suspected suicide, (b) (4) The respective proportions of abuse cases and misuse cases out of total cases involving phenobarbital were (b) (4) and (b) (4) Among barbiturates, phenobarbital had the highest numbers of total cases and abuse cases, followed by schedule III butalbital. As a reminder, secobarbital and butabarbital were discontinued in October 2020. Misuse cases involving phenobarbital numbered 223, slightly lower than the number of misuse cases involving butalbital. Phenobarbital had a lower proportion of abuse or misuse cases than that for schedule II and schedule III barbiturate comparators. When comparing with schedule IV benzodiazepines (study period: 2009 to 2018), phenobarbital also had a lower proportion of abuse cases out of total cases. Of note, we focused on the comparisons of percentages or rates when comparing benzodiazepines with phenobarbital because it is not appropriate to compare case counts for the commonly used benzodiazepines drug class with phenobarbital, a single active pharmaceutical ingredient with relatively low utilization. **(Table 3.2.1)**.

Table 3.2.1 Total Exposure Cases, Abuse Cases, and Misuse Cases Involving Phenobarbital and Other Selected Comparators, U.S. Poison Control Center (PCC) Data, 2012-2021*

Products	Total exposure cases	Abuse cases	Proportion of abuse cases among total exposure cases	Misuse cases	Proportion of misuse cases among total exposure cases
	N	N	(%)	N	(%)
Phenobarbital	(b) (4)				
Schedule II barbiturate comparators					
Amobarbital					
Pentobarbital					
Secobarbital[a]					
Schedule III barbiturate comparators					
Butabarbital[a]					
Butalbital					
Schedule IV comparators					
*Benzodiazepines drug class**					

*Cases involving any benzodiazepine (schedule IV) had a study period from 2009-2018 and were restricted to ages 6 and older. Misuse data are not available for benzodiazepine comparator because we did not analyze misuse cases by year in the 2020 benzodiazepine comparative review.

[a]Secobarbital and Butabarbital were discontinued in October 2020

Utilization-adjusted rates of abuse cases

Due to the small number of abuse cases and prescriptions dispensed for schedule II barbiturate comparators and schedule III butabarbital, we only examined utilization-adjusted rates of abuse cases involving phenobarbital, schedule III butalbital, and schedule IV benzodiazepines, using aggregate data over the five-year period (2014 to 2018) **(Table 3.2.2)**. Consistent with results in the unadjusted analysis, phenobarbital had a higher five-year rate of total abuse cases (b) (4) prescriptions dispensed than butalbital's rate. Benzodiazepines had a higher five-year rate of total abuse cases than that for phenobarbital (2.4 times higher). A similar trend was also observed for single-substance abuse cases, although differences in five-year rates among phenobarbital, schedule III butalbital, and schedule IV benzodiazepines were attenuated when limited to single-substance cases. Of note, we also examined *annual* rates of total abuse cases and single-substance abuse cases for phenobarbital and comparators, although annual numbers of barbiturate-involved abuse cases were low. Results are provided in in **Appendix 8.2, Table 8.2.5**.

Table 3.2.2 Rate of Abuse Cases Per 1 Million Prescriptions Dispensed of Phenobarbital and Selected Comparators, by Total Abuse Cases and Single-Substance Abuse Cases, U.S. Poison Control Center (PCC) Data, Five-Year Period (2014 to 2018)*

Drug	Total Abuse Cases Per Million Prescriptions Dispensed	Single-Substance Abuse Cases Per Million Prescriptions Dispensed
	(b) (4)	
Phenobarbital		
Schedule III barbiturate comparator		
Butalbital		
Schedule IV comparator		
Benzodiazepines drug class*		

*Cases involving any benzodiazepines (schedule IV) had a study period from 2009-2018 and were restricted to ages 6 and older.

Based on calls to U.S. poison centers, the annual numbers of total abuse or single-substance abuse cases involving phenobarbital or schedule II and schedule III barbiturate comparators were low and declined from 2012 to 2021. As a reminder, secobarbital and butabarbital were discontinued in October 2020. Annual total abuse or single-substance abuse cases involving schedule IV benzodiazepines, as a class, also declined from 2014 to 2018 **(Table 3.2.3).**

Table 3.2.3 Trends in Abuse Cases Involving Phenobarbital and Selected Comparators, by Total Abuse Cases and Single-Substance Abuse Cases, U.S. Poison Control Center (PCC) Data, 2012 to 2021*

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total abuse cases (N)										
Phenobarbital	(b) (4)									
Schedule II barbiturate comparators										
Amobarbital										
Pentobarbital										
Secobarbital[a]										
Schedule III barbiturate comparators										
Butabarbital[a]										
Butalbital										
Schedule IV comparators										
*Benzodiazepines drug class**										
Single-substance abuse cases (N)										
Phenobarbital										
Schedule II barbiturate comparators										
Amobarbital										
Pentobarbital										
Secobarbital[a]										
Schedule II barbiturate comparators										
Butabarbital[a]										
Butalbital										
Schedule IV comparators										
*Benzodiazepines drug class**										

*Cases involving any benzodiazepines (schedule IV) had a study period from 2009-2018 and were restricted to ages 6 and older.

[a]Secobarbital and Butabarbital were discontinued in October 2020

The annual numbers of total misuse and single-substance misuse cases involving phenobarbital were low and declined from 2012 to 2021 and were similar to or slightly lower than schedule III butalbital. Schedule II barbiturate comparators and schedule III butabarbital were involved in very few misuse cases during the study period (**Table 3.2.4).**

Table 3.2.4 Trends in Misuse Cases Involving Phenobarbital and Selected Comparators, by Total Misuse Cases and Single-Substance Misuse Cases, U.S. Poison Control Center (PCC) Data, 2012 to 2021*

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Total misuse cases (N)										
Phenobarbital	(b) (4)									
Schedule II barbiturate comparators										
Amobarbital										
Pentobarbital										
Secobarbital[a]										
Schedule III barbiturate comparators										
Butabarbital[a]										
Butalbital										
Schedule IV comparators										
*Benzodiazepines drug class**										
Single-substance misuse cases (N)										
Phenobarbital										
Schedule II barbiturate comparators										
Amobarbital										
Pentobarbital										
Secobarbital[a]										
Schedule III barbiturate comparators										
Butabarbital[a]										
Butalbital										
Schedule IV comparators										
*Benzodiazepines drug class**										

*Cases involving any benzodiazepines (schedule IV) were not included in this table because we did not analyze misuse cases by year in the 2020 benzodiazepine comparative review.
[a]Secobarbital and Butabarbital were discontinued in October 2020

3.2.2 *Selected Characteristics of Abuse Cases Involving Phenobarbital and Selected Comparators*

During the ten-year period, in approximately (b) (4) of phenobarbital-involved abuse cases, PCC specialists documented phenobarbital as a single substance exposure (**Table 3.2.5**). The percentage of phenobarbital-involved abuse cases that were single substance was similar to schedule III butalbital, and higher than the percentage for the rest of comparators (b) (4)). The affected individual was male in (b) (4) of abuse cases involving phenobarbital and typically in the age range 20 to 39. This was consistent with abuse cases involving barbiturate or benzodiazepine comparators, except for cases involving schedule III butalbital where the proportion of cases involving males was lower, and the ages involved skewed older.

Table 3.2.5 Select Characteristics of Abuse Cases Involving Phenobarbital and Other Selected Comparators, U.S. Poison Control Center Data, 2012 to 2021*

Products	Number of Abuse Cases		Gender	Age Group in Years						
	Total abuse cases N	Single-substance N (%)	Male N (%)	0-5 N (%)	6-11 N (%)	12-19 N (%)	20-39 N (%)	40-64 N (%)	65+ N (%)	Unknown N (%)
Phenobarbital										(b) (4)
Schedule II barbiturate comparators										
Amobarbital										
Pentobarbital										
Secobarbital[a]										
Schedule III barbiturate comparators										
Butabarbital[a]										
Butalbital										
Schedule IV comparators										
*Benzodiazepines drug class**										

*Cases involving any benzodiazepines (schedule IV) had a study period from 2009-2018 and were restricted to ages 6 and older.
[a]Secobarbital and Butabarbital were discontinued in October 2020

Oral was the most common route among phenobarbital single-substance abuse cases ([(b) (4)] as it was for the comparators (**Table 3.2.6**). The inhalation or injection routes were rare for phenobarbital single-substance abuse cases [(b) (4)] Route of exposure definitions are included in **Appendix 8.2, Table 8.2.3.**

Among single-substance phenobarbital abuse cases with a related medical outcome, minor effect (i.e., symptoms that are minimally bothersome to patients and usually resolved rapidly) was the most common category of medical outcome ([(b) (4)] followed by moderate effect (i.e., symptoms that are prolonged and involved some treatments). When looking at single-substance abuse cases involving barbiturate comparators, moderate effect was the most common category of medical outcome [(b) (4)] followed by minor effect [(b) (4)] (**Table 3.2.6**). It is important to note that NPDS does not capture all cases of abuse that warrant medical attention, because not every case generates a call to a PCC. The most severe events, resulting in out-of-hospital overdose death, may be unlikely to generate a call to a PCC.[4] Medical outcome definitions are included in **Appendix 8.2, Table 8.2.3.**

Of [(b) (4)] single-substance abuse cases involving phenobarbital, approximately [(b) (4)] were admitted to a health care facility. The percentage of abuse cases involving phenobarbital that were admitted to a health care facility was also generally similar to that of barbiturate comparators ([(b) (4)] Among abuse cases involving phenobarbital that were admitted to a health care facility, admission to a noncritical care unit was the most common ([(b) (4)] followed by critical care unit and psychiatric facility. This pattern was also generally similar to barbiturate comparators, except for pentobarbital (**Table 3.2.6**).

Of note, cases with unknown status (categorized either as some related clinical effects, but patient not followed, patient lost to follow-up, patient did not arrive at healthcare facility, or missing data) accounted for approximately [(b) (4)] of single-substance abuse cases involving phenobarbital and approximately [(b) (4)] of single-substance abuse cases involving barbiturate comparators. While the proportion of unknown status is consistent with the proportion we see for abuse cases involving many other substances, the high proportion of unknown status, adds some uncertainty to the comparisons of phenobarbital versus comparisons on the distribution of medical outcome severity, as well as admission to health care facility.

Table 3.2.6 Summary of Single-Substance, Abuse Cases Involving Phenobarbital and Other Selected Comparators, U.S. Poison Control Center Data, 2012 to 2021*

Variable	Phenobarbital	Amobarbital	Pentobarbital	Secobarbital	Butabarbital	Butalbital (b) (4)
Route of Exposure [a]						
Ingestion						
Inhalation						
Injection						
Other						
Unknown						
Medical Outcome Severity						
No effect						
Minor effect [b]						
Moderate effect [b]						
Major effect [b]						
Death [b]						
Some related clinical effects, but patient not followed [c]						
No reported clinical effects, but patient not followed [d]						
Unrelated clinical effects						
Healthcare Facility Admissions						
Treated/evaluated and released						
Critical care unit						
Noncritical care unit						
Psychiatric unit						
Patient lost to follow-up/ left against medical advice						
Patient refused referral/ did not arrive at healthcare facility						
Unknown (missing data)						

[a] Percentages may not sum to 100 since some exposures involve more than one route
[b] Determined to be related to the exposure by PCC personnel
[c] Included medical outcome classified as not followed, minimal clinical effects possible (no more than minor effect possible) or unable to follow, judged as a potentially toxic exposure
[d] Included medical outcome classified as not followed, judged as nontoxic exposure (clinical effects not expected)
*Secobarbital and Butabarbital were discontinued in October 2020. Cases involving any benzodiazepines (schedule IV) were not included in this table because variable categories included in the 2020 benzodiazepine comparative review were different from current analysis.

3.3 National Vital Statistics System Mortality Data

The annual numbers of overdose deaths involving barbiturates and overdose deaths involving benzodiazepines both increased during the study period (2011 to 2020). The increase in overdose deaths involving barbiturates was modest, whereas overdose deaths involving benzodiazepines increased approximately 2-fold during this period. The annual number of overdose deaths involving benzodiazepines remained higher than overdose deaths involving barbiturates (approximately 20 to 30 times) **(Table 3.3.1).**

Utilization-adjusted analysis rates of overdose deaths

After adjusting for prescriptions dispensed, the rate of overdose deaths documenting barbiturate involvement was higher than the rate of overdose deaths documenting benzodiazepine involvement during the study period examined (2014 to 2018, using available data on benzodiazepine prescriptions). The annual *prescription-adjusted* rates of overdose deaths involving barbiturates increased around 1.5-fold from 2013 to 2020, similar to the trend in annual rates of overdose deaths documenting benzodiazepine involvement from 2014 to 2018 **(Table 3.3.1).**

Table 3.3.1 Deaths with Documented Underlying Cause of Death due to Drug Poisoning[a] Involving Barbiturates or Benzodiazepines, U.S. Residents, NVSS-M, 2011 to 2020

Year	Barbiturates		Benzodiazepines	
	Number of deaths	Death rates per 1 million prescriptions dispensed	Number of deaths	Death rates per 1 million prescriptions dispensed[b]
2011	(b) (4)			
2012				
2013				
2014				
2015				
2016				
2017				
2018				
2019				
2020				

[a]Drug poisoning underlying cause of death ICD-10 codes: X40-X44, X60-X64, X85, Y10-Y14
Single drug substance defined by ICD-10 codes: T42.3 (Barbiturates); T42.4 (Benzodiazepines)
[b]Prescription dispensed data for schedule IV benzodiazepine comparator were available from 2014 to 2018.

3.4 EPIDEMIOLOGY DATA SUBMITTED BY THE APPLICANT

The NDA original submission section 2.7.4.3.6, Drug Abuse, cited seven articles in statements about abuse, misuse, addiction, diversion, or overdose involving phenobarbital or barbiturates in general. Our full-text review found that two were study reports containing epidemiologic data on phenobarbital's involvement in at least one of the outcomes of interest.[6] [7] Of note, one additional article classified cases of abuse, dependence, and self-harm as a single outcome category, and so it did not meet our case definition of abuse.[8] **Appendix 8.3** contains details on the study design and findings from these three articles.

Two articles met our inclusion criteria. The first study had a small sample size: in interviews of 42 clients at methadone maintenance clinics in eastern U.S. cities in 1987, phenobarbital abuse or diversion was reported by one of 20 clients who self-reported having obtained phenobarbital by prescription. The second study reported on diversion of a combination product, phenobarbital/dextroamphetamine, and it is not clear how to interpret this finding to diversion of single-entity phenobarbital since dextroamphetamine is in CSA schedule II because of its high abuse potential.

4 DISCUSSION

4.1 SUMMARY OF FINDINGS AND INTERPRETATION

4.1.1 *Drug utilization*

We examined utilization data for oral and injectable barbiturates that are for human use but could be prescribed by veterinarians; veterinary barbiturate products were not captured in the data sources used in the analyses. Based on manufacturer sales data, the majority of oral barbiturates were used in outpatient retail and mail-order/specialty pharmacies while the majority of injectable barbiturates were used in the non-federal hospitals. The utilization of oral barbiturates in outpatient pharmacies decreased by (b) (4) from 2013 through 2021 and remained consistently lower than the utilization of non-injectable benzodiazepines in retail pharmacies from 2014 through 2018. For context, an estimated (b) (4) oral barbiturate prescriptions and (b) (4) oral phenobarbital prescriptions were dispensed in 2018, compared to (b) (4) non-injectable benzodiazepine[x] prescriptions dispensed in the same year. In 2021, an estimated total of (b) (4) oral barbiturate prescriptions were dispensed from outpatient pharmacies. Of these, oral phenobarbital and butalbital accounted for approximately (b) (4) and (b) (4) respectively; oral butabarbital and secobarbital had minimal use. Overall utilization of oral phenobarbital and butalbital decreased by (b) (4) and (b) (4) respectively, from 2013 to 2021. Single-ingredient oral phenobarbital accounted for the vast majority ((b) (4) of total oral phenobarbital prescriptions dispensed in 2021, but (b) (4) of these prescriptions were written by veterinarians; note that prescriptions were dispensed for human drug products only. In contrast, veterinarians accounted for a minimal proportion of prescriptions written for combination phenobarbital, butalbital, butabarbital, or secobarbital.

In non-federal hospitals, injectable phenobarbital accounted for (b) (4) of total (b) (4) patients who received any injectable barbiturate, and the utilization of injectable phenobarbital doubled from 2016 to 2021. Patients younger than 2 years of age accounted for (b) (4) of total patients who received injectable phenobarbital in 2021 and phenobarbital utilization among this age group decreased by (b) (4) from 2016 to 2021. Notably, utilization of injectable barbiturates among pediatric patients may be underestimated in the hospital data. Although these data were based on a robust sample of non-federal hospitals, children's hospitals and other standalone specialty hospitals are not included in the data source.

4.1.2 *Epidemiologic data*

Patterns in phenobarbital abuse, misuse, abuse-related morbidity
From 2012 to 2021, each year U.S. PCCs documented few abuse and misuse cases that involved phenobarbital and even fewer involving barbiturate comparators: there were (b) (4) total abuse cases involving phenobarbital. Phenobarbital had a lower proportion of abuse or misuse cases among total cases than that for barbiturate and benzodiazepine comparators. Due to the small

[x] Source: excerpt from Office of Surveillance and Epidemiology. Division of Epidemiology. Comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances. FDA Internal Document; December 7, 2020. Symphony Health Metys™. 2013-2019. Extracted October 2020. File: 2020-1972 SH Benzo 8F molecule TRx 2020-10-07.xlsx

number of cases and prescriptions dispensed for schedule II barbiturates and schedule III butabarbital, we restricted the utilization-adjusted analyses to phenobarbital, butalbital, and benzodiazepines, using aggregate data for the five-year period, 2014 to 2018. After adjusting for utilization, phenobarbital had a slightly higher five-year rate of abuse cases (b) (4) prescriptions dispensed than butalbital's rate but lower than benzodiazepines' rate (benzodiazepines were 2.4 times higher).

Overall, data from exposure calls to PCCs suggest that nonfatal, adverse events associated with abuse involving phenobarbital occur primarily in the context of polysubstance use, but less so than for comparators. Specifically, poison center data showed that approximately (b) (4) of abuse cases involving phenobarbital also involved other substances, per documentation by PCC specialists. This was slightly lower than most barbiturate comparators ((b) (4) and schedule IV benzodiazepines ((b) (4) Generally, the proportion of phenobarbital polysubstance abuse cases was similar to schedule III butalbital. It is important to note that PCC case data has been shown to undercount fatal adverse events (see section 4.2.3).[4] In addition, among abuse cases involving phenobarbital, the affected individual was likely to be in the age range 20 to 39 years.

Among PCC abuse cases involving phenobarbital that were admitted to a health care facility, admission to a noncritical care unit was the most common ((b) (4) followed by critical care unit and psychiatric facility. Among single-substance phenobarbital abuse cases with a related medical outcome, minor effect was the most common category of medical outcome, followed by moderate effect.

Patterns in overdose deaths documenting barbiturate involvement
The annual number of overdose deaths involving barbiturates remained lower than overdose deaths involving benzodiazepines during the ten-year period (2011 to 2020), approximately 20 to 30 times lower depending on the year. In contrast, utilization-adjusted rates of overdose deaths involving barbiturates were higher than for benzodiazepines during the study period examined (2014 to 2018, using available data on benzodiazepines).

Time trends
PCC cases of abuse and misuse involving phenobarbital and all comparators declined over the study period, proportional to declines in utilization in outpatient pharmacies. This also was consistent with overall declines in human exposure cases received by PCCs in recent years.[9] In contrast, overdose deaths involving barbiturates and overdose deaths involving benzodiazepine increased during the study period, before and after adjusting for utilization. Specifically, the annual prescription-adjusted rates of overdose deaths involving barbiturates increased around 1.5 times, from (b) (4) in 2013 to (b) (4) in 2020. The annual rates of overdose deaths involving benzodiazepines also increased around 1.5 times from 2014 to 2018. However, factors such as increasing involvement of more dangerous illicit substances in polysubstance overdose deaths and better documentation of individual drugs on the death certificate may have contributed to the observed increasing trend in overdose deaths involving barbiturates or benzodiazepines.

Route of abuse
In the PCC data, among single-substance abuse cases, the oral route was the most common route of abuse for phenobarbital ([(b) (4)] and comparators [(b) (4)]. The inhalation or injection route was rare for phenobarbital single-substance abuse cases ([(b) (4)]

Literature Review
We searched for references to published study reports submitted by the Applicant and reviewed for evidence on the scope and patterns of misuse and abuse of phenobarbital. These studies were poor quality and could not inform our review because of major methodological limitations. Specific limitations included lack of a relevant outcome definition (e.g., used falsified prescriptions as a proxy measure of abuse or a composite outcome of self-harm, abuse, and dependence) or very small sample size.

4.2 Data and Methods Considerations

In this review, we used several data sources to examine the scope of use and nonmedical use, as well as the scope of the harm and public health burden associated with phenobarbital versus with comparator drugs. Specifically, the dispensed prescriptions data represent U.S. retail and mail order/specialty pharmacies and are projected to national estimates. The hospital data represent prescription drug use from the inpatient and outpatient settings of non-federal hospitals and are projected to national estimates. PCC case data (NPDS) is a national data source that provides detailed information on abuse and related harms involving phenobarbital and comparators during the study period, by using standard procedures for data collection and management to collect information from callers. Finally, mortality data (NVSS-M) provide a comprehensive description of deaths in the U.S. population.

4.2.1 *Comparisons of Estimates of Abuse-Related Outcomes*

We encourage cautious interpretation of the comparative analyses of utilization-adjusted rates of outcomes involving phenobarbital versus comparators. Phenobarbital and other barbiturates as a class had a considerably lower utilization compared to benzodiazepines ([(b) (4)] prescriptions for phenobarbital, [(b) (4)] prescriptions for barbiturates, and [(b) (4)] prescriptions for benzodiazepines in outpatient pharmacies in 2018). Benzodiazepines' higher utilization may have led to the class having more widespread familiarity and access among people who use drugs and greater detection of involvement if providers are more likely to look for benzodiazepine involvement in adverse outcomes. Another limitation was that we were unable to compare phenobarbital rates to some of the barbiturate comparators because their extremely low levels of utilization and events precluded calculation of reliable rates.

As previously mentioned, we used qualitative comparisons, not statistical testing, in comparative analyses of events or rates of events involving phenobarbital versus comparators. Variances for the prescription dispensing estimates are not available to us, and therefore formal statistical comparisons of utilization-adjusted abuse rates are not possible. Furthermore, conventional statistical hypothesis testing is complicated by comparing multiple comparator drugs across multiple outcomes in various, diverse data sources. P-values are based on probability, and the probability of a Type 1 error (incorrectly concluding that a finding is significant when it actually

only occurred by chance) increases with an increasing number of tests. Given the many comparators and outcome measures, we believe that a qualitative synthesis of descriptive data is the most appropriate interpretation.

4.2.2 *Drug Utilization Data*

Each data source has strengths and limitations that may impact interpretation of the findings. Drug use data findings should be interpreted within the context of the known limitations of the databases used. The drug use analyses only focused on data from outpatient retail and mail-order/specialty pharmacies where oral barbiturates were primarily used, and non-federal hospitals where injectable barbiturates were primarily used. Therefore, these data may not represent the utilization patterns in other settings of care such as clinics, long-term care pharmacies, and standalone children's and specialty hospitals. Therefore, our data analyses may underestimate the true extent of barbiturate utilization, especially in the pediatric population.

4.2.3 *Abuse Cases Documented by Poison Control Centers*

It is important to keep in mind that NPDS data rely on calls seeking medical advice after an exposure; therefore, it is expected that many abuse cases do not generate a call to a PCC. In addition to exposures resulting in no or very mild adverse effects, exposures associated with the most severe effects—unattended, out-of-hospital overdose death—may be particularly unlikely to generate a call to a PCC.[4] Therefore, PCC data may disproportionately undercount cases involving drugs or substances with the highest risk of such fatal overdoses. Additionally, there is a potential for detection bias (*i.e.,* bias that occurs when an exposure influences the way outcome information is collected or assessed). For example, familiarity with the involved drug and its effects may influence whether an affected individual, bystander, or healthcare professional calls a PCC for advice. Also, a nontrivial proportion of single-substance abuse cases had missing data on certain clinical characteristics, such as medical outcome and level of healthcare facility ([(b) (4)] for phenobarbital and [(b) (4)] for barbiturate comparators). This adds some uncertainty to the comparisons of phenobarbital versus comparators with respect to the distribution of these case characteristics.

4.2.4 *Overdose Deaths*

One important limitation to consider when using death certificate data is that variation exists in the death investigation, including whether an autopsy is conducted, differences across and within jurisdictions, which toxicology tests are ordered, interpretation of toxicology results, and determination of which drugs to include on the death certificate, as well as in other decision-making by the medical certifier.[10 11] This variation could result in bias for certain populations, such as underreporting for populations less likely to be suspected of drug overdose and improvements in reporting could affect trends over time. In addition, it is important to recognize that not all involved or contributing substances may be tested for, or if detected, be documented on the death certificate. Finally, drug overdose deaths often involve multiple drugs (i.e., polysubstance overdose deaths). For example, an overdose death that involved a barbiturate may also involve other drugs. This also adds some uncertainty to the comparison of barbiturates versus benzodiazepines regarding number of drug overdose deaths. Due to time constraints, we

did not conduct additional analyses to examine the extent to which other substances were documented among barbiturate-involved overdose deaths.

4.2.5 *Consideration of Epidemiologic Data for CSA Scheduling and Labeling*

Although data sources we examined provide evidence of phenobarbital abuse and adverse outcomes, it is important to note that our review findings alone may not be sufficient to inform CSA scheduling and labeling. As discussed above, low utilization and small case numbers for phenobarbital and barbiturate comparators compared with commonly prescribed benzodiazepines made our comparative analyses complicated to interpret. Therefore, caution should be taken when comparing phenobarbital with benzodiazepines and using that as the guide for labeling and a boxed warning. In addition, due to time constraints to meet the priority review milestones, we were unable to quantify related clinical effects for abuse cases involving phenobarbital, which may inform signs and symptoms of overdose, particularly respiratory depression. According to FDA product labeling for Butisol Sodium (schedule III butabarbital)[xi], barbiturates are respiratory depressants, and acute overdosage with barbiturates is manifested by central nervous system and respiratory depression. Data from the forthcoming review by the OSE Division of Pharmacovigilance and from pre-clinical and clinical studies of phenobarbital may help to characterize clinical effects and describe overdose deaths involving phenobarbital for product labeling.

5 CONCLUSIONS

From postmarketing data readily available to FDA and evaluable in the timeframe of a priority review, evidence suggests that phenobarbital is abused, primarily with other substances, and this abuse is associated with adverse outcomes, including overdose deaths. Specifically, in U.S. PCC data, there were more phenobarbital abuse cases and higher utilization-adjusted rates of abuse than for barbiturate comparators, but rates were lower than for schedule IV benzodiazepines during the study period examined (2012 to 2021). Cautious interpretation of these findings is warranted because outpatient drug utilization data also suggest that phenobarbital and barbiturate comparators have relatively low utilization compared with benzodiazepines, and the total number of prescriptions dispensed in outpatient pharmacies for barbiturates also declined over time. Among U.S. drug overdose deaths with documented involvement of either barbiturates or benzodiazepines, as a class, from 2011 to 2020, barbiturates had lower overdose-death involvement than benzodiazepines, but had higher utilization-adjusted rates of overdose deaths. These data may be helpful in conjunction with pre-clinical and clinical data to determine changes in CSA scheduling and labeling for NDA 215910.

6 RECOMMENDATIONS

These epidemiologic data support adding warnings about misuse, abuse, and overdose to the label, including potentially a boxed warning about these risks. Considering findings from other disciplines in conjunction with our findings will be important for recommending a boxed

[xi] FDA approved labeling text for NDA 793/S- 025 (Butisol Sodium oral soln) Final 9.18.07. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/000793s025lbl.pdf. Accessed 5/31/2022

warning because the low utilization of phenobarbital and other barbiturates may have contributed to the relatively low levels of abuse observed.

Our recommendations for labeling are as follows, similar to Xanax (alprazolam)[xii]. Other barbiturate labels do not have sections 5, 9, and 17 so we used the Xanax label as a guide for our proposal.

1. Consider adding risk of abuse and misuse to Section 5 Warning and Precaution to product labeling for phenobarbital products
2. Consider adding risk of abuse and misuse to Section 9 Drug Abuse and Dependence to the product labeling to phenobarbital products
3. Consider adding risk of abuse and misuse to Section 17 Patient Counseling Information to the product labeling to phenobarbital products

Suggested language for further discussion is included below:

The use of barbiturates, including DRUG exposes users to the risks of abuse, misuse, which can lead to overdose or death.

[xii] FDA approved labeling text for NDA 018276 (Xanax oral tablets) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018276s055lbl.pdf. Accessed 06/03/2022

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8 APPENDICES

8.1 DRUG UTILIZATION DATABASE

8.1.1 *Drug Utilization Database Descriptions and Limitations*

IQVIA National Sales Perspectives (NSP)

The IQVIA National Sales Perspectives™ measures the volume of prescription drug products moving from distributors and manufacturers into various outlets within the retail and non-retail markets. It is the industry standard for measuring pharmaceutical spending because it captures ~89% of the total pharmaceutical market. Any capture of non-pharmaceutical product sales is a collection of convenience and not by database design. As such, NSP's coverage on over-the-counter (OTC) products is generally less than 50%, though it may be higher for OTC products with an NDC number.

Sales volume is expressed in terms of sales dollars, eaches, extended units, and share of market. Outlets within the retail channel include chain drug stores, independent drug stores, mass merchandisers, and food stores. Outlets within the non-retail channel include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. Outlets within the mail channel are mail service pharmacies. NSP is used to monitor the actual volume amount of a product that is being distributed in any channel of the pharmaceutical marketplace. NSP captures ~86% of the sales within the retail channel, ~97% of the sales within the non-retail channel, and 90% within the mail channel. Except for the mail channel, these data are estimated based on national projections. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys™

Metys™ Powered by IDV® is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point — all while delivering insights faster than any other tool in the industry. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning.

The dispensed prescriptions in the sample represent approximately 84% of all U.S. retail prescriptions, 72% of all U.S. mail order prescriptions, 76% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order/specialty, and long-term care prescriptions are projected to the national level.

IQVIA Hospital Visit Analyzer

Hospital Visit Analyzer (HVA) provides un-matched insights into patient visits and treatments that occur in Short-Term, General Non-Federal Hospitals (STGNFs). With history back to 2005, HVA is an accounting system specific to each hospital that tracks all billable events that take

place during a visit, including drugs administered, devices used, all patient diagnoses, and procedures/tests performed. The greatest advantage of HVA is the ability to see drug and device use within the hospital, which is often not captured by UB-04 forms.

IQVIA has the largest panel of hospitals, with approximately 350-400 facilities contributing patient visit records to HVA per year. Data are collected on approximately 18M+ patients across 60M+ hospital visits per year. Both inpatient and outpatient, as well as all pay types are captured for 100% of visits within each hospital on the panel. These data are then projected to national estimates. Data are updated monthly, with a lag of 75 days after the end of hospital discharge (inpatient) or encounter (outpatient).

Limitations of Drug Utilization Data

Drug use data findings should be interpreted within the context of the known limitations of the databases used. Dispensed prescription estimates are nationally projected based on a sample of prescription claims from U.S. retail and mail-order/specialty pharmacies, and should be interpreted with caution as they are based on a small sample size, particularly for the pediatric population. The data cannot be validated due to lack of access to medical records in the database. Summarization of these projected estimates across time periods and/or products may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time.

The HVA hospital sample does not include children's hospitals or other standalone specialty hospitals and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the HVA hospital data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. Moreover, summarization of patient estimates across patient age groups, time periods, and/or products may double count patients due to patients aging or receiving multiple products during the study period.

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8.2 NATIONAL POISON DATABASE SYSTEM (NPDS)

8.2.1 *NPDS Description*

The American Association of Poison Control Centers (AAPCC) maintains the NPDS, which captures data on all cases received by U.S. poison control centers (PCCs) on a near real-time basis. PCCs' healthcare professionals are available, free of charge, to callers through the Poison Help Line 24 hours per day. Currently, AAPCC's 55 PCCs serve the entire U.S. population, including all 50 states and U.S. territories. PCCs classify cases by type, as either information (involving no actual exposure) or exposure (involving an actual exposure to a substance or product by a human or animal). Each exposure is assigned to a generic code that represents a broad group of related products; the exposure may also have a Micromedex POISINDEX product code entered if an exact product or substance is reported and available in the product database.[13] PCC healthcare professionals systematically follow-up on reported exposures to provide clinical care recommendation and document clinical effects, treatments, and medical outcome. NPDS and regional poison centers have quality control (QC) measures in place to maximize accuracy and completeness of collected data. The database is described in detail elsewhere.[14]

AAPCC-NPDS is a nationwide public health resource that includes detailed clinical data on exposure to misuse and abuse of pharmaceutical products and other substances; however, it is subject to many limitations. PCC case data should not be interpreted as representing the complete incidence of national exposures or cases of misuse/abuse related to any substance. This data source captures data from events in which the exposure resulted in a contact to PCC and relies on information electively shared by patients, healthcare personnel, or other individuals. Of notes, some poison centers utilize online chat and text messaging. Polysubstance exposures can complicate attribution of patients' clinical symptoms to a single drug. Thus, related clinical effects were described after restricting the analyses to single-substance exposure cases. Although PCCs perform follow-up, they are not able to verify the accuracy of every report.[15] Drug exposures resulting in unattended or out-of-hospital death are unlikely to be reported to a PCC, and therefore, fatal poisonings are expected to be substantially under-reported in PCC case data. There has been declining PCC utilization since mid-2007, particularly for less serious exposures. Possible contributing factors to this decline may include increasing use of text rather than voice communication, and an increasing use of and reliance on internet resources.

[13] Micromedex POISINDEX® System maintains and updates the NPDS products database.
[14] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol* 2018;56(12): 1213-1415.
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Table 8.2.1 AAPCC/NPDS Phenobarbital and Selected Comparators

Description	Product Code (Generic Code) **Note: These product codes must be redacted for public release**
Phenobarbital	(b) (4)

Description	Product Code (Generic Code) **Note: These product codes must be redacted for public release**
	(b) (4)

Description	Product Code (Generic Code) **Note: These product codes must be redacted for public release**
	(b) (4)
Schedule II barbiturate comparators	
Amobarbital	
Pentobarbital	
Secobarbital	
Schedule III barbiturate comparators	
Butabarbital	
Butalbital	

Description	Product Code (Generic Code) **Note: These product codes must be redacted for public release**
	(b) (4)
Schedule IV benzodiazepine comparators	
Benzodiazepines	
Excluded product codes, injectable (N=66)	

Table 8.2.2 NPDS Search Parameters-Benzodiazepines

Report name	**Case Log (Generic Code)**
Month/year of query	6/2020
Date range for query (benzodiazepines) Formulation: We included any formulations, except injections or injectable solution formulations	1/1/2009- 12/31/2018
Case type	Exposure
Case status	Closed
Species	Human
Minimum Age	6 years

Source: excerpt from Office of Surveillance and Epidemiology. Division of Epidemiology. Comparative review of benzodiazepine use, abuse, misuse, addiction, and overdose, relative to other controlled substances. FDA Internal Document; December 7, 2020.

Table 8.2.3 National Poison Data System Definitions for Exposure Reason, Medical Outcome, and Route of Exposure Categories

Exposure Reasons	Definitions
Unintentional	Exposure results from an unforeseen or unplanned event. The following eight coding options are available for unintentional exposures: general, environmental, occupational, therapeutic error, misuse, bite/sting, food poisoning, unknown.
Intentional	A purposeful action results in an exposure. The following four coding options are available for intentional exposures: suspected suicidal, misuse, abuse, unknown. • **Misuse**: an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. • **Abuse**: an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect; include recreational use of a substance for any effect.
Adverse reaction	Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to the active ingredient(s), inactive ingredient(s) or excipient of a drug, chemical, cosmetic, food or other substance when the exposure involves the normal, prescribed, labeled or recommended use of the substance.
Other	Involves contaminant/tampering, malicious, or withdrawal.
Unknown	This category is used when the reason for the exposure cannot be determined or if no other category is appropriate.
Clinical effect relatedness	**Definitions**
	Related to the exposure • Timing of clinical effect is reasonable for reported exposure • Severity of effect is consistent with reported exposure • Effect is consistent with anticipated substance toxicity • Clinical assessment of relationship was made by a physician Note: An assessment of Related does not necessarily serve as confirmation of causality.
Medical Outcome	**Definitions**
Some related clinical effects, but patient not followed*	Medical outcome classified as not followed, minimal clinical effects possible (no more than minor effect possible) or unable to follow, judged as a potentially toxic exposure.
No reported clinical effects, but patient not followed*	Medical outcome classified as not followed, judged as nontoxic exposure (clinical effects not expected).
Minor effect	The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement.

Moderate effect	The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening, and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement.
Major effect	The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse.
Death	The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication.
Route of Exposure	**Definitions**
Ingestion	An exposure by the oral route. Exposures in which the material was put in the mouth but unlikely to have reached the stomach are also classified as ingestions. Ingestion accompanied by aspiration are coded as aspiration. If aspiration is coded, ingestion is automatically coded by the data collection software program. It is not an error to code both ingestion and aspiration. *Includes:* A gasoline ingestion in a child that results in aspiration is coded as both ingestion and aspiration
Inhalation/nasal	An exposure by the pulmonary route (tracheal or nasal). This route usually pertains to gaseous or vaporized agents. *Includes:* Insufflation of cocaine *Excludes:* Ingestions accompanied by aspiration (code Aspiration)
Injection	An exposure resulting from the injection of a substance into the body.
Other	Any other route of exposure not listed. *Includes:* Penetrating (stab, gunshot) injuries
Unknown	The route of exposure is unknown.

Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2020.12.07. December 7, 2020. American Association of Poison Control Centers. (2022). National Poison Data System. https://www npds.us/

*Adapted from NPDS Data Dictionary 2020

Table 8.2.4 AAPCC-NPDS Definitions of Level of Health Care Facility

Level of Health Care Facility	Definitions
Admitted to critical care unit	The patient is admitted to a critical or intensive care unit. Select this response even if the regional poison center assessment is that the patient did not require critical care (e.g. admitted to intensive care units only because there were no other beds, or as a suicide precaution).
Admitted to noncritical care unit	The patient is observed or treated by a physician and subsequently admitted to a noncritical care unit. If the patient is transferred to another hospital and then admitted to a noncritical care unit, code the Initial Health Care Facility and Final Health Care Facility. Select admitted to a noncritical care unit as this is the highest level of care rendered. DO NOT select treated/evaluated and released even though the patient was released from the initial HCF.
Admitted to psychiatric care facility	The patient is observed or treated by a physician and subsequently admitted primarily to receive psychiatric care or evaluation.
Patient refused referral/did not arrive at HCF	The patient declined to follow the PCC referral recommendation or failed to arrive at the HCF to which the patient was referred. The specific HCF to which the patient was referred to may be coded, but this code is not required. If the patient arrives at an HCF different from the referral HCF, do not select this response. Enter the specific HCF code of the facility where the patient did arrive, and code the actual disposition (e.g., treated/evaluated and released, admitted to critical care unit, etc.) This coding option is not valid for patients with Management Site = already in (en route to) HCF when PPC called.
Patient lost to follow-up/left AMA	The patient is lost to follow-up or the patient has left the HCF against medical advice (AMA).

Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2020.12.07. December 7, 2020. American Association of Poison Control Centers. (2022). National Poison Data System. https://www.npds.us/

Table 8.2.5 Rates of Abuse Cases Per 1 Million Prescriptions Dispensed of Phenobarbital and Selected Comparators, by Total Abuse Cases and Single-Substance Abuse Cases, U.S. Poison Control Center (PCC) Data, 2013 to 2021*

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Rate of total abuse cases (N)									
Phenobarbital									(b) (4)
Schedule III barbiturate comparators									
Butalbital									
Schedule IV comparators									
*Benzodiazepines drug class**									
Rate of single-substance abuse cases (N)									
Phenobarbital									(b) (4)
Schedule III barbiturate comparators									
Butalbital									
Schedule IV comparators									
*Benzodiazepines drug class**									
Consistent with results in the unadjusted analysis, from 2013 to 2018, phenobarbital had a higher annual rate of total abuse cases per 1 million prescriptions dispensed than butalbital's rate. Starting in 2019, butalbital's rates were higher than phenobarbital's rates. Benzodiazepines had greater number of annual rates of total abuse cases than that for phenobarbital (1.5 to 3 times higher) during the study period examined. A similar trend was also observed for single-substance abuse cases, although differences in annual rates among phenobarbital, schedule III butalbital, and schedule IV benzodiazepines were attenuated when limited to single-substance cases.									

*Cases involving any benzodiazepines (schedule IV) had a study period from 2009-2018 and were restricted to ages 6 and older.

8.3 ARTICLES INCLUDED IN THE OBSERVATIONAL STUDY LITERATURE REVIEW

First author, year	Data Source (include years)	Study Design	Population	Outcomes	Notable findings	Comments
Iguchi, 1993	Original data collection from patients at methadone maintenance clinics in Baltimore (Balt.), New York City (NYC), and Philadelphia (Phila.), July 1987 to January 1988	Cross-sectional survey (Phase 1) and semi-structured interview (Phase 2)	Surveyed 547 patients who received therapy at least three times per week at methadone maintenance clinics in Balt., NYC, and Phila. Of these, N=42 interviewed for Phase 2.	Phase 1: endorsement of any use, in past six months or lifetime, of one or more of: diazepam, lorazepam, alprazolam, clorazepate, oxazepam, chlordiazepoxide, pentobarbital, secobarbital, amobarbital/secobarbital, and phenobarbital. Phase 2: self-reported preferred drug for "high," among people who reported lifetime use of seven or more of the drugs.	Self-reported lifetime use of any of the drugs was 94% (Balt.), 86% (NYC), 78% (Phila.). Prevalence of lifetime and past-six-month use of phenobarbital was not reported, but it was not in the top three in any center. Of all drugs, lifetime use of diazepam was most common (73% or more in each center). Other top drugs lorazepam (70% Balt.), alprazolam (46% Balt.), amobarbital/secobarbital (42% Phila., 51% NYC), secobarbital (37% Phila., 51% NYC). In Phase 2, 20 of 42 participants reported obtaining phenobarbital by Rx, and one (5%) of them sold or abused the Rx.	Study report lacked a measure of medical or nonmedical use of phenobarbital, and so is not informative on the extent of use of phenobarbital, in medical or nonmedical contexts, among patients receiving regular methadone treatments.
Davis, 1991	Drug Abuse Warning Network (DAWN): 564 hospital emergency departments (ED) and 62	Serial cross-sectional analyses of surveillance databases	ED: people presenting to an ED at one of 24 metro areas throughout the U.S.	Case involving drug 'misuse,' defined as "*use of a substance for any of the following reasons: psychic effect,*	Average annual number (rate per 100,000 dispensed prescriptions: Drug-misuse deaths: phenobarbital 162 (2.7), secobarbital 123 (20.7), pentobarbital 52 (11.8),	Outcome definition includes self-harm, as well as drug abuse and dependence. This complicates comparisons of the extent of abuse across drugs or time periods.

First author, year	Data Source (include years)	Study Design	Population	Outcomes	Notable findings	Comments
	medical examiner facilities (ME) that reported consistently from 1976 through 1985. Outpatient prescription data from National Prescription Audit, IMS America.		ME: Decedents from 23 metro areas across the U.S. whose deaths were investigated by the ME.	*dependence, or suicide attempt/gesture."* ED cases captured any drug the individual took. ME cases captured any drug found by toxicology.	amobarbital 65 (21.0), All benzodiazepines 400 (0.5). Misuse ED visits, by drug: phenobarbital 1,493 (2.4), secobarbital 927 (15.7), pentobarbital 195 (4.4), amobarbital 439 (14.1), all benzodiazepines 15,114 (2.0). From 1976-1985, there were declines in cases involving barbiturates, barbiturate Rx dispensings, and case rates per 100,000 Rx dispensings.	To classify drug involvement, used any drug reported to the ED in course of treating patient, or any drug detected by toxicology. Some drugs noted may not have actually been involved in the case. Also, some drugs may have been missed by the surveillance data collection.
Baumevieille, 1997	Survey of pharmacists at network of 130 pharmacies in Aquitaine, France, Dec 1992 to Nov 1993	Cross-sectional survey	People filling prescriptions in 130 pharmacies in Aquitaine France (pharmacies geographically representative of region)	Falsified prescription, as pharmacist determined	Over two-thirds of pharmacies reported at least one falsified Rx. In total there were 392 falsified Rx for 594 products. The products with the most falsified Rx were phenobarbital/dextroamphetamine: 117 Rx (19.7%), flunitrazepam: 58 (9.8%), clobenzorex: 31 (5.2%). No data on phenobarbital SE.	Combination product containing phenobarbital and another drug with abuse potential, dextroamphetamine, is not marketed in the U.S. Falsified prescriptions are a proxy measure of abuse. Not a U.S. study.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 29, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215910
Product Name and Strength:	Sezaby (phenobarbital) for injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sun Pharma Advanced Research Co Ltd (SPARC)
FDA Received Date:	February 17, 2022 and April 27, 2022
OSE RCM #:	2022-398
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Sezaby (phenobarbital) for injection, the Division of Neurology 2 (DN 2) requested that we review the proposed Sezaby prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY AND BACKGROUND HISTORY

NDA 215910 is a 505(b)(2) NDA and the Applicant is relying on published literature.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 ASSESSMENT OF PRESENTATION OF ESTABLISHED NAME

During our initial review of the labels and labeling we identified that the established name is presented as the salt form (i.e., phenobarbital sodium) instead of the active moiety (i.e. phenobarbital). However, in accordance with USP Salt Naming Policy[a], when an active ingredient in a drug product is a salt, the name of the active moiety (or neutral form), and not the name of the salt (e.g., "newdrug tablets" instead of "newdrug hydrochloride tablets") should be used.

[a] Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. 2015. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/naming-drug-products-containing-salt-drug-substances

We contacted the Office of Pharmaceutical Quality (OPQ) via email on June 14, 2022, to discuss the appropriate presentation of the established name. OPQ noted that the marketed (unapproved) products are labeled based on the salt form consistent with the USP monograph "Phenobarbital Sodium Injection" and has an extensive history of use. OPQ further noted that there was a monograph for phenobarbital sodium for injection from May 2018 to November 2021 when Sun Pharma initiated development. However, USP "omitted" that monograph December 2021 because there are no marketed phenobarbital sodium for injection products. Therefore, OPQ recommends presenting the established name based on the salt to be consistent with the marketed (unapproved) products and the extensive history of use. We agree with OPQ's recommendation to present the established name as the salt form "Phenobarbital Sodium" as proposed by the Applicant.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 (Table 2) for the Division and in Section 6 (Table 3) for Sun Pharma Advanced Research Co Ltd.

5 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) – General Issues			
1.	The placeholder, PROPRIETARY NAME, is used throughout the labeling.	The proposed proprietary name, Sezaby was found acceptable on May 13, 2022.[b]	The placeholder, PROPRIETARY NAME, should be replaced with the conditionally acceptable name, Sezaby, throughout the PI labeling.
2.	We note that inconsistent terminology is used throughout the PI when describing the administration technique (e.g., "(b) (4) ,	Inconsistent terminology may lead to improper administration medication errors.	We recommend that consistent administration language is used throughout the PI. We defer to the team to determine the appropriate terminology.

[b] Weitzman, B. Proprietary Name Review for Sezaby (NDA 215910). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 13. PNR ID No. 2022-1044724447

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	“ (b) (4)		
Highlights of Prescribing Information (HPI)			
1.	In the Dosage and Administration section of the HPI, we note that the loading dose should be infused over 15 minutes. However, as currently presented, the infusion time for the maintenance dose is not included (e.g., over xx minutes).	Lack of an infusion time for the maintenance dose may lead to administration medication errors (i.e., risk of product being infused too quickly).	We recommend including a statement such as “infuse over xx minutes” for the maintenance dose or something similar, if applicable. We defer to the clinical team for final determination related to the infusion time for the maintenance dose.
2.	In the Dosage and Administration section of the HPI, health care providers are not instructed to reconstitute the product with 10 mL 0.9% Sodium Chloride Injection, USP.	We are concerned there is a risk for preparation errors related to reconstitution of the product.	We recommend adding a new bullet point to the HPI that describes the reconstitution instructions. For example: “Must be reconstituted with 10 mL 0.9 % Sodium Chloride Injection USP prior to administration. (2.3)”
3.	In the Dosage Forms and Strengths section of the HPI the dosage form is presented as (b) (4), the package type term (b) (4) is used to describe the package type, and the strength statement is presented as (b) (4)	“ (b) (4) is not the appropriate dosage form for this product. The appropriate dosage form for this product is “For Injection” as the dosage form is a lyophilized powder. See USP General Chapter <1121> Nomenclature. (Available from https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/1121Nomenclature.pdf). Additionally, (b) (4) is not a recommended	We recommend revising the Dosage Form and Strengths section to read as follows or something similar: “For injection: 100 mg of phenobarbital sodium lyophilized powder in a single-dose vial for reconstitution (3)”

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		package type term and is inconsistent with the package term "single-dose" used in other sections of the PI and container and carton labeling. Lastly, the strength statement (b) (4) represents the final concentration after reconstitution rather than the amount of drug in the vial (i.e., 100 mg per vial) and is inconsistent with the strength statement on the container and carton labeling.	
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.1 (Recommended Dosage), we note that the Loading dose should be infused over 15 minutes. However, as currently presented, the infusion time for the maintenance dose is not included (e.g., over xx minutes).	Lack of an infusion time for the maintenance dose may lead to administration medication errors (i.e., risk of product being infused too quickly).	We recommend including a statement such as "infuse over xx minutes" for the maintenance dose or something similar, if applicable. We defer to the clinical team for final determination related to the infusion time for the maintenance dose.
2.	In Section 2.1 (Recommended Dosage), the statement (b) (4) lacks clarity. (b) (4)	While the instructions state that a (b) (4) it is not clear when the *initial* maintenance dose should be delivered after either a loading or subsequent loading dose.	We recommend clarifying the appropriate timing of the initial maintenance dose. We also recommend clarifying the instructions as to how subsequent maintenance doses are to be administered (e.g., also in a large peripheral vein?).

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) However, as currently presented, there are no administration site instructions for the maintenance dose.	Additionally, the instructions are not clear as to how the maintenance dose is to be administered (e.g., also in a large peripheral vein?).	We defer to the clinical team for final determination. If the team determines this information should be added, we recommend revising the Dosage and Administration section of the HPI for consistency with the FPI as space allows.
3.	In Section (b) (4) (Storage of Reconstituted Solutions), the storage statements can be improved for clarity. Specifically, we note that the terms "room temperature" and "refrigerated" are not included in the storage statement, and the intent of the instruction "Discard any unused portion of the reconstituted solution after the recommended storage duration" is unclear. Furthermore, we note a similar, more clearly written discard instruction is already included in Section (b) (4)): "Discard any unused portion of the reconstituted solution left in the vial."	Unclear storage information may lead to improper storage and use of expired product (e.g., this unclear language may lead someone to think the remaining contents of the vial can be saved for future use).	We recommend removing the (b) (4) from the storage instruction "protect it from (b) (4) light" to be consistent with the container and carton labeling. Additionally, to increase clarity we recommend revising Section (b) (4) to read: "Administer immediately after reconstitution. If reconstituted solution is not administered immediately, the vial should be placed back in the original carton to protect it from light and stored at room temperature at 20°C to 25°C (68°F to 77°F) for up to 8 hours or in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours."

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Lastly, we note the storage instruction "protect from (b) (4) light" uses (b) (4) (b) (4)		
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16.2 (Storage and Handling) does not clearly specify that the storage information is for unopened vials. Additionally, we note the storage instruction "protect from (b) (4) light" uses (b) (4) (b) (4)	This may be improved to increase clarity and to prevent wrong product storage and risk for deteriorated drug medication errors.	We recommend removing the (b) (4) from the storage instruction "protect from (b) (4) light" to be consistent with the container and carton labeling. Additionally, consider revising Section 16.2 to read as follows: "Store unopened vials of SEZABY in original cartons at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]. Retain in the original carton until use to protect from light." "For information on storage of the reconstituted SEZABY, see Dosage and Administration (2.4)."

6 RECOMMENDATIONS FOR SUN PHARMA ADVANCED RESEARCH CO LTD

Table 3. Identified Issues and Recommendations for Sun Pharma Advanced Research Co Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The labels and labeling contain the placeholder, "Brand."	We reference our May 17, 2022, Proprietary Name Conditionally Acceptable Letter informing you that the proprietary name, Sezaby, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Sezaby, and use the intend-to-market font, color, etc.
2.	As currently presented, the dosage form (i.e., for injection) is placed inside the parenthesis with the established name, whereas the dosage form is located outside of the parenthesis in the prescribing information.	The presentation of the established name and dosage form are inconsistent with the presentation in the prescribing information.	To be in alignment with the PI, relocate the dosage form to appear outside of the parenthesis as follows: "(phenobarbital sodium) for injection"
3.	The proposed format for the expiration date (that is, MM YYYY) does not specify whether the month (that is, MM) will be displayed using numerical (for example, 06), or alphabetical (for example, JU) characters.	We are concerned that the current presentation of the expiration date may cause confusion. For example, presentation of the month as 'MM' does not clearly communicate whether 'MA' or 'JU' is for the months of March or May and the months of June or July, respectively. Therefore, we are unable to assess the expiration date format from a medication safety perspective, which may increase the risk for deteriorated drug medication errors.	Provide more information regarding the expiration format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if

Table 3. Identified Issues and Recommendations for Sun Pharma Advanced Research Co Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date
4.	As currently presented the "Discard unused portion" statement is separated from the package type "single-dose vial."	Inclusion of this discard statement immediately after "single-dose vial" helps minimize the risk of the entire contents of the vial being given as a single dose.	We recommend combining the statements "Discard unused portion" and "single-dose vial" to appear together as "Single-dose vial. Discard unused portion." If space is needed on the container label, the font size of the "Rx Only" statement may be decreased. See also recommendation #4 under the carton labeling section of the table.
5.	The recommended dosage statement can be improved.	To ensure consistency with the prescribing information.	Revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."
6.	The storage instructions "store vial in original carton" and "protect from light" can be improved.	These statements can be connected to improve clarity of the storage instructions.	Consider rephrasing the storage information to read "Store vial at controlled room temperature 20°C to 25°C (68°F to 77°F) (see USP Controlled Room Temperature) in original carton to protect from light."
7.	The reconstitution instructions are inconsistent between the container label and	The instructions may be improved to increase readability as well as to reduce the risk of	We recommend revising the reconstitution instructions to read:

Table 3. Identified Issues and Recommendations for Sun Pharma Advanced Research Co Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	carton labeling and can be improved for clarity.	reconstitution and administration medication errors.	"Reconstitute with 10 mL 0.9% Sodium Chloride Injection, USP, resulting in a final concentration of 100 mg/10 mL (10 mg/mL) of phenobarbital sodium."
Carton Labeling			
1.	The "reconstituted solution" storage statement does not include the Fahrenheit temperature range. Additionally, symbols (hyphens) are included in the temperature range.	Not all US practitioners may be familiar with the Celsius temperature scale, therefore, all temperature ranges for which the product can be stored should be clearly displayed in both Fahrenheit and Celsius to prevent the risk of administration of deteriorated drug product. Additionally, symbols may be misinterpreted and are error-prone.	To increase clarity, revise the storage statement to include both temperature scales and to replace hyphens with their intended meaning "to". Revise to read: "Use the reconstituted solution within 8 hours when stored at room temperature at 20°C to 25°C (68°F to 77°F) or within 24 hours when stored refrigerated at 2°C to 8°C (36°F to 46°F)."
2.	The statement (b) (4) appears above the tradename. Additionally, this statement and the "Sparc" name/logo appear with equal or more prominence than the important information on the PDP and back panels of the carton labeling.	Important information may be easily overlooked and difficult to read.	Ensure the statement (b) (4) and the "Sparc" name/logo do not appear more prominent than the critical information (e.g., established name, route of administration and reconstitution statements "for slow intravenous use only after reconstitution", etc.). Additionally, consider removing the statement (b) (4) as this is not required on the carton labeling.

Table 3. Identified Issues and Recommendations for Sun Pharma Advanced Research Co Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			However, if you wish to retain this statement, we recommend moving it away from the proprietary name.
3.	The controlled substance symbol lacks prominence.	The "symbol on labels shall be clear and large enough to afford easy identification of the schedule of the controlled substance upon inspection without removal from the dispenser's shelf" (per 21 CFR 1302.04).	Consider slightly increasing the prominence (i.e., larger font size) of the controlled substance symbol. When increasing the prominence of the controlled substance symbol, ensure the symbol does not interfere with the readability of the proprietary name, established name, or strength.
4.	As currently presented, the net quantity statement does not appear on the principal display panel.	Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the carton.	We recommend including a net quantity statement by revising "single-dose vial" to read "One single-dose vial. Discard unused portion."
Packaging			
1.	We note that as presently configured, the 100 mg/vial may contain a significant excess amount of drug product when used for administration of the maintenance dose of 1.5 mg/kg every 8 hours for a total of 4.5 mg/kg.	Excess drug product will result in waste and could potentially contribute to medication error over-dosing.	We recommend (b) (4) (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Sezaby that Sun Pharma Advanced Research Co Ltd submitted on February 17, 2022.

Table 4. Relevant Product Information for Sezaby	
Initial Approval Date	N/A
Active Ingredient	phenobarbital
Indication	Treatment of neonatal seizure
Route of Administration	Intravenous
Dosage Form	For injection
Strength	100 mg/vial (post reconstitution concentration: 100 mg/10 mL)
Dose and Frequency	Loading dose: 20 mg/kg infused intravenously over 15 minutes. If electrographic seizures persist or recur 15 minutes after completion of the initial loading dose, a second infusion of 20 mg/kg is administered over the subsequent 15 minutes for a total loading dose of 40 mg/kg. Maintenance dose: 1.5 mg/kg every 8 hours (total daily dose 4.5 mg/kg/day) for 5 days.
How Supplied	Single-dose vial
Storage	Store the vials in original cartons at USP controlled room temperature [20°C to 25°C (68°F to 77°F) with excursions between 15°C and 30°C (59°F and 86°F) permitted]. Retain in the original carton until use to protect from (b) (4) light.
Container Closure	Glass vial with rubber stopper and crimp seal

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Sezaby labels and labeling submitted by Sun Pharma Advanced Research Co Ltd.

- Container label received on February 17, 2022.
- Carton labeling received on February 17, 2022.
- Prescribing Information (Image not shown) received on April 27, 2022, available from
  Clean: \\CDSESUB1\evsprod\nda215910\0006\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-clean.docx
  Track: \\CDSESUB1\evsprod\nda215910\0006\m1\us\114-labeling\draft-labeling\draft-label-text\draft-label-text-tracked.docx

F.2 Label and Labeling Images

Container label

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BEVERLY WEITZMAN
07/29/2022 10:34:45 AM

STEPHANIE L DEGRAW
07/29/2022 11:54:23 AM

Clinical Inspection Summary

Date	July 27, 2022
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Josephine Little, Pharm.D., Regulatory Project Manager Amy Kao, M.D., Clinical Reviewer Phil Sheridan, M.D., Clinical Team Leader Division of Neurology 2
NDA #	215910
Applicant	Sun Pharma Advanced Research Company, Ltd.
Drug	Phenobarbital Injection
NME	No
Therapeutic Classification	Anticonvulsant
Proposed Indication	Treatment of Neonatal Seizure
Consultation Request Dates	03/24/2022
Summary Goal Date	07/01/2022
Update Summary Goal Date	08/01/2022
Action Goal Date	08/17/2022
PDUFA Date	08/17/2022
Updated Action Goal Date	11/17/2022
Updated PDUFA Date	11/17/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor-investigator Dr. Haas and clinical investigators (CIs) Drs. Rasmussen and Kuperman were inspected in support of this application (NDA 215910). Despite some protocol deviations observed at each site, the study appears to have been conducted adequately, and the clinical data generated from these CI sites and reported by the sponsor appear to be reliable in support of the respective indications.

II. BACKGROUND

Phenobarbital is the first-line therapy for neonatal seizures. Currently, the phenobarbital product marketed in the USA is manufactured by West-Ward Pharmaceuticals Corporation, which contains benzyl alcohol as preservative and propylene glycol as solvent. It is believed that benzyl alcohol and benzoic acid are not metabolized and cleared adequately by neonates and subsequently could be accumulated in neonates, causing severe metabolic acidosis.

Sun Pharma Advanced Research Company, Ltd. (SPARC) has developed a phenobarbital sodium for injection, which is a lyophilized powder that does not contain benzyl alcohol and propylene glycol. SPARC reported that they have conducted a single dose crossover study in healthy adults and proven the bioequivalence in PK of total and unbound phenobarbital between SPARC's phenobarbital sodium for injection formulation and West-Ward's phenobarbital sodium injection formulation (PHEN-20-01 Study).

The principal investigator, Dr. Richard Haas, at the University of California San Diego sponsored a Phase 2 randomized double-blind active-controlled safety and efficacy study of phenobarbital versus levetiracetam in neonatal seizures (NEOLEV2).

SPARC has obtained right of reference of Study NEOLEV2. SPARC has authorized Sun Pharmaceutical Industries Inc. (SUN) as their US agent to submit this New Drug Application (NDA) for phenobarbital sodium for injection in the indication of neonatal seizures. This indication was granted Orphan Drug Designation on October 2, 2019, Fast Track designation on August 24, 2021, and a Rare Pediatric Disease Designation on August 26, 2021.

Clinical investigator (CI) inspections were requested for Study NEOLEV2. The following is a brief description of the study.

Protocol 111361-NEOLEV2

Title: "Efficacy of Intravenous Levetiracetam in the Treatment of Neonatal Seizures: A Phase 2b Study of Levetiracetam in the Treatment of Neonatal Seizures."

Subjects: 106 were randomized

Study Sites: 6 centers in 2 countries (USA and New Zealand)

Study Initiation Date: June 04, 2013

Study End Date: October 31, 2017

This Phase 2 randomized, double blinded, and active controlled study was submitted to demonstrate the efficacy and safety of phenobarbital (lyophilized powder) in subjects with neonatal seizures. Neonates recognized as having seizures or as being at risk of developing seizures were recruited (via their parents) and started on continuous video electroencephalogram (EEG) monitoring. The EEG data was then reviewed continuously for electroencephalographic seizures by study investigators and by EEG technicians from a commercial EEG monitoring company (CortiCare). Eligible subjects were randomized in a 60:40 fashion to levetiracetam (LEV) or phenobarbital (PB) group. Treatment was initiated at the onset of electrographically confirmed seizure activity and continued for up to 5 days.

Subjects randomized to the levetiracetam (LEV) group received an IV loading dose of 40mg/kg given over 15 minutes at the onset of electrographically confirmed seizure activity. If electrographic seizures were confirmed to persist or recur more than 15 minutes after the first infusion was completed, a further 20mg/kg load of LEV was administered IV over 15 minutes. Maintenance LEV at 10 mg/kg was given IV every 8 (q8) hours and continued for at least 5 days. If seizures persisted or recurred more than 15 minutes after the second LEV infusion was completed, a PB loading dose of 20 mg/kg was administered IV over 15 minutes. If seizures persisted or recurred more than 15 minutes after the first loading dose of PB was completed, a second 20 mg/kg load was administered IV over 15 minutes. This resulted in PB being started within 1 hour of the onset of seizures when loading with LEV was ineffective. Subjects given PB loading doses were started on maintenance PB with 1.5 mg/kg/dose given IV q8 hours and continued at least until the end of the study. If electrographic seizures were still apparent following treatment with both LEV and PB, or if they recurred during the 5 days during which the study protocol was active, the subject was considered to have failed the

experimental treatment regime. They would be discontinued and follow the institutional specific standard seizure management.

Primary Efficacy Endpoint: the rate of achieving and maintaining electrographic seizure freedom for 24 hours following initiation of treatment and who did not go on to require a second anticonvulsant agent based on an independent review of video EEGs by two neurophysiologists, with a third neurophysiologist adjudicator, if necessary.

Key Secondary Efficacy Endpoint: seizure freedom for 1 hour and 48 hours.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, inspection history and reported protocol deviations.

RESULTS

1. **Richard Haas, M.D. (Sponsor-Investigator)**
   Site #002
   University of California
   San Diego Medical Center
   200 W. Arbor Drive
   San Diego, CA, 92103

   Site #003
   Rady Children's Hospital - San Diego
   3020 Children's Way
   San Diego, CA 92123
   Inspection dates: 05/09/2022 to 05/13/2022

For Protocol 111361-NEOLEV2, at Site #002, 26 subjects were screened, 9 were enrolled, and 6 subjects completed the study. Three subjects were discontinued. Subject #(b) (6) (in levetiracetam group) discontinued due to transferring to another hospital. Two subjects (Subject #(b) (6) in levetiracetam group and Subject #(b) (6) in phenobarbital group) discontinued due to failing the experimental treatment regime, which was the criteria for discontinuation. These two subjects subsequently followed the institutional specific standard seizure management protocol for treatment. All discontinuations and the reasons for discontinuations were reported to FDA.

For Protocol 111361-NEOLEV2, at Site #003, 56 subjects were screened, 30 were enrolled, and 16 subjects completed the study. Fourteen subjects were discontinued. All discontinuations and the reasons for discontinuations were reported to FDA.

This inspection covered Dr. Haas' responsibilities as a sponsor-investigator and was performed as a data audit. For the sponsor portion, it covered documentation for IND 109622, monitoring reports, monitoring procedures, monitoring logs, training for clinical sites and monitors, data collection and management, protocol adherence, communications with the FDA, sponsor correspondence, and sponsor reporting. For the CI portion, it reviewed the informed consent forms, inclusion/exclusion criteria, primary efficacy endpoints, adverse event and serious adverse event reporting, concomitant

medication information, delegation logs, case report forms, financial disclosure forms, investigational product accountability, investigator agreements, Institutional Review Board (IRB)

submissions, reporting, and approvals as well as other IRB correspondence.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. The inspection observed that the investigational drug disposition records were not adequate with respect to dates, quantity, and use by subjects.

Reviewer's comment: This observation as it relates to the investigational drug disposition appears to be more related to good documentation practices and is less likely to have an impact on data reliability.

2. Maynard Rasmussen, M.D.
Site #004
Sharp Mary Birch Hospital for
Women and Newborns
3003 Health Center Drive
San Diego, CA, USA, 92123-2700
Inspection dates: 05/02/2022 to 05/06/2022

For Protocol 111361-NEOLEV2, at this site, 80 subjects were screened and enrolled, 19 were randomized, and 14 subjects completed the study. Five subjects were discontinued. The number and reasons of discontinuations were verifiable.

The inspection reviewed informed consent forms, inclusion/exclusion criteria, treatment assignment and randomization, protocol deviations, subject discontinuations, primary endpoint information on seizure occurrence, and adverse events for all randomized subjects. An audit was also performed of concomitant medication information and laboratory values, some of which were verified against the data line listings provided by the sponsor; the investigational product accountability and storage; the study regulatory binders; correspondence with the IRB and sponsor; and other available study-related documentation.

The primary and key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. The inspection observed that the documentation of the destruction of unused doses of the study drug was not adequate. Also, the accountability documentation for study drug kits for three subjects did not include disposition of the unused maintenance doses of levetiracetam.

Reviewer's comment: The observations related to documentation of the destruction of unused doses of the study drug and drug accountability appear to be more related to good documentation practice and is less likely to have an impact on data reliability.

3. Rachel Kuperman, M.D.
Site #006
UCSF Benioff Children's Hospital– Oakland
747 52nd St
Oakland, CA 94609
Inspection dates: 06/15-17, 22-23, 27/2022

At this site for Protocol 111361-NEOLEV2, 59 subjects were screened and enrolled, 15 were randomized, and 8 subjects completed the study. Seven subjects were discontinued. The number and reasons of discontinuations were verifiable.

The inspection reviewed the informed consent forms for all 59 enrolled subjects. It also reviewed other source data, including study eligibility, treatment assignment, discontinuations, adverse events, and study test article accountability for 20 enrolled subjects.

There was no evidence of under-reporting of adverse events. The inspection was not able to review the primary efficacy endpoint data. Seizure and vital sign data were collected via continuous video EEG monitoring. This data was stored on a dedicated drive at the University of California, San Diego (with the sponsor-investigator) and was not readily available for review during the inspection.

It was observed that two subjects (Subject #(b) (6) and #(b) (6)) were not eligible for the study because the subjects did not meet the eligibility criterion of postnatal age <14 days. They were 16 days and 18 days old, respectively, at the time of enrollment. It was also observed that Subject #(b) (6) was randomized to the levetiracetam group but was administered phenobarbital for the NEOLEV-2 study.

Finally, for three subjects, legally effective informed consent was not obtained from the subjects' legally authorized representative before enrollment. Specifically, they were enrolled and received study-related tests after a verbal consent was obtained but not followed by a written consent.

Reviewer's comment: Subject #(b) (6) was withdrawn from the study due to clinical suspicion of possible underlying metabolic disorder and was not included in the per-protocol analysis. Subject #(b) (6) was withdrawn from the study once the site realized that the subject did not meet the study eligibility criteria. These discontinuations were reported to FDA. The observation that Subject #(b) (6) did not receive levetiracetam as allocated is an isolated event.

The violation about not obtaining legally effective informed consent from the subjects' legally authorized representatives before enrollment was reported to IRB.

{See appended electronic signature page}

Jenn W. Sellers, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Division Director
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
DARRTS: NDA 215910
DN II/Project Manager/Josephine Little
DN II/Medical Officer/Amy Kao
DN II/Clinical Team Leader/Phil Sheridan
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENN W SELLERS
07/27/2022 01:05:12 PM

PHILLIP D KRONSTEIN
07/27/2022 01:25:40 PM

KASSA AYALEW
07/27/2022 02:05:06 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 19, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Phil Sheridan, Cross Discipline Team Lead; DN2
Josephine Little, RPM, DN2

Subject: QT Consult to NDA 215910 (SDN 006)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 6/14/2022 regarding the sponsor's product labeling for QTc interval prolongation. We reviewed the following materials:

- Sponsor's product labeling (NDA 215910 (SDN 001)) and
- Previous IRT review(s) for NDA 215910 dated 04/26/2022 in DARRTS.

1 Responses for the Division

1) Please assist with editing the language in the Applicant's proposed label in Section 5.6 QT Prolongation and Section 12.2 Pharmacodynamics (Cardiac Electrophysiology), including the proposed inclusion of (b) (4). The Applicant's proposed labeling is attached.

IRT's response*:* Our suggestions to the product labeling are shown below in Section 3. These suggestions follow a draft guidance on QTc information in product labeling which is currently undergoing internal OND review. We defer final labeling decisions to your Division.

2) Please assist with drafting language for a postmarketing requirement to further characterize QTc interval effects of phenobarbital.

IRT's response: We propose the following language for the PMR.

> An evaluation of the effects of PROPRIETARY NAME on the QTc interval designed accordingly to ICH E14 guidance for industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2015) and E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (February 2022).

2 BACKGROUND

Sun Pharma Advanced Research Company, Ltd. (SPARC), has developed a new formulation of phenobarbital for the treatment of neonatal seizures. SPARC proposes QT-related labeling language (b) (4)

(b) (4).

Notably, the clinical QT data provided does not support QT characterization.

A review of the submitted nonclinical and clinical data is presented in our previous consult review (4/26/2022 in DARRTS).

3 Proposed Label

Our changes are highlighted (**addition**, ~~deletion~~). Each section is followed by a rationale for the changes made and follow internal guidance on QTc Information in Product Labeling. Please note that this is a suggestion only and we defer final labeling decisions to the Division.

(b) (4)

Reviewer's comments: Recommendations follow those suggestions in draft internal guidance on QTc Information in Product Labeling.

(b) (4)

(b) (4)

Reviewer's comments: We recognize that phenobarbital products have been marketed in the US since 1912, however, the limited information provided in the NDA suggests a potential for QTc prolongation. We therefore recommend that the sponsor characterizes the effects on the QTc interval as described in ICH E14. We defer the timing of such a characterization to the review division.

(b) (4)

Reviewer's comments: Suggestions are consistent with section 5.6.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
07/19/2022 10:28:47 AM

CHRISTINE E GARNETT
07/19/2022 10:34:40 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	June 15, 2022
Reviewer:	Karen Long, PharmD, Safety Evaluator Division of Pharmacovigilance I (DPV I)
Team Leader:	Allen Brinker, MD, MS DPV I
Product Name:	Phenobarbital
Subject:	Abuse, misuse, diversion, dependence, withdrawal, overdose, toxicity
Application Type/Number:	NDA 215910
Applicant:	Sun Pharmaceutical Industries, Inc.
OSE RCM #:	2022-706 (CSS), 2022-839 (CVM)
SS ID #:	2022-706, 2022-839

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EXECUTIVE SUMMARY

This review provides a descriptive analysis of FAERS and medical literature cases of phenobarbital abuse, misuse, diversion, overdose, dependence, withdrawal, toxicity, or elevated levels. The Division of Pharmacovigilance (DPV) received two consult requests through the Office of Surveillance and Epidemiology (OSE) for this data analysis, one from the Controlled Substances Staff and one from the Center for Veterinary Medicine. This DPV postmarket safety review supplements a concurrent consult to the Division of Epidemiology (DEPI) to evaluate drug utilization data and epidemiology data regarding abuse, misuse, diversion, and overdose for the barbiturate drug class and a concurrent consult to the Division of Mitigation and Medication Error Surveillance (DMAMES) to evaluate medication errors.

DPV included 57 FAERS and medical literature cases for analysis from January 1, 2012 to April 30, 2022 describing 1) abuse, misuse, dependence, withdrawal, or overdose or 2) toxicity or elevated levels with phenobarbital; toxicity was defined as adverse events related to supratherapeutic doses/levels or central nervous system (CNS)-related adverse events that may suggest abuse potential at therapeutic doses/levels. Among the 57 cases, DPV identified 40 cases describing abuse (32), misuse (5), dependence (9), withdrawal (3), or overdose (32) with phenobarbital [one case can report more than one event] and 17 cases describing toxicity or elevated levels with phenobarbital. Most cases (56/57) reported a regulatory serious outcome, including death (18), life-threatening (3), hospitalization (33), disability (1), required intervention (1), and other serious (35).

Most cases (49/57) involved multiple drugs or substances and the mean number of concomitant drugs or substances was higher in the cases reporting abuse, misuse, dependence, withdrawal, or overdose (mean 5.1) compared to cases reporting toxicity or elevated levels (mean 2.4). The most frequently reported categories of concomitant drugs included opioids (24), antiepileptic drugs (23), benzodiazepines (22), muscle relaxants (12), and antidepressants (11). Phenobarbital in isolation was reported in one case of abuse, one case of misuse/overdose, two cases of dependence/ withdrawal, and four cases of toxicity or elevated levels.

Most cases reported use of oral phenobarbital or did not report a route of administration, and we identified only one case of intravenous phenobarbital use. Most cases were reported in adults (n=37, pediatric n=9, unknown n=11) with a mean age of 36.1 years (median 37, range 3 months-88.6 years). Most cases (27/57) reported seizure as the reason for phenobarbital use. We identified higher doses and phenobarbital levels in cases reporting abuse, misuse, dependence, withdrawal, or overdose compared to cases reporting toxicity or elevated levels, which corresponded to a higher severity of reported adverse events. Most reported adverse events were related to injury/poisoning, nervous system disorders, psychiatric disorders, cardiovascular disorders, and respiratory disorders.

DPV identified two cases describing abuse, misuse, or overdose of veterinary phenobarbital (canine and equine) in humans; both cases presented with CNS depression, involved ingestion of other substances (opiates and alcohol), and required hospitalization for the events. DPV did not identify any cases of severe withdrawal resulting in seizures, delirium, or death. DPV also did not identify any cases of toxicity or overdose resulting from accidental ingestion of phenobarbital or medication errors related to confusion in dosing and administration.

Although phenobarbital labeling includes extensive information regarding phenobarbital tolerance, dependence, withdrawal, and overdose, additional labeling regarding abuse potential may be reasonable and help inform prescribers and patients of these risks, particularly when used in combination with other drugs/substances of abuse (e.g., opioids, benzodiazepines, alcohol, etc.).

1 INTRODUCTION

This review provides a descriptive analysis of FAERS and medical literature cases of phenobarbital abuse, misuse, diversion, overdose, dependence, withdrawal, or toxicity. The Division of Pharmacovigilance received the following two consult requests through the Office of Surveillance and Epidemiology (OSE) for this data analysis:

- **Controlled Substance Staff (CSS)** consult, OSE RCM# 2022-706
  - Request to review FAERS for cases of phenobarbital abuse, misuse, diversion, overdose, dependence, and withdrawal
  - Data to inform the CSS review of an application for phenobarbital injection solution for the treatment of neonatal seizures submitted for drug approval under rare pediatric disease priority review
  - DPV postmarket safety review supplements concurrent consult to the Division of Epidemiology (DEPI) to evaluate drug utilization data and epidemiology data regarding abuse, misuse, diversion, and overdose for the barbiturate drug class

- **Center for Veterinary Medicine (CVM)** consult, OSE RCM# 2022-839
  - Request to review FAERS for cases of phenobarbital abuse, diversion, accidental exposure, and medication errors
  - Data to inform the CVM review of an application for veterinary phenobarbital oral tablets for the treatment of seizures in dogs submitted for drug approval
  - DPV postmarket safety review supplements concurrent consult to the Division of Mitigation and Medication Error Surveillance (DMAMES) to evaluate medication errors

1.1 BACKGROUND AND REGULATORY HISTORY

Phenobarbital is a long-acting barbiturate that is an unapproved prescription drug product; it was first used as a sedative hypnotic and antiepileptic drug (AED) in 1912.[1] FDA permits some unapproved prescription drugs to be marketed if the drug is subject to an open drug efficacy study implementation (DESI) program proceeding, health care professionals rely on the drug to treat serious medical conditions when there is no FDA-approved drug to treat the condition, or there is insufficient supply of an FDA-approved drug.[2]

Phenobarbital injection and oral tablets/solution are currently marketed in the United States as unapproved prescription drug products by several manufacturers. The injection is available as 65 mg/mL and 130 mg/mL vials, containing alcohol, propylene glycol, and benzyl alcohol in water for injection. Phenobarbital injection in its current formulation with the preservative benzyl alcohol is not recommended for use in neonates because of the risk for fatal "gasping syndrome" characterized by a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse; this information is currently labeled in the WARNINGS section of phenobarbital injection labeling. Phenobarbital tablets are available in various doses (15, 16.2, 30, 32.4, 60, 64.8, 97.2, and 100 mg) and oral solution is available as 20 mg/5ml.[3,4,5,6]

In February 2022, Sun Pharmaceutical Industries, Inc. submitted NDA 215910 under rare pediatric disease priority review for a preservative-free phenobarbital injection solution 100 mg per vial for the treatment of neonatal seizures. The CSS team consulted OSE to evaluate drug utilization, epidemiology, and postmarketing data regarding phenobarbital abuse, misuse, diversion, and overdose, dependence, and withdrawal to inform their review of the NDA for appropriate drug scheduling and safety labeling. This DPV postmarket safety review supplements a concurrent consult to DEPI to evaluate drug utilization data and epidemiology data regarding abuse, misuse, diversion, and overdose for the barbiturate drug class.

The CVM team also received a New Animal Drug Application (NADA) for phenobarbital oral tablets for treatment of seizures in dogs, with an intent to market a 100-count and 1000-count bottles. The CVM team consulted OSE to evaluate postmarket data regarding phenobarbital diversion, abuse, misuse, accidental exposures, and medication errors and use of veterinary phenobarbital in humans. This DPV postmarket safety review supplements a concurrent consult to DMAMES to evaluate medication errors

Phenobarbital is a Schedule IV controlled substance under the Controlled Substances Act (CSA), while other barbiturates are in Schedule II, III, or IV. **Table 1** summarizes the drug schedules, FDA regulatory status, formulation, and clinical use for single ingredient barbiturate products.

Table 1. Summary of Single Ingredient Barbiturate Products

Drug	Schedule	FDA Regulatory Status	Formulation	Clinical Use
Amobarbital[7]	II	Unapproved	Injection	Sedative, hypnotic, preanesthetic
Butabarbital[8,9,10]	III	Previously approved, now discontinued	Oral	Sedative, hypnotic
Methohexital[11]	IV	Approved	Injection	Intravenous: anesthesia, hypnotic Rectal or intramuscular: anesthesia
Pentobarbital[12]	II	Approved	Injection	Sedative, hypnotic, preanesthetic, anticonvulsant
Phenobarbital[3,4,5,6]	IV	Unapproved	Injection, Oral	Injection: sedative, hypnotic, preanesthetic, anticonvulsant Oral: sedative, anticonvulsant
Secobarbital[8,9,10]	II	Previously approved, now discontinued	Injection, Oral	Hypnotic, preanesthetic

1.2 RELEVANT PRODUCT LABELING

Phenobarbital currently has the following excerpted information related to abuse, misuse, dependence, and overdose in the labeling (full labeling is provided in **Appendix A**):[3,4]

Phenobarbital sodium injection
WARNINGS: Habit Forming

DRUG ABUSE AND DEPENDENCE:

- Barbiturates may be habit forming. Tolerance and psychological dependence and physical dependence may occur especially following prolonged use of high doses of barbiturates.
- The symptoms of barbiturate withdrawal can be severe and may cause death.
- Drug dependence to barbiturates arises from repeated administration of a barbiturate or agent with barbiturate-like effect on a continuous basis, generally in amounts exceeding therapeutic dose levels.
- Individuals subject to barbiturate abuse and dependence include alcoholics and opiate abusers as well as other sedative-hypnotics and amphetamine abusers.

OVERDOSAGE:

- The toxic dose of barbiturates varies considerably. Barbiturate intoxication may be confused with alcoholism, bromide intoxication and various neurological disorders.
- For sedation, therapeutic blood levels of phenobarbital range from 5-40 μg/mL; the lethal blood level is greater than 80 μg/mL and usually ranges from 100-200 μg/mL.
- Acute overdosage with barbiturates is manifested by CNS [central nervous system] and respiratory depression which may progress to Cheyne-Stokes respiration, areflexia, constriction of the pupils to a slight degree (though in severe poisoning, they may show paralytic dilation), oliguria, tachycardia, hypotension, lowered body temperature and coma. Typical shock syndrome (apnea, circulatory collapse, respiratory arrest and death) may occur.

Phenobarbital tablets
PRECAUTIONS: This drug should also be administered cautiously to patients with a history of drug dependence or abuse.

DRUG ABUSE AND DEPENDENCE:

- **Dependence**: Prolonged, uninterrupted use of barbiturates (particularly the short-acting drugs), even in therapeutic doses, may result in psychic and physical dependence. Withdrawal symptoms due to physical dependence following chronic use of large doses of barbiturates may include delirium, convulsions, and death.

OVERDOSAGE

- The signs and symptoms of barbiturate poisoning are referable especially to the central nervous system and the cardiovascular system. Moderate intoxication resembles alcoholic inebriation. In severe intoxication, the patient is comatose, the level of reflex activity conforming in a general way to the intensity of the central depression.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

DPV included cases meeting any of the definitions described in **Table 2**. Standard definitions were obtained from FDA Guidances (Assessment of Abuse Potential of Drugs; Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products – Content and Format)[13,14] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V).[15] DPV also included cases reporting drug toxicity as defined in **Table 2** or elevated levels of phenobarbital.

Table 2. Definitions of Drug Abuse, Misuse, Addiction, Tolerance, Dependence, Withdrawal, Diversion, and Overdose for DPV Review

Term	Definition
Standard definitions from FDA Guidances[13,14]	
Drug abuse	Intentional, non-therapeutic use of a drug or substance, even once, to achieve a desired psychological or physiological effect
Drug misuse	Intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed
Drug addiction	A cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence
Tolerance	Physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose)
Physical dependence	State that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug
Psychological (or psychic) dependence	State in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug
Withdrawal	Characteristic withdrawal syndrome for that drug occurring in response to 1) abrupt discontinuation or a significant dose reduction of that drug or 2) administration of an antagonist or taking the drug itself to alleviate withdrawal symptoms
Diagnostic Criteria for Withdrawal From DSM-V[15]	

Table 2. Definitions of Drug Abuse, Misuse, Addiction, Tolerance, Dependence, Withdrawal, Diversion, and Overdose for DPV Review	
Term	**Definition**
Sedative, Hypnotic, or Anxiolytic Withdrawal	Diagnostic Criteria for Sedative, Hypnotic, or Anxiolytic Withdrawal A. Cessation of (or reduction in) sedative, hypnotic, or anxiolytic use that has been prolonged B. Two (or more) of the following, developing within several hours to a few days after the cessation of (or reduction in) sedative, hypnotic, or anxiolytic use described in Criterion A: 1. Autonomic hyperactivity (e.g., sweating or pulse rate >100 bpm) 2. Hand tremor 3. Insomnia 4. Nausea or vomiting 5. Transient visual, tactile, or auditory hallucinations or illusions 6. Psychomotor agitation 7. Anxiety 8. Grand mal seizures C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance
Other Definitions	
Drug diversion[16]	Illegal distribution or abuse of prescription drugs or their use for purposes not intended by the prescriber
Overdose[17]	Fatal or non-fatal injury to the body that occurs when a drug is taken in excessive amounts; for purposes of this review, intentional overdose cases in context of abuse/misuse were analyzed together
Toxicity	For purposes of this review, toxicity was defined as: • Adverse event related to supratherapeutic doses/levels OR • Central nervous system (CNS)-related adverse event that may suggest abuse potential at therapeutic doses/levels[13] o e.g., euphoria, feeling drunk, hallucination, feeling abnormal, somnolence, mood disorders and disturbances, psychosis, confusion, disorientation, etc. • AND adverse event was not in the context of abuse, misuse, or intentional overdose

DPV excluded cases reporting any of the following exclusion criteria:

- Reports describing abuse, misuse, dependence, or withdrawal of another drug/substance and any of the following
  - Phenobarbital was used for the treatment of withdrawal symptoms from another drug/substance
  - Phenobarbital is listed as a concomitant medication, and it is clearly stated that phenobarbital use was not involved in abuse, misuse, dependence, or withdrawal events (e.g., a patient only abused opiates or benzodiazepines)
- Reports describing events related to DSM-V criteria for sedative, hypnotic, or anxiolytic withdrawal in a clinical setting not related to abuse, misuse, dependence, or withdrawal; for example:
  - Seizures related to underlying medical conditions when phenobarbital is used for the treatment of seizure/epilepsy
  - Fever and nausea/vomiting related to gastrointestinal infection

    - Tachycardia and hypertension related to cardiac condition
- Reports from the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS)
    - Note: these exposures are captured in the concurrent DEPI review
- Reports describing transplacental exposure of phenobarbital
- Reports describing use of veterinary phenobarbital in animals

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 3**.

Table 3. FAERS Search Strategy*	
Date of search	May 3, 2022
Time period of search	Start date† - End date January 1, 2012 – April 30, 2022†
Search type	*RxLogix PV Reports Quick Query*
Product terms	Product Active Ingredient: PHENOBARBITAL, PHENOBARBITAL CALCIUM, PHENOBARBITAL DIETHYLAMINE, PHENOBARBITAL SODIUM
MedDRA search terms (Version 25.0)	**SMQ:** Drug abuse, dependence and withdrawal (SMQ) Broad search **PTs related to abuse/misuse:** Euphoric mood; Feeling drunk; Feeling of relaxation; Acute psychosis; Transient psychosis; Delusion of grandeur; Delusional perception; Delusion; Mixed delusion; Paranoia; Inappropriate affect; Mania; Depersonalisation/derealisation disorder; Disinhibition; Feeling jittery; Flight of ideas; Mood altered **PTs related to barbiturate withdrawal:** Autonomic nervous system imbalance; Hyperhidrosis; Tachycardia; Neonatal tachycardia; Sinus tachycardia; Neonatal Sinus tachycardia; Rebound tachycardia; Heart rate increased; Hypertension; Hypertension neonatal; Withdrawal hypertension; Blood pressure increased; Pyrexia; Hyperpyrexia; Body temperature increased; Tachypnoea; Neonatal tachypnoea; Respiratory rate increased; Tremor; Tremor neonatal; Insomnia; Nausea; Vomiting; Hallucination; Hallucination, auditory; Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Illusion; Psychomotor hyperactivity; Agitation; Agitation neonatal; Delirium; Anxiety; Seizure; Neonatal seizures; Generalised tonic-clonic seizure; Clonic convulsion; Tonic convulsion; Drug withdrawal convulsions; Status epilepticus
Other criteria†	Country derived: USA
Narrative search	Contains: vet, veterinar, dog, canine, animal Cases were screened for use of veterinary phenobarbital in humans

* See Appendix B for a description of the FAERS database.
† Previous 10-year time frame of U.S. reports selected to correspond to data lock dates used in concurrent review of U.S. drug utilization and epidemiologic databases by DEPI
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term

2.3 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in **Table 4**. The focus of the literature review included: 1) identification of case reports of abuse or misuse of stand-alone phenobarbital and 2) identification of articles or opinion pieces outlining concern for the abuse or misuse of stand-alone phenobarbital. Studies in animals and acute overdose in the setting of self-harm were not included. The search was limited to articles published since January 1, 2000.

Table 4. Literature Search Strategy	
Date of search	June 7, 2022
Database	NIH NLM PubMed, Embase (FDA access)
Search terms	'phenobarbital' AND 'abuse'
Years included in search	January 1, 2000 through search date (June 7, 2022)

3 RESULTS

3.1 FAERS AND LITERATURE CASES

The FAERS search retrieved 681 reports and literature searches retrieved 297 (PubMed) and 610 (Embase) articles. After applying the FAERS case definition in Section 2.1, the literature inclusion criteria in Section 2.3, and accounting for duplicate reports, 57 cases were included in the analysis (see **Figure 1**).

Figure 1. FAERS Case Selection

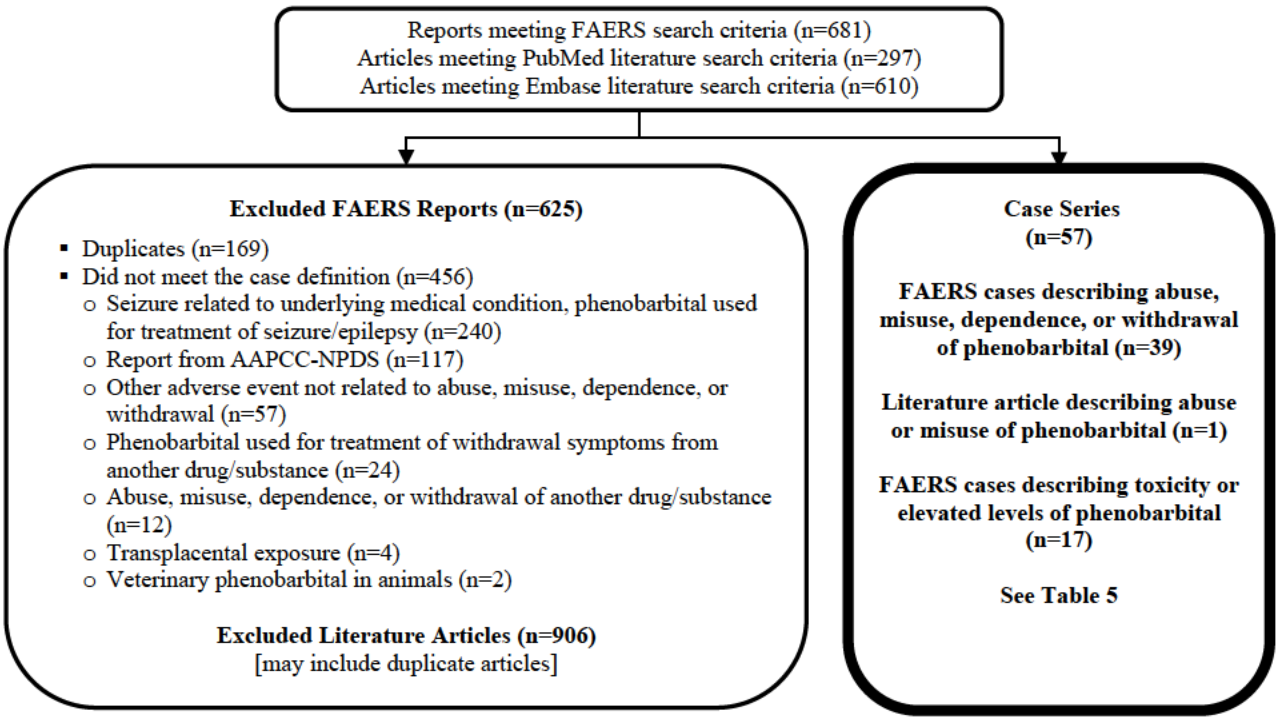


Table 5 summarizes the 57 FAERS and medical literature cases describing abuse, misuse, dependence, withdrawal, overdose, toxicity, or elevated levels with phenobarbital for this case series.

Appendix C contains a line listing of the 57 cases in this case series.

Table 5. Descriptive Characteristics of Abuse, Misuse, Dependence, Withdrawal, Overdose, Toxicity, or Elevated Levels With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA From January 1, 2012 – April 30, 2022 or Published From January 1, 2000 – June 7, 2022 (N=57)

	Abuse, misuse, dependence, withdrawal, or overdose cases (n=40)	**Toxicity or elevated level cases (n=17)**
Age (years)	(n=30)	(n=15)
Mean	38.2	31.9
Median	35.5	37
Range	4 months – 88.6 years	3 months – 73 years
Sex	(n=37)	(n=16)
Female	16	8
Male	21	8
Report type and case source[*]		
FAERS	39	17
15-Day	33	12
Periodic	5	5
Direct	1	
Literature	1	
Dose (mg)[†]	(n=6)	(n=10)
Mean	539.7	205.9
Median	180	204.6
Range	"34.2"-2400	97-300
Route	(n=22)	(n=16)
Oral	21	16
Intravenous	1	0
Reason for use[‡]	(n=20)	(n=15)
Seizure	12	15
Drug withdrawal	2	0
Sedative	2	0
Anxiety	1	0
"Assisted suicide"	1	0
"Child abuse"	1	0
Insomnia	1	0
Peak phenobarbital level (mcg/ml)	(n=7)	(n=11)
Mean	105.6	56.2
Median	113	47.2
Range	25-147.9	28-103

Table 5. Descriptive Characteristics of Abuse, Misuse, Dependence, Withdrawal, Overdose, Toxicity, or Elevated Levels With Phenobarbital in This FAERS and Medical Literature Case Series, Received by FDA From January 1, 2012 – April 30, 2022 or Published From January 1, 2000 – June 7, 2022 (N=57)

	Abuse, misuse, dependence, withdrawal, or overdose cases (n=40)	Toxicity or elevated level cases (n=17)
Number of total drugs/substances involved		
Mean	5.1	2.4
Median	4	2
Range	1-15	1-5
Phenobarbital alone	4	4
Categories of concomitant drugs/substances§		
Opioid	24	0
Antiepileptic drug	12	11
Benzodiazepine	20	2
Muscle relaxant	11	1
Antidepressant	10	1
Antihistamine/anticholinergic	7	1
Antipsychotic	7	1
Gabapentin	6	1
Barbiturate	5	0
Alcohol	4	0
Sedative hypnotic	4	0
Acetaminophen	2	0
Heroin	2	0
Dextromethorphan	1	0
Methamphetamine	1	0
Synthetic cannabinoid	1	0
Serious outcome(s)‖	(n=39)	(n=17)
Death	17	1
Life-threatening	2	1
Hospitalization	25	8
Disability	1	0
Other serious	25	10
Required intervention	1	0

* FAERS - includes any case identified in either FAERS alone or in both FAERS and the literature
Literature - includes cases only identified in the literature

† Two cases reported unknown amount of phenobarbital: one case of abuse/overdose reported oral ingestion of "100 phenobarb tablets" and one case of dependence/withdrawal reported an intravenous dose of 0.33 mg/kg/24 hours. One other case of abuse/overdose reported a dose of "34.2 mg", which is presumed to be 32.4 mg.

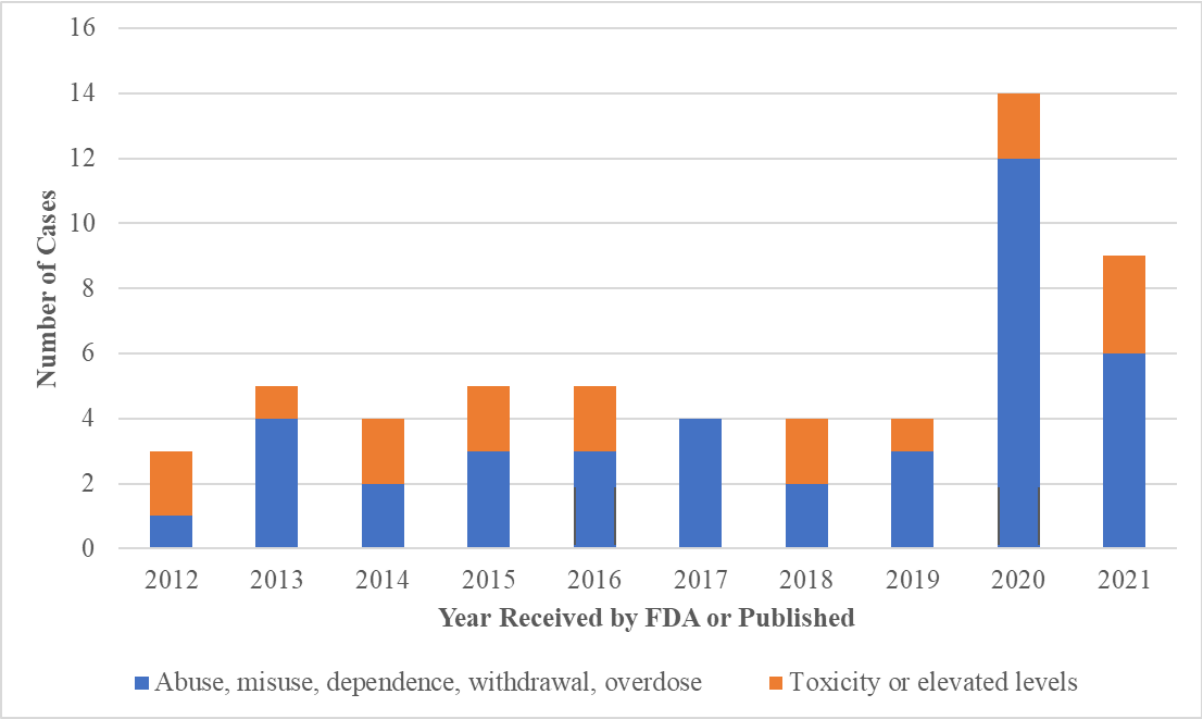
‡ For cases not reporting a reason for use, use for seizure was assumed if patient was on other antiepileptic agents or had medical history of seizure.

§ One case can report more than one category of concomitant drugs/substances.

‖ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome and causality has not been assessed to determine the role of phenobarbital with the reported serious regulatory outcome. The one case from literature only (not included in FAERS) reported hospitalization; this case was included in the total count of serious regulatory outcomes for hospitalization.

Figure 2 displays the number of FAERS or medical literature cases by initial FDA received year or publication date. Reports were relatively consistent from 2012-2019 and peaked in 2020. The increased number of reports in 2020 were driven by five reports submitted through "Purdue bankruptcy claims process" and three published literature articles. In 2021, four literature articles were published.

Figure 2. Number of FAERS or Medical Literature Cases by Year



3.1.1 Cases Describing Abuse, Misuse, Dependence, Withdrawal, or Overdose With Phenobarbital (n=40)

DPV identified 40 FAERS and medical literature cases describing abuse (32), misuse (5), dependence (9), withdrawal (3), or overdose (32) with phenobarbital; one case can report more than one event. Most cases (36/40) reported use of other concomitant medications/substances and the most frequently reported categories included opioids (24), benzodiazepines (20), antiepileptic drugs (12), muscle relaxants (11), and antidepressants (10); one case can report more than one category. Most cases occurred in adults (n=27, pediatric n=4, unknown n=9), with a mean age of 38.2 (median 35.5, range 4 months-88.6 years). Most cases (39/40) reported a regulatory serious outcome, including death (17), life-threatening (2), hospitalization (25), disability (1), required intervention (1), and other serious (25).

Phenobarbital dosing was only reported in 6/40 cases (mean 539.7 mg, median 180, range 34.2-2400). Phenobarbital peak levels were only reported in 7/40 cases (mean 105.6 mcg/ml, median 113, range 25-147.9). Most cases did not provide sufficient information for case evaluation, including temporal relationship to phenobarbital or other drug/substance use.

Cases reporting use of phenobarbital alone, phenobarbital withdrawal, and use of veterinary phenobarbital are discussed below.

Table 6 lists the most frequently reported MedDRA PTs by System Organ Class reported in FAERS cases describing abuse, misuse, dependence, withdrawal, or overdose with phenobarbital. Most cases reported events related to injury/poisoning, psychiatric disorders, nervous system disorders, cardiovascular disorders, and respiratory disorders. Note: a case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.

Table 6. Most Frequently Reported MedDRA PTs by System Organ Class in FAERS Cases Describing Abuse, Misuse, Dependence, Withdrawal, or Overdose With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	**Number of FAERS Reports***
Injury, poisoning and procedural complications	**53**
Toxicity to various agents	18
Overdose	13
Intentional overdose	5
Off label use	3
Intentional product misuse	2
Clavicle fracture	1
Contusion	1
Eye contusion	1
Fall	1
Injury	1
Intentional dose omission	1
Intentional product use issue	1
Product prescribing error	1
Product use issue	1
Rib fracture	1
Road traffic accident	1
Wrong technique in product usage process	1
Psychiatric disorders	**48**

Table 6. Most Frequently Reported MedDRA PTs by System Organ Class in FAERS Cases Describing Abuse, Misuse, Dependence, Withdrawal, or Overdose With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Drug dependence	10
Completed suicide	5
Drug abuse	5
Substance abuse	4
Anxiety	3
Confusional state	3
Suicide attempt	3
Aggression	2
Agitation	2
Depression	2
Abnormal behaviour	1
Agitated depression	1
Alcohol abuse	1
Conversion disorder	1
Disorientation	1
Hallucination	1
Major depression	1
Suicidal ideation	1
Withdrawal syndrome	1
Nervous system disorders	**41**
Coma	4
Seizure	4
Ataxia	3
Dysarthria	3
Somnolence	3
Altered state of consciousness	2
Mental impairment	2
Nystagmus	2
Unresponsive to stimuli	2
Brain injury	1
Brain oedema	1
Coma scale abnormal	1
Depressed level of consciousness	1
Dizziness postural	1
Generalised tonic-clonic seizure	1
Headache	1
Hyperreflexia	1
Hypotonia	1
Insomnia	1
Lethargy	1
Loss of consciousness	1
Memory impairment	1
Migraine	1
Neuralgia	1
Psychomotor hyperactivity	1

Table 6. Most Frequently Reported MedDRA PTs by System Organ Class in FAERS Cases Describing Abuse, Misuse, Dependence, Withdrawal, or Overdose With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Cardiac disorders, Vascular disorders	**19**
Tachycardia	5
Hypotension	3
Cyanosis	2
Hypertension	2
Blood pressure systolic decreased	1
Blood pressure systolic increased	1
Bradycardia	1
Cardiac arrest	1
Cardiac hypertrophy	1
Palpitations	1
Pulse abnormal	1
Respiratory, thoracic and mediastinal disorders	**13**
Respiratory depression	3
Apnoea	2
Hypoxia	2
Tachypnoea	2
Hypercapnia	1
Pulmonary congestion	1
Pulmonary oedema	1
Respiratory failure	1
* A case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.	

3.1.1.1 Cases Reporting Phenobarbital Alone (n=4)

DPV identified four FAERS cases reporting abuse, misuse, dependence, withdrawal, or overdose of **phenobarbital alone**; these four cases are summarized in **Table 7**. One case reported misuse and overdose, one reported abuse, and two reported dependence and withdrawal. Three of the four cases required hospitalization for the event.

Table 7. Summary of FAERS Cases Reporting Abuse, Misuse, Dependence, Withdrawal, or Overdose of Phenobarbital Alone (N=4)			
FAERS Case # Received Year	**Age/Sex**	**Scenario**	**Description**
10258396v1 2014	4 months Male	Misuse, overdose	Literature case;[18] Hospitalized with altered consciousness, somnolence, lethargy, hypotension, hypothermia, respiratory depression, and hypotonia secondary to misuse and overdose of unknown dose of phenobarbital (mother administered her own medication to infant for "fussiness"). Medical history of stable hydrocephalus secondary to intraventricular hemorrhage; not on any medications. Urine toxicology screen positive for barbiturates and serum phenobarbital level was 138 mcg/mL (normal 15-30). Mother admitted to administering her own phenobarbital to the patient to seek attention from patient's father. Patient was admitted to the intensive care unit and received mechanical ventilation and supportive care. Events were reported as resolved.
18707947v1 2021	30 years Female	Abuse	Patient reported previous multiple occurrences of abuse with phenobarbital to get "high" and "delusion." Medical history of epilepsy and "scar tissue"; concomitant medications lamotrigine and clobazam. Patient was hospitalized for elevated lamotrigine levels and was "behaviorally off" and told doctor she has been on phenobarbital since age 6 and has "misused" it in the past multiple times to get "high" and "delusion."
12752161v3 2016	4 years Male	Withdrawal, dependence	Hospitalized with withdrawal symptoms ("behavioral issues") from unknown dose of phenobarbital for epilepsy. Medical history of tuberous sclerosis complex, epilepsy, autism spectrum disorder; concomitant medication vigabatrin. When patient was taken off phenobarbital it "led to constipation, hyperactivity, and violent actions such as kicking, throwing arms and biting." Patient placed back on phenobarbital and also started risperidone. Events were reported as resolved.
13260257v1 2017	41 years Female	Withdrawal, dependence	Hospitalized with withdrawal symptoms ("horrible head pain") from phenobarbital 120 mg PO daily for benzodiazepine withdrawal. Medical history of acute benzodiazepine withdrawal and Lyme disease; concomitant medications amitriptyline, several herbals/dietary supplements. Patient was hospitalized for "horrible head pain as she cut her phenobarbital dose at that time." Patient had been receiving phenobarbital 120 mg PO daily for approximately 22 months prior. Approximately 29 months after receiving phenobarbital, the patient "was trying to taper off of the phenobarbital and was micro tapering her dose for a long time by shaving off 0.001 grams at a time with a razor blade and she had been aware of and investigation the fact that there is not a consistency in the tablets and wanted to know if she was cutting the active pharmaceutical ingredient and not just the fillers." At the time of the report, the patient "was disabled and couldn't go to the doctor and her phenobarbital therapy was ongoing and was tapered to a 50% of the initial dose." Event resolution was unknown.

3.1.1.2 Other Cases Reporting Phenobarbital Withdrawal (N=1)

In addition to the two cases of withdrawal described in **Table 7** above, DPV identified one other case (FAERS #18095269v1, 2020) of withdrawal and dependence reported with intravenous phenobarbital in combination with several concomitant medications. The literature case[19] reported a pediatric patient of unknown age and sex experienced withdrawal (unknown events) from intravenous phenobarbital 0.33 mg/kg/24hr, dexmedetomidine at a cumulative dose of 67.9 mcg/kg for 3 days, benzodiazepine equivalent of lorazepam 0.01 mg/kg/24hr, and opioid equivalent of morphine 0.3 mg/kg/24hr for sedation. The patient was placed on an oral clonidine transition protocol to wean off the intravenous sedatives, and the event of withdrawal was reported as recovering/resolving.

3.1.1.3 Cases Reporting Use of Veterinary Phenobarbital (n=2)

DPV identified two cases describing abuse, misuse, or overdose of **veterinary phenobarbital (canine and equine) in humans**, summarized in **Table 8**. Both cases presented with CNS depression, involved ingestion of other substances (opiates and alcohol), and required hospitalization for the events.

Table 8. Summary of FAERS and Medical Literature Cases Reporting Abuse, Misuse, or Overdose of Veterinary Phenobarbital (N=2)

FAERS Case # Received Year	Age/Sex	Scenario	Description
8510608v1 2012	32 years Male	Abuse, misuse, overdose	Hospitalized with depressed level of consciousness, somnolence, confusional state, ataxia, and dysarthria secondary to abuse, misuse, and overdose of veterinary (canine) phenobarbital for insomnia (dose estimated 240 mg PO if ingesting 30 mg tablets). Medical history of substance abuse (heroin, Suboxone, and Vicodin); concomitant medications not reported. Patient was brought in by ambulance for difficulty to be aroused by parents and was somnolent, ataxic, and confused with slurred speech. Patient stated he had "been taking his dog's seizure medication (phenobarbital) to help him sleep" and "took approximately 8 tablets of phenobarbital" the night before admission. Patient stated he "had taken phenobarbital for insomnia on prior occasions." Urine toxicology screen was positive for barbiturates and opiates and phenobarbital level was 109.6 mcg/mL (normal 15-30). Treatment was not reported, but the patient did not receive gastrointestinal decontamination because he presented too far from ingestion. Events were reported as resolved.

Table 8. Summary of FAERS and Medical Literature Cases Reporting Abuse, Misuse, or Overdose of Veterinary Phenobarbital (N=2)			
Literature case[20] 2015	47 years Male	Abuse, overdose	Hospitalized for motor vehicle accident and coma secondary to abuse and overdose of unknown dose of veterinary (equine) phenobarbital and ethanol. Medical history of extensive alcohol use disorder, vocational and social difficulties, no psychiatric history; concomitant medications not reported. Patient was found at the scene unresponsive and with a "near empty bottle of highly concentrated phenobarbital liquid at a concentration of 250 mg/ml labeled for equine administration." Urine toxicology screen was positive for barbiturates and ethanol on admission. Patient's initial ethanol level measured 174 mg/dL (normal <10) and a phenobarbital serum level was 124 mcg/mL (normal 15-30). Patient was admitted to the intensive care unit and received mechanical ventilation, sedation with dexmedetomidine and lorazepam, and hemodialysis for phenobarbital removal. Patient experienced hypotension, confusion, and agitation while receiving supportive care. Events were reported as resolved. Note: patient had access to the product from his occupation (assistant horse trainer); the concentration of the veterinary phenobarbital (250 mg/ml) is substantially more concentrated than typically seen in preparations for human ingestion (20 mg/5 mL).

3.1.2 Cases Describing Toxicity or Elevated Levels With Phenobarbital (n=17)

DPV identified 17 FAERS and medical literature cases describing toxicity or elevated levels with phenobarbital. Most cases (13/17) reported use of other concomitant medications and the most frequently reported categories included antiepileptics (11) and benzodiazepines (2). Most cases occurred in adults (n=10, pediatric n=5, unknown n=2), with a mean age of 31.9 (median 37, range 3 months-73 years). All 17 cases reported a regulatory serious outcome, including death (1), life-threatening (1), hospitalization (8), and other serious (10).

The 17 cases described toxicity with or without elevated phenobarbital levels, primarily manifesting as neurological adverse events including feeling "drunk," "high," depressed level of consciousness, and ataxia/gait disturbances. Five cases reported potential drug interactions with either phenytoin, cannabidiol, pregabalin, valproate, or chloramphenicol that led to elevated levels or toxicity. Phenobarbital dosing was reported in 10/17 cases (mean 205.9 mg, median 204.6, range 97-300). Phenobarbital peak levels were reported in 11/17 cases (mean 56.2 mcg/ml, median 47.2, range 28-103).

We identified one FAERS case (#8950866v1) reporting a prescribing error – a 73-year-old male was switched from mephobarbital 100 mg TID to phenobarbital 100 mg TID and was hospitalized for ataxia with elevated phenobarbital level of 45.1 mcg/ml. It was noted mephobarbital and phenobarbital are not dose equivalent and the dosing conversion was not appropriate; phenobarbital dose was changed to 120 mg BID and the events improved.

We identified two FAERS cases reporting potential product issues leading to elevated levels. One case (#8695232v3) described a 3-year-old male who required an emergency department

visit for declining activity and alertness, decreased oral intake, and lethargy and was found to have an elevated phenobarbital level of 97 mcg/ml. The patient recently switched to a phenobarbital product from a new pharmacy and crystals were noted in the bottle of phenobarbital solution, suggesting an overly concentrated solution. The other case (19855629v1) described a 40-year-old male who was hospitalized with phenobarbital toxicity and elevated levels ">60" mcg/ml. The pharmacist was concern that the phenobarbital tablet had a "higher concentration of phenobarbital than marked on the package" because the patient had been on a stable dose for years.

Table 9 lists the most frequently reported MedDRA PTs by System Organ Class reported in the FAERS cases describing toxicity or elevated levels with phenobarbital. Most cases reported events related to nervous system disorders, injury/poisoning, investigations, and psychiatric disorders. Note: a case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.

Table 9. Most Frequently Reported MedDRA PTs by System Organ Class With in FAERS Cases Describing Toxicity or Elevated Levels With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*
Nervous system disorders	**37**
Seizure	6
Somnolence	5
Ataxia	2
Coma	2
Dysarthria	2
Feeling drunk	2
Lethargy	2
Balance disorder	1
Choreoathetosis	1
Depressed level of consciousness	1
Dizziness	1
Drug withdrawal convulsions	1
Dysmetria	1
Gait disturbance	1
Generalised tonic-clonic seizure	1
Headache	1
Hypoaesthesia	1
Mental status changes	1
Nystagmus	1
Sedation	1
Slow speech	1
Tonic convulsion	1
Unresponsive to stimuli	1
Injury, poisoning and procedural complications	**15**

Table 9. Most Frequently Reported MedDRA PTs by System Organ Class With in FAERS Cases Describing Toxicity or Elevated Levels With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Toxicity to various agents	9
Fall	1
Incorrect dose administered	1
Intentional product misuse	1
Overdose	1
Product dose omission issue	1
Product prescribing error	1
Investigations	**9**
Anticonvulsant drug level increased	6
Drug level increased	2
Drug level decreased	1
Psychiatric disorders	**6**
Abnormal behaviour	1
Confusional state	1
Euphoric mood	1
Hallucinations, mixed	1
Laziness	1
Listless	1
Gastrointestinal disorders	**5**
Diarrhoea	2
Abdominal pain upper	1
Constipation	1
Intestinal perforation	1
Metabolism and nutrition disorders	**5**
Decreased appetite	1
Dehydration	1
Feeding disorder	1
Hypophagia	1
Metabolic acidosis	1
* A case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.	

3.1.3 Fatal Cases (n=18)

DPV identified 18 fatal FAERS and medical literature cases describing abuse (15), misuse (1), dependence (4), overdose (16), or toxicity (1) with phenobarbital; one case can report more than one event. All 18 cases reported use of other concomitant medications/substances and the most frequently reported categories included opioids (16), benzodiazepines (11), antidepressants (9), antiepileptic drugs (6), muscle relaxants (5), antihistamines/anticholinergics (4), and sedative hypnotics (4); one case can report more than one category. Most cases occurred in adults (n=12, pediatric n=1, unknown n=5), with a mean age of 44.4 (median 43, range 3 months-88.6 years). All 18 cases reported a regulatory serious outcome, including death (18), life-threatening (1), hospitalization (5), and other serious (14).

Most cases (16/18) did not report a phenobarbital dose; one case reported a dose of 100 tablets and one reported "34.2" mg, which is presumed to be 32.4 mg. None of the 18 fatal cases reported peak phenobarbital levels. Most cases did not provide sufficient information for case evaluation, including temporal relationship to phenobarbital or other drug/substance use.

Table 10 lists the most frequently reported MedDRA PTs by System Organ Class reported in fatal FAERS cases describing abuse, misuse, dependence, overdose, or toxicity with phenobarbital. Most cases reported events related to injury/poisoning, psychiatric disorders, nervous system disorders, respiratory disorders, and cardiovascular disorders. Note: a case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.

Table 10. Most Frequently Reported MedDRA PTs by System Organ Class in Fatal FAERS Cases Describing Abuse, Misuse, Dependence, Withdrawal, Overdose, Toxicity, or Elevated Levels With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports*
Injury, poisoning and procedural complications	**33**
Toxicity to various agents	12
Overdose	8
Clavicle fracture	1
Rib fracture	1
Subdural haematoma	1
Eye contusion	1
Fall	1
Injury	1
Road traffic accident	1
Contusion	1
Skin abrasion	1
Skin laceration	1
Intentional product misuse	1
Off label use	1
Intentional overdose	1
Psychiatric disorders	**30**
Drug dependence	8
Completed suicide	5
Substance abuse	4
Anxiety	3
Drug abuse	2
Learning disability	1
Depression	1
Major depression	1
Hallucination	1
Aggression	1
Alcohol abuse	1
Insomnia	1
Suicidal ideation	1
Nervous system disorders	**11**

Table 10. Most Frequently Reported MedDRA PTs by System Organ Class in Fatal FAERS Cases Describing Abuse, Misuse, Dependence, Withdrawal, Overdose, Toxicity, or Elevated Levels With Phenobarbital Received by FDA From January 1, 2012 – April 30, 2022, Sorted by Decreasing Number of FAERS Reports per PT	
MedDRA PT	**Number of FAERS Reports***
Coma	2
Unresponsive to stimuli	2
Seizure	2
Migraine	1
Brain oedema	1
Depressed level of consciousness	1
Loss of consciousness	1
Dizziness postural	1
Respiratory, thoracic and mediastinal disorders	**10**
Respiratory depression	2
Lung consolidation	1
Pulmonary congestion	1
Pulmonary oedema	1
Apnoea	1
Tachypnoea	1
Hypercapnia	1
Hypoxia	1
Respiratory failure	1
Vascular disorders	**7**
Cyanosis	2
Arteriosclerosis	1
Shock	1
Visceral congestion	1
Subgaleal haemorrhage	1
Hypertension	1
Cardiac disorders	**6**
Tachycardia	2
Bradycardia	1
Cardiac arrest	1
Palpitations	1
Cardiac hypertrophy	1
* A case can contain more than one MedDRA PT and causality has not been assessed to determine the role of phenobarbital with the reported MedDRA PTs.	

3.2 ADDITIONAL LITERATURE ARTICLES

Broadly, the literature search was dominated by articles noting the use of phenobarbital for the treatment/prophylaxis of alcohol withdrawal seizures and for maintenance therapy for opioid and barbiturate dependence/abuse ***in adults***. The published literature was also notable for articles on the use of phenobarbital for various clinical conditions ***in newborns*** associated with in utero exposure to opioids (i.e., neonatal opioid withdrawal). Following review, two articles met the stated inclusion criteria in Section 2.3.

One article by Alleva et al. (2015)[20] reported a case of diversion and abuse of veterinary (equine) phenobarbital with ethanol leading to a motor vehicle accident; this case was included in the case series and discussed in Section 3.1.1.3.

The other article meeting the inclusion criteria was an opinion article by Bhalla et al. (2015).[21] These authors – writing from an international perspective – offer their perspective on regulation of phenobarbital. The article includes discussion of abuse liability. Some text is reproduced as follows:

> *"Epilepsy is a major chronic noncommunicable neurologic disorder. Although a simple, safe, efficacious, and low-cost treatment has been available for nearly 100 years, the treatment gap remains been available for nearly 100 years, the treatment gap remains disturbingly high in many low- and middle-income countries. Treatment gap is generally defined as a "difference between the number of people with active epilepsy and the number being appropriately treated." There are many reasons for this treatment gap; one important reason is an overly restrictive regulation on barbiturates such as phenobarbital (PB). These restrictive regulations deserve a wider and open discussion, even though epileptologists and others are intensely engaged on reducing the epilepsy treatment gap. With this article, we provide our viewpoint with an aim of raising an extremely important issue: undue regulatory restriction on phenobarbital, an essential lifesaving antiepileptic drug (AED)."*

4 DISCUSSION

DPV included 57 FAERS and medical literature cases for analysis from January 1, 2012 to April 30, 2022 describing 1) abuse, misuse, dependence, withdrawal, or overdose or 2) toxicity or elevated levels with phenobarbital. Among the 57 cases, DPV identified 40 cases describing abuse (32), misuse (5), dependence (9), withdrawal (3), or overdose (32) with phenobarbital [one case can report more than one event] and 17 cases describing toxicity or elevated levels with phenobarbital. Most cases (56/57) reported a regulatory serious outcome, including death (18), life-threatening (3), hospitalization (33), disability (1), required intervention (1), and other serious (35).

Most cases (49/57) involved multiple drugs or substances and the mean number of concomitant drugs or substances was higher in the cases reporting abuse, misuse, dependence, withdrawal, or overdose (mean 5.1) compared to cases reporting toxicity or elevated levels (mean 2.4). All 18 fatal cases reported use of other concomitant medications/substances. The most frequently reported categories of concomitant drugs in all cases included opioids (24), antiepileptic drugs (23), benzodiazepines (22), muscle relaxants (12), and antidepressants (11). Phenobarbital in isolation was reported in one case of abuse, one case of misuse/overdose, two cases of dependence/ withdrawal, and four cases of toxicity or elevated levels.

Most cases reported use of oral phenobarbital or did not report a route of administration. DPV identified only one case of intravenous phenobarbital use, reporting withdrawal and dependence of multiple drugs used for sedation (phenobarbital, dexmedetomidine, opioids, benzodiazepines). Most cases were reported in adults (n=37, pediatric n=9, unknown n=11) with a mean age of 36.1 years (median 37, range 3 months-88.6 years). Most cases (27/57) reported seizure as the

reason for phenobarbital use. The number of cases were relatively consistent between 2012-2019 and peaked in 2020, which appears to have been stimulated by cases of abuse, misuse, dependence, or withdrawal submitted through Purdue bankruptcy claims process.

We identified higher doses and phenobarbital levels in cases reporting abuse, misuse, dependence, withdrawal, or overdose compared to cases reporting toxicity or elevated levels, which corresponded to a higher severity of reported adverse events. Most reported adverse events were related to injury/poisoning (e.g., toxicity to various agents, overdose), nervous system disorders (e.g., somnolence, coma, ataxia), psychiatric disorders (e.g., drug dependence and abuse, suicide, confusion, abnormal behavior), cardiovascular disorders (e.g., tachycardia, hypotension), and respiratory disorders (e.g., respiratory depression/failure, hypoxia). The 17 cases describing toxicity with or without elevated phenobarbital levels primarily manifested as neurological adverse events including feeling "drunk," "high," depressed level of consciousness, and ataxia/gait disturbances, which may suggest phenobarbital produces effects that may be sought out for abuse purposes.[13]

DPV identified two cases describing abuse, misuse, or overdose of veterinary phenobarbital (canine and equine) in humans; both cases presented with CNS depression, involved ingestion of other substances (opiates and alcohol), and required hospitalization for the events. DPV did not identify any cases of severe withdrawal resulting in seizures, delirium, or death. DPV also did not identify any cases of toxicity or overdose resulting from accidental ingestion of phenobarbital or medication errors related to confusion in dosing and administration. DPV identified five cases of potential drug interactions with either phenytoin, cannabidiol, pregabalin, valproate, or chloramphenicol that led to elevated levels or toxicity of phenobarbital.

Phenobarbital injection and oral tablet/solution labeling includes extensive information regarding phenobarbital tolerance, dependence, withdrawal, and overdose, however, there is not substantial information regarding abuse potential. The injection labeling states "Individuals subject to barbiturate abuse and dependence include alcoholics and opiate abusers as well as other sedative-hypnotics and amphetamine abusers" and the tablet labeling states "This drug should also be administered cautiously to patients with a history of drug dependence or abuse."[3,4] Additional labeling regarding abuse potential may be reasonable and help inform prescribers and patients of these risks, particularly when used in combination with other drugs/substances of abuse (e.g., opioids, benzodiazepines, alcohol, etc.).

5 CONCLUSION

In conclusion, we identified 57 FAERS and medical literature cases from 2012-2022 included in our analysis: 40 cases describing abuse, misuse, dependence, withdrawal, or overdose of phenobarbital and 17 cases describing toxicity or elevated levels with phenobarbital. Most cases (49/57) reported use of multiple concomitant drugs or substances that may have contributed to the reported events. Most cases (56/57) reported a regulatory serious outcome, including death (18), life-threatening (3), hospitalization (33), disability (1), required intervention (1), and other serious (35). Most reported adverse events were related to injury/poisoning, nervous system disorders, psychiatric disorders, cardiovascular disorders, and respiratory disorders.

DPV identified two cases describing misuse/abuse/overdose of veterinary (canine and equine) phenobarbital in humans. DPV did not identify any cases of severe withdrawal resulting in seizures, delirium, or death, or any cases of toxicity or overdose resulting from accidental ingestion of phenobarbital or medication errors related to confusion in dosing and administration.

Although phenobarbital labeling includes extensive information regarding phenobarbital tolerance, dependence, withdrawal, and overdose, additional labeling regarding abuse potential may be reasonable and help inform prescribers and patients of these risks, particularly when used in combination with other drugs/substances of abuse (e.g., opioids, benzodiazepines, alcohol, etc.).

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7 APPENDICES

7.1 APPENDIX A. PHENOBARBITAL LABELING

Phenobarbital Sodium Injection[3]

WARNINGS

Habit Forming

Barbiturates may be habit forming. Tolerance and psychological and physical dependence may occur with continued use (see DRUG ABUSE AND DEPENDENCE and CLINICAL PHARMACOLOGY). Patients who are psychologically dependent on barbiturates may increase the dosage or decrease the dosage interval without consulting a physician and may subsequently develop a physical dependence on barbiturates. To minimize the possibility of overdosage or the development of dependence, the prescribing and dispensing of sedative-hypnotic barbiturates should be limited to the amount required for the interval until the next appointment. Abrupt cessation after prolonged use in the dependent person may result in withdrawal symptoms, including delirium, convulsions and possibly death. Barbiturates should be withdrawn gradually from any patient known to be taking excessive dosage over long periods of time (see DRUG ABUSE AND DEPENDENCE).

DRUG ABUSE AND DEPENDENCE

Phenobarbital Sodium Injection is a Schedule IV controlled substance.

Barbiturates may be habit forming. Tolerance and psychological dependence and physical dependence may occur especially following prolonged use of high doses of barbiturates. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxicating dosage and fatal dosage becomes smaller. Symptoms of acute intoxication with barbiturates include unsteady gait, slurred speech and sustained nystagmus. Mental signs of chronic intoxication include confusion, poor judgment, irritability, insomnia and somatic complaints. Symptoms of barbiturate dependence are similar to those of chronic alcoholism. If an individual appears to be intoxicated with alcohol to a degree that is radically disproportionate to the amount of alcohol in his or her blood, the use of barbiturates should be suspected. The lethal dose of a barbiturate is far less if alcohol is also ingested.

The symptoms of barbiturate withdrawal can be severe and may cause death. Minor withdrawal symptoms may appear 8 to 12 hours after the last dose of a barbiturate. These symptoms usually appear in the following order: anxiety, muscle twitching, tremor of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia and orthostatic hypotension. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Individuals susceptible to barbiturate abuse and dependence include alcoholics and opiate abusers, as well as other sedative-hypnotic and amphetamine abusers.

Drug dependence to barbiturates arises from repeated administration of a barbiturate or agent with barbiturate-like effect on a continuous basis, generally in amounts exceeding therapeutic

dose levels. The characteristics of drug dependence to barbiturates include: (a) a strong desire or need to continue taking the drug, (b) a tendency to increase the dose, (c) a psychic dependence on the effects of the drug related to subjective and individual appreciation of those effects and (d) a physical dependence on the effects of the drug requiring its presence for maintenance of homeostasis and resulting in a definite, characteristic and self-limited abstinence syndrome when the drug is withdrawn.

Individuals subject to barbiturate abuse and dependence include alcoholics and opiate abusers as well as other sedative-hypnotics and amphetamine abusers.

Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. In all cases, withdrawal takes an extended period of time. One method involves substituting a 30 mg dose of phenobarbital for each 100 to 200 mg dose of barbiturate that the patient has been taking. The total daily amount of phenobarbital is then administered in 3 to 4 divided doses, not to exceed 600 mg daily. Should signs of withdrawal occur on the first day of treatment, a loading dose of 100 to 200 mg of phenobarbital may be administered IM in addition to the oral dose. After stabilization on phenobarbital, the total daily dose is decreased by 30 mg a day as long as withdrawal is proceeding smoothly. If withdrawal symptoms appear, dosage is maintained at that level or increased slightly until symptoms disappear. A modification of this regimen involves initiating treatment at the patient's regular dosage level and decreasing the daily dosage by 10 percent if tolerated by the patient. The symptoms of withdrawal can be severe and may cause death. Minor withdrawal symptoms (e.g., anxiety, muscle twitching, tremors, nausea, etc.) may appear 8-12 hours after the last dose of a barbiturate. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to five days after abrupt cessation of the barbiturate. The intensity of withdrawal symptoms gradually declines over a period of two weeks.

Infants physically dependent on barbiturates may be given phenobarbital 3 to 10 mg/kg/day. After withdrawal symptoms (hyperactivity, disturbed sleep, tremors, hyperreflexia) are relieved, the dosage of phenobarbital should be gradually decreased and completely withdrawn over a 2-week period.

OVERDOSAGE

The toxic dose of barbiturates varies considerably. Barbiturate intoxication may be confused with alcoholism, bromide intoxication and various neurological disorders.

For sedation, therapeutic blood levels of phenobarbital range from 5-40 μg/mL; the lethal blood level is greater than 80 μg/mL and usually ranges from 100-200 μg/mL.

Acute overdosage with barbiturates is manifested by CNS and respiratory depression which may progress to Cheyne-Stokes respiration, areflexia, constriction of the pupils to a slight degree (though in severe poisoning, they may show paralytic dilation), oliguria, tachycardia, hypotension, lowered body temperature and coma. Typical shock syndrome (apnea, circulatory collapse, respiratory arrest and death) may occur.

In extreme overdose, all electrical activity in the brain may cease, in which case a "flat" EEG normally equated with clinical death cannot be accepted. This effect is fully reversible unless hypoxic damage occurs. Consideration should be given to the possibility of barbiturate intoxication even in situations that appear to involve trauma.

Complications such as pneumonia, pulmonary edema, cardiac arrhythmias, congestive heart failure and renal failure may occur. Uremia may increase CNS sensitivity to barbiturates if renal function is impaired. Differential diagnosis should include hypoglycemia, head trauma, cerebrovascular accidents, convulsive states and diabetic coma. To obtain up-to-date information about the treatment of overdosage, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdose, interaction among drugs and the unusual drug kinetics in your patient.

Treatment of overdosage is mainly supportive and consists of the following:

1. Maintenance of an adequate airway, with assisted respiration and oxygen administration as necessary.
2. Monitoring of vital signs and fluid balance.
3. Fluid therapy and other standard treatment for shock, if needed.
4. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of phenobarbital.
5. Although not recommended as a routine procedure, hemodialysis may be used in severe barbiturate intoxication or if the patient is anuric or in shock. Hemoperfusion through an anion-exchange resin or activated charcoal has been successful. Peritoneal dialysis is significantly less effective in removing barbiturates.
6. Patient should be rolled from side to side every 30 minutes.
7. Antibiotics should be given if pneumonia is suspected.
8. Appropriate nursing care to prevent hypostatic pneumonia, decubiti, aspiration and other complications of patients with altered states of consciousness.
9. The use of analeptic agents is not recommended.

Phenobarbital tablets[4]

PRECAUTIONS
This drug should also be administered cautiously to patients with a history of drug dependence or abuse (see DRUG ABUSE AND DEPENDENCE).

DRUG ABUSE AND DEPENDENCE
Controlled Substance: Phenobarbital is a Schedule IV drug.

Dependence
Prolonged, uninterrupted use of barbiturates (particularly the short-acting drugs), even in therapeutic doses, may result in psychic and physical dependence. Withdrawal symptoms due to physical dependence following chronic use of large doses of barbiturates may include delirium, convulsions, and death.

OVERDOSAGE
The signs and symptoms of barbiturate poisoning are referable especially to the central nervous system and the cardiovascular system. Moderate intoxication resembles alcoholic inebriation. In severe intoxication, the patient is comatose, the level of reflex activity conforming in a general way to the intensity of the central depression. The deep reflexes may persist for some time despite coexistent coma. The Babinski sign is often positive. The EEG may be of the "burst-suppression" type, with brief periods of electrical silence. The pupils may be constricted and react to light, but late in the course of barbiturate poisoning they may show hypoxic paralytic dilatation. Respiration is affected early.

Breathing may be either slow or rapid and shallow; Cheyne-Stokes rhythm may be present. Respiratory minute volume is diminished, and hypoxia and respiratory acidosis may develop. The blood pressure falls, owing partly to depression of medullary vasomotor centers; partly to a direct action of the drug on the myocardium, sympathetic ganglia, and vascular smooth muscle; partly to hypoxia.

The patient thus develops a typical shock syndrome, with a weak and rapid pulse, cold and clammy skin, and a rise in the hematocrit. Respiratory complications (atelectasis, pulmonary edema, and bronchopneumonia) and renal failure are much dreaded and not infrequent concomitant of severe barbiturate poisoning. There is usually hypothermia, sometimes with temperatures as low as 32°C.

Treatment
General management should consist of symptomatic and supportive therapy, including gastric lavage, administration of intravenous fluids, and maintenance of blood pressure, body temperature and adequate respiratory exchange. Dialysis will increase the rate of removal of barbiturates from the body fluids. Antibiotics may be required to control pulmonary complications.

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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council 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 LINE LISTING OF ABUSE, MISUSE, DEPENDENCE, WITHDRAWAL, OVERDOSE, TOXICITY, OR ELEVATED LEVELS WITH PHENOBARBITAL CASE SERIES (N=57)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
Cases Reporting Abuse, Misuse, Dependence, Withdrawal, or Overdose (n=40)									
1	23-JUN-2014	10258396	1	US-H14001-14-00087	15-DAY	0.33333	MALE	USA	HO
2	15-SEP-2016	12752161	3	US-LUNDBECK-DKLU2019211	PERIODIC	4	MALE	USA	OT,HO
3	07-APR-2021	19104914	8	NVSC2021CA075560	15-DAY	11	MALE	USA	HO,OT
4	05-MAR-2013	9140232	2	US-PFIZER INC-2013073333	15-DAY	18	FEMALE	USA	OT,HO
5	09-AUG-2017	13854269	1	US-BAUSCH-BL-2017-023704	15-DAY	23	MALE	USA	HO
6	31-MAY-2021	19347427	1	US-PURDUE-USA-2020-0158747	PERIODIC	23.512	MALE	USA	DE,OT
7	06-MAY-2021	19220243	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2021R1-294826	15-DAY	24	MALE	USA	OT,DE
8	06-MAR-2013	9144609	2	US-PFIZER INC-2013069349	15-DAY	24	MALE	USA	HO,OT
9	01-MAR-2013	9133514	2	US-PFIZER INC-2013069327	15-DAY	26	FEMALE	USA	HO,OT
10	10-MAR-2016	12168942	1	US-PFIZER INC-2016137590	15-DAY	26	MALE	USA	HO
11	18-SEP-2020	18285499	1	US-PURDUE-USA-2020-0166965	15-DAY	29.097	MALE	USA	OT,DE
12	18-JUL-2020	18038582	1	US-AUROBINDO-AUR-APL-2010-02937	15-DAY	30	FEMALE	USA	OT,HO
13	06-JAN-2021	18707947	1	US-GLAXOSMITHKLINE-US2020AMR259199	15-DAY	30.53	FEMALE	USA	HO
14	10-JUL-2020	18010761	3	US-PURDUE-USA-2020-0156226	15-DAY	31.247	MALE	USA	DE,OT
15	10-APR-2012	8510608	1	473265	DIRECT	32	MALE	USA	RI,HO
16	02-APR-2020	17618596	4	US-NAPPMUNDI-USA-2020-0150732	15-DAY	39.088	MALE	USA	DE,OT,HO
17	22-FEB-2017	13260257	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-17-00404	15-DAY	41	FEMALE	USA	DS,HO,OT
18	15-JAN-2013	9014691	1	US-ROXANE LABORATORIES, INC.-2013-RO-00052RO	15-DAY	43	FEMALE	USA	DE
19	30-MAY-2017	13594172	1	US-IMPAX LABORATORIES, INC-2017-IPXL-01478	15-DAY	47	FEMALE	USA	HO
20	25-JAN-2015	10735329	1	US-JNJFOC-20150109239	15-DAY	50	FEMALE	USA	LT
21	28-JAN-2021	18798087	1	US-CIPLA LTD.-2021US00611	15-DAY	51	MALE	USA	OT
22	30-JUL-2020	18090028	1	US-AUROBINDO-AUR-APL-2020-037075	15-DAY	52	FEMALE	USA	DE,OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
23	29-JAN-2021	18805228	1	US-HIKMA PHARMACEUTICALS USA INC.-US-H14001-21-00408	PERIODIC	52	FEMALE	USA	OT,HO
24	02-OCT-2018	15454935	1	US-ENDO PHARMACEUTICALS INC-2018-041336	15-DAY	53	FEMALE	USA	DE
25	05-MAR-2019	16034724	1	US-ALKEM LABORATORIES LIMITED-US-ALKEM-2019-01667	15-DAY	56	FEMALE	USA	OT,DE
26	30-AUG-2017	13919342	2	US-JNJFOC-20170819177	15-DAY	56	MALE	USA	HO
27	03-DEC-2020	18575815	1	US-PURDUE-USA-2020-0170869	15-DAY	57.259	FEMALE	USA	OT,DE
28	10-OCT-2018	15484433	1	US-ALLERGAN-1839513US	15-DAY	80	MALE	USA	LT,OT,DE,HO
29	28-OCT-2020	18438913	1	US-PURDUE-USA-2020-0173099	15-DAY	88.564	MALE	USA	DE,OT,HO
30	11-DEC-2019	17142563	1	US-PURDUE PHARMA-USA-2019-0149341	15-DAY	UNK	UNK	USA	DE,OT
31	09-DEC-2016	13011677	1	US-STRIDES ARCOLAB LIMITED-2016SP013768	15-DAY	UNK	UNK	USA	HO
32	30-JUL-2020	18095269	1	US-MYLANLABS-2020M1068324	15-DAY	UNK, PEDS	UNK	USA	HO
33	21-AUG-2020	18182633	1	US-PURDUE-USA-2020-0162612	15-DAY	UNK	FEMALE	USA	DE,OT,HO
34	25-FEB-2019	16001720	2	US-ALLERGAN-1851081US	PERIODIC	UNK	FEMALE	USA	
35	06-MAR-2015	10891723	1	US-JNJFOC-20150220172	15-DAY	UNK	FEMALE	USA	HO,OT
36	04-MAR-2014	10025471	1	RB-53633-2013	PERIODIC	UNK	MALE	USA	DE
37	18-SEP-2020	18283667	1	US-PURDUE-USA-2020-0166604	15-DAY	UNK	MALE	USA	HO,DE,OT
38	04-AUG-2020	18109769	3	US-PURDUE-USA-2020-0159424	15-DAY	UNK	MALE	USA	OT,HO
39	28-JUL-2020	18081636	2	US-PURDUE-USA-2020-0156483	15-DAY	UNK	MALE	USA	DE,OT
40	2015	Literature	NA	NA	Literature	47	MALE	USA	HO
Cases Reporting Toxicity or Elevated Phenobarbital Levels (n=17)									
41	01-MAR-2021	18954932	1	US-SUN PHARMACEUTICAL INDUSTRIES LTD-2021R1-282832	15-DAY	0.25	FEMALE	USA	OT,DE
42	31-MAY-2019	16375341	3	US-GW PHARMA-201905USGW1626	15-DAY	2	FEMALE	USA	OT
43	07-DEC-2015	11813147	1	15-040	15-DAY	3	FEMALE	USA	OT
44	31-JUL-2012	8695232	3	US-ENDO PHARMACEUTICALS INC.-PHEB20120009	15-DAY	3.15	MALE	USA	OT
45	16-AUG-2020	18156816	1	FDA-CDER-CTU-2020-72260	DIRECT	7	FEMALE	USA	OT
46	19-FEB-2015	10833770	1	US-PFIZER INC-2015057547	15-DAY	18	FEMALE	USA	HO
47	15-FEB-2016	12076292	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-16-00222	15-DAY	23	MALE	USA	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
48	14-OCT-2013	9619502	1	US-PFIZER INC-2013292314	15-DAY	37	MALE	USA	OT
49	29-JUL-2020	18087799	1	US-GW PHARMA-202007USGW02603	15-DAY	40	MALE	USA	HO
50	20-SEP-2021	19855629	1	FDA-CDER-CTU-2021-69147	DIRECT	40	MALE	USA	HO,LT
51	23-FEB-2018	14565327	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-18-01074	15-DAY	53	MALE	USA	OT
52	16-FEB-2018	14538001	4	US-UCBSA-2015032528	15-DAY	54.66	FEMALE	USA	HO
53	29-JAN-2014	9853847	1	US-ENDO PHARMACEUTICALS INC.-PHEB20140002	15-DAY	55.58	FEMALE	USA	HO,OT
54	26-OCT-2016	12891231	1	FDA-CDER-CTU-10144	DIRECT	68.14	MALE	USA	HO
55	30-NOV-2012	8950866	1	495602	DIRECT	73	MALE	USA	HO
56	04-FEB-2021	18845674	2	US-GW PHARMA-202101USGW00341	15-DAY	UNK	UNK	USA	HO
57	31-MAR-2014	10050294	1	545023	DIRECT	UNK	FEMALE	USA	OT

* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.

Abbreviations: DE=death, HO=hospitalization, LT= life-threatening, DS= disability, RI=required intervention, OT=other medically significant
NA=not applicable, UNK=unknown

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/s/

KAREN M LONG
06/15/2022 10:41:56 AM

ALLEN D BRINKER
06/15/2022 10:48:08 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/1/2022

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215910

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Record Review (RRR) of the analytical site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

The Office of Regulatory Affairs (ORA) inspected the clinical site in October 2019. The inspection was conducted under the following submissions: (b) (4).

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations:

(b) (4)

After review of the inspectional findings and the site's written response, OSIS determined that all study data be accepted for Agency review (FINAL OSIS EIR Review – October 2019 Inspection).

OSIS notes that the current study was conducted within approximately 1 year of the previous

inspection

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Axis Clinicals	1711 Center Avenue West Dilworth, MN
		(b) (4)

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/s/

JAMES J LUMALCURI
06/01/2022 09:29:58 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 26, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Harold Sano
DN2

Subject: QT Consult to NDA 215910 (SDN 001 (New NDA))

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 3/21/2022 regarding the proposed QT labeling language and need for further QT assessment. We reviewed the following materials:

- Siniscalchi et al. Clin Drug Investig (NDA 215910 / eCTD 0001; link);
- Sharpe et al. Pediatrics (NDA 215910 / eCTD 0001; link);
- Study protocol 16-1-1 (NDA 215910 / eCTD 0001; link);
- Pharmacology written summary (NDA 215910 / eCTD 0001; link);
- Summary of clinical pharmacology studies (NDA 215910 / eCTD 0001; link);
- Summary of clinical safety (NDA 215910 / eCTD 0001; link); and
- Annotated label (NDA 215910 / eCTD 0001; link).

1 Responses for the Review Division

Question: Per the sponsor, phenobarbital prolongs the QT interval (see summary of clinical safety), and QT related labeling language is proposed for sections 5.6 and 12.2. Please provide your thoughts on and recommendations for the need to conduct additional studies (either prior to taking action or as a PMR) to characterize the QT effects of this product as it could be the first approval of phenobarbital.

IRT's response: The available nonclinical data and the limited clinical ECG data suggests a possibility for QTc prolongation. The literature report is inadequate to support a thorough characterization of phenobarbital's clinical QT effects because of the uncertainties about clinical exposure; the limited ECG data collected; and the lack of placebo and positive controls. No

safety ECGs were collected on treatment in the bioavailability study and the summary of safety data collected in NEOLEV-2 does not describe collection of ECGs. Consequently, there is insufficient information to provide specific labeling recommendations.

We recognize that phenobarbital products have been marketed in the US since 1912, however, the limited information provided in the NDA suggests a potential for QTc prolongation. We therefore recommend that the sponsor characterizes the effects on the QTc interval as described in ICH E14. We defer the timing of such a characterization to the review division.

2 Internal Comments for the Division

Not applicable.

3 BACKGROUND

3.1 Product Information

Phenobarbital products have been marketed in the US since 1912, however, there is no single-agent phenobarbital product approved by the FDA. Sun Pharma Advanced Research Company, Ltd. (SPARC), has developed a new formulation of phenobarbital for the treatment of neonatal seizures. SPARC asserts that the new formulation, which does not include preservatives such as benzyl alcohol, will have an improved safety profile in neonates compared to other phenobarbital formulations due to the limited ability of neonates to metabolize preservatives like benzol alcohol present in currently marketed formulations. To support efficacy, SPARC conducted a relative BA study showing bioequivalence to the marketed phenobarbital formulation included in the NEOLEV2 study that evaluated seizure reduction in neonates.

The proposed therapeutic dose includes a loading dose and a maintenance dose after electrolyte abnormalities have been corrected or excluded. The initial loading dose is 20 mg/kg over 15 min followed by another loading dose if seizures persist or recur 15 min after completion of the first loading dose. The maintenance dose is 1.5 mg/kg every 8 h for 5 days. The proposed therapeutic dose is similar to the dosing regimen evaluated in NEOLEV2. Model predicted Cmax is ~22 ug/mL and ~45 ug/mL following the initial and second loading dose.

SPARC proposes QT-related labeling language (b) (4) (b) (4) (b) (4). Notably, the clinical QT data provided does not support QT characterization (see section 3.3):

(b) (4)

(b) (4)

3.2 Nonclinical Cardiac Safety

Barbiturates at high concentrations, which are known to produce anesthesia, have direct electrophysiological effects on the heart. In one study examining the effects of phenobarbital on the cardiac rapid delayed rectifier potassium ion current (IKr) expressed by human ether-à-gogo gene (hERG) stably expressed in HEK 293 cells, phenobarbital blocked tail currents with an IC50 value of 3 mM (~700 µg/mL). This suggests that phenobarbital may have arrhythmogenic potential, especially when administered to patients with a predisposed condition or in the case of drug-drug interactions (12). In a second study, the effects of combined AEDs known to inhibit IKr were examined in gestational day 10 of C57BL mouse embryos in culture. Phenobarbital also exhibited a higher potential to cause prolongation of the cardiac repolarization, a marker associated with developing irregular rhythm during longer exposure periods when combined with phenytoin, carbamazepine, and dimethadione (13).

Reviewer's Comment: The reported results for the hERG assay for phenobarbital suggests a potential for direct inhibition (safety margin: ~26x) of the hERG potassium channel (Cmax.free: ~115 uM; PB: 35-50%; MW: 254.22 g/mol).

3.3 Clinical Cardiac Safety

There is one report in the literature that examined the association of phenobarbital and the length of the QTc interval. Siniscalchi and collaborators (2014) (41) performed an open-label, parallel group, prospective study of adult subjects with a clinical diagnosis of late post-stroke seizures. The twenty-five subjects who were treated with phenobarbital exhibited longer QTc interval than those post-stroke patients who were treated with levetiracetam (460.0 ± 57.2 vs. 421.5 ± 50.1 ms; p\0.05). A QTc interval >500 ms was recorded in 3/25 patients treated with phenobarbital, 1/24 patients treated with levetiracetam, and 1/50 patients who received no treatment. A QTc interval between 480 and 500 ms was recorded in 6/25 patients treated with phenobarbital, and 3/24 patients treated with levetiracetam.

In general, a QTc interval over the 99th percentile is considered abnormally prolonged. Approximate 99th percentile QTc values for otherwise healthy postpubertal individuals are 470 ms for males and 480 ms for females. Asymptomatic (eg., no syncope or Torsades) mild QT prolongation (<500 ms and <60 ms increase from baseline) is typically managed with outpatient observation. QTc >440 ms but <500 ms occurs in approximately 10% to 20% of the general population (42).

In contrast a broader survey examining the effects of anticonvulsant drugs published in 2013 (43) did not find any clinical studies that specifically evaluated the effect of phenobarbital on QT interval but found that primidone, the active metabolite of which is phenobarbital, was associated with shortening of the QT interval (44, 45). There has been an anecdotal report of successful treatment of subjects with congenital long QT syndrome with primidone and primidone treatment was associated with reduction of the QT interval and suppression of ventricular arrhythmias (45).

Reviewer's comment: *SPARC references a single open-label, parallel-group, multi-center study in adult patients with a clinical diagnosis of late post-stroke seizure. Patients were randomized to phenobarbital (group A; n = 25, mean dose 130 mg) or levetiracetam (group B; n = 24, mean*

dose 1650 mg). A control group (group C; n = 50) of patients with cerebral post-stroke injury and no seizure were also enrolled. A single 12-lead ECG was collected in the morning and semi-automatically annotated by a blinded cardiologist using a global median approach. While a higher mean QTcF was reported in patients receiving phenobarbital compared to levetiracetam (460.0 ± 57.2 vs. 421.5 ± 50.1 msec), this study is inadequate to characterize the QTc effects of phenobarbital due to limited ECG sampling, no information about ECG collection relative to dosing, no placebo or positive control and unclear how the exposure of phenobarbital compares to the expected exposures with the new formulation.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

LARS JOHANNESEN
04/26/2022 01:41:02 PM

CHRISTINE E GARNETT
04/26/2022 01:53:48 PM