CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215910Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	215910
SERIAL NUMBER:	0001
DATE RECEIVED BY CENTER:	2/17/22
PRODUCT:	Phenobarbital
INTENDED CLINICAL POPULATION:	Neonatal seizures
SPONSOR:	Sun Pharmaceuticals, LLC
CLINICAL REVIEW DIVISION:	Neurology 2
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
DN2 DIVISION DIRECTOR:	Nick Kozauer
PROJECT MANAGER:	Josephine Little

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I. INTRODUCTION AND DRUG HISTORY

Phenobarbital is used as first-line therapy in the treatment of neonatal seizures, but the currently available unapproved formulation contains benzyl alcohol and propylene glycol, both of which represent safety risks for neonates. The current formulation developed by Sun does not contain these excipients but is a lyophilized powder containing 100 mg of phenobarbital sodium to be reconstituted before administration with 10 mL of 0.9% sodium chloride. There are no issues related to excipients or impurities. In the PIND 132342 written responses (February 1, 2017), the sponsor was told:

> If previous human experience in neonates is considered sufficient to address safety, there would be no need for you to conduct standard nonclinical studies to support clinical development of phenobarbital, provided that there are no other issues (e.g., excipients or impurities) that would require nonclinical safety assessment. However, a 505(b)(2) application must contain sufficient nonclinical safety data to write labeling which meets current requirements, as defined in 21 CFR 201.57. The adequacy of published literature for this purpose will be a matter of review.

Because of the indication, nonclinical information referred to in labeling is limited to that in sections 8.4, 12.1, and 13.1.

II. LABELING INFORMATION

8.4

The adverse developmental effects of phenobarbital (PB) exposure during the early postnatal period are well-established based on studies in rats reported in the literature. In published studies provided in the submission, PB exposure during the period of synaptogenesis was shown to increase the number of apoptotic neurons in the developing rat brain and produce neurobehavioral deficits that persisted into adulthood (Bittigau et al., Proc Natl Acad Sci 99:15089–15094, 2002). These effects have also been reported for other anticonvulsants and anesthetic agents with diverse mechanisms of action, including other GABAA agonists (benzodiazepines) as well as voltage-gated sodium channel blockers (phenytoin and lamotrigine), and NMDA receptor antagonist (ketamine and nitrous oxide). As described in one review of the neurobehavioral effects of PB included in the submission (Gutherz et al., Epilepsy Behav 37:265-269, 2014), “One of the most consistent findings is impaired spatial memory in PB-exposed animals tested as adults; exposure from [postnatal day] P6 to P10, from P7 to P14, or from P2 to P21 all disrupted adult spatial memory in the Morris water maze or radial arm maze. Deficits in other memory tasks (i.e., delayed alternation, fear conditioning, reversal learning) have also been reported after PB exposure in early life.” These postnatal ages coincide with what has been determined to be the critical period for the pro-apoptotic effect of PB and other agents. This period of peak susceptibility is thought to correspond to the period of synaptogenesis, which in rats extends from shortly before birth to about 2 weeks after birth and in humans starts in the third trimester and ends several years after birth (Jevtovic-Todorovic et al, J Neurosci 23:876–882, 2003). The most commonly used age (postnatal day, PND) for induction of apoptotic neurodegeneration in rats following a single dose, PND 7, is thought to correspond neurodevelopmentally to approximately the first 6 months after a term birth in humans (ibid).

Neonatal PB exposure in rodents has also been reported to alter male and female reproductive function. Administration of PB (20 mg/kg sc) to rats during early postnatal development (PND 1-8) resulted in disruption of testosterone secretory profiles and estrous cyclicity, changes in steroidogenesis, and impaired fertility in adulthood (Gupta and Yaffe, Pediatr Res 15:1488-1491, 1981), and administration of PB to neonatal hamsters produced deficits in male sexual behavior (Clemens et al, Dev. Psychobiol 12:49, 1979).

12.1

Literature was provided to support an mechanism of action for anticonvulsant effects, which involves facilitation of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission. These effects have long been recognized and several published reviews on mechanisms of action of barbiturates were referenced in the NDA submission. GABA binding to its recognition site on the GABAA receptor complex results in chloride channel opening and the influx of chloride anions into the neuron. Barbiturates such as phenobarbital have been shown to prolong the opening time of the channel, leading to hyperpolarization and a decrease in electrical transmission. Barbiturates also enhance the affinity of GABAA receptors for GABA. Although the precise sites of action of barbiturates have not yet been defined and other effects, such as blockade of non-NMDA (AMPA/kainate) receptors and voltage-activated calcium channels, have been described, a relatively recent review by two experts in the field (Loscher and Rogawski, Epilepsia, 53(Suppl. 8):12–25, 2012) concluded that "potentiation of synaptic GABAergic transmission is the most likely mechanism of the anticonvulsant action of phenobarbital."

13.1

Carcinogenicity

The carcinogenicity of orally administered PB has been investigated in multiple rodent studies. In literature provided by the sponsor, PB was consistently reported to produce hepatocellular adenomas and carcinomas in mice and hepatocellular adenomas in rats after lifetime exposure. Oral administration of PB was also reported to promote liver carcinogenesis in rodents, as well as patas monkeys. The conclusion reached in an extensive review of the carcinogenicity data for PB by the IARC (Vol 79, 2001) was that "There is sufficient evidence in experimental animals for the carcinogenicity of phenobarbital."

(b) (4)

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The identification of PB as an animal carcinogen is considered adequate for labeling purposes.

Fertility

There are no reports of standard fertility studies of PB in published literature; however, in a published study in which rats were administered PB (up to 60 mg/kg/day sc) for 28 days prior to mating and throughout mating and gestation, no adverse effects on fertility were reported (Livezey et al, Am J Obstet Gynecol 167:1611–1615, 1992).

III. RECOMMENDATIONS

The literature information provided in the NDA is adequate for describing risks to the indicated patient population based on nonclinical studies. This information should be included in the relevant sections of labeling.

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/

J EDWARD FISHER
11/15/2022 10:10:06 AM

LOIS M FREED
11/15/2022 10:15:03 AM
I concur. Labeling recommendations have been provided separately.