CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216513Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Not Ready for Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 216513
Assessment 1

Drug Product Name	Pheburane (sodium Phenylbutyrate) oral pellets
Dosage Forms	Pellets
Strength	84 g/bottle (483 mg Sodium phenylbutyrate /g of pellets)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Medunic Canada Inc., Canada
US agent, if applicable	ICON Clinical Research LLC Attn: Jordan Samaniego, Raleigh, NC

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Aug 13, 2021	OPQ
Amendment	Oct 8, 2021	ONDP, DP
Amendment	Nov 10, 2021	ONDP, DP
Amendment	Nov 12, 2021	DS, OPMA, Facilities, Process, Biopharm
Amendment	Nov 29, 2021	ONDP, DP
Amendment	Jan 10, 2022	OPMA, Process
Amendment	Feb 8, 2022	Biopharm
Amendment	Feb 11, 2022	OPMA
Amendment	Feb 24, 2022	ONDP, DP
Amendment	Mar 7, 2022	ONDP, DP
Amendment - Labeling	Mar 11, 2022	ONDP, DP
Amendment	Mar 14, 2022	ONDP, DP
Amendment	Mar 18, 2022	ONDP, DP
Amendment	Mar 22, 2022	ONDP, DP
Amendment	Mar 30, 2022	OPMA, Process
Amendment - labeling	Apr 13, 2022	ONDP, DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sharon Kelly	Donna Christner
Drug Product	Jane Chang	Hong Cai
Manufacturing/ Microbiology	Amit Kokate	Yubing Tang
Biopharmaceutics	Kamrun Nahar	Vidula Kolhatkar
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Hitesh Shroff	

Laboratory (OTR)	N/A	N/A
Environmental	Jane Chang	Hong Cai

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	Adequate: Last Reviewed on Dec 13, 2021 by Sharon Kelly	LOA: Mar 1, 2021
	III			Active	N/A	LOA: Mar 4, 2021

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Pheburane (sodium phenylbutyrate) oral pellets, 84 g per bottle.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "**Approval**" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is satisfactory from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for "**Approval**".

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Pheburane is a nitrogen-binding agent. It is supplied as white to off-white pellets in a child-resistant high-density polyethylene bottle with (b) (4) desiccant in the cap. A calibrated dosing spoon is co-packaged with the drug product in the carton. The drug product can be directly swallowed with a drink or sprinkled onto a spoonful of apple sauce or carrot puree. Each gram of pellets contains 483 mg of sodium phenylbutyrate. Each bottle contains 174 g of pellets equivalent to 84 g of Sodium phenylbutyrate.

Sodium phenylbutyrate has a bitter taste resulting in patient compliance with treatment with children. The proposed pellets are coated with a taste masking coating and bioequivalent to Buphenyl.

FDA has granted Orphan Drug designation to Pheburane for the proposed indication (OD 12-3721).

This NDA is submitted via 505(b)(2) pathway because it relies on the Agency's previous finding of safety and efficacy of the listed drug, Buphenyl and/or on published literature. The proposed drug product. Pheburane, is a drug/device combination product per 21 CFR 3.2(e).

Proposed Indication(s) including	PHEBURANE is a nitrogen-binding agent indicated as adjunctive therapy in the chronic management of urea cycle disorders for adults and pediatric patients.

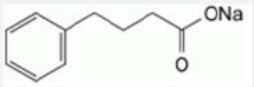
Intended Patient Population	
Duration of Treatment	As needed
Maximum Daily Dose	The usual total daily dose of sodium phenylbutyrate is: • 450 - 600 mg/kg/day (b) (4) weighing less than 20 kg • 9.9 - 13.0 g/m^2/day (b) (4) weighing more than 20 kg, (b) (4). The total daily dose of the drug product should be divided (b) (4) and given with (b) (4) meal or feeding (b) (4).
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, Sodium Phenylbutyrate, is a white to yellowish-white powder. It has no chiral centers. It is freely soluble in water, sparingly soluble in ethanol and practically insoluble in ether. Its pH value is between 6.5 and 7.5. Based on the FTIR spectra of 4 different batches of the drug substance the applicant showed that the same polymorph is produced by the proposed manufacturing process.

Its chemical name is 4-phenylbutyric acid sodium salt. Its chemical structure, molecular formula and molecular weight are shown below.



Molecular formula: $C_{10}H_{11}NaO_2$
Molecular Weight: 186.2 g/mol

The drug substance is manufactured using the proposed manufacturing process under cGMP conditions, tested and released by (b) (4) (b) (4) as described in DMF# (b) (4) The detailed CMC information including physicochemical properties, manufacturing process, characterization, specification, batch analyses of three batches, container closure system and stability results of the drug substance are provided in the DMF # (b) (4) from the manufacturer. A letter of authorization was provided.

The CMC information provided in the DMF was reviewed and the drug substance reviewer concluded that the submitted information is adequate to support the drug product (see the DMF # (b) (4) Review #14, 12/13/2021, S. Kelly, Ph.D.).

A retest period for sodium phenylbutyrate of (b) (4) is acceptable (b) (4) (b) (4) (b) (4) (See **Drug Substance Review**)

Drug Product: Adequate

Pheburane is indicted as an Adjunctive therapy in chronic management of urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) and argininosuccinate synthetase (AS).

Pheburane is white to off-white pellets for oral administration in plastic bottles. Each bottle contains 174 g of pellets equivalent to 84.1 g of sodium phenylbutyrate. Each gram of pellets contain 483 mg of sodium phenylbutyrate. The drug product contains the following inactive ingredients: Sugar spheres (b) (4) (sucrose (b) (4) Hypromellose, Ethylcellulose (b) (4) Macrogol / PEG 1500 and Povidone K25. All ingredients in the drug product are compendial. There are no novel excipients.

(b) (4)

Pheburane is supplied in 250 mL white high-density polyethylene (HDPE) bottle closed with a child-resistant twist-off cap with (b) (4) desiccant co-packaged with a calibrated dosing spoon for measurement of 0.25 g to 3.00 g in 0.25 g increment.

The identity, strength, purity and quality of the drug product are controlled by the drug product specification. The release and stability specifications include the following tests: appearance by visual inspection, identity by HPLC and IR; strength by HPLC, purity via assessment of impurities by HPLC, and microbial enumeration and specified organism per USP <61> and USP <62>; (b) (4) ICP-MS and dissolution per USP <711>. The in-house developed, non-compendial analytical methods were validated per ICH Q2(R1). The specifications for Pheburane were reviewed by the drug product reviewer and determined to be adequate.

A risk assessment for (b) (4) impurities indicated a low risk for the presence of (b) (4) in the drug product. Thus, no (b) (4) impurities control is required in the drug product specification.

In 4 lots of drug products 7 elemental impurities were found to be below ICH Q3D levels (b) (4) Therefore, (b) (4) is controlled to NMT (b) (4) ppm per the drug product specification.

The compatibility study results support that Pheburane can be sprinkled onto soft food such as apple sauce or carrot puree prior to oral administration without significant degradation in quality. The taste-masking coating starts to

progressively dissolve after approximately 10 seconds thus it is recommended that Pheburane with food should be ingested immediately.

On the basis of the satisfactory long-term and accelerated stability study results a 36-month expiration dating period is granted when the drug product is stored at 20 to 25ºC (68 to 77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature]. (See the **Drug Product review**).

Labeling: Inadequate

The label/labeling is satisfactory from the CMC perspective. (See **Labeling Review and Labeling Addendum**)

Manufacturing: Adequate

Facilities: Adequate

Pheburane is manufactured (b) (4) (b) (4)

A typical batch of Pheburane oral pellets manufacturing process includes the following steps: (b) (4) (b) (4)

The primary packaging involves filling 174 g of Pheburane oral pellets into a 250 mL HDPE bottle with a child resistant cap with a desiccant in the cap. A calibrated dosing spoon is included in the secondary packaging.

The applicant provided a flow diagram and a detailed drug product manufacturing process description with all incoming materials, unit operations, in-process controls, process parameters and equipment used.

The proposed drug substance manufacturing and testing facility as well as drug product manufacturing, testing and packaging facilities are recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

The OPMA reviewer concluded that the applicant has submitted adequate CMC information regarding Pheburane oral pellets manufacturing process and facilities. (See **Manufacturing Integrated Assessment** review)

Biopharmaceutics: Adequate

Pheburane is formulated as immediate release pellets for oral administration. The drug product dissolution is assessed by UPS Apparatus 2 (Paddle) method. and the acceptance criterion is Q= (b)(4)% in 30 minutes for batch release and stability. The active ingredient sodium phenylbutyrate is a very soluble in water. The dissolution method did not show significant discriminating ability due to very rapid drug release. On the basis of the totality of the dissolution information provided, the proposed dissolution method and the acceptance criterion of Q= (b)(4)% in 30 minutes for batch release and stability are determined to be adequate.

The drug product used in the bioequivalence studies comparing Pheburane (the proposed product) with Buphenyl (listed drug) is identical to the commercial product. Hence, no bridging study is required.

The Dissolution study comparing sodium phenylbutyrate with Pheburane demonstrated that Pheburane taste-masking is progressively dissolved after approximately 10 seconds and then at a reduced rate over (b)(4)minutes. Therefore, it is important that food sprinkled with Pheburane is administered immediately before the taste masking coating starts to dissolve.

The biopharm reviewer concluded that NDA 216513 for Pheburane (sodium phenylbutyrate) oral pellets is adequate form the Biopharmaceutics perspective. (See **Biopharmaceutics Review**)

Microbiology: Adequate

Pheburane oral pellets is a non-sterile product. The drug product specification include microbial enumeration test for total aerobic microbial count and total combined yeast/molds count per USP <61> and test for specified micro-organisms Escherichia Coli per USP <62>. The acceptance criteria will adhere to USP <1111> for non-sterile products. Microbial limits testing will be performed at release and stability. The stability data of the registration batches, post-approval stability protocol and microbiological purity specifications were reviewed and deemed acceptable. (See the **Manufacturing Integrated Assessment** review).

Environmental Assessment: Adequate

The drug product is an alternative treatment option for urea cycle disorders. Therefore, it will not increase the use of the active moiety. The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31(a) is appropriate for the submitted application, and a statement of no extraordinary circumstances has been submitted. Per 21 CFR 25.15(d), the claim of categorical exclusion is acceptable. (See the **Drug Product** Review).

Post-marketing Commitments (PMC): None

Lifecycle Management Considerations: None

C. Risk Assessment

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters • Container/closure system	L		Low to None	None
Elemental Impurity: (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Low to None	

D. List of Deficiencies: None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
April 20, 2022

Hitesh N. Shroff -S
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QUALITY REVIEW

BIOPHARMACEUTICS
NDA: NDA 216513
Drug Product Name / Strength: Pheburane (Sodium phenylbutyrate) granules/ 483 mg/g
Route of Administration: Oral
Applicant Name: Medunik Canada Inc.
Indication: Treatment of urea cycle disorders
Submission date: 08/13/2021
Primary Reviewer: Kamrun Nahar, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.
Recommendation: Adequate

BACKGROUND:
The Applicant is seeking approval under 505(b)(2) regulatory pathways for Pheburane (Sodium phenylbutyrate) granules/ 483 mg/g referencing BUPHENYL (sodium phenylbutyrate) powder, NDA# 020573 held by HORIZON THERAPEUTICS LLC for oral administration, indicated for the treatment of urea cycle disorders. This Application received "Orphan drug designation" for the treatment of Urea cycle disorders.

REVIEW SUMMARY:
The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data:

1) Dissolution Method and Acceptance Criteria:
The Applicant used FDA database-based dissolution method for the sodium phenylbutyrate oral suspension which is the same method as the USP monograph for Sodium phenylbutyrate oral powder. The dissolution method is as follows- USP apparatus II (paddle), 75 rpm, 900 mL of Simulated intestinal fluid without pancreatin as the dissolution media at 37°C. The Applicant's proposed a dissolution acceptance criterion of "Q= (b)(4)% in 30 minutes" for batch at release and at stability. The Applicant did not provide discriminating ability of the dissolution method.
In vitro studies have demonstrated that the coating starts to progressively dissolve after approximately 10 seconds. Also, dissolution data showed > (b)(4)% drug is released within 15 minutes time point. As the formulation is showing very rapid release of the drug, demonstration of discriminating ability was not much feasible. Overall, considering high solubility of sodium phenylbutyrate, rapid dissolution rate with low variability, dissolution method is deemed adequate. Dissolution acceptance criteria is set as "Q= (b)(4)% in 30 minutes".

The approved dissolution method and acceptance criterion for quality control testing of the proposed sodium phenylbutyrate for oral suspension:

Apparatus	Rotation Speed (rpm)	Medium and volume	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	75	Simulated intestinal fluid without	37±0.5°C	Q (b)(4)% in 30 minutes

		pancreatin/ 900 mL		

2) Bridging of Formulations:

The proposed product used in the bioequivalence studies comparing Pheburane (the proposed product) vs Buphenyl (listed drug) is identical to the commercial product. Hence, no bridging study is required.

3) Waiver request:

No waiver was requested Pheburane (Sodium phenylbutyrate) granules/ 483 mg/g.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 216513, Pheburane (sodium phenylbutyrate) oral granules 483 mg/g is **adequate**.

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed:

1. Seq 0001, dated 08/13/2021
2. Seq 0008, dated 11/12/2021
3. Seq 0012, dated 02/08/2022

Highlight Key Outstanding Issues from Last Cycle: None

I. Solubility Per Biopharmaceutical Classification System (BCS):

The proposed product contains 483 mg of sodium phenylbutyrate. The solubility data showed that (b) (4) the label claimed amount (b) (4) is dissolved in all the pH conditions. Hence, Sodium phenylbutyrate is considered as a highly soluble compound across physiological pH range 1.2 to 6.8.

Table 1: Sodium phenylbutyrate solubility data

Medium pH before dissolution	Medium pH after dissolution	Amount dissolved (% of theoretical amount*, average of 3 samples)
6.83	6.77	(b) (4)
5.56	6.13	
4.53	5.51	
3.54	5.32	
1.95	5.92	
1.00	4.94	

* (b) (4)

II. Dosage Form:

The proposed drug product Pheburane granules are white to off-white immediate release granules in strength of 483 mg/g contained in HDPE plastic bottle closed with a (b) (4) child proof resistant twist-off cap. Each bottle contains 84 g of sodium Phenylbutyrate.

Table 2: Components of Pheburane granules

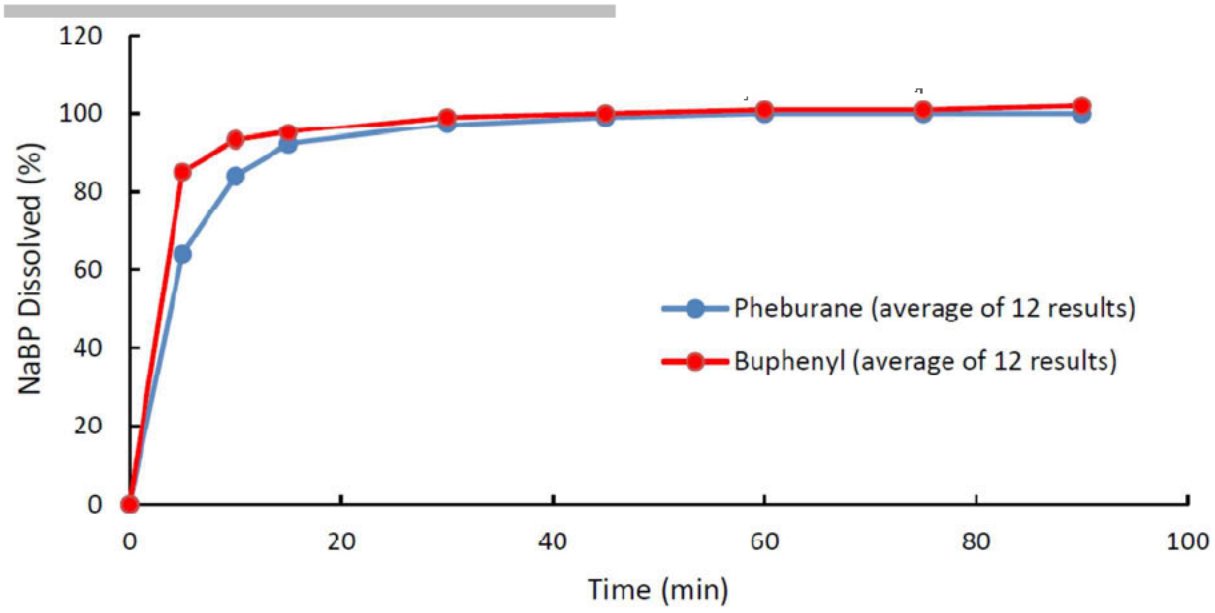
Name of Ingredients	Quantity (per g of granules)	Quantity (per bottle of 174 g)	Quantity (% basis)	Function	Reference
Active ingredient					
Sodium 4-phenylbutyrate	483 mg	84 (b) (4) g	48.3%	Drug substance	USP
Other ingredients					
Sugar spheres (b) (4) (sucrose (b) (4))	(b) (4)				NF
Hypromellose (b) (4) 2910, (b) (4) (b) (4)					USP
Ethylcellulose (b) (4) (b) (4)					USP
Macrogol / PEG 1500					NF
Povidone K25 (b) (4) (b) (4)					USP

III. Equivalence between Pheburane vs Buphenyl:

To compare the dissolution profile of the US listed product Buphenyl vs the proposed product Pheburane, the Applicant conducted dissolution using the FDA database-based dissolution method (USP apparatus II (paddle), 75 rpm, 900 mL of simulated intestinal fluid, pH 6.8) and Pheburane validated dissolution medium at acidic pH 1.2.

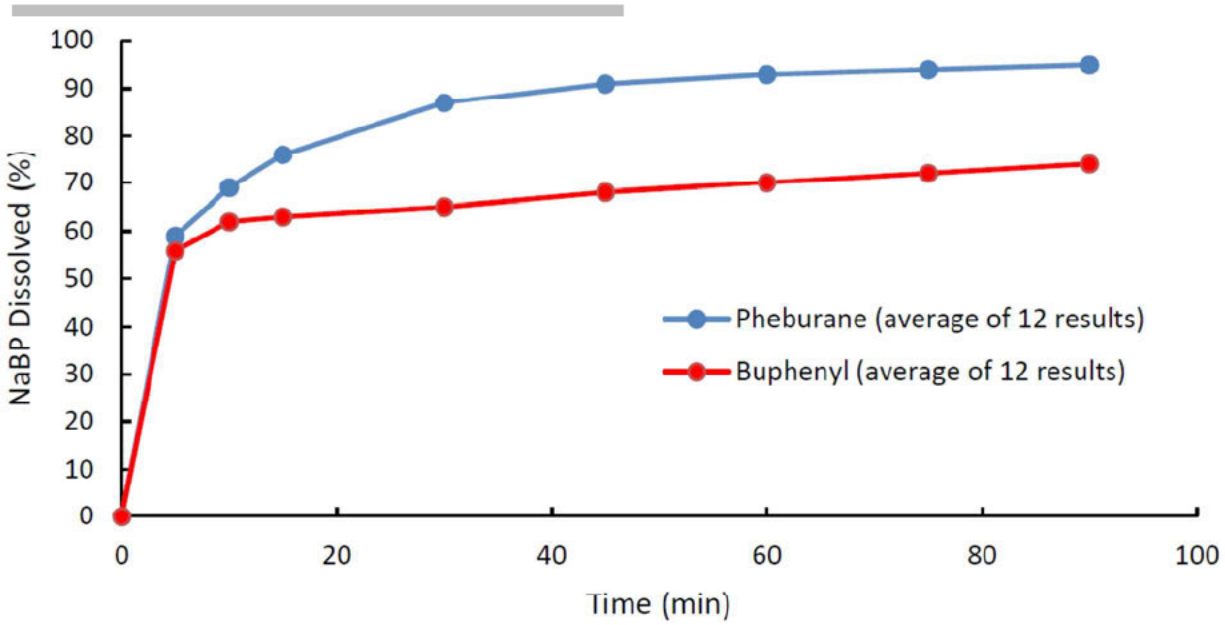
Dissolution data using the FDA database-based dissolution method showed that both Buphenyl and Pheburane did not show many differences in drug release with a similarity factor (f2)>50, indicating dissolution profile similarity.

Figure 1: Dissolution profiles of Buphenyl and Pheburane using the FDA database-based dissolution method



Dissolution data at acidic pH 1.2 showed the proposed product Pheburane showed faster drug release compared to the US listed product Buphenyl. However, this method failed to meet difference factor (f1) and similarity factor (f2) criteria. The Applicant stated that two different dissolution methods under two different pH conditions, i.e., FDA database dissolution method at pH 6.8 and Pheburane validated dissolution media under pH 1.2 showed two different dissolution results. Nevertheless, bioequivalence between Pheburane and Buphenyl was established by clinical bioequivalence study#200009. Refer to the clinical pharmacology review for detail information.

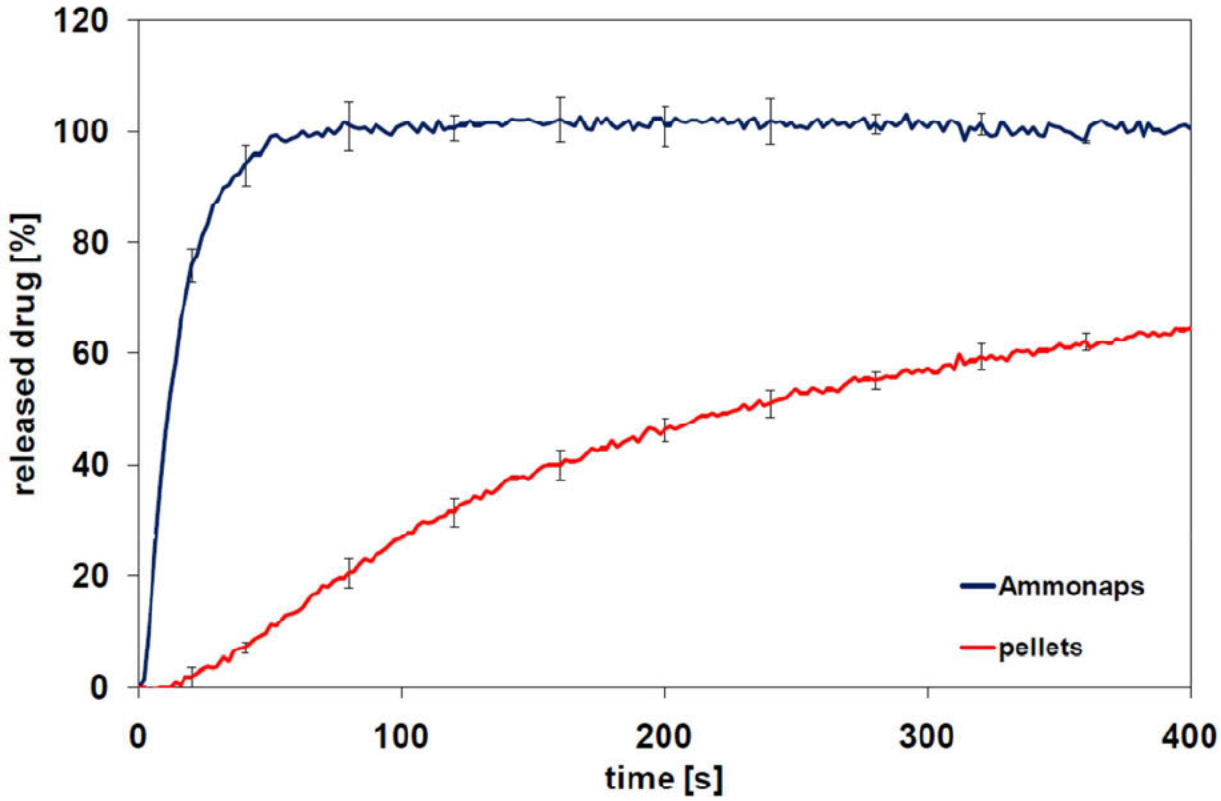
Figure 2: Dissolution profiles of Pheburane and Buphenyl using acidic pH 1.2



Real time dissolution profiles and taste masking efficiency:

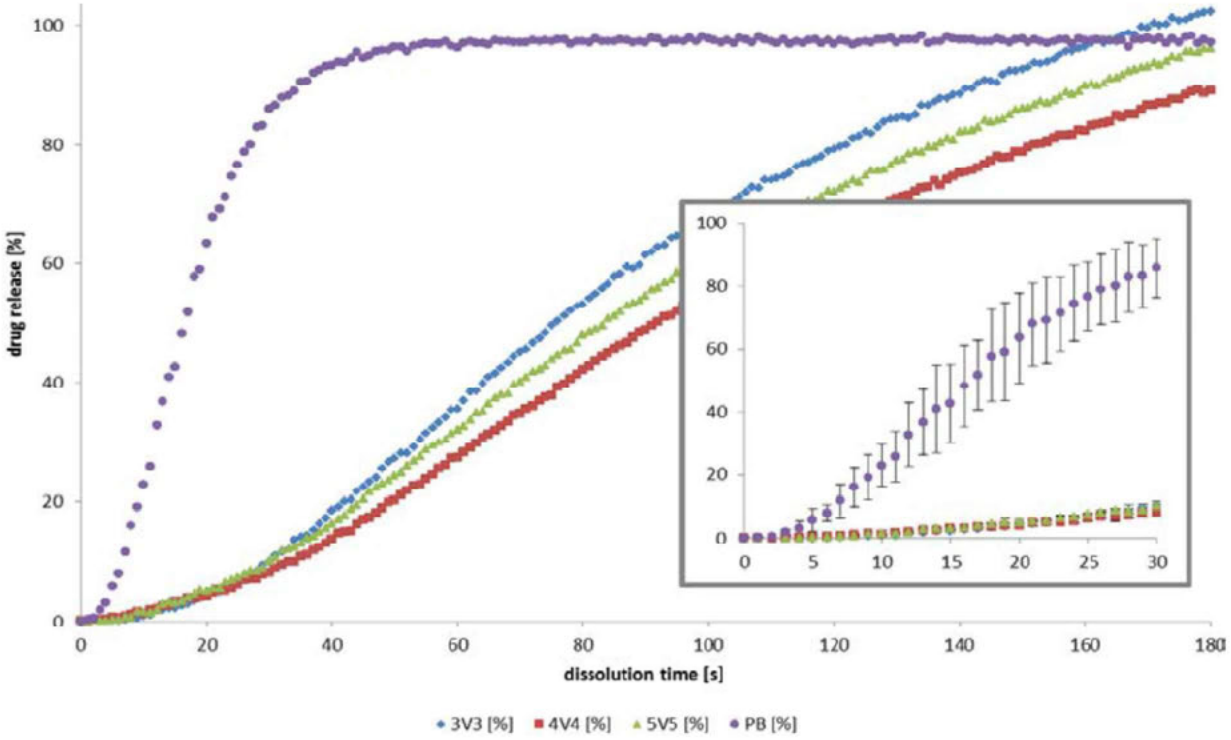
The Applicant evaluated the taste masking efficiency between Pheburane and Ammonaps granules (approved in European Union) using the electronic tongue (b) (4) (b) (4) In addition, the drug release of these two products were evaluated by dissolution study by using fibre-optic UV spectroscopy for real-time measurements. Ammonaps granules showed drug release immediately and fully within less than 60 seconds. Whereas the proposed product Pheburane showed lower drug release compared to Ammonaps.

Figure 3: Sodium phenylbutyrate release from the uncoated granules (Ammonaps-European Union approved product) vs the proposed product Pheburane batch#44049G02



When the dissolution was performed using pure sodium phenylbutyrate (PB) and three different Pheburane batches, it was observed that Pheburane showed slower drug release than the pure compound.

Figure 4: Dissolution behavior of pure sodium phenylbutyrate (PB) and three different Pheburane batches



This study concludes that the newly developed granules are taste-masked showing a lag-time of about 10 seconds and then a reduced release rate over (b) (4) minutes. In the label, the Applicant states that (b) (4) (b) (4)

IV. Dissolution Method:

Dissolution method development history:
Historically the Applicant used a different dissolution methos, (b) (4) (b) (4) The Applicant used this method to compare US listed product Buphenyl vs European listed product Ammonaps. Dissolution data showed that both products have similar drug release.

Later, the Applicant adopted FDA database-based dissolution method which is the same as the USP monograph dissolution method for the sodium phenylbutyrate oral powder, which is as follows, USP apparatus II (paddle), 75 rpm, simulated intestinal fluid (SIF), 900 mL at 37°C with an acceptance criterion of "Q (b) (4) % in 30 minutes".

The Applicant was asked to provide the dissolution method development report. In response, they stated that they have adopted USP monograph dissolution method, additional dissolution method development work was not performed.

Dissolution profile of the clinical batch#6336901 using the FDA database-based method showed that (b) (4)% drug is released within 15 minutes time point. In vitro studies have demonstrated that the coating starts to progressively dissolve after approximately 10 seconds. Also, dissolution data showed (b) (4)% drug is released within 15 minutes time point. As the formulation is showing very rapid release of the drug, demonstration of discriminating ability was not much feasible.

In conclusion, sodium phenylbutyrate is a highly soluble compound. The dissolution method is not considered to have discriminating ability. Dissolution data showed very rapid drug release, i.e., (b) (4) drug release in 15 minutes time with low variability. Hence, based on the totality of the information, dissolution method is deemed adequate.

Dissolution acceptance criterion:

The Applicant's proposed a dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes" as quality control for batch release and stability testing of the proposed drug product. Dissolution profile data of the clinical batch# 6336901 at different time points, n=12, showed very rapid drug release, i.e., >(b) (4)% drug release in 15 minutes time with low variability. For immediate release solid oral drug products containing a high solubility drug substance, the dissolution criterion is Q= (b) (4)% in 30 minutes is recommended. Therefore, based on the dissolution data, the proposed dissolution acceptance criterion is deemed adequate.

Table 3: The list process validations, clinical study, stability, and commercial lots of the proposed product

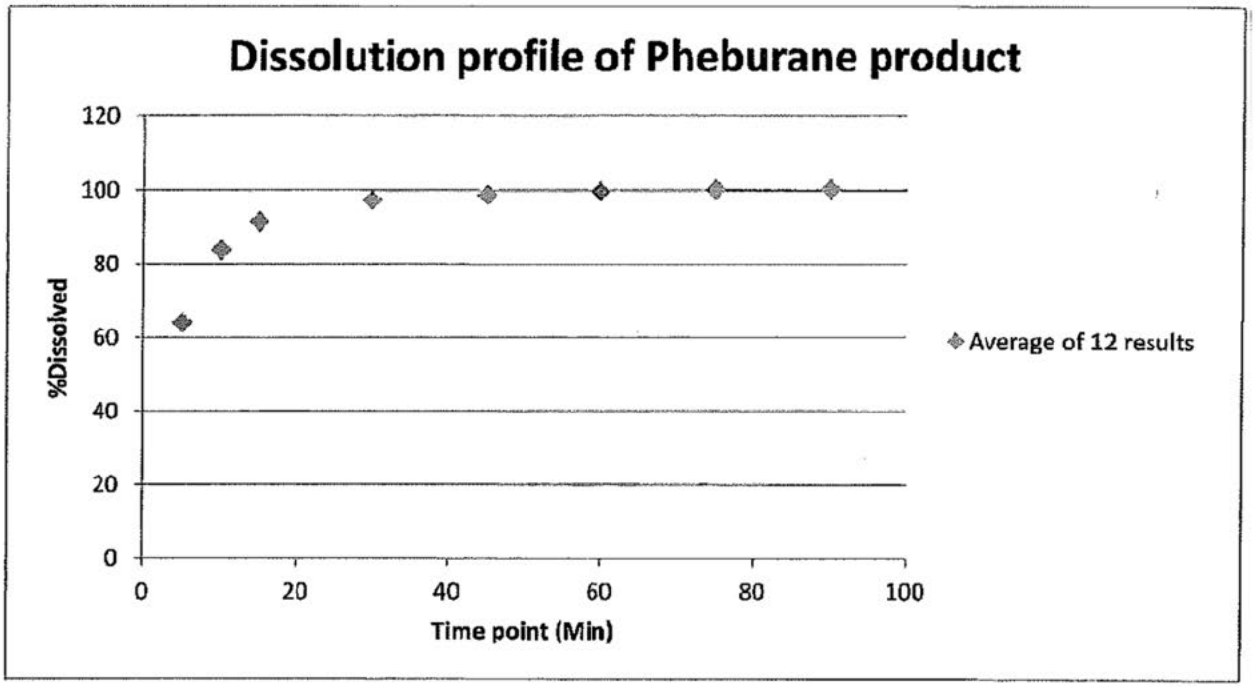
Batch	API manufacturer*/ API Batch No.	Batch size (kg)	Date of Manufacture	Use
Process Validation Batches				
5793601V1	(b) (4) 0142516P	(b) (4)	Nov. 2016	Process validation Stability
5793602V2	(b) (4) 0142516P		Nov. 2016	Process validation Stability
5793603V3	(b) (4) 0142516P		Nov. 2016	Process validation Stability
Clinical Batches				
4602502V2	(b) (4) 166 656	(b) (4)	May 2011	Bioequivalence study LUC1001 / Stability
6016901	(b) (4) 0051917P/0161917P		March 2018	Bioequivalence study 180443
6336901	(b) (4) 0131118P		June 2019	Bioequivalence study 200009
Stability Batches				
6230801	(b) (4) 0174217P/0081917P	(b) (4)	Feb. 2019	Stability
6230804	(b) (4) 0174217P/0011118P		Feb. 2019	Stability
6230802	(b) (4) 0174217P		Feb. 2019	Stability
6230803	(b) (4) 0174217P		Feb. 2019	Stability
5835701	(b) (4) 608045/702048		May 2017	Stability
Commercial Registration Batches				
6382901	(b) (4) 006019P/0182819P	(b) (4)	May 2020	Commercial
6382902	(b) (4) 0182819P		May 2020	Commercial
6382903	(b) (4) 0182819P/0242819P		May 2020	Commercial

(b) (4) is, an alternate manufacturer of Sodium Pheburane used in other jurisdictions. The pharmaceutical development was done using API from this source.

Table 4: Dissolution profiles of Pheburane, batch#6336901, n=12 using FDA database-based dissolution method

Name	Obtained results (% Dissolved)							
	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
Vessel 1	(b) (4)							
Vessel 2								
Vessel 3								
Vessel 4								
Vessel 5								
Vessel 6								
Vessel 7								
Vessel 8								
Vessel 9								
Vessel 10								
Vessel 11								
Vessel 12								
Average:	64	84	92	97	99	100	100	100

Figure 5: Dissolution profiles of Pheburane, batch#6336901, n=12 using FDA database-based dissolution method



The approved dissolution method and acceptance criterion for quality control and stability testing of the proposed sodium phenylbutyrate for oral suspension:

Apparatus	Rotation Speed (rpm)	Medium/ volume	Temperature	Acceptance Criterion
USP Apparatus 2 (Paddle)	75	Simulated intestinal fluid (SIF)/ 900 mL	37±0.5°C	Q (b) (4)% in 30 minutes

Appendix 1. Dissolution Data

Dissolution data:

1. \\CDSESUB1\evsprod\nda214860\0008\m1\us\1111-quality-info-amend-cmc-ir1-27oct2021.pdf
2. \\CDSESUB1\evsprod\nda216513\0001\m3\32-body-data\32p-drug-prod\pheburane-granules\32p2-pharm-dev\pharmaceutical-development-20-242t-r00.pdf

Appendix 2. Information Request and Responses

Information Request (10/12/2021)**:**

Information request:

1. Provide the solubility data of Sodium phenylbutyrate across the physiological pH range 1.2-6.8 in aqueous media.
2. Provide dissolution method development report. Dissolution development report should include detailed description of the dissolution method being proposed for the evaluation of the product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the proposed drug product (e.g., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, media pH, sink conditions, use of sinker and enzyme, if applicable, etc. It is recommended the use of at least twelve dosage units per testing variable and sampling time points (e.g., 10, 15, 20, 30, 45 60 min. etc.).
3. Provide complete dissolution data [individual (n=12), mean, range, %RSD at each time point and mean profiles] of the proposed sodium phenylbutyrate formulation pivotal clinical lots, development, and primary registration lots using the proposed QC dissolution method. Clearly identify batch no. in your response.

Applicant's Response (11/22/2021):

1. \\CDSESUB1\evsprod\nda216513\0008\m1\us\111-info-amend\response-document-ir-12oct2021.pdf
2. \\CDSESUB1\evsprod\nda216513\0016\m1\us\111-info-amend\response-ir-12oct2021.pdf

Reviewer's assessment IR#1: Adequate

The Applicant provided solubility data of the sodium phenylbutyrate across the physiological pH range (b) (4) in aqueous media. The solubility table is provided in the current review. The response is adequate.

Reviewer's assessment IR#2: Adequate

In response, the Applicant mentioned that they have adopted FDA database-based dissoltuion method which is the same dissoltuion method as the USP method. The Applicant did not conduct additional development work. Their response is assessed the review.

Reviewer's assessment IR#3: Adequate

The Applicant was asked to provide complete profile of the development, clinical and registration batches. In response, they provided dissolution data of the registration and stability batches at 30 minutes time point. All these batches showed > (b) (4)% drug release at 30 minutes time points.

CHAPTER IV: LABELING

See Chapter IV (Labeling) of the NDA IQA Guide

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0001 (SDN-1)	08/13/2021
eCTD-0006 (SDN-6)	11/05/2021

1.0 PRESCRIBING INFORMATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Drug name [201.57(a)(2)]		
Established name[1]	Inadequate	Established name should be revised to "sodium phenylbutyrate oral pellets"
Dosage form, route of administration	Inadequate	Dosage Form should be revised to "pellets"
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	Adequate	The year that FDA initially approves an NME should be listed. The drug substance was first approved in 1996 for NDA 20573.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Inadequate	Dosage form terminology under this heading (i.e., oral pellets) should be identical to the dosage form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 13)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of	Inadequate	The name of the salt is included. Strength is based on the salt to be consistent with the approved products (for historical reason).

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		The amount of the salt in each bottle is used for strength.
Whether the drug product is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	N/A

Conclusion: Unsatisfactory

In the NDA, the applicant uses two terms "granules" and "pellets" (e.g., 3.2.P.2 Drug Product, page 11) for the drug product description. (b) (4) (b) (4) (b) (4) This assessor recommends "pellets" as the dosage form based on the following:

1. Per USP <1151> definition of Granules vs. Pellets.
   - Granules are solid dosage forms that are composed of agglomerations of smaller particles.
   - Pellets are small solid dosage forms. They can have a spherical or nearly spherical shape, although such a shape is not required. Spherical pellets are sometimes referred to as beads. Pellets may be designed with the drug substance dispersed in a matrix or the pellets may be coated with an appropriate polymer.
2. The NDA 216513 drug product is manufactured by (b) (4) (b) (4) (b) (4)
3. The dosage form "pellets" is consistent with:
   - NDA 214358 PRADAXA® (dabigatran etexilate) oral pellets.
   - NDA 21153 Nexium (esomeprazole magnesium) delayed-release capsules, which is listed as "CAPSULES, DELAYED REL PELLETS" in Orange Book. Based on the labeling, the drug product contains sugar spheres as an excipient.

Thus, the established name of the drug product should be "sodium phenylbutyrate oral pellets".

OPQ/ONDP and DMEPA discussed the following options for expression of strength (emails dated 9/24/2021, 10/20/2021, and 11/1/2021):

(b) (4)

(b) (4)

A final recommendation for Option 3 was reached by both parties. Of note, the strength is based on the salt to be consistent with the approved products for historical reason.

The recommended revisions are shown below:

PRODUCT TITLE:

(b) (4)

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Instruction for swallowing with a drink or solid food is included, including immediately taking the drug after sprinkling onto solid food.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Solid food, i.e., apple sauce or carrot puree, that can be taken with the drug is included.
For parenteral products: include statement: "Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	There is no USP monograph for the dosage form "oral pellets".
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug.	N/A	N/A
For hazardous products, include the statement "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs".	N/A	N/A

Assessment: ***Inadequate***

Food compatibility study supports sprinkling the drug product onto apple sauce or carrot puree for administration (see NDA 216513 Drug Product R01). However, the statement (b) (4) (b) (4) (b) (4) should be removed.

The term (b) (4) should be replaced with "oral pellets" or "pellets", for example:

(b) (4)

Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Available dosage forms	Inadequate	Dosage form terminology in this section (i.e., oral pellets) should be identical to the dosage form terminology in the product title in HL (see Labeling Review Tool, page 26).
Strengths in metric system.	Inadequate	Metric system is used for strengths. However, strength should be based on the amount of salt per bottle.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Adequate	Strength is based on the salt to be consistent with the approved products (for historical reason). The name of the salt is included for clarity.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and color and clarity of the solution, when applicable.	Inadequate	Color is included. However, the solid form (b) (4) should be replaced with "pellets".
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

(b) (4)

Section 11: DESCRIPTION

(b) (4)

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Inadequate	"Pheburane (sodium phenylbutyrate) oral pellets" should be included. Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Inadequate	Dosage form terminology under this heading (i.e., oral pellets) should be identical to the dosage form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 48)
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)*	Inadequate	Strength is not provided. Strength should be based on the salt to be consistent with the approved products (for historical reason). Equivalence statement should be included for clarity.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any) in alphabetical order]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	Adequate	Inactive ingredients are not required if it is for oral use. However, it is recommended that this information be included to be consistent with other NDAs.
Sterility statement [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	N/A	N/A

Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Inadequate	Not provided. The pharmacological class for phenylbutyric acid as a nitrogen binding agent is listed in Established Pharmacologic Class (EPC) terms in eLIST.
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F)]	Inadequate	Molecular weight should include two decimal places, i.e., 186.19.
If radioactive, statement of important nuclear characteristics [21 CFR 201.57(c)(12)(i)(G)]	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	N/A	N/A
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	There is no USP monograph for the dosage form "oral pellets".

*Per 201.57(c)(12)(i)(C): The same qualitative and/or quantitative ingredient information as required under 201.100(b) for drug labels or 610.60 and 610.61 of this chapter for biological product labels

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

(b) (4)

(b) (4)

Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Dosage form	Inadequate	Dosage form terminology (i.e., oral pellets) under this heading should be identical to the dosage form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 59)
Strength(s) in metric system. If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Inadequate	Strengths in metric system are provided. Strength is based on the salt to be consistent with the approved products (for historical reason). However, strength should be based on the amount of salt per bottle.
Available units (e.g., bottles of 100 tablets)	Adequate	"(b) (4) provided. However, (b) (4) should be replaced with "oral pellets".
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Inadequate	(b) (4) should be replaced with "white to off-white oral pellets".
Special handling (e.g., protect from light,	N/A	N/A

refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."		
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Adequate	The desiccant is in the cap and not mixed with the pellets.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Acceptable storage condition is provided. However, revision for the shelf-life of the open bottle is recommended.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging (if manufacturer choose to include)	Adequate	The primary packaging is with a child resistant HDPE bottle.

Conclusion: Unsatisfactory

The applicant provided in-use data, which show no change in assay and impurities over 45 days after first opening the bottle (see NDA 216513 Drug Product R01). The applicant proposes a shelf-life of 45 days after opening the bottle. This information is recommended for Section 16.

The recommended revisions are shown below:

(b) (4)

(b) (4)

Section 17: PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information in Proposed Labeling	Assessor's Comments
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	Inadequate	The street address should be included.

Conclusion: Unsatisfactory

The street address should be included.

(b) (4)

(b) (4)

Item	Information in Proposed Labeling	Assessor's Comments
Established name	Inadequate	Established name should be "sodium phenylbutyrate oral pellets".
Special preparation instructions (if applicable)	N/A	No information
Storage and handling information (if applicable)	Adequate	Correct information is provided. However, it is recommended that the temperature range in Fahrenheit be listed first.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	The desiccant is in the cap and not mixed with the pellets.
Active ingredient(s) (if applicable)	Inadequate	Not provided
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	Not provided
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Inadequate	The street address should be included.

Conclusion: Unsatisfactory

The recommended revisions are shown below:

(b) (4)

3.0 CARTON AND CONTAINER LABELS

3.1 CONTAINER LABEL

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Inadequate	Established name should be "sodium phenylbutyrate oral pellets".
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Adequate	"oral" provided
Strength(s) in metric system	Inadequate	Strengths in metric system. However, "84 g (b) (4) per bottle" should not be in parenthesis and should be located immediately beneath the established name.
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Inadequate	Strength should be based on the salt content per bottle (see page 2). Strength based on the salt is to be consistent with the approved products (for historical reason). Salt equivalence statement should be revised. See Assessment below.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Inadequate	Net content (174 g) is provided. However, (b) (4) should be replaced with "pellets".
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR	N/A	Not required for oral drugs

201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]		
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	NDC: 71770-200-10
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Adequate	None
Bar code [21CFR 201.25(c)(2)]*	Inadequate	Not included
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Inadequate	Replace (b) (4) (b) (4) with "Recommended Dosage: See Prescribing Information"
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Inadequate	The street address should be included.
And others, if space is available	Inadequate	For clarity, minor edit for " (b) (4) (b) (4) (b) (4). Add "Date of first opening: _____/_____/_____"
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	N/A	N/A

*Requests for an exemption can be made [21 CFR 201.25(d)(ii)(2)]. The bar code requirement does not apply to prescription drug samples [21 CFR 201.25(b)(1)(i)(A)].

Conclusion: **Unsatisfactory**

In an email communication dated 8/9/2019 with DMEPA assessor for labeling of another NDA, the DMEPA assessor stated that based on DMEPA management's involvement with the Labeling Workgroup, it was recently determined that the usual dosage statement be changed from (b) (4) to "Recommended Dosage: See Prescribing Information".

The recommended revisions are shown below:

1. The dosage form should be "pellets". [(b) (4)] Use parenthesis to enclose "sodium phenylbutyrate" for the established name. Revise the proprietary name, established name, and strength as following:

   Pheburane®
   (sodium phenylbutyrate) oral pellets
   84 g per bottle*

2. On the side panel, add a statement "*Each bottle contains 84 g of sodium phenylbutyrate (equivalent to 74 g of phenylbutyrate) in 174 g of oral pellets. Each gram of pellets contains 483 mg of sodium phenylbutyrate (equivalent to 423 mg of phenylbutyrate)."
3. Replace the statement "[(b) (4)]" with "Recommended Dosage: See Prescribing Information".
4. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual bottle as required per 21CFR 201.25(c)(2).
5. Replace the statement "[(b) (4)], with "Date of first opening: ___/___/_____. Discard unused Pheburane 45 days after first opening of the bottle".
6. Include the street address for the distributor.
7. Delete statements '[(b) (4)], and "[(b) (4)] [(b) (4)], from the principal display panel.

3.2 CARTON LABELS

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Inadequate	Established name should be "sodium phenylbutyrate oral pellets".
Strength(s) in metric system	Inadequate	Strengths in metric system. However, "84 g (b) (4) per bottle" should not be in parenthesis and should be located immediately beneath the established name.
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Adequate	"oral" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Inadequate	Strength should be based on the salt content per bottle (see page 2). Strength based on the salt is to be consistent with the approved products (for historical reason). Salt equivalence statement should be revised. See Assessment for container label.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Inadequate	Net content (174 g) is provided. However, (b) (4) should be replaced with "pellets".
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Inadequate	Established name, which is the title of the USP/NF monograph, should be used for each inactive ingredient.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	NDC 71770-200-10

Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	No comment
Bar code [21 CFR 201.25(c)(2)]	Adequate	Provided
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Inadequate	Replace (b) (4) (b) (4) with "Recommended Dosage: See Prescribing Information"
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Inadequate	Add "See accompanying patient instructions for use"
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Adequate	provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Inadequate	The street address should be included.
And others, if space is available	Inadequate	For clarity, minor edit for "After the first opening, Pheburane® should be used within 45 days".

Conclusion: Unsatisfactory

Items 1, 2, 3, 6, and 7 on page 14 for the recommended revisions for the container label are also applicable to carton label. In addition, the following revisions are recommended:

1. The title of a USP/NF monograph should be used as the established name for inactive ingredients. Please replace the list of inactive ingredients (b) (4) (b) (4)" with "ethylcellulose, hypromellose, polyethylene glycol 1500, povidone K25, and sugar spheres". Relocate the list of inactive ingredients following the salt equivalency statement.
2. Add a statement to the principal display panel "Pharmacist: Dispense the enclosed instructions for use with each prescription".

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

1. Replace the title from [redacted] with "PHEBURANE® (sodium phenylbutyrate) oral pellets". That is, "pellets" is the dosage form and the established name should be "sodium phenylbutyrate oral pellets".

b) Full Prescribing Information

Section 3: Dosage Forms and Strengths

2. The same dosage form terminology, i.e., oral pellets" as the product title in Highlights should be used. Strength should be expressed as the amount of salt per bottle. A description of the identifying characteristics of the dosage form should be included. That is, 84 g of sodium phenylbutyrate per bottle as white to off-white pellets.

Section 11: Description

3. The proprietary name and established name, i.e., Pheburane (sodium phenylbutyrate) oral pellets, should be provided. Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
4. Include an equivalence statement for active moiety content.
5. Include the pharmacological class, i.e., a nitrogen binding agent.
6. Include excipients in alphabetical order.

Section 16: How Supplied/Storage and Handling

7. Delete promotional language [redacted] and inactive ingredients.
8. The same dosage form terminology, i.e., oral pellets" as the product title in Highlights should be used.
9. The strength should be expressed as the amount of salt per bottle, i.e., 84 g of sodium phenylbutyrate per bottle. Include an equivalence statement for active moiety content.

B. Regarding the Container/Carton Labels

1. Address the following for container and carton labels:
   a. The dosage form should be "pellets", [redacted] Use parenthesis to enclose "sodium phenylbutyrate" for the established name. Revise the proprietary name, established name, and strength as following:

      Pheburane®
      (sodium phenylbutyrate) oral pellets
      84 g per bottle*

   b. On the side panel, add a statement "*Each bottle contains 84 g of sodium phenylbutyrate (equivalent to 74 g of phenylbutyrate) in 174 g of oral

pellets. Each gram of pellets contains 483 mg of sodium phenylbutyrate (equivalent to 423 mg of phenylbutyrate)."

c. Replace the statement [redacted] with "Recommended Dosage: See Prescribing Information".
d. Include the street address for the distributor.
e. Delete statements "[redacted]" and "[redacted]" from the principal display panel.

2. Address the following for container label:
   a. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual bottle as required per 21CFR 201.25(c)(2).
   b. Replace the statement "[redacted]" with "Date of first opening: ___/___/_____. Discard unused Pheburane 45 days after first opening of the bottle".
3. Address the following for carton label:
   a. The title of a USP/NF monograph should be used as the established name for inactive ingredients. Please replace the list of inactive ingredients [redacted] with "ethylcellulose, hypromellose, polyethylene glycol 1500, povidone K25, and sugar spheres". Relocate the list of inactive ingredients following the salt equivalency statement.
   b. Add a statement to the principal display panel "Pharmacist: Dispense the enclosed instructions for use with each prescription".

OVERALL ASSESSMENT:

Issues on dosage form, established name, strength, and missing information, including an active moiety equivalence statement, a pharmacological class, and bar code, are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Reviewer
ONDP/DNDP II
03/02/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Hong Cai, Ph.D.
Chief, Branch 4
ONDP/DNDP II
03/02/2022

Jane Chang

Digitally signed by Jane Chang
Date: 3/02/2022 11:22:18AM
GUID: 5034f819000053b21e2574590781f330

Hong Cai

Digitally signed by Hong Cai
Date: 3/02/2022 11:35:38AM
GUID: 55919d6500e16bdaad5825645e4f22ff

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

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

DATE: April 20, 2022

TO: Addendum of Assessment #1 of NDA 216513 Quality Assessment - Labeling

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II

THROUGH Hong Cai, Ph.D.
Chief, OPQ/ONDP/DNDP II/Branch 4

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 02-Mar-2022, made a recommendation of not ready for approval of this NDA because of labeling deficiencies (see NDA 216513 Labeling R01 Section 4.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0022, eCTD-0025, and eCTD-0028.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC labeling/label perspective.

Assessment Notes

Assessor Comment: Labeling deficiencies from Quality Assessment were identified in Assessment Cycle #1 dated 02-Mar-2022 (see NDA 216513 Labeling R01 Section 4.0). Subsequently, labeling amendments, as listed below, were submitted. These amendments are the subject of this addendum.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received	Information
eCTD-0022 (SDN-22)	03/11/2022	Container and carton labels
eCTD-0025 (SDN-25)	03/22/2022	Container and carton labels
eCTD-0028 (SDN-28)	04/13/2022	PI and PPI

1.0 PRESCRIBING INFORMATION

The information provided in eCTD-0028 dated 04/13/2022 is summarized below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Drug name [201.57(a)(2)]		
Established name[1]	Adequate	"sodium phenylbutyrate oral pellets" provided
Dosage form, route of administration	Adequate	"oral pellets" provided
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	Adequate	The year that FDA initially approves an NME should be listed. The drug substance was first approved in 1996 for NDA 20573.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage Forms and Strengths in metric system	Adequate	Dosage form terminology under this heading (i.e., oral pellets) should be identical to the dosage

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

		form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 13)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	The name of the salt is included. Strength is based on the salt to be consistent with the approved products (for historical reason). The amount of the salt in each bottle is used for strength.
Whether the drug product is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	N/A

Conclusion: Satisfactory

Information in HIGHLIGHTS section meets the regulatory requirements.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions	Adequate	Instruction for swallowing with a drink or solid food is included, including immediately taking the drug after sprinkling onto solid food.

needed to maintain the stability of the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Solid food, i.e., apple sauce or carrot puree, that can be taken with the drug is included.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	There is no USP monograph for the dosage form "oral pellets".

Assessment: ***Adequate***

Correct dosage form "pellets" is used. Food compatibility study supports sprinkling the drug product onto apple sauce or carrot puree for administration (see NDA 216513 Drug Product R01). However, the statement regarding (b) (4) (b) (4) (b) (4)" appears to be promotional, which should be addressed by OND.

From OPQ perspective, the information in Administration Instructions is acceptable.

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Available dosage forms	Adequate	Dosage form terminology in this section (i.e., oral pellets) should be identical to the dosage form terminology in the product title in HL (see Labeling Review Tool, page 26).
Strengths in metric system.	Adequate	Metric system is used for strength. Strength is based on the amount of salt per bottle.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Adequate	Strength is based on the salt to be consistent with the approved products (for historical reason). The name of the salt is included for clarity.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, and color and	Adequate	Color and the physical form (pellets) of the product are included.

clarity of the solution, when applicable.		

Conclusion: **Satisfactory**

Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.3 Section 11: DESCRIPTION

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	Adequate	"Pheburane (sodium phenylbutyrate) oral pellets" provided. Per 201.10(g)(1), the established name shall accompany the proprietary name. The established name shall be used at least once in the running text in association with such proprietary name or designation.
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	Adequate	Dosage form terminology under this heading (i.e., oral pellets) should be identical to the dosage form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 48)
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)*	Adequate	Strength is based on the salt to be consistent with the approved products (for historical reason). Equivalence statement should be included for clarity.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)]	Adequate	The established names of inactive ingredients are provided in alphabetical order.

[quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any) in alphabetical order]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).		
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Adequate	The pharmacological class for phenylbutyric acid as a nitrogen binding agent is listed in Established Pharmacologic Class (EPC) terms in eLIST.
Chemical name, structural formula, molecular weight [21 CFR 201.57(c)(12)(i)(F)]	Adequate	No comment
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	There is no USP monograph for the dosage form "oral pellets".

Conclusion: **Satisfactory**

Information in DESCRIPTION meets the regulatory requirements.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Dosage form	Adequate	Dosage form terminology (i.e., oral pellets) under this heading should be identical to the dosage form terminology in the product title in HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) (see Labeling Review Tool, page 59)
Strength(s) in metric system. If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety.	Adequate	Strength, which is based on the amount of salt per bottle, in metric system is provided. Strength is based on the salt to be consistent with the approved products (for historical reason).
Available units (e.g., bottles of 100 tablets)	Adequate	'(b) (4) (b) (4)' provided.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable, NDC number. Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Adequate	"white to off-white (b) (4) pellets" provided
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with	N/A	N/A

x numerical citation to "OSHA Hazardous Drugs."		
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	Adequate	The desiccant is in the cap and not mixed with the pellets.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Acceptable storage condition is provided. The in-use period of the open bottle is also provided.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
Include information about child-resistant packaging (if manufacturer choose to include)	Adequate	The primary packaging is with a child resistant HDPE bottle.

Conclusion: Satisfactory

A written verification that the child-resistant packaging (CRP) meets the standards of U.S. Consumer Product Safety Commission (CPSC) under 16 CFR 1700 is provided in 3.2.P.7 (see also NDA 216513 DP R01 dated 3/25/2022). Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information in Proposed Labeling	Assessor's Comments
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	Adequate	No comment

Conclusion: Satisfactory

The information in Section 17 meets the regulatory expectation.

2.0 PATIENT LABELING (MEDICATION GUIDE)

The information provided in eCTD-0028 dated 04/13/2022 is summarized below.

(b) (4)

Conclusion: Satisfactory

The information meets the regulatory expectation.

3.0 CARTON AND CONTAINER LABELS

3.1 CONTAINER LABEL

Container label provided in eCTD-0022 (SDN-22) is shown below.

(b) (4)

Assessment: ***Inadequate***

The container issues identified in NDA 216513 Labeling R01 Section 4.0 have been addressed except for the dosage form. The applicant continued using "granules" as the dosage form because Pheburane is currently approved/marketed with the 'granules' nomenclature in many countries, including Canada and Europe. The response is unacceptable. See NDA 216513 Labeling R01 on determination of dosage form.

The following comment was conveyed to the applicant on 3/16/2022:

1. We acknowledge that you would like to use "granules" as the dosage form for Pheburane since it is currently approved/marketed with the 'granules' nomenclature in many countries, including Canada and Europe. However, approval of US drugs must follow US regulations, including the dosage form. The dosage form of Pheburane is "pellets" based on the following:
   a. Per USP <1151> definitions of granules and pellets:
      i. Granules are solid dosage forms that are composed of agglomerations of smaller particles.
      ii. Pellets are small solid dosage forms. They can have a spherical or nearly spherical shape, although such a shape is not required. Spherical pellets are sometimes referred to as beads. Pellets may be designed with the drug substance dispersed in a matrix or the pellets may be coated with an appropriate polymer.
   b. Pheburane drug product is manufactured by (b) (4)

(b) (4)

Replace (b) (4) with "pellets" for container and carton labels.

In SDN-25, updated container label was provided, as shown below.

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"Pheburane (sodium phenylbutyrate) oral pellets" provided
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	Adequate	"oral" provided
Strength(s) in metric system	Adequate	Strengths, 84 g per bottle, provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Adequate	Strength should be based on the salt content per bottle to be consistent with the approved products (for historical reason). Salt equivalence statement is provided.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Net content (174 g of oral pellets) is provided.
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii),	N/A	Not required for oral drugs

21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]		
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	NDC: 71770-200-10
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Adequate	"Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" provided
Bar code [21CFR 201.25(c)(2)]*	Adequate	Provided
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	"Recommended Dosage: See Prescribing Information" provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"Distributed by: Medunik USA, Inc. 919 Conestoga Road Bryn Mawr, PA 19010" provided
And others, if space is available	Adequate	"Date of first opening: _____/_____/_____. Discard unused Phenburane 45 days after first opening the bottle" provided

Conclusion: Satisfactory

The information for container label meets the regulatory expectations.

3.2 CARTON LABEL

Carton label provided in eCTD-0022 (SDN-22) is shown below.

(b) (4)

[redacted]

Assessment: ***Inadequate***

The carton issues identified in NDA 216513 Labeling R01 Section 4.0 have been addressed except for the dosage form. See page 10.

In SDN-25, updated carton label was provided, as shown below.

(b) (4)

Items	Information in Proposed Labeling	Assessor's Comments
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Adequate	"Pheburane (sodium phenylbutyrate) oral pellets" provided
Strength(s) in metric system	Adequate	Strengths, 84 g per bottle, provided
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	Adequate	"oral" provided
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Adequate	Strength should be based on the salt content per bottle to be consistent with the approved products (for historical reason). Salt equivalence statement is provided.

Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	Adequate	Net content (174 g of oral pellets) is provided.
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Adequate	"ethylcellulose, hypromellose, polyethylene glycol 1500, povidone K25, and sugar spheres" provided in alphabetical order. Titles of the USP monographs are used as the established names.
"Rx only" displayed on principal display [21 CFR 201.100(b)(1)]	Adequate	Provided
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	Adequate	NDC 71770-200-10
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Adequate	Space allocated
Storage conditions.	Adequate	"Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature]" provided.
Bar code [21 CFR 201.25(c)(2)]	Adequate	Provided
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Adequate	"Recommended Dosage: See Prescribing Information" and "Use only the enclosed measuring spoon designed for use with this product" provided
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	"Pharmacist: Dispense the enclosed instructions for use with each prescription" provided
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Adequate	provided
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Adequate	"Distributed by: Medunik USA, Inc. 919 Conestoga Road Bryn Mawr, PA 19010" provided
And others, if space is available	Adequate	"After the first opening, Pheburane® should be used within 45 days" provided

Conclusion: Satisfactory

The information for carton label meets the regulatory expectations.

Jane Chang

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Hong Cai

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