CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215025Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Clinical Review and Evaluation

Application Type	Original NDA 505(b)(2)
Application Number(s)	215025
Priority or Standard	Standard
Submission Date	8/21/2020
Received Date	8/21/2020
PDUFA Goal Date	6/21/2021
Division/Office	Division of Rare Diseases and Medical Genetics (DRDMG)/Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (ORPURM)
Review Completion Date	6/9/2021
Established/Proper Name	Sodium Phenylacetate and Sodium Benzoate, 10%/10%
Trade Name	N/A
Pharmacologic Class	Nitrogen binding agent
Applicant	MAIA Pharmaceuticals, Inc.
Dosage form	Solution for Injection
Applicant proposed Dosing Regimen	Sodium Phenylacetate and Sodium Benzoate Injection must be diluted with sterile 10% Dextrose Injection (D10W) before administration. Sodium Phenylacetate and Sodium Benzoate Injection should be administered as a loading dose infusion over 90 to 120 minutes, followed by the same dose repeated as a maintenance infusion administered over 24 hours. The loading dose and maintenance dose for Sodium Phenylacetate and Sodium Benzoate are both 250 mg/kg for patients 0 to 20 kg and 5.5 g/m^2 for patients > 20 kg
Applicant Proposed Indication	Adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle
Applicant Proposed SNOMED CT Indication	36444000 | Disorder of the urea cycle metabolism (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication	Adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle
Recommended SNOMED CT Indication Disease	36444000 | Disorder of the urea cycle metabolism (disorder)
Recommended Dosing Regimen	Same as proposed

Table of Contents

Reviewers of Clinical Review and Evaluation

Clinical Reviewer	Christine Yuen-Yi Hon, Pharm.D.
Clinical Team Leader	Anita Zaidi, M.D.
Deputy Division Director	Patroula Smpokou, M.D.

Additional Reviewers of NDA Application (see separate reviews in DARRTS)

Nonclinical Reviewer	Jonathan Cohen, Ph.D.
Nonclinical Team Leader	Bayo Laniyonu, Ph.D.
OPQ	Gaetan Ladouceur/Donna Christner
Drug Substance	Zhengfang Ge/Wendy Wilson
Drug Product	Yan Xu/Joanne Wang
Process/Facilities	BreOnna DeLaine-Elias/Neal Sweeney
Microbiology	Zhengfang Ge/Wendy Wilson
Biopharm	Bryan Ericksen/Vidula Kolhatkar
DPMH	Christos Mastroyannis/Tamara Johnson
OND Policy	Julieann Dubeau

OPQ=Office of Pharmaceutical Quality
DPMH=Division of Pediatrics and Mental Health

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
eCTD	electronic common technical document
FDA	Food and Drug Administration
IND	Investigational New Drug
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Experience Report
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10%, [2g/20 mL; 2g/20 mL], is a sterile, concentrated, clear and almost colorless aqueous solution of sodium phenylacetate and sodium benzoate that is being developed under the 505(b)(2) pathway. It has the same active ingredient as the listed drug Ammonul (sodium phenylacetate and sodium benzoate) Injection.The reference listed drug (LD) is commercially available Ammonul (sodium phenylacetate and sodium benzoate) Injection, 10%/10% in a 50-mL single dose vial [5g/50 mL; 5g/50 mL] (NDA# 020645, Bausch Health US, LLC).

The Applicant currently markets a generic Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10% [5g/50mL; 5g/50 mL] in a 50 mL fill volume, under its approved ANDA 208521. However, the proposed drug product of Sodium Phenylacetate and Sodium Benzoate Injection is a different strength [2g/20 mL; 2g/20 mL] with a different fill volume [20 mL in a 20 mL vial].

1.2. Conclusions on the Substantial Evidence of Effectiveness

This 505b2 NDA relies upon the Agency's findings of safety and effectiveness for the listed drug, Ammonul, which is considered to be bioequivalent to the proposed product. Substantial evidence of effectiveness has previously been established for Ammonul for the treatment of hyperammonemia in patients with urea cycle disorders. The proposed product in this NDA is found to be chemically equivalent to Ammonul and a waiver of clinical studies was granted by the OPQ review team.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Urea cycle disorders (UCD) are a group of genetic conditions characterized by deficiencies of the enzymes and transporters involved in the urea cycle. The severity of the defect results in the rapid accumulation of ammonia. Infants with UCD appear normal at birth but rapidly develop cerebral edema and related symptoms. Acute symptoms from hyperammonemia progress from somnolence to lethargy and coma. A significant portion of neonates with severe hyperammonemia have seizures, which may be subclinical and nonconvulsive. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes a respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem.

Sodium phenylacetate and sodium benzoate are nitrogen scavenging products that are used in combination (as an intravenous infusion) or each as monotherapy (as oral agents) to trap nitrogen into urine-excretable forms. Sodium benzoate combines with glycine to make hippurate, and sodium phenylacetate combines with glutamine to make phenacetyglutamine, which are excreted in the urine, thus, enabling ammonia detoxification.

The listed drug (LD), Ammonul (sodium phenylacetate and sodium benzoate) Injection, 10%/10% (5g/50mL; 5g/50mL) (NDA 020645) was initially approved by the FDA in 2005 as an adjunctive therapy in the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle. The applicant submitted a 505(b)(2) application for a new product formulation (new strength and fill volume) of Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/20mL;2g/20mL). No new efficacy or safety studies were submitted as the applicant referenced the LD. Assessment of safety information from Ammonul PADER for the reporting period from 17 February 2019 to 16 February 2021 and published literature from the current submission did not identify any new safety information that warrants labeling changes.

No bridging of formulations or BA/BE studies are necessary and the Applicant was granted a biowaiver by the OPQ review team. The Applicant provided a side-by-side comparison of formulations including pH and osmolality data to compare the proposed product with the LD, Ammonul. These data are adequate according to the OPQ review team and a biowaiver was granted per 21 CFR 320.24(b)(6). A bioequivalence study is not needed. Overall, the OPQ review team's assessment is that the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/20mL;2g/20mL).

The benefit-risk determination for sodium phenylacetate and sodium benzoate as an adjunctive therapy in the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle remains unchanged with the submission of this NDA and remains favorable to allow for approval. The applicant referenced the LD for efficacy and safety and bioequivalence was demonstrated based on chemistry considerations (no clinical bioequivalence study is warranted). No new safety concerns were identified in this review. Therefore, an approval action is recommended.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

□	The patient experience data that were submitted as part of the application include:	N/A
X	Patient experience data were not submitted in this application	

2 Therapeutic Context

2.1. Analysis of Condition

Urea cycle disorders (UCD) are a group of genetic conditions characterized by deficiencies of the enzymes and transporters involved in the urea cycle. These include deficiencies of the enzymes carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS1), argininosuccinate lyase (ASL), and arginase (ARG1); the cofactor producer N-acetylglutamate synthse (NAGS); and the acid transporters ornithine translocase (ORNT1) and citrin. The incidence of UCDs is estimated to be 1:35,000 births in the United States.[1]

Severity of the urea cycle defect is influenced by the position of the defective protein in the pathway and the severity of the enzymatic deficiency. Severe deficiency or total absence of activity of CPS1, OTC, ASS1, ASL, or NAGS results in the rapid accumulation of ammonia during the first few days of life.[2] Infants with an early-onset, severe UCD appear normal at birth but rapidly develop life-threatening hyperammonemia which causes cerebral edema and resultant neurologic symptoms: vomiting, seizures, somnolence/lethargy, coma. Abnormal posturing and encephalopathy are often related to the degree of central nervous system (CNS) swelling and pressure on the brain stem. A significant portion of neonates with severe hyperammonemia have seizures, which may be subclinical and nonconvulsive. Hyperventilation, secondary to cerebral edema, is a common early finding in a hyperammonemic attack, which causes a respiratory alkalosis. Hypoventilation and respiratory arrest follow as pressure increases on the brain stem. Defects in the enzyme arginase cause hyperargininemia with neonatal hyperammonemia reported infrequently. Defects in ORNT1 and citrin may both cause hyperammonemia.[2]

Historically the outcome of newborns with hyperammonemia was considered poor due to late diagnosis and inadequate treatment options; acute hyperammonemia from severe UCDs can progress to coma and death without treatment.[3] With rapid identification of newborns with these conditions through newborn metabolic screening and current treatment strategies, survival of neonates with hyperammonemia due to a UCD has improved dramatically in the last few decades.

2.2. Analysis of Current Treatment Options

Current emergency management of patients with hyperammonemia includes the removal of excess ammonia by dialysis or hemofiltration, reversal of the catabolic state through caloric supplementation and dietary optimization, and pharmacologic scavenging of excess nitrogen though the use ammonia scavenger medications.[2,4] Sodium phenylacetate and sodium benzoate are each nitrogen scavengers that are used in combination (and separately as monotherapy) to trap nitrogen in excretable forms. Sodium benzoate combines with glycine to make hippurate, and sodium phenylacetate combines with glutamine to make

phenacetyglutamine, which are excreted in the urine and, thus, facilitate nitrogen excretion and ammonia removal.[4,5]

Ammonul (sodium phenylacetate and sodium benzoate) Injection, 10%/10% (NDA 020645) was initially approved by the FDA in 2005 as an adjunctive therapy in the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle. Ammonul is available in 50-mL single-dose vials. In 2016, two generic sodium phenylacetate and sodium benzoate 10%/10% products (ANDAs 205880 and 207096) were subsequently approved under 505(j) of the Federal Food, Drug, and Cosmetic (FD&C) Act. A third generic product (ANDA 208521), which is from the current Applicant MAIA Pharmaceuticals Inc., was approved under 505(j) FD&C Act in 2017. All three generic products are available in 50-mL single-dose vials.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant currently markets a generic Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10% [5g/50mL; 5g/50 mL] in a 50 mL fill volume under ANDA 208521, which was approved under 505(j) of the FD&C Act in 2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

On May 26, 2020, a Type B pre-NDA meeting was held between the Agency and the Applicant to discuss the proposed regulatory pathway and the adequacy of the proposed 505b2 NDA. Because the proposed strength (total amount of drug substances) and fill volume are different than the listed drug (Ammonul), an ANDA application under section 505(j) is not appropriate, and because FDA has not approved a pending suitability petition allowing the submission of an ANDA for a product with the proposed differences, the Agency agreed that the 505(b)(2) NDA regulatory pathway is the appropriate pathway for submission and review of this product.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable since no clinical data were submitted for review.

4.2. Product Quality (see separate review by OPQ for details)

Sodium phenylacetate and Sodium benzoate are the drug substances in Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/ 20mL; 2g/ 20mL). The following content constitutes the final assessments of this NDA by the OPQ (biopharmaceutics) review team.

The detailed CMC information including physicochemical properties, manufacturing process, characterization, specification, Certificate of Analysis, container closure system and stability of both drug substances is provided in the DMFs from their manufacturers. The letters of authorization were provided. The CMC information provided in the NDA and DMFs was reviewed and deemed by the OPQ review team to be adequate for NDA review. A (b) (4)-month retest period for Sodium phenylacetate and Sodium benzoate is supported by their stability study results.

The Applicant provided a side-by-side comparison of formulations and pH and osmolality data to compare the proposed product with the listed drug, Ammonul. A waiver from the requirements for submitting evidence of in vivo bioavailability or bioequivalence is granted under 21 CFR 320.22(b)(1) because the Applicant's formulation contains the same active ingredients (sodium phenylacetate and sodium benzoate) at the same concentrations (100mg/mL and 100mg/mL) and the same inactive ingredients at the same concentrations as the listed drug. No bridging of formulations is necessary.

Overall, the OPQ review team (biopharmaceutics) has determined that the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Sodium phenylacetate and Sodium benzoate Injection, 10%/10% (2g/20mL;2g/20mL).

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

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

The label/labeling is satisfactory from the CMC perspective.

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

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

Not applicable. No nonclinical information was submitted for review. As a 505(b)(2) application, the applicant is relying the Agency's previous findings of safety and effectiveness for the listed drug, Ammonul, including all pertinent nonclinical information. See Jonathan Cohen's filing review in DAARTS dated 10/20/20 for more details.

6 Clinical Pharmacology

No BA/BE studies were submitted by the applicant and this is considered acceptable as a waiver of in vivo clinical studies was granted according to 21 CFR 320.24(b)(6). See CMC section above and separate CMC review for more details.

7 Sources of Clinical Data and Review Strategy

7.1. Review Strategy

This application is a 505(b)(2) NDA and relies on FDA's findings of the efficacy and safety of the listed drug (LD), Ammonul, which was demonstrated by the Applicant to be chemically equivalent to the proposed product (and a waiver of BA/BE studies was granted). Since clinical studies were not needed, efficacy or safety trials or BA/BE trials have not been submitted for review which is acceptable. The Applicant provided additional safety review of published literature for sodium phenylacetate and sodium benzoate from 10/1/2019 (revision date of Ammonul labeling submitted to the NDA) to 12/4/2020 (120-day safety update). The current review focuses on the safety evaluation of these published articles to identify if there are additional safety data that could be useful to inform product labeling.The review also includes post marketing safety from recent Ammonul Periodic Adverse Drug Experience Reports (PADERs) dated 14 April 2020 and April 14 2021 for the reporting periods between 17 February 2019 and 16 February 2021. Those reports are summarized below.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

No efficacy studies were submitted for review and this is acceptable

8.2. Review of Safety

Assessment of safety information from the Ammonul PADERs for the reporting periods between 17 February 2019 and 16 February 2021 and published literature submitted in this NDA did not identify any new safety information that warrants labeling upates to the safety sections.

Published Literature

Evaluation of the recent published literature for sodium phenylacetate and sodium benzoate safety information did not identify any new safety signals.

Using various keywords related to safety of drug products, the Applicant performed Embase keyword searches for the period between 10/1/2019 to 12/4/2020 and identified 1,917 literature reports. Titles and abstracts of these reports were reviewed, and a total of 9 articles were obtained for detailed review and submitted to the NDA.

The reviewer performed assessment of these 9 articles and found relevant safety information in 3 of them; two were case reports and one was a clinical trial report. The two case reports describe the use of intravenous (IV) sodium phenylacetate and sodium benzoate as ammonia scavenger in reducing ammonia levels in two infants with UCDs, one with citrullinemia Type 1[6] and the other with CPS1 (carbamoyl phosphate synthase) deficiency.[7] No new safety signals were identified in these two patients. The infant with CPS1 deficiency died from persistently elevated ammonia levels. The clinical trial report describes the efficacy and safety results of oral sodium benzoate (different drug) in the management of hyperammonemia in children with decompensated chronic liver disease.[8] Because oral sodium benzoate is a different drug (and given via a different route) from IV sodium phenylacetate and sodium benzoate and the oral bioavailability of sodium benzoate is not known, adverse events observed in the clinical trial using sodium benzoate are not directly relevant or applicable to this NDA.

PADERs from the Listed Drug, Ammonul

In the Ammonul PADERs dated 14 April 2020 and 14 April 2021 for the reporting periods between 17 February 2019 and 16 February 2021, three serious and unlabeled adverse events (AEs) were reported; two of the AEs were fatal. No change in the product labeling resulted from these PADERs.

Case 1 (PADER dated 14 April 2020):
A 34-year-old male patient with acute myeloid leukemia (AML) type 1 received Ammonul at a dose of 11 g daily for hyperammonemic coma in the context of induction chemotherapy for AML on 11 (b) (6). The patient experienced refractory hyperammonemia and progression of his leukemia and subsequently died on (b) (6). An autopsy was not performed. The patient received multiple concomitant medications including sodium phenylbutyrate, N-carbamyl glutamate, carnitine, L-arginine, vancomycin, ceftazidime, voriconazole, cisatracurium, midazolam, morphine, noradrenaline, hemisuccinate, hydrocortisone, fludrocortisone, non-fractionated heparin, and intra lipid. The AEs of hyperammonemia and leukemia were considered serious, and no causality assessment was reported.

The role of Ammonul in this patient's death is unknown but it is unlikely that the AEs were directly related to Ammonul use. The patient's underlying severe conditions (AML, suspected infection, hyperammonemic coma) and multiple concomitant medications administered are all contributing factors to this fatal event. The review team does not believe that labeling changes are warranted based on this AE.

Case 2 (PADER dated 14 April 2021):
A fatal event was reported in a case with very limited information. No further clinical analysis was provided in the periodic report.

Case 3 (PADER dated 14 April 2021):
A 3-year-old female, diagnosed with citrullinemia type I, was treated with sodium phenylacetate and sodium benzoate 10%/10% injection and arginine on (b) (6); the patient experienced convulsions and was put back on hemodialysis on the same day (details not submitted). An unknown formulation of sodium phenylbutyrate was started on an unknown date and for an unknown indication. The dose, frequency, and route for all three medications were not known. The initial suspect for convulsions was an overdose of arginine, but an overdose of phenylbutyrate was suspected at the time of the report. It is not known what actions were taken in response to the AEs. The outcome of the hemodialysis, remaining events, and final therapy were not known. The AEs of hemodialysis, seizure, and overdose were assessed as serious, but causality assessment was not reported.

The contribution of Ammonul to the AEs of hemodialysis and seizures cannot be determined due to the missing information. The contributory role of concurrent medications including phenylbutyrate and arginine and the patient's underlying condition cannot be ruled out. Based on the patient's clinical presentation, serious medical condition, and concomitant medications and interventions (hemodialysis), it is difficult to make an assessment of causality in this case but it is unlikely that Ammonul was directly responsible for these AEs although it could have contributed. Convulsion is a known adverse reaction associated with the use of Ammonul and is already included in the product labeling. No labeling changes are proposed.

9 Advisory Committee Meeting and Other External Consultations

This application was not referred to an FDA Advisory Committee as no controversial issues that would benefit from an advisory committee discussion were identified.

10 Pediatrics

No pediatric studies were conducted as part of this NDA. The product is currently approved for pediatric patients including patients in the early neonatal period.

11 Prescription Drug Labeling

See agreed-upon final labeling

12 Risk Evaluation and Mitigation Strategies (REMS)

None warranted

13 Postmarketing Requirements and Commitments

None warranted.

14 Deputy Division Director (DRDMG) Comments

I concur with the review team's recommendation for an approval action of this 505b2 NDA which relies on the Agency's findings of safety and effectiveness of the listed drug, Ammonul. The Applicant has demonstrated that the proposed product is chemically equivalent to the listed drug, Ammonul, and the OPQ review team has determined that a (bio)waiver of BA/BE studies is appropriate. Based on the OPQ determination that the two products are chemically equivalent, no clinical studies are needed for approval. No new/unexpected/serious safety signals were identified through post-marketing safety surveillance for Ammonul (the listed drug) that warrant an update to the relevant sections of the label. The benefit-risk determination for Ammonul (the listed drug) for the proposed (and previously approved) indication remains favorable and supports approval. The label is final and has been agreed upon with the Applicant.

15 Appendices

15.1. References

1. Summer ML, Koelker S, Freedenberg D et al. The incidence of urea cycle disorders. *Mol Genet Metab* 2013;110:179-80.
2. Urea cycle disorders overview. GeneReviews®. Accessed January 29, 2021. https://www.ncbi.nlm.nih.gov/books/NBK1217/
3. Urea cycle disorders. StatPearls. Accessed April 2, 2021. https://www.ncbi.nlm.nih.gov/books/NBK482363/
4. Summar ML and Mew NA. Inborn errors of metabolism with hyperammonemia. Urea cycle defects and related disorders. *Pediatr Clin N Am* 2018;65:231-46.
5. Häberle J, Boddaert N, Burlina A et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis* 2012;7:32.
6. Nguyen JM, Kaushal S, Glinton KE et al. A somnolent neonate with hypothermia and posturing. *Clin Pediatr* 2020;59:841-3.
7. Fong NWY and Jamuar SS. Novel compound heterozygous pathogenic variants in the *CPS1* gene in a newborn with Carbamoyl Phosphate Synthetase 1 Deficiency. Abstracts from the 51st European Society of Human Genetics Conference: Electronic Posters. *Eur J Human Genet* 2019;27:931.
8. Snehavardhan P, Lal BB, Sood V et al. Efficacy and safety of sodium benzoate in the management of hyperammonemia in decompensated chronic liver disease of the childhood – a double-blind randomized controlled trial. *JPGN* 2020;70:165-70.

15.2. Financial Disclosure

Not applicable as no clinical studies were submitted in this NDA.

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/

CHRISTINE Y HON
06/09/2021 01:02:58 PM

ANITA A ZAIDI
06/10/2021 09:09:43 AM

PATROULA I SMPOKOU
06/10/2021 09:58:43 AM