PHEBURANE® WRITTEN TESTIMONY

Urea Cycle Disorders (UCD) are inherited deficiencies in enzymes of the urea cycle, the process that clears the blood from toxic ammonia resulting from protein metabolism. Hyperammonemia, increased plasma level of ammonia, is the main life-threatening manifestation of the deficient urea cycle seen in all UCD patients who are not under metabolic control. Ammonia is toxic to neurons and other brain cells, and severe, prolonged and/or repeated episodes of hyperammonemic coma can lead to brain damage, impairment of intellectual function and ultimately death.

Sodium phenylbutyrate (NaBP), a nitrogen scavenger drug established decades ago as the gold standard adjunctive therapy to the standard of care, which includes dietary management, has changed the prognosis of this condition by saving patients' lives and drastically improving their outcomes.

Sodium phenylbutyrate non-coated formulation had been used since 1987 under an Investigational New Drug (IND) and was approved for marketing as Buphenyl® in the United States in 1996. However, bad taste or taste aversion are amongst the most frequent adverse events (AE) reported with commercial non-coated formulations of NaPB. The non-coated formulations of NaPB are extremely bitter and may cause taste disturbance (ageusia) and vomiting at intake. The intolerable taste makes their chronic use very difficult to the extent that compliance to the treatment can be jeopardized and, thus, trigger serious and life-threatening hyperammonemia crisis especially in children.

Since commercial non-coated formulations of NaPB granules have an offensive taste, an improved palatable tasteless pellet formulation of sodium phenylbutyrate Pheburane® was developed (see Figure 1) to improve adherence and patient outcomes, whereby coating of individual pellets results in a formulation which has no immediate taste (i.e. when swallowing the drug). Pheburane® dissolution in mouth allows for a lag time of 10 seconds before a slow progressive release of 60% of the drug over 8 minutes, compared to the non-coated formulations of NaPB where the drug is completely released within less than 60 seconds. This product was approved for marketing in the EU under the same brand name in July 2013, in Canada in January 2015 and in several other countries.

Figure 1

Data from a French Compassionate Program, also known as ''Autorisation Temporaire d'Utilisation de cohorte'' (ATUc) demonstrated that in comparison with the non-coated formulation used before entering the cohort, Pheburane® improved acceptability (greater acceptability score: see Figure 3) and ease of administration (swallowed without any reconstitution), and resulted in no vomiting in patients who had previously reported vomiting with the non-coated NaPB. Pheburane® also improved control of ammonia plasma levels with no hyperammonemia crisis for up to 30 months of treatment, even in patients who had previously experienced hyperammonemic episodes on the non-coated NaPB formulation (see Figure 2).

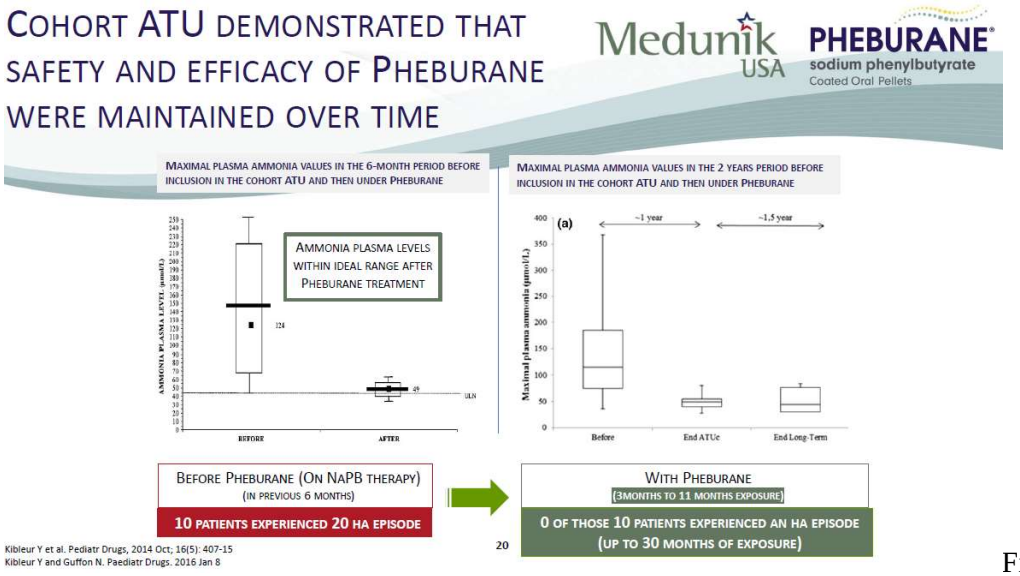

Figure 2

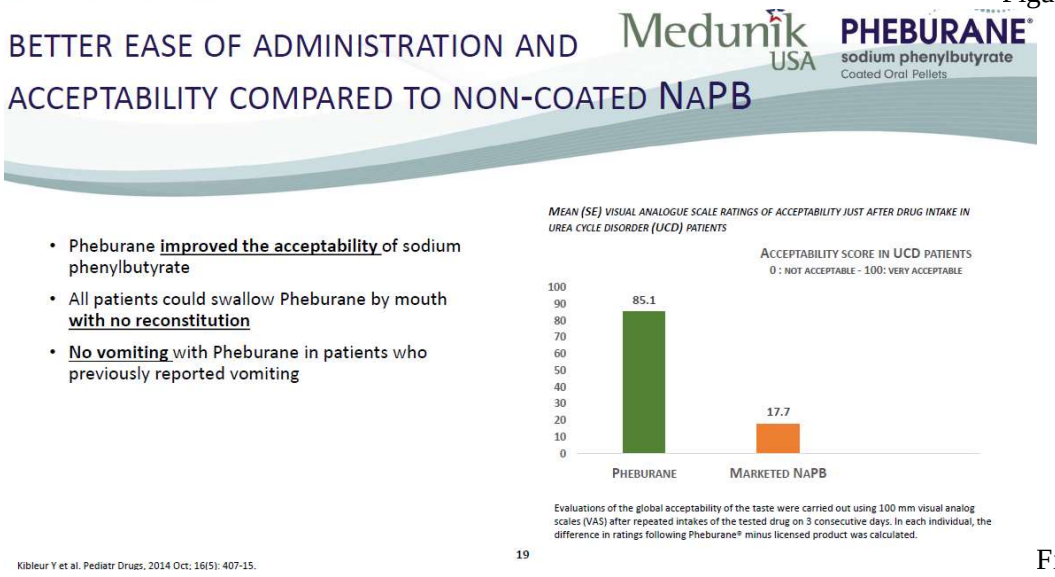

Figure 3

Medunik dedicated to improving the management of orphan diseases, offers Pheburane® the first palatable FDA approved sodium phenylbutyrate for UCD patients in order to help them to improve their compliance thus their outcomes. Therefore, we respectfully request to include Pheburane® as preferred in your products list agreement (PLA)

AMGEN Written Testimony

- Urea Cycle Disorders (UCDs) are devastating, inherited diseases that interrupt the removal of excess nitrogen from the body and exhibit a broad spectrum of serious clinical manifestations ranging from impaired cognition to permanent brain damage, coma, and death. In healthy individuals, protein is metabolized to amino acids and subsequently ammonia – a neurotoxin – which is then converted to urea and excreted in the urine. However, those living with UCDs are not able to convert ammonia to urea and they require individualized treatment plans including protein restriction and medication called nitrogen scavengers that remove ammonia. [1]

- Chronic compliance and adherence are critical components of better UCD patient outcomes. RAVICTI has demonstrated ammonia control over a chronic period of years in adults, pediatric patients, toddlers, infants, and newborns. In addition, data on RAVICTI demonstrate a significant reduction in hyperammonemic crises, significant decreases in clinical manifestations (when compared to sodium phenylbutyrate), significantly improved brain executive function, and improved growth and development. Data concerning some these UCD management objectives does not exist for any other nitrogen scavenger. [2]

- As a rare disease impacting 1 in 35,000 lives births in the U.S., families often spend years trying to get a proper diagnosis. Hospitals don't often check for ammonia because clinical manifestations are not associated with hyperammonemia by the attending physician, leading to misdiagnosis and prolonged time to treatment. [3]

- Many patients are children under the age of 18, in the formative years of their life, where having a well-controlled disease is essential to growth and development. Patients and families often live in fear of a single hyperammonemic crisis, which can result in hospitalization, permanent brain damage, or death. Even mildly elevated ammonia for a prolonged period may result in devastating impacts. [3,4]

- The robust clinical RAVICTI trial programs, championed by the patient community, were designed to address the issues of compliance and adherence. RAVICTI is nearly odorless and nearly tasteless with no time limitation placed on ingestion of the medication, whereas the taste-masked versions of sodium phenylbutyrate have a very limited time frame during which the taste is actually masked. In addition, RAVICTI can be administered via a G-tube while the taste-masked versions cannot. [5, 6, 7, 8, 9]

- Moreover, RAVICTI is approved for all subtypes of UCDs expect for NAGS. Taste-masked versions are only approved for three UCD subtypes. [7]

- Taste-masked sodium phenylbutyrate products were approved via bioequivalence studies (505(b)(2); there are no monotherapy (a single nitrogen scavenger) studies for any sodium phenylbutyrate product regarding chronic ammonia control. [8, 9, 10, 11]

- Due to the grave risks involved with switching stable UCD patients to a new therapy, we ask that the board strongly consider allowing any existing, stable RAVICTI patients to maintain access to their current therapy

1) Urea Cycle Disorders Overview. Nicholas Ah Mew, et al. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. 2003 Apr 29 [updated 2017 Jun 22].

2) Long-term safety and efficacy of glycerol phenylbutyrate for the management of urea cycle disorder patients. George A Diaz, et al. Mol Genet Metab. 2019 Aug; 127(4): 336-345.

3) Perspectives on urea cycle disorder management: Results of a clinician survey. Gregory M Enns, et al. Mol Genet Metab. 2019 Sep-Oct; 128(1-2): 102-108.

4) Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. Brendan Lee, et al. Genet Med. 2015 Jul;17(7): 561-568.

5) Glycerol phenylbutyrate for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle. Nicola Longo and Robert J Holt. Expert Opinion on Orphan Drugs. 2017 Vol. 5: 12, 999 – 1010.

6) Rare disease clinical research network's urea cycle consortium delivers a successful clinical trial to improve alternate pathway therapy. Pramod K Mistry. Hepatology. 2013 Jun;57(6): 2100-2.

7) RAVICTI (glycerol phenylbutyrate) Prescribing Information

8) Olpruva (sodium phenylbutyrate) Prescribing Information

9) Pheburane (sodium phenylbutyrate) Prescribing Information

10) Acer Therapeutics and Relief Therapeutics Announce U.S. FDA Approval of OLPRUVA™for Patients with Urea Cycle Disorders - Acer Therapeutics (acertx.com)

11) US Food and Drug Administration. NDA approval for Pheburane (sodium phenylbutyrate) oral pellets. August 13, 2021. Accessed October 25, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/216513Orig1s000ltr.pdf.

Recordati Rare Diseases, Inc. ("RRD") submits this request to **Oregon Medicaid**, in support of patients with rare urea cycle disorders (UCDs). As detailed below, the **availability of ammonia lowering medication is essential to patients who suffer from UCDs**. RRD is seeking Carbaglu®(carglumic acid) tablets for oral suspension 200mg, **to be in parity with** generic carglumic acid for (i) adjunctive treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA), (ii) adjunctive treatment of acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency, and (iii) maintenance treatment of chronic hyperammonemia due to NAGS deficiency. RRD makes this request for Carbaglu® **to be in parity with** generic carglumic acid, since it is currently approved for use in the three noted indications[1], while the generic carglumic acid is only approved for individuals with NAGS deficiency[2].

Hyperammonemia is a medical emergency AND therapies need to be started as soon as possible. Individuals with NAGS deficiency, PA and MMA do not break down nitrogen correctly resulting in toxic ammonia accumulation. The incidence of NAGS deficiency is <1:2,000,000, for PA it is 1: 100,000, and MMA is 1: 50,000 (Ah Mew, et al., 2017 Chapman, et al., 2018)[3,4]. According to www.babysfirsttest.org's website,[5] **Oregon** has newborn screening for PA and MMA but not NAGS Deficiency. Therefore, checking the ammonia level of newborns is one of the key ways to identify these rare genetic conditions.

To put this into perspective, we are aware of less than 25 individuals with NAGS deficiency in the US. NAGS deficiency is typically identified in decompensating neonates that require hospitalization and immediate implementation of a complex management strategy. The guidelines for diagnosis and management of UCDs by Haberle in 2012 are still in effect and provide that Carbaglu® is recommended as first-line for the treatment of NAGS deficiency. Haberle also pointed out that there is potential toxicity of repeated boluses of sodium benzoate or phenylacetate[6]. In our retrospective, unblinded, pivotal trial of 23 NAGS deficiency patients, Carbaglu® ensured control of metabolic parameters, prevented metabolic decompensation and neurological sequelae, and no serious safety issues were identified[7]. For PA and MMA, the guidelines were published by Forny in 2021 and include carglumic acid for acute metabolic decompensation[8].

Those with inborn errors of metabolism must balance dietary needs for growth and development while simultaneously managing ammonia levels that result from normal catabolism or which are elevated due to stress, illness, and growth. Treatment requires both consistent daily dosing and management of triggers. Since 2010, the standard of care has included daily Carbaglu® tablets for those with NAGS deficiency and in 2021, the FDA approved the use for acute hyperammonemia with PA and MMA. In an NIH study by Dr. Mendel Tuchman, which is also the same study referenced in our PI, Carbaglu® enhanced ammonia lowering, along with the standard of care. These are fragile patients at high risk, who should have Carbaglu® and other management strategies available to them. The most common adverse reactions with Carbaglu® (>9%) are: vomiting, abdominal pain, pyrexia, tonsillitis, anemia, diarrhea, ear infection, infections, nasopharyngitis, hemoglobin decreased, and headache.) For more information, please refer to the complete **Prescribing Information for Carbaglu®** attached here.

As the only carglumic acid approved for NAGS deficiency management AND from hyperammonemia due to propionic acidemia or methylmalonic acidemia, RRD requests that Carbaglu® **be in parity with** generic carglumic acid, given the key differences in the indication set forth above.

References:

1. Carbaglu **full Prescribing Information**: https://www.carbaglu.com/PI. Accessed on 4 September 2024.

2. https://carglumicacid.com/wp-content/uploads/carglumic-acid-prescribing-info.pdf. Accessed on 4 September 2024.

3. Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. 2003 Apr 29 [Updated 2017 Jun 22]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1217/

4. Chapman KA, Gramer G, Viall S, Summar ML. Incidence of maple syrup urine disease, propionic acidemia, and methylmalonic aciduria from newborn screening data. Mol Genet Metab Rep. 2018 Apr 5;15:106-109. doi: 10.1016/j.ymgmr.2018.03.011. PMID: 30023298; PMCID: PMC6047110.

5. https://www.babysfirsttest.org/newborn-screening/states/alaska

6. Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, Mandel H, Martinelli D, Pintos-Morell G, Santer R, Skouma A, Servais A, Tal G, Rubio V, Huemer M, Dionisi-Vici C. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019 Nov;42(6):1192-1230. doi: 10.1002/jimd.12100. Epub 2019 May 15. PMID: 30982989.

7. Guffon N, et al. Treatment of NAGs Deficiency: Retrospective Data on 23 Patients Treated with Carglumic Acid over 16 years. Molecular Genetics and Metabolism. SIMD Poster Number 42, March 2011. DOI:10.1016/j.ymgme.2010.11.160

8. Forny P, Hörster F, Ballhausen D, Chakrapani A, Chapman KA, Dionisi-Vici C, Dixon M, Grünert SC, Grunewald S, Haliloglu G, Hochuli M, Honzik T, Karall D, Martinelli D, Molema F, Sass JO, Scholl-Bürgi S, Tal G, Williams M, Huemer M, Baumgartner MR. Guidelines for the diagnosis and management of methylmalonic acidaemia and propionic acidaemia: First revision. J Inherit Metab Dis. 2021 May;44(3):566-592. doi: 10.1002/jimd.12370. Epub 2021 Mar 9. Erratum in: J Inherit Metab Dis. 2022 Jul;45(4):862. PMID: 33595124; PMCID: PMC8252715.