Efficacy Supplement Review

Date	September 2, 2025
From	Jennifer E. Shields M.D., MPH
Medical Team Leader	Anita Zaidi M.D.
NDA #	214860, S-007
Applicant	Acer Therapeutics
Date of Submission	December 20, 2024
PDUFA Goal Date	October 10, 2025
Product name (generic)	Olpruva (sodium phenylbutyrate)
Dosage forms / Strength	For oral suspension: 0.5 g, 1 g, 2 g, 3 g, 4 g, 5 g, 6 g, and 6.67 g of sodium phenylbutyrate as pellets in packets for reconstitution
Proposed Indication(s)	Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing 7 kg or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).
Recommended:	adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients 1 year of age and older weighing 7 kg or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS).

The Applicant submitted this Prior Approval Efficacy Supplement on December 20th, 2024, in accordance with PREA PMRs 4380-1 and 4380-3 to revise labeling to include 0.5 g and 1 g dose strengths and include instructions on administration via gastrotomy tubes. Additionally, the Applicant proposed expanding the indicated population from patients weighing 20 kg or greater to pediatric patients weighing 7 kg or greater.

4380-1 Develop dosage strength(s) to accommodate the recommended dosing for pediatric patients who weigh <20 kg and patients who weigh =20 kg with a body surface area <1.2 m^2.

4380-3 Conduct in vitro studies to determine the feasibility of administering Olpruva (sodium phenylbutyrate) for oral suspension through enteral feeding tubes.

The Office of Product Quality (OPQ) agreed with the addition of the oral suspension 0.5 g and 1g pediatric dose strengths and administration of the drug product through gastrostomy tubes (full review available in Panorama). The Division of Medication Error Prevention and Analysis (DMEPA) approved the revisions from a medication error perspective. In their review dated June 3, 2025 (reference ID: 5602292 in DARRTs), DMEPA suggested additional improvements in the product labeling regarding symbols in display of ranges, consistency in measurement terms, and including gastrotomy tubes as an administration vehicle for completeness. the Division of Pharmacovigilance conducted a review of the postmarketing data in FAERS on February 11, 2025 (reference ID: 5528642 in DARRTs) and did not identify any new safety signals that would require additional labeling changes.
The Department of Pediatric and Maternal Health (DPMH) was consulted for this review and expressed concern regarding the amount of free water consumption required for proper administration of the drug in patients less than 1 year old. Each dose must be taken with at least 120 mL of water, resulting in the potential for 360 mL to 720 mL of free water intake per day. The American Academy of Pediatrics recommends that children younger than 6 months should not ingest free water, and children 6 months to 12 months should limit free water intake to no more than 120 - 240 mL/day. OPQ also assessed that reduction of the free water used in suspension of the drug is not possible as it would increase the viscosity and thickness of the Mix-aid solution to levels not safe for swallowing, especially for patients with dysphagia. Additionally, the Applicant evaluated other potential dosing vehicles besides water but eliminated these options from consideration due to compatibility issues such as pH incompatibility with the product's taste-masking agent, leaving water with Mix-aid as the optimal vehicles despite the resulting large fluid volume requirements.

This reviewer agrees with DPMH reviewer concerns and recommends broadening the indication to patients that are both older than 1 year old and weighing 7 kg or greater only and including a limitation of use statement concerning product use in patient younger than 1 year of age due to the unsafe amount of water required for the product administration. The Applicant agreed with the proposed indication and the limitations of use.

The recommended updates to the prescribing information based on the information reviewed included:

"Section 1:
OLPRUVA is a nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients 1 year of age and older weighing 7 kg or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase.

Limitations of Use: OLPRUVA is not recommended for patients younger than 1 year of age due to the volume of free water required for daily administration

Section 2:
Gastrostomy Tube

For gastrostomy tube administration via size 12 French, 14 French or 16 French gastrostomy tube (individual doses of 0.5 g to 6.67 g):

1. *Pour the entire contents of the Mix-Aid packet into approximately 120 mL of water in a cup and stir, forming a Mix-Aid/water suspension.*

For individual OLPRUVA doses < 2 g, *use 10 mL of the Mix-Aid/water suspension to prime the gastrostomy tube, another 10 mL of the Mix-Aid/water suspension to suspend and administer the OLPRUVA dose, and then another 10 mL of the Mix-Aid/water suspension to flush the gastrostomy tube 3 times. Discard unused portion of Mix-Aid/water suspension.*

2. *Prepare the OLPRUVA dose in a separate cup by mixing the entire contents of the OLPRUVA packet(s) with the appropriate amount of the Mix-Aid/water suspension and stir.*
3. *Prime the gastrostomy tube with the appropriate amount of the remaining Mix-Aid/water suspension using a new enteral syringe.*
4. *Draw up the entire contents of the OLPRUVA dose into an enteral syringe and administer via the gastrostomy tube.*
5. *After the entire dose of OLPRUVA has been administered through the gastrostomy tube, rinse the gastrostomy tube three times with the appropriate amount of the remaining Mix-Aid/water suspension.*

Section 8.4:
The safety and effectiveness of OLPRUVA have not been established in pediatric patients less than 1 year of age or who weigh less than 7 kg. OLPRUVA is not recommended in patients younger than 1 year of age because the total daily volume of free water necessary for administration has the potential to cause hyponatremia which may result in serious complications such as lethargy or seizures [see Dosage and Administration (2.5)].

Section 16:
OLPRUVA (sodium phenylbutyrate) for oral suspension is available in dosage strengths of 0.5 g, 1 g, 2 g, 3 g, 4 g, 5 g, 6 g, and 6.67 g of sodium phenylbutyrate as white to off-white pellets."

The Patient Prescribing Information, Instructions for Use (IFU), carton/container labels were updated to reflect the changes listed above including the limitations to the indication, administration through gastrotomy tubes, and new dosage strengths.
On September 16, 2025, the Pediatric Review Committee (PeRC) discussed the Division recommendations to broaden the indicated population to patients older than 1 year of age and weighing greater than 7 kg only, to include limitation of use statement and waive the requirement to study patients younger than 1 year of age due to the safety concerns with free water needed for appropriate administration of this product and availability of alternative formulations of sodium phenylbutyrate for patients <1 year of age. PeRC agreed with the Division's recommendations (reference ID: 5667720 in DARRTs).

Review of the Applicant's proposed label, packaging and product labeling was conducted DMEPA reviewer. The reviewer concluded that proposed agreed upon labels and labeling were acceptable.

Recommendation

- Recommended Regulatory Action
  - Approval
    Recommended changes to labeling for OLPRUVA include broadening of the indicated population to patients older than 1 year of age and weighing greater than 7 kg and including limitation of use statement "*OLPRUVA is not recommended for patients younger than 1 year of age due to the volume of free water required for daily administration"*
  - Grant waiver for studying patients younger than 1 year old or weighing less than 7 kg. Release, reissue PMR 4380-1 and consider it fulfilled
  - Consider PMR 4380-3 fulfilled.

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/

JENNIFER E SHIELDS
10/01/2025 07:39:24 AM

ANITA A BAILEY ZAIDI
10/01/2025 07:52:10 AM