



National Tay-Sachs &
Allied Diseases Association

Use of 4-phenylbutyric acid (4-PBA) in the GM2 Gangliosidosis

The following information is intended for individuals living with rare diseases and their healthcare providers (HCPs) who are considering the off-label drug (OLDU) use of 4-phenylbutyric acid (4-PBA) for GM2 gangliosidosis. This document is not intended to provide medical advice; individuals interested in the use of 4-PBA off-label should discuss this with their HCPs. This information is for individuals affected in the US; the approval status of medications may vary by country. Countries outside of the US may have regulations or processes in place to access medications via OLDU as well.

NTSAD does not advocate for or against OLDU of specific drugs for any individuals.

- Background
 - Additional drug name: sodium phenylbutyrate; brand names: Ammonaps, Buphenyl, Olpruva, Pheburane, RELYVRIO (AMX0035: sodium phenylbutyrate and taurursodiol); generic name: phenylbutyric acid; more synonyms: <https://go.drugbank.com/drugs/DB06819>, <https://pubchem.ncbi.nlm.nih.gov/compound/Phenylbutyric-acid>.
 - This small molecule drug acts as a nitrogen scavenger by binding to glutamine, and its chaperone activity is thought to promote proper protein folding in the endoplasmic reticulum (ER) and reduce ER stress. Chemical chaperones may help to stabilize mutant proteins. Mechanisms of action are reviewed in Kolb et al. (2015).
 - The drug was developed by UCyclid (part of Medicis Pharmaceutical) and approved by the FDA in 1996 to reduce hyperammonemia in urea cycle defects. Hyperion acquired BUPHENYL® from UCyclid Pharma in 2013.
 - A nonclinical study demonstrated that 4-PBA treatment mitigated ER stress-induced neurodegeneration in the spinal cord of the *Hexb*^{-/-} mouse model of Sandhoff disease, a type of GM2 gangliosidosis (Weaver et al., 2025). The study further revealed that 4-PBA enhanced motor neuromuscular function and lifespan, reduced apoptosis in spinal cord neurons, and increased the number of choline acetyltransferase (ChAT)-positive neurons. The authors suggested that 4-PBA may be a promising therapy for Sandhoff disease and related lysosomal disorders.

- The *Hexb*^{-/-} mouse used by Weaver et al. (2025) is a well-characterized animal model for both Tay-Sachs disease and Sandhoff disease, recapitulating the severe neurodegenerative phenotype observed in humans.
 - In addition to GM2 gangliosidoses, 4-PBA has been studied in cystic fibrosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy (SMA) (Lim et al., 2004; Ricobaraza et al., 2019; Paganoni et al., 2020; Paganoni et al., 2022; Brahe et al., 2005).
 - 4-PBA is thought to have a general neuroprotective effect (Mimori et al., 2012).
 - Many neurodegenerative diseases are believed to share a common pathophysiology; thus, a general neuroprotective drug like 4-PBA may be effective in treating multiple disorders.
- Approved uses
 - 4-PBA is an FDA-approved drug for the treatment of urea cycle disorders. Urea cycle disorders are inherited conditions that impair the body's ability to convert toxic ammonia into nontoxic urea for elimination in urine.
 - This drug was approved under the trade name Buphenyl.
 - Other brand names include: Ammonaps, Buphenyl, Olpruva 2 Gm Pack, and Pheburane.
 - The FDA initially approved Relyvrio (also known as AMX0035), a combination of sodium phenylbutyrate/taurursodiol, for ALS patients in 2022, based on limited data from a Phase 2 clinical trial. However, Relyvrio was withdrawn from the market in 2024 after it failed to outperform the placebo in a larger Phase 3 clinical trial.
 - Additional drug information, including its pharmacology, various properties, and toxicity, can be found at:
<https://go.drugbank.com/drugs/DB06819> or
<https://pubchem.ncbi.nlm.nih.gov/compound/Phenylbutyric-acid>.
 - Known drug interactions/contraindications can be found at:
<https://go.drugbank.com/drugs/DB06819>.
 - Available data in GM2 gangliosidoses
 - The only data currently available for 4-PBA in the GM2 gangliosidoses are those described in the publication by Weaver et al. (2025) (cited below), from the laboratory of Dr. Suleiman A. Igdoura at McMaster University in Hamilton, ON, Canada.
 - Neurodegenerative diseases, like the GM2 gangliosidoses and GM1 gangliosidosis, share common pathophysiologic features. Thus, 4-PBA

may potentially treat multiple lysosomal diseases, most of which exhibit neurodegeneration.

- On-label recommended dosing (per package insert)
 - Recommendations for BUPHENYL® (sodium phenylbutyrate) tablets and BUPHENYL® (sodium phenylbutyrate) powder are available here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020572s016,020573s015lbl.pdf. This document states that the usual total daily dose of BUPHENYL tablets and powder for patients with urea cycle disorders is 450–600 mg/kg/day in patients weighing less than 20 kg, or 9.9–13.0 g/m²/day (up to 20g/day) in larger patients and that the tablets and powder are to be taken in equally divided amounts with each meal or feeding (i.e., three to six times per day). Note the contraindications and warnings included.
 - Common adverse reactions include amenorrhea/menstrual dysfunction in female patients, decreased appetite, body odor, and bad taste or taste aversion. Gastrointestinal symptoms can occur and can include abdominal pain, gastritis, nausea, and vomiting; these often improve with continued use.
 - 4-PBA contains sodium, so care should be used in patients with congestive heart failure, renal insufficiency, or conditions where there is sodium retention with edema.
 - 4-PBA may be effective in lower doses in individuals with GM2 gangliosidosis or other lysosomal diseases, so starting at a lower dose and titrating upwards as tolerated is a reasonable approach.
 - HCPs should consider monitoring a Comprehensive Metabolic Panel, Complete Blood Count, and plasma amino acids during treatment as a general safety measure.
 - The on-target effect of 4-PBA can be evaluated by measuring specific Hex A (Tay-Sachs and Sandhoff) activity in white blood cells (WBCs) from blood samples. Prior to initiating 4-PBA, it is important to measure the HexA activity in WBCs from two separate blood samples to determine a 'baseline' to assess the therapeutic response in subsequent HexA measurements.
 - The pharmacodynamic effects of 4-PBA can be evaluated by measuring lysoGM2 (substrate accumulation), neurofilament light chain and tau (neuronal injury), and glial fibrillary acidic protein (astrocyte injury) (Welford *et al.*, 2022).

- This document is intended to provide information and references regarding 4-PBA. For general information on off-label drug use, please see our general guidelines document. For information on additional off-label drugs, please refer to our other drug-specific documents, which will be made available on NTSAD's website once they are completed.
- This document was organized by the National Tay-Sachs & Allied Diseases Association (NTSAD) Research Committee working group. It was authored by Cynthia Perreault-Micale, PhD, and Valerie Greger, PhD, from NTSAD with input from other NTSAD Research Committee members and members of the NTSAD Scientific Advisory Committee.
- If you have additional questions, please contact research@ntsad.org.

References:

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