



National Tay-Sachs &  
Allied Diseases Association

## Use of 4-phenylbutyric acid (4-PBA) in GM2 Gangliosidoses

The following information is intended for individuals and families living with rare diseases who are considering the off-label drug use (OLDU) of 4-phenylbutyric acid (4-PBA) for GM2 gangliosidoses. 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
  - 4-PBA (sodium phenylbutyrate) is an oral therapy that may help stabilize abnormal proteins.
  - The drug was developed by UCyclid (part of Medicis Pharmaceutical) and approved by the FDA in 1996 to lower abnormal ammonia levels in children with a category of diseases called urea cycle defects. Hyperion acquired BUPHENYL® from UCyclid Pharma in 2013.
  - A study in 2025 showed that 4-PBA treatment slowed spinal cord neurodegeneration, enhanced neuromuscular function and lifespan, and had other positive effects in a mouse model of Sandhoff disease, a type of GM2 gangliosidosis (Weaver et al., 2025). The authors suggested that 4-PBA may be a promising therapy for Sandhoff disease and related lysosomal disorders.
  - 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 protective effect on the nervous system (Mimori *et al.*, 2012).
  - Many neurodegenerative diseases have common disease mechanisms; 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 where the body cannot clear ammonia properly.
  - 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 may be found at:  
<https://go.drugbank.com/drugs/DB06819> or  
<https://pubchem.ncbi.nlm.nih.gov/compound/Phenylbutyric-acid>.
  - Known drug interactions/contraindications may be found at:  
<https://go.drugbank.com/drugs/DB06819>.
  
- Available data in GM2 gangliosidosis
  - The only data currently available for 4-PBA in the GM2 gangliosidosis 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 gangliosidosis and GM1 gangliosidosis, share common features. Thus, 4-PBA may potentially treat multiple lysosomal diseases, most of which exhibit neurodegeneration.
  
- On-label recommended dosing (per package insert)
  - For urea cycle disorders, the typical dose is based on body weight. It is usually taken three to six times per day with meals.
  - 4-PBA may be effective in lower doses in individuals with GM2 gangliosidosis or other lysosomal diseases, so starting at a lower dose and then increasing as tolerated is a reasonable approach.
  - Common adverse reactions include change in menstrual cycle in women, decreased appetite, body odor, and bad taste or taste aversion. Gastrointestinal symptoms can occur and can include abdominal pain, inflammation of the stomach lining, nausea, and vomiting; these often improve with continued use.

- 4-PBA contains sodium, so care should be used in patients with congestive heart failure, kidney problems, or conditions where there is swelling from sodium retention.
- Doctors may order blood tests to check liver and kidney function, blood counts, and amino acid levels.  
If 4-PBA is being used for Tay-Sachs or Sandhoff diseases, doctors may also check enzyme activity (HexA) before and during treatment, and measure certain markers of nerve health or injury.
- This document is intended to provide information and references regarding 4-PBA. For general information on OLDU, please see our general guidelines document entitled “Off-label Drug Use General Information” and available at <https://ntsad.org/resources-for-professionals/off-label-drug-information/>. For information on additional off-label drugs, please refer to our other drug-specific documents, also available on the NTSAD website at: <https://ntsad.org/resources-for-professionals/off-label-drug-information/>.
- 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. It was thoughtfully edited by Karen Grinzaid, MS, CGC, CCRC, to make appropriate for patients.
- If you have additional questions, please contact [research@ntsad.org](mailto:research@ntsad.org).

#### References:

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