Oscar Clinical Guideline: Urea Cycle Disorder (UCD) Treatment Agents (PG187, Ver. 4)

Urea Cycle Disorder (UCD) Treatment Agents

- Buphenyl (sodium phenylbutyrate)
- Olpruva (sodium phenylbutyrate)
- Pheburane (sodium phenylbutyrate)
- Ravicti (glycerol phenylbutyrate)
- Sodium Phenylbutyrate [generic Buphenyl]

Summary

Urea cycle disorders (UCDs) are rare genetic conditions characterized by deficiencies of enzymes necessary for urea synthesis, resulting in hyperammonemia and central nervous system damage. Severe neonatal-onset UCDs typically present in the first month of life with lethargy, vomiting, seizures, coma, and cerebral edema. Partial enzyme deficiencies associated with late-onset UCDs may manifest later, often triggered by stressors. If untreated, UCDs can be fatal due to hyperammonemic encephalopathy.

Early diagnosis and urgent treatment of UCDs is critical to improve outcomes. Key therapies include hemodialysis, sodium phenylbutyrate, sodium phenylacetate, sodium benzoate, protein restriction, and amino acid supplementation. Hemodialysis most rapidly removes ammonia but drug therapy can be tried first. Overall survival is around 80% for neonatal-onset UCDs with treatment initiation before repeated hyperammonemic episodes. However, most survivors have later cognitive or neurologic deficits. In late-onset UCDs, survival exceeds 90% with treatment, but neurologic impairment may continue progressing.

Many patients require lifelong sodium phenylbutyrate to help manage chronic hyperammonemia. Glycerol phenylbutyrate is an alternative that provides additional waste nitrogen excretion but does not treat acute hyperammonemia. Increased exposure to its metabolite phenylacetate may risk neurotoxicity. Recurrent hyperammonemic episodes should be urgently treated as medical emergencies with all ammonia-lowering therapies.

Definitions

"Acute Hyperammonemia" refers to sudden onset of severely elevated blood ammonia levels that can quickly cause brain damage or death if left untreated.

"Amino Acid Supplementation" refers to medical supplementation with essential amino acids.

"Ammonia" refers to a compound made in the body during protein metabolism and normally converted to urea by the liver.

"Dietary Protein Restriction" refers to limiting protein intake in the diet as a therapeutic strategy to reduce ammonia production.

"Hyperammonemia" refers to abnormally high levels of ammonia in the blood.

"Late-onset" refers to onset of the disorder after the first 28 days of life, often partially deficient enzymes.

"Neonatal-onset" refers to onset of the disorder within the first 28 days of life.

"Orphan Drug" refers to an FDA designation for drugs treating rare diseases affecting less than 200,000 people in the US.

"Urea Cycle Disorder (UCD)" refers to a group of rare genetic conditions characterized by deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia, resulting in toxic accumulation of ammonia.

"[s]" indicates state mandates may apply.

Clinical Indications

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Urea Cycle Disorder

The Plan considers Urea Cycle Disorder (UCD) Treatment Agents medically necessary when ALL of the following criteria are met:

1. Prescribed by or in consultation with a specialist experienced in the treatment of urea cycle disorders (e.g. geneticist, metabolic disorders); *AND*
2. Confirmed diagnosis of a urea cycle disorder, defined by ALL of the following:
    a. Elevated plasma ammonia levels per age; *and*
    b. Normal anion gap; *and*
    c. Normal blood glucose level; *and*
    d. Supportive amino acid profile, urine organic acids, enzymatic testing, or genetic testing; *AND*
3. Dietary protein restriction and/or amino acid supplementation alone cannot adequately manage the disorder; *AND*
4. Agent is prescribed as adjunctive therapy to dietary restriction; *AND*
5. Agent will not be used to treat acute hyperammonemia; *AND*
6. The member is unable to use, or has tried and failed generic sodium phenylbutyrate OR pheburane[s], unless the request is for:
    a. Sodium Phenylbutyrate [generic Buphenyl]; *or*
    b. Pheburane; *or*
    c. Brand Ravicti, and member has experienced unsatisfactory therapeutic response or clinically significant adverse effects to generic glycerol phenylbutyrate from at least two (2) different manufacturers (if available); *or*

d. Brand Buphenyl, and member has experienced unsatisfactory therapeutic response or clinically significant adverse effects to generic sodium phenylbutyrate from at least two (2) different manufacturers (if available); *or*
e. Is established on requested agent with documented positive response; *AND*

7. Agent is being prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication; *AND*
8. The member meets ALL of the following, as applicable:
    a. For neonates, the requested agent is FDA approved for use in neonates and the prescribed dose is within FDA labeled dosing for neonates; *and*
    b. For Olpruva (sodium phenylbutyrate), and the member weighs 7 kg or greater; *and*
    c. For members requiring doses or frequencies exceeding FDA labeled dosing, the prescribed regimen is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, the requested product will be authorized for up to 6-months.[s]

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Urea Cycle Disorder

The Plan considers Urea Cycle Disorder (UCD) Treatment Agents medically necessary when ALL of the following criteria are met:

1. The member previously met applicable Initial Authorization criteria; *AND*
2. The agent is prescribed by or in consultation with a specialist experienced in the treatment of urea cycle disorders (e.g. geneticist, metabolic disorders); *AND*
3. The member has achieved or maintained disease stability or improvement as indicated by normalized or controlled plasma ammonia levels; *AND*
4. Agent will NOT be used to treat acute hyperammonemia; *AND*
5. The member requires ongoing therapy in conjunction with dietary management.

If the above reauthorization criteria are met, the requested product will be authorized for up to 12 months.[s]

Experimental or Investigational / Not Medically Necessary[s]

Urea Cycle Disorder (UCD) Treatment Agents for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Absence of positive response to therapy
- Alzheimer's Disease (AD)
- Amyotrophic Lateral Sclerosis (ALS)
- Cirrhosis of the Liver / Hepatic Encephalopathy (HE)
- Cystic Fibrosis (CF)
- Huntington's Disease (HD)
- Lack of confirmed urea cycle enzyme deficiency diagnosis
- Parkinson's Disease (PD)
- Spinal Muscular Atrophy (SMA)
- Therapeutic Agent Toxicity
- Use for acute hyperammonemia

References

1. Ah Mew N, McCarter R, Izem R, et al. Comparing Treatment Options for Urea Cycle Disorders [Internet]. Washington (DC): Patient-Centered Outcomes Research Institute (PCORI); 2020 Dec.
2. Batshaw ML, Berry GT. Use of citrulline as a diagnostic marker in the prospective treatment of urea cycle disorders. J Pediatr 1991;118(6):914–7.
3. Batshaw ML, Tuchman M, Summar M, et al. A longitudinal study of urea cycle disorders. Mol Genet Metab 2014; 113:127.
4. Berry SA, Longo N, Diaz GA, et al. Safety and efficacy of glycerol phenylbutyrate for management of urea cycle disorders in patients aged 2months to 2years. Mol Genet Metab 2017; 122:46.
5. Buphenyl (sodium phenylbutyrate) tablets, powder [prescribing information]. Deerfield, IL: Horizon Therapeutics USA Inc; March 2023.
6. Burrage LC, Jain M, Gandolfo L, et al. Sodium phenylbutyrate decreases plasma branched-chain amino acids in patients with urea cycle disorders. Mol Genet Metab 2014; 113:131.
7. Daniotti M, la Marca G, Fiorini P, Filippi L. New developments in the treatment of hyperammonemia: emerging use of carglumic acid. Int J Gen Med 2011; 4:21.
8. Gropman AL, Summar M, Leonard JV. Neurological implications of urea cycle disorders. J Inherit Metab Dis 2007;30(6):865–79.
9. Häberle J. Clinical practice: the management of hyperammonemia. Eur J Pediatr 2011; 170:21.
10. 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.
11. Lilliu F. Treatment of organic acidurias and urea cycle disorders. J Matern Fetal Neonatal Med 2010; 23 Suppl 3:73.
12. Olpruva (sodium phenylbutyrate) [prescribing information]. Newton, MA: Acer Therapeutics Inc; October 2025.
13. Pheburane (sodium phenylbutyrate) [prescribing information]. Princeton, NJ: Medunik USA Inc; August 2023.

14. Pheburane (sodium phenylbutyrate) [prescribing information]. Bryn Mawr, PA: Medunik USA Inc; June 2022.
15. Ravicti (glycerol phenylbutyrate) [prescribing information]. Lake Forest, IL: Horizon Therapeutics USA Inc; September 2021.
16. Smith W, Diaz GA, Lichter-Konecki U, et al. Ammonia control in children ages 2 months through 5 years with urea cycle disorders: comparison of sodium phenylbutyrate and glycerol phenylbutyrate. J Pediatr 2013; 162:1228.
17. Summar M, Tuchman M. Proceedings of a consensus conference for the management of patients with urea cycle disorders. J Pediatr 2001;138(1 Suppl):S6–10.
18. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr 2001;138(1 Suppl):S30–9.

Appendix

Table 1: Common ICD-10-CM Codes for Urea Cycle Disorder (UCD) Treatment Agents

Code	Description
E72.20	Disorder of urea cycle metabolism, unspecified
E72.21	Argininemia
E72.22	Arginosuccinic aciduria
E72.23	Citrullinemia
E72.29	Other disorders of urea cycle metabolism
E72.4	Disorders of ornithine metabolism

Table 2: Main Enzymatic Deficiencies Causing Urea Cycle Disorders[‡]

Disorder	Also Known As	MIM Number[‡]
Carbamyl phosphate synthetase I (CPSI) deficiency		237300
Ornithine transcarbamylase (OTC) deficiency		311250
Argininosuccinate synthetase (ASS) deficiency	Classic citrullinemia, Type I citrullinemia (CTLN1)	215700
Argininosuccinate lyase (ASL) deficiency	Argininosuccinic aciduria	207900
N-acetyl glutamate synthetase (NAGS) deficiency		237310
Arginase deficiency	Argininemia	207800

↕ *The table summarizes the main enzymatic deficiencies that can lead to urea cycle disorders. For complete gene, molecular, and chromosomal location information on these disorders, please refer to the Online Mendelian Inheritance in Man® (OMIM®) database.*

Clinical Guideline Revision / History Information

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