Oscar Clinical Guideline: Urea Cycle Disorder (UCD) Treatment Agents (PG187, Ver. 1)

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 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.

Medical Necessity Criteria for Initial Authorization

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. Member is unable to use, or has tried and failed generic sodium phenylbutyrate **OR** Pheburane, unless request is for:
    a. Sodium Phenylbutyrate [generic Buphenyl]
    b. Pheburane
    c. Brand Buphenyl[ɳ], and member has experienced unsatisfactory therapeutic response or clinically significant adverse effects to generic sodium phenylbutyrate from at least two different manufacturers (if available)
    d. is established on requested agent with documented positive response; ***AND***

    [ɳ]For (Brand) Buphenyl requests, in addition to meeting the criteria here-in, is also subject to Oscar Clinical Guideline: Brand Medically Necessary Drugs (PG186).
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.
    a. For neonates, the requested agent is FDA approved for use in neonates and the prescribed dose is within FDA labeled dosing for neonates

b. For Olpruva, and the member meets **BOTH** of the following:
    i. weighing 20 kg or greater; ***and***
    ii. with a body surface area (BSA) of 1.2 m^2 or greater
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
d. For members with partial UCD deficiencies, the prescribing physician has provided information indicating the requested agent is appropriate for the member's type of UCD. Information must include:
    i. Specific UCD mutation or enzyme deficiency
    ii. Rationale for using the requested medication for the member's type of partial UCD (e.g. expected clearance of toxic metabolites, reduced risk of hyperammonemia)
    iii. Any available lab results, ammonia levels, or prior response to the requested medication supporting its use in the member's type of partial UCD

If the above prior authorization criteria are met, the requested product will be authorized for 6-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12-months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The member previously met Initial Authorization criteria; ***AND***
2. 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.

Experimental or Investigational / Not Medically Necessary

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

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.*

References

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