Carbaglu (carglumic acid)  
Prior Authorization  
Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Medicaid, Health Insurance Marketplace, KeyRx and FocusRx formularies.

This is a FlexRx Standard and GenRx Standard program.

FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing &amp; Administration</th>
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</thead>
<tbody>
<tr>
<td>Carbaglu® (carglumic acid) tablets for oral suspension</td>
<td>Adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS)</td>
<td>Acute hyperammonemia: Initial dose 100 mg/kg/day to 250 mg/kg/day. Titrate based on plasma ammonia level and clinical symptoms</td>
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<td></td>
<td>Maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS)</td>
<td>Chronic hyperammonemia: 10 mg/kg/day to 100 mg/kg/day. Titrate to target normal plasma ammonia level for age</td>
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*Divide the total daily dose into two to four doses

CLINICAL RATIONALE

Urea cycle disorders (UCDs) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and nitrogen-containing molecules. UCDs are caused by deficiency in the enzymes of the urea cycle: (carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetylglutamate synthetase [NAGS]. N-acetylglutamate (NAG) is the product of N-acetylglutamate synthase (NAGS), the enzyme for co-factor in NAG production. The UCDs listed above result in the accumulation of ammonia (hyperammonemia) during the first few days of life. In severe disease, infants rapidly develop cerebral edema and signs of lethargy, anorexia, hypoventilation, hypothermia, seizures, neurologic posturing, and coma whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.²³

Diagnosis is based upon clinical suspicion and biochemical and genetic testing. A normal anion gap and plasma glucose in the presence of a plasma ammonia concentration of 150 µmol/L (>260 µg/dl) or higher in neonates and > 100 µmol/L (175 µg/dl) in older children and adults is indicative of UCD. The diagnosis of a specific UCD can be confirmed by enzyme analysis of tissue samples. Specifically, NAGS deficiencies can be confirmed by liver biopsy. Molecular genetic testing is also available for all urea cycle defects.⁴

Initial approach to treatment consists of rehydration and maintaining good urine output without overhydration; removing nitrogen (ammonia) from the body using medications and/or hemodialysis; stopping protein intake and minimize catabolism; and stimulating anabolism and uptake of nitrogen precursors by muscles. Respiratory status should be closely monitored because clinical condition can deteriorate rapidly. Glucocorticoids increase protein catabolism and should not be routinely used. Valproic acid increases serum ammonia levels and should not be used to treat seizures. Excessive ammonia is removed by hemodialysis and medications.
Hemodialysis is the quickest and most efficient method and should be used if ammonia is rapidly increasing, the acute hyperammonemia is resistant to initial drug therapy, and/or the ammonia is persistently above the range of 350 to 400 micromol/L.  

Pharmacological therapy for hyperammonemia consists of initial intravenous administration of a combination preparation of sodium phenylacetate and sodium benzoate (Ammonul) followed by maintenance with oral sodium phenylbutyrate (Buphenyl) or glycerol phenylbutyrate (Ravicti). Carglumic acid (Carbaglu) is effective in treating NAGS deficiency.

Long term management options to prevent hyperammonemia include: dietary restriction of protein, use of specialized formulas, and oral nitrogen-scavenging agents. According to guidelines, not all patients who recover from a hyperammonemic episode require chronic nitrogen scavengers but they should be considered.

REFERENCES
Carbaglu (carglumic acid) Prior Authorization

OBJECTIVE
The intent of the Carbaglu (carglumic acid) Prior Authorization (PA) program is to appropriately select patients for treatment according to product labeling and/or clinical studies and/or clinical practice guidelines.

TARGET AGENT
Carbaglu (carglumic acid)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation
Carbaglu will be approved when ALL the following are met:
1. The patient has a diagnosis of N-acetylglutamate synthase (NAGS) deficiency confirmed by enzyme analysis (via liver biopsy) OR genetic testing
   AND
2. The patient has a diagnosis of hyperammonemia AND ALL of the following:
   a. The patient has elevated ammonia levels according to the patient’s age
      [Neonate: plasma ammonia level 150 µmol/L (>260 µg/dl) or higher; Older child or adult: plasma ammonia level> 100 µmol/L (>175 µg/dl)]
      AND
   b. The patient has a normal anion gap
      AND
   c. The patient has a normal blood glucose level
      AND
3. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, when clinically appropriate, essential amino acid supplementation
   AND
4. The prescriber is a specialist in metabolic diseases or a pediatric geneticist or the prescriber has consulted with a specialist in metabolic diseases or a pediatric geneticist
   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. The requested dose is within the FDA-labeled dose for the requested agent

Length of Approval: 12 months

Renewal Evaluation
Carbaglu will be approved when ALL the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics Prior Authorization process
   AND
2. The patient has a plasma ammonia level within the normal range
   AND
3. The prescriber is a specialist in metabolic diseases or a pediatric geneticist or the prescriber has consulted with a specialist in metabolic diseases or a pediatric geneticist
   AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
5. The requested dose is within the FDA labeled dose for the requested agent

Length of Approval: 12 months