



Urea Cycle Disorders Prior Authorization Program Summary

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

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date
03-01-2024

Date of Origin
08-01-2017

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Buphenyl® (sodium phenylbutyrate)* Oral tablet Powder for oral, nasogastric, or gastrostomy tube administration	Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). All patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). All patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. Buphenyl must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.	* generic available	2
Olpruva™ (sodium phenylbutyrate) Oral suspension packet	Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing 20 kg or greater and with a body surface area (BSA) of 1.2 m ² or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) Limitations of Use: Episodes of acute hyperammonemia may occur in patients while on Olpruva. Olpruva is not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.		8
Pheburane® (sodium phenylbutyrate) Oral pellets	Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)		7
Ravicti®	Chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.		1

Agent(s)	FDA Indication(s)	Notes	Ref#
(glycerol phenylbutyrate)	Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).		
Oral liquid	<p>Limitations of Use:</p> <ul style="list-style-type: none"> Not indicated for the treatment of acute hyperammonemia in patients with UCDS because more rapidly-acting interventions are essential to reduce plasma ammonia levels. Safety and efficacy for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established. 		

See package insert for FDA prescribing information: <https://dailymed.nlm.nih.gov/dailymed/index.cfm>

CLINICAL RATIONALE

Urea Cycle Disorders	<p>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 other nitrogen-containing molecules. Severe deficiency, or total absence, of any of the enzymes in the urea cycle (carbamoyl phosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG1]) or the cofactor producer (N-acetyl glutamate synthetase [NAGS]) results 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, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma, whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.(3,4,5)</p> <p>The most important diagnostic step in UCDs is clinical suspicion of hyperammonemia. Laboratory data useful in the diagnosis of UCD includes, but is not limited to, plasma ammonia, anion gap, and plasma glucose. A normal anion gap and normal blood glucose in the presence of a plasma ammonia concentration of 150 micromol/L (greater than 260 micrograms/dL) or higher in neonates and greater than 100 micromol/L (175 micrograms/dL) in older children and adults is indicative of UCD. The diagnosis of a specific UCD can be confirmed by genetic testing. Specifically, NAGS, OTC, and CPS1 deficiencies can be confirmed by liver biopsy.(3,4,5)</p> <p>Pharmacologic therapy for acute hyperammonemia consists of initial IV administration of a combination preparation of sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. If chronic therapy is warranted, the patient can then be switched to nitrogen scavengers such as sodium phenylbutyrate, glycerol phenylbutyrate, and carglumic acid.(4,5,6) Sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti) are metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine to form phenylacetylglutamine, which is then excreted by the kidneys. On a molar basis it is comparable to urea, which makes it an alternate vehicle for excreting waste nitrogen.(1,2)</p> <p>Long term management options to prevent hyperammonemia includes dietary modification and nutritional oversight (e.g., protein restriction, limitation of alcohol intake, essential amino acid supplementation if clinically appropriate).(4-6) Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become more brittle as time goes on.(4,5)</p>
Safety	Buphenyl (sodium phenylbutyrate) is contraindicated for management of acute hyperammonemia, which is a medical emergency.(2)

	Pheburane and Olpruva (sodium phenylbutyrate) have no noted contraindications.(7,8)
	Ravicti (glycerol phenylbutyrate) is contraindicated in patients with known hypersensitivity to phenylbutyrate.(1)

REFERENCES

Number	Reference
1	Ravicti prescribing information. Horizon Therapeutics USA, Inc. September 2021.
2	Buphenyl prescribing information. Horizon Therapeutics USA, Inc. July 2022.
3	Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. April 2003 [Updated June 2017]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/ .
4	Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. Available at: https://www.rarediseasesnetwork.org/cms/ucdc/Healthcare-Professionals/Urea-Cycle-Treatment-Guidelines .
5	Summar M. Urea Cycle Disorders. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/ .
6	Haberle J, Burlina A, Chakrapani A, et al. Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders: First Revision. J Inher Metab Dis. 2019;42(6):1041-1230.
7	Pheburane prescribing information. Medunik USA, Inc. June 2022.
8	Olpruva prescribing information. Acer Therapeutics Inc. December 2022.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Ravicti	glycerol phenylbutyrate liquid	1.1 GM/ML	M ; N ; O ; Y	N		
Pheburane	sodium phenylbutyrate oral pellets	483 MG/GM	M ; N ; O ; Y	N		
Buphenyl	sodium phenylbutyrate oral powder	3 GM/TSP	M ; N ; O ; Y	O ; Y		
Olpruva	sodium phenylbutyrate packet for susp	2 GM ; 3 GM ; 4 GM ; 5 GM ; 6 GM ; 6.67 GM	M ; N ; O ; Y	N		
Buphenyl	sodium phenylbutyrate tab	500 MG	M ; N ; O ; Y	O ; Y		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Buphenyl	sodium phenylbutyrate oral powder	3 GM/TSP	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Buphenyl	sodium phenylbutyrate tab	500 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
			Marketplace/BasicRx ; KeyRx
Olpruva	sodium phenylbutyrate packet for susp	2 GM ; 3 GM ; 4 GM ; 5 GM ; 6 GM ; 6.67 GM	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pheburane	sodium phenylbutyrate oral pellets	483 MG/GM	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ravicti	glycerol phenylbutyrate liquid	1.1 GM/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	<p>Initial Evaluation</p> <p>Target Agent(s) will be approved when ALL of the following are met:</p> <ol style="list-style-type: none"> The patient has a diagnosis of hyperammonemia AND ALL of the following: <ol style="list-style-type: none"> The patient has elevated ammonia levels according to the patient's age [Neonate: plasma ammonia level 150 micromol/L (greater than 260 micrograms/dL) or higher; Older child or adult: plasma ammonia level greater than 100 micromol/L (175 micrograms/dL)] AND The patient has a normal anion gap AND The patient has a normal blood glucose level AND The patient has a diagnosis of ONE of the following urea cycle disorders confirmed by enzyme analysis OR genetic testing: <ol style="list-style-type: none"> carbamoyl phosphate synthetase I deficiency [CPSID] OR ornithine transcarbamylase deficiency [OTCD] OR argininosuccinic acid synthetase deficiency [ASSD] OR argininosuccinic acid lyase deficiency [ASLD] OR arginase deficiency [ARG1D] AND The requested agent will NOT be used as treatment of acute hyperammonemia AND 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 The patient will be using the requested agent as adjunctive therapy to dietary protein restriction AND ONE of the following: <ol style="list-style-type: none"> If the requested agent is Buphenyl or Olpruva, then ONE of the following: <ol style="list-style-type: none"> The patient has tried and had an inadequate response to generic sodium phenylbutyrate OR The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the brand agent OR The patient has an FDA labeled contraindication to generic sodium phenylbutyrate that is not expected to occur with the brand agent OR The prescriber has provided information to support the use of the requested brand agent over generic sodium phenylbutyrate OR The patient is currently being treated with the requested agent as indicated by ALL of the following: <ol style="list-style-type: none"> A statement by the prescriber that the patient is currently taking the requested agent AND

Module	Clinical Criteria for Approval
	<p style="margin-left: 40px;">B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent AND</p> <p style="margin-left: 40px;">C. The prescriber states that a change in therapy is expected to be ineffective or cause harm OR</p> <p style="margin-left: 20px;">6. The prescriber has provided documentation that generic sodium phenylbutyrate cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm OR</p> <p style="margin-left: 20px;">B. If the requested agent is Ravicti, ONE of the following:</p> <ol style="list-style-type: none"> 1. The patient has tried and had an inadequate response to generic sodium phenylbutyrate AND Pheburane OR 2. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate AND Pheburane OR 3. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate AND Pheburane OR 4. The patient is currently being treated with the requested agent as indicated by ALL of the following: <ol style="list-style-type: none"> A. A statement by the prescriber that the patient is currently taking the requested agent AND B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent AND C. The prescriber states that a change in therapy is expected to be ineffective or cause harm OR 5. The prescriber has provided documentation that generic sodium phenylbutyrate AND Pheburane cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm AND <p style="margin-left: 20px;">7. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND</p> <p style="margin-left: 20px;">8. The patient does NOT have any FDA labeled contraindications to the requested agent AND</p> <p style="margin-left: 20px;">9. The requested quantity (dose) is within FDA labeled dosing for the requested indication</p> <p>Length of Approval: 12 months</p> <p>Renewal Evaluation</p> <p>Target Agent(s) will be approved when ALL of the following are met:</p> <ol style="list-style-type: none"> 1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process AND 2. The patient has had clinical benefit with the requested agent (e.g., plasma ammonia level within the normal range) AND 3. The requested agent will NOT be used as treatment of acute hyperammonemia AND 4. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction AND 5. ONE of the following: <ol style="list-style-type: none"> A. If the requested agent is Buphenyl or Olpruva, then ONE of the following: <ol style="list-style-type: none"> 1. The patient has tried and had an inadequate response to generic sodium phenylbutyrate OR 2. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the brand agent OR 3. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate that is not expected to occur with the brand agent OR

Module	Clinical Criteria for Approval
	<ol style="list-style-type: none"> 4. The prescriber has provided information to support the use of the requested brand agent over generic sodium phenylbutyrate OR 5. The patient is currently being treated with the requested agent as indicated by ALL of the following: <ol style="list-style-type: none"> A. A statement by the prescriber that the patient is currently taking the requested agent AND B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent AND C. The prescriber states that a change in therapy is expected to be ineffective or cause harm OR 6. The prescriber has provided documentation that generic sodium phenylbutyrate cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm OR <p>B. If the requested agent is Ravicti, ONE of the following:</p> <ol style="list-style-type: none"> 1. The patient has tried and had an inadequate response to generic sodium phenylbutyrate AND Pheburane OR 2. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate AND Pheburane OR 3. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate AND Pheburane OR 4. The patient is currently being treated with the requested agent as indicated by ALL of the following: <ol style="list-style-type: none"> A. A statement by the prescriber that the patient is currently taking the requested agent AND B. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent AND C. The prescriber states that a change in therapy is expected to be ineffective or cause harm OR 5. The prescriber has provided documentation that generic sodium phenylbutyrate AND Pheburane cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm AND 6. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND 7. The patient does NOT have any FDA labeled contraindications to the requested agent AND 8. The requested quantity (dose) is within FDA labeled dosing for the requested indication <p>Length of Approval: 12 months</p>

