crinecerfont (Crenessity™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO322

Description

Crinecerfont (Crenessity) is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist orally administered twice daily.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
crinecerfont (Crenessity)	Adjunct to glucocorticoid replacement to control androgens in adults and pediatrics with classic congenital adrenal hyperplasia (CAH)	25 mg capsules 50 mg capsules 100 mg capsules	60 capsules/30 days
		50 mg/mL solution	120 mL/30days

Initial Evaluation

I. **Crinecerfont (Crenessity)** may be considered medically necessary when the following criteria are met:
   A. Member is 4 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of classic 21-hydroxylase deficiency **congenital adrenal hyperplasia (CAH)** confirmed by one of the following:
      1. Positive newborn screening; **OR**
      2. Positive laboratory testing (e.g., Elevated 17-hydroxyprogesterone (17-OHP) level, positive CYP21A2 genotype, cosyntropin stimulation test, etc.); **AND**
   D. Member is currently taking long-term (> 6 months), supraphysiological glucocorticoid treatment for congenital adrenal hyperplasia (e.g., hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone); **AND**
   E. Provider attestation that medication will be used as adjunctive treatment with glucocorticoid replacement therapy; **AND**
   F. Provider attestation that the medication will not be used in combination with a strong CYP3A4 or CYP2B6 inducer(s) (e.g., carbamazepine, phenobarbital, valproic acid, phenytoin, rifampin, ritonavir); **OR**
      1. Provider attestation that the appropriate dose adjustment will be made while using a strong CYP3A4 or CYP2B6 inducer(s)

II. Crinecerfont (Crenessity) is considered investigational when used for all other conditions, including but not limited to:
   A. Crinecerfont (Crenessity) is used in conditions other than classic CAH that require long-term glucocorticoid therapy.
   B. Non-classic CAH
   C. Crinecerfont (Crenessity) used in classic CAH not due to 21-hydroxylase deficiency

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in glucocorticoid dose, reduction in 17-hydroxyprogesterone (17-OHP) level, reduction in androstenedione level]; **AND**
IV. Provider attestation that the member will continue to use crinecerfont (Crenessity) in combination with glucocorticoid replacement therapy; **AND**
V. Provider attestation that the medication will not be used in combination with a strong CYP3A4 or CYP2B6 inducer(s) (e.g., carbamazepine, phenobarbital, valproic acid, phenytoin, rifampin, ritonavir); **OR**
   - Provider attestation that the appropriate dose adjustment will be made while using a strong CYP3A4 or CYP2B6 inducer(s)

Supporting Evidence

I. Crinecerfont (Crenessity) is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist, FDA-approved as adjunct therapy with glucocorticoid replacement in patients with classic congenital adrenal hyperplasia (CAH) due to a 21-hydroxylase deficiency. The CAHtalyst trial did not enroll any participants under 4 years old; therefore, there is no efficacy and safety data supporting the use of crinecerfont (Crenessity) in this population.
II. In the United States, all newborns are screened for 21-hydroxylase deficiency CAH between two to four days after birth. According to 2018 guidelines from the Endocrine Society (ES), a referral to a pediatric endocrinologist is recommended if an infant has a positive newborn screening for CAH.
III. Evaluation of cosyntropin stimulation testing can be done to confirm the diagnosis after positive newborn screening. In symptomatic patients beyond infancy, screening of early-morning baseline serum 17-OHP levels is recommended, and typically done using liquid chromatography-

tandem mass spectrometry. For patients with borderline 17-OHP levels, a complete adrenocortical profile is recommended after a cosyntropin stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects. Genotyping is also a diagnostic tool for patients with CAH if cosyntropin stimulation tests are ambiguous or cannot be accurately performed.

IV. The 2018 Endocrine Society guidelines recommend hydrocortisone as the preferred first-line maintenance therapy for growing individuals with classic CAH. However, the guidelines recommend against the use of oral hydrocortisone suspension and chronic use of long-acting potent glucocorticoids in this population due to the increased risk of growth suppression in children. In adults with classic CAH, daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids are recommended. Clinical practice guidelines from the American Academy of Family Physicians (AAFP) also provide similar recommendations for first-line treatment.

V. Crinecerfont (Crenessity) was studied in two Phase 3, multicenter, randomized, double-blind, placebo-controlled trials.

- One trial included adults 18 years and older (CAHtalyst Adult); and the other included individual aged 2 to 17 years (CAHtalyst Pediatric). The CAHtalyst Adult trial included 182 participants, with an average age of 30 years, who received supraphysiological daily glucocorticoid dose >13 mg/m^2 of HC-equivalent. Participants were randomized 2:1 to receive crinecerfont (Crenessity) or placebo for 24 weeks. During treatment, baseline glucocorticoid regimen was strategically reduced to achieve the lowest glucocorticoid dose possible while still maintaining androstenedione control. The primary endpoint for the CAHtalyst Adult trial was the percentage change in the daily glucocorticoid dose from baseline to week 24 while maintaining androstenedione control. By the end of week 24, the crinecerfont (Crenessity) arm achieved a statistically significant percentage change in glucocorticoid dose compared to placebo (-27.3 vs -10.3; P<0.001).
- The CAHtalyst Pediatric trial included 103 participants, averaging 12 years of age, who received daily glucocorticoid dose >12 mg/m^2 of HC-equivalent. Similarly to CAHtalyst Adult trial, the glucocorticoid regimen was reduced but had a target dose of 8-10 mg/m^2 of HC-equivalent while maintaining androstenedione control by week 28. The primary endpoint in the pediatric trial was the change in androstenedione levels from baseline to week 4. By week 4, CAHtalyst Pediatric trial also achieved a statistically significant primary endpoint (-197 vs 71; P<0.001).

VI. Crinecerfont (Crenessity) is the first adjunctive agent approved for the management of classic CAH. The current mainstay approach for managing classic CAH is glucocorticoid and/or mineralocorticoid replacement therapy.

VII. The CAHtalyst trials specifically excluded concomitant therapy use of strong inducers of CYP3A4 or CYP2B6. There is no safety data from clinical trials that demonstrates appropriate concomitant use of crinecerfont (Crenessity) with certain CYP inducers. However, the FDA label

includes instructions for dose adjustment with concomitant use of CYP inducers with crinecerfont (Crenessity). A dose increase of up to two times the standard recommended dose is advised when crinecerfont (Crenessity) is used in combination with a strong CYP3A4 inducer, and a dose increase of 1.5 times the standard recommended dose is advised when used in combination with a moderate CYP3A4 inducer (see appendix for examples).

Investigational or Not Medically Necessary Uses

I. Crinecerfont (Crenessity) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Crinecerfont (Crenessity) is used in any conditions other than classic CAH that require long-term glucocorticoid therapy.
      i. There are no current data or investigations on the use of crinecerfont (Crenessity) in any conditions other than CAH that requires chronic glucocorticoid replacement therapy. CAHtalyst trials excluded any conditions outside CAH that require glucocorticoid dosing; thus, there is no efficacy and safety evidence to suggest clinical benefit of crinecerfont (Crenessity) in any other conditions.
   B. Non-classic CAH
      i. Non-classic CAH is considered the mild form of the condition. Patients with non-classic CAH often exhibit mild to no symptoms or clinical presentation. The risks of treatment may outweigh the benefits in this population; thus, this indication is considered experimental and investigational at this time.
   C. Crinecerfont (Crenessity) used in classic CAH not due to 21-hydroxylase deficiency
      i. Crinecerfont (Crenessity) was only studied in patients who have 21-hydroxylase deficiency classic CAH.
      ii. There is a lack of evidence to support the use to crinecerfont (Crenessity) in CAH due to other enzyme deficiency.

Appendix

I. Table 1: CYP3A4 and CYP2B6 inducers

	CYP3A4 inducers	CYP2B6 inducers
Strong inducers	Carbamazepine Dexamethasone Fosphenytoin Lumacaftor Midostaurin Mitotane Phenobarbital Phenytoin Primidone Rifampin	Carbamazepine Fosphenytoin Nevirapine Phenobarbital Phenytoin

	St. John's Wort	
Moderate inducers	Bosentan Dexamethasone Efavirenz Etravirine Modafinil Nafcillin	Alpelisib Rifampin

** This table includes only common examples and is not a comprehensive list.*

References

1. Crenessity product dossier. Neurocrine Biosciences, Inc; August 2024.
2. Crenessity. Package Insert. Neurocrine Biosciences, Inc; December 2024.
3. Endocrine Society. Congenital Adrenal Hyperplasia Guideline Resources. September 19, 2018. Accessed February 19, 2025. Congenital Adrenal Hyperplasia Guideline Resources | Endocrine Society
4. Deaton, M.A, Glorioso, J.E., & Mclean, D.B. Congenital Adrenal Hyperplasia: Not Really a Zebra. *American Family Physician*. 1999;59(5):1190-1196. https://www.aafp.org/pubs/afp/issues/1999/0301/p1190.html.
5. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia. N Eng J Med. 2024;391:504-514. DOI: 10.1056/NEJMoa2404656.
6. Sarafoglou K, Kim MS, Lodish M, et al. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. N Eng J Med. 2024;391:493-503. DOI: 10.1056/NEJMoa2404655.
7. Sharma L, Momodu II, & Singh G. Congenital Adrenal Hyperplasia. National Library of Medicine. Update January 27, 2025. Accessed February 20, 2025. Congenital Adrenal Hyperplasia - StatPearls - NCBI Bookshelf

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2025