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Subject: Crinecerfont (Crenessity) Capsule and Oral Solution

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Congenital adrenal hyperplasia (CAH) is a genetic enzyme deficiency, which results in altered production of one or more adrenal steroids (e.g., cortisol, mineralocorticoids, androgens). The two major types of CAH are classic and non-classic. Non-classic is a mild, common form of CAH with clinical presentation in childhood or early adulthood; however, classic is a rarer, more serious form of the disease and is typically identified as part of newborn screening. The prevalence of classic type 21-hydroxylase deficiency CAH is 1 per 15,000 live births. Symptoms of classic CAH include reduced cortisol production which leads to adrenal crisis and problems regulating blood pressure, blood glucose, energy production, and increased risk of illness during periods of stress. Additional complications include increased androgen production resulting in patients being born with atypical genitalia, usually enlarged, and altered urinary anatomy requiring surgical intervention. Long-term complications include early puberty, accelerated growth with short stature, and fertility issues. Management includes chronic treatment with glucocorticoid (e.g., hydrocortisone) and mineralocorticoid (e.g., fludrocortisone) replacement therapy.

On December 13, 2024, the FDA approved crinecerfont (Crenessity) as adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic CAH. Crinecerfont (Crenessity) is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist that blocks the binding of CRF to CRF type 1 receptors in the pituitary. The blockade inhibits adrenocorticotropic hormone (ACTH) secretion from the pituitary, thereby reducing ACTH-mediated adrenal androgen production.

As summarized in the prescribing information, the efficacy and safety of crinecerfont (Crenessity) was evaluated in two randomized, double-blind, placebo-controlled trials; one in the adult population and one in the pediatric population. The adult study (Study 1; NCT#04490915) enrolled 182 patients with

classic CAH due to 21-hydroxylase deficiency on supraphysiological glucocorticoid doses and with androgen concentrations in the normal range or with inadequate androgen control. Patients were randomized to receive crinecerfont (Crenessity) 100 mg twice daily (N=122) or placebo (N=60) for 24 weeks. During the first 4 weeks of crinecerfont (Crenessity) treatment, patients maintained a stable glucocorticoid regimen except for stress dosing as needed. During Weeks 4 to 12, the glucocorticoid dose was reduced as frequently as every 2 weeks without regard to androstenedione levels, with the goal to achieve a glucocorticoid dose of 8 to 10 mg/m^2/day in hydrocortisone dose equivalents by Week 12. From Weeks 12 to 20, the glucocorticoid dose was further adjusted, if needed, to achieve androstenedione control by Week 24. The mean (range) age was 31 years (range: 18 to 58 years), 51% were male, 90% were Caucasian, and 8% were Hispanic or Latino. At baseline, the mean (SD) glucocorticoid total daily dose in hydrocortisone equivalents was 32 (9) mg/day (18 [5] mg/m^2/day), with mean (SD) androstenedione levels of 620 (729) ng/dL prior to the morning glucocorticoid dose. The efficacy of crinecerfont (Crenessity) was assessed by the least-squares (LS) mean (SEM) percent change from baseline in the total glucocorticoid daily dose while androstenedione was controlled (≤120% of baseline or ≤upper limit of normal [ULN]) after 24 weeks. The LS mean percent change from baseline in daily glucocorticoid dose was greater in the crinecerfont (Crenessity) group at -27% compared to -10% in the placebo group, as shown in Table 1.

At week 24, there was a greater percentage of patients achieving a reduction to a physiologic glucocorticoid daily dose (≤11 mg/m^2/day hydrocortisone equivalents) while androstenedione was controlled (≤120% of baseline or ≤ULN) with crinecerfont (Crenessity) compared to placebo (63% vs 18%, p<0.0001). At Week 4, following a treatment period at a stable glucocorticoid dose regimen, the LS mean change from baseline in serum androstenedione in the crinecerfont (Crenessity) group was significantly different at -299 ng/dL compared to the LS mean increase from baseline in the placebo group of 46 ng/dL, as shown in Table 2.

Table 1: Percent Change from Baseline in Glucocorticoid Daily Dose while Maintaining Androstenedione Control at Week 24 in Adults with Classic CAH

	Treatment Group	Mean (SD) Baseline (mg/m^2/day)	LS Mean (SEM) Percent Change From Baseline (%)	Placebo-Subtracted LS Mean Difference (95% CI) (%)
Glucocorticoid Daily Dose*	Crinecerfont (N=122)	18 (5)	-27 (2)	-17 (-24, -10) p<0.0001
	Placebo (N=60)	18 (6)	-10 (3)	

CI=confidence interval; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean

*In hydrocortisone equivalents (4x equivalency factor for (methyl)predniso(lo)ne, 60x for dexamethasone) adjusted for body surface area.

Table 2: Change from Baseline in Serum Androstenedione (ng/dL) at Week 4* in Adults with Classic CAH

	Treatment Group	Mean (SD) Baseline	LS Mean (SEM) Change from Baseline	Placebo-subtracted LS Mean Difference (95% CI)
Serum Androstenedione (ng/dL)†	Crinecerfont (N=122)	634 (796)	-299 (38)	-345 (-457, -232) p< 0.0001
	Placebo (N=60)	590 (572)	46 (51)	

CI=confidence interval; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean

*End of glucocorticoid stable period.

†Obtained prior to the morning glucocorticoid dose.

The pediatric study (Study 2; NCT#04806451) enrolled 103 patients 4 to 17 years of age with classic CAH due to 21-hydroxylase deficiency and inadequate androgen control on supraphysiological glucocorticoid doses. Patients were randomized to receive either crinecerfont (Crenessity) twice daily (N=69) or placebo (N=34) for 28 weeks, using weight-based dosing (50 mg twice daily via oral solution for patients 20 to < 55 kg [crinecerfont N=37; placebo N=14], or 100 mg twice daily via oral capsules for patients ≥ 55 kg [crinecerfont N=32; placebo N=20]). During the first 4 weeks of crinecerfont (Crenessity) treatment, patients were maintained on a stable glucocorticoid regimen except for stress dosing, as needed. The primary efficacy endpoint was the change from baseline in serum androstenedione at Week 4. From Weeks 4 to 20, the glucocorticoid dose could be reduced as frequently as every 4 weeks provided androstenedione levels were controlled. The goal was to achieve a glucocorticoid dose of 8 to 10 mg/m^2 /day (hydrocortisone dose equivalents) by Week 28 while maintaining androstenedione control. The mean (range) age was 12 years (range: 4 to 17 years), 41% were Tanner Stage 1 or 2, 52% were male, 63% were Caucasian, and 11% were Hispanic or Latino. With respect to concurrent glucocorticoid use at baseline, 92% of patients were receiving hydrocortisone alone and 8% were receiving prednisone [or equivalent] (with or without hydrocortisone). At baseline, patients were receiving a mean (SD) glucocorticoid total daily dose in hydrocortisone equivalents of 16 (4) mg/m^2/day and had a mean (SD) androstenedione level of 431 (461) ng/dL and mean (SD) serum 17-hydroxyprogesterone level of 8682 (6847) ng/dL prior to the morning glucocorticoid dose. At Week 4, following a treatment period at a stable glucocorticoid dose regimen, the LS mean reduction from baseline in serum androstenedione in the crinecerfont (Crenessity) group was significantly different at -197 ng/dL compared to the increase of 71 ng/dL in the placebo group, as shown in Table 3.

At Week 4, following a treatment period at a stable glucocorticoid regimen, the LS mean reduction (SEM) from baseline in serum 17-hydroxyprogesterone in the crinecerfont (Crenessity) group was statistically different at -5865 (572) ng/dL compared to the increase of 556 (818) ng/dL in the placebo group (LS Mean Treatment Difference -6421, 95% CI -8387, -4454, p< 0.0001). The LS mean percent change from baseline in the total glucocorticoid daily dose while androstenedione was controlled (≤120% of baseline or ≤ULN) at Week 28 in the crinecerfont (Crenessity) group was statistically different at -18% compared to the increase of 6% in the placebo group, as shown in Table 4.

Table 3: Change from Baseline in Serum Androstenedione (ng/dL) at Week 4* in Pediatric Patients with Classic CAH

	Treatment Group	Mean (SD) Baseline	LS Mean (SEM) Change from Baseline	Placebo-subtracted LS Mean Difference (95% CI)
Serum Androstenedione (ng/dL)†	Crinecerfont (N=69)	405 (464)	-197 (40)	-268 (-403, -132) p=0.0002
	Placebo (N=34)	483 (456)	71 (56)	

CI=confidence interval; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean

*End of glucocorticoid stable period.

†Obtained prior to the morning glucocorticoid dose.

Table 4: Percent Change from Baseline in Glucocorticoid Daily Dose while Maintaining Androstenedione Control at Week 28 in Pediatric Patients with Classic CAH

	Treatment Group	Mean (SD) Baseline (mg/m^2/day)	LS Mean (SEM) Percent Change from Baseline (%)	Placebo-Subtracted LS Mean Difference (95% CI) (%)
Glucocorticoid Daily Dose*	Crinecerfont (N=69)	17 (4)	-18 (2)	-24 (-30, -17) p< 0.0001
	Placebo (N=34)	16 (3)	6 (3)	

CI=confidence interval; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean

*In hydrocortisone equivalents (4x equivalency factor for (methyl)predniso(lo)ne) adjusted for body surface area.

The most common adverse reactions associated with crinecerfont (Crenessity) in adults are fatigue, headache, dizziness, arthralgia, back pain, decreased appetite, and myalgia and in pediatrics are headache, abdominal pain, fatigue, nasal congestion, and epistaxis.

POSITION STATEMENT:

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of crinecerfont (Crenessity) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria (“1” to “7”):

1. Member is 4 years of age or older
2. Diagnosis of classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency as confirmed by **ONE** of the following ("a," "b," or "c"): - laboratory documentation must be provided
    a. Positive infant screening with second-tier confirmation (e.g., liquid chromatography–tandem mass spectrometry)
    b. Cosyntropin (ACTH) stimulation test
    c. Genetic testing (e.g., *CYP21A2* gene mutation consistent with CAH)
3. Member is receiving a supraphysiologic glucocorticoid regimen as follows ("a" or "b") - documentation must be provided
    a. Pediatric: Total glucocorticoid dose greater than 12 mg/m^2/day of hydrocortisone dose equivalents
    b. Adult: Total glucocorticoid dose greater than 13 mg/m^2/day of hydrocortisone dose equivalents
4. Crinecerfont (Crenessity) will be prescribed in conjunction with glucocorticoid replacement therapy
5. The medication is prescribed by an endocrinologist or specialist with expertise in the diagnosis and management of classic CAH
6. The provider attests that the member's complete medication list has been reviewed and modified, if possible, to prevent coadministration of crinecerfont with CYP3A4 moderate inducers (e.g., dexamethasone, efavirenz, modafinil, nafcillin) and CYP3A4 strong inducers (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wart)
7. Total daily dose does not exceed the following ("a," "b," or "c"):
    a. Weight 10 kg to less than 20 kg: 50 mg daily without a CYP3A4 inducer, 75 mg daily with a moderate CYP3A4 inducer, or 100 mg daily with a strong CYP3A4 inducer
    b. Weight 20 kg to less than 55 kg: 100 mg daily without a CYP3A4 inducer, 150 mg daily with a moderate CYP3A4 inducer, or 200 mg daily with a strong CYP3A4 inducer
    c. Weight greater than or equal to 55 kg and adults: 200 mg daily without a CYP3A4 inducer, 300 mg daily with a moderate CYP3A4 inducer, or 400 mg daily with a strong CYP3A4 inducer

Duration of approval: 6 months

Continuation of crinecerfont (Crenessity) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria ("1" to "6"):

- Authorization or reauthorization for crinecerfont (Crenessity) has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of classic congenital adrenal hyperplasia (if another health plan, documentation of a health plan-paid claim for crinecerfont (Crenessity) during the 90 days immediately before the authorization request must be submitted); **OR** the member previously met **ALL** indication-specific initiation criteria
- The member has had a beneficial response to therapy (e.g., improvement in androgen control, reduction in glucocorticoid daily dose) – documentation must be provided
- The member is taking and will continue a glucocorticoid replacement regimen

- The medication is prescribed by an endocrinologist or specialist with expertise in the diagnosis and management of classic CAH
- The provider attests that the member's complete medication list has been reviewed and modified, if possible, to prevent coadministration of crinecerfont with CYP3A4 moderate inducers (e.g., dexamethasone, efavirenz, modafinil, nafcillin) and CYP3A4 strong inducers (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wart)
- Total daily dose does not exceed the following ("a," "b," or "c"):
    a. Weight 10 kg to less than 20 kg: 50 mg daily without a CYP3A4 inducer, 75 mg daily with a moderate CYP3A4 inducer, or 100 mg daily with a strong CYP3A4 inducer
    b. Weight 20 kg to less than 55 kg: 100 mg daily without a CYP3A4 inducer, 150 mg daily with a moderate CYP3A4 inducer, or 200 mg daily with a strong CYP3A4 inducer
    c. Weight greater than or equal to 55 kg and adults: 200 mg daily without a CYP3A4 inducer, 300 mg daily with a moderate CYP3A4 inducer, or 400 mg daily with a strong CYP3A4 inducer

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Crinecerfont (Crenessity) is a corticotropin-releasing factor type 1 receptor antagonist indicated as adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

- Crinecerfont (Crenessity) is administered orally, twice daily, with a meal in the morning and evening. The dose is 100 mg orally twice daily for adults and weight-based for pediatric patients as follows:
    a. Weight 10 kg to less than 20 kg: 25 mg orally twice daily
    b. Weight 20 kg to less than 55 kg: 50 mg orally twice daily
    c. Weight greater than or equal to 55 kg: 100 mg orally twice daily

- Capsules should be swallowed whole, and unopened bottles of solutions should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Once a bottle is opened for use, it may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature (15°C to 25°C [59°F to 77°F]) for up to 30 days. Discard any unused oral solution after 30 days of first opening the bottle.

Dose Adjustments

- Dosage adjustments of crinecerfont (Crenessity) are necessary if administered with CYP3A4 inducers. The dosage adjustments are as follow for strong and moderate CYP3A4 inducers.
    - If administered with a moderate CYP3A4 inducer, crinecerfont (Crenessity) is dosed as follows:

        - Weight 10 kg to less than 20 kg: 25 mg orally in the morning and 50 mg orally in the evening
        - Weight 20 kg to less than 55 kg: 50 mg orally in the morning and 100 mg orally in the evening
        - Weight greater than or equal to 55 kg and adults: 100 mg orally in the morning and 200 mg orally in the evening
    - If administered with a strong CYP3A4 inducer, crinecerfont (Crenessity) is dosed as follows:
        - Weight 10 kg to less than 20 kg: 50 mg orally twice daily
        - Weight 20 kg to less than 55 kg: 100 mg orally twice daily
        - Weight greater than or equal to 55 kg and adults: 200 mg orally twice daily
- Crinecerfont (Crenessity) is not recommended in patients with severe renal impairment or end-stage renal disease.

Drug Availability

- Capsules: 25 mg (60-count bottle, NDC 70370-5025-1), 50 mg (60-count bottle, NDC 70370-5050-1), 100 mg (30-count bottle, NDC 70370-5100-1)
- Oral Solution: 50 mg/mL in an amber polyethylene terephthalate (PET) bottle contains 30 mL oral solution (NDC 70370-5250-1)

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Crinecerfont (Crenessity) is contraindicated in patients with hypersensitivity to the product or any excipients.

Precautions/Warnings

- **Hypersensitivity Reactions:** A hypersensitivity reaction, including throat tightness, angioedema, and generalized rash, occurred in a patient after 3 days of treatment with crinecerfont (Crenessity). If a clinically significant hypersensitivity reaction occurs, initiate appropriate therapy and discontinue crinecerfont (Crenessity).
- **Risk of Acute Adrenal Insufficiency or Adrenal Crisis with Inadequate Concomitant Glucocorticoid Therapy:** Continue glucocorticoids upon initiation of and during treatment with crinecerfont (Crenessity). Do not reduce the glucocorticoid dose below the dose required for cortisol replacement. Acute adrenal insufficiency or adrenal crisis, which can potentially be fatal or life-threatening, can occur in patients with underlying adrenal insufficiency who are on inadequate daily glucocorticoid doses, especially in situations associated with increased cortisol need, such as acute intercurrent illness, serious trauma, or surgical procedures. Any adjustment of daily glucocorticoid dosage after initiation of crinecerfont (Crenessity) should be performed under the supervision of a health care provider. Use glucocorticoid stress doses in case of increased cortisol need (e.g., acute intercurrent illness, serious trauma, surgical procedures). In the placebo-controlled clinical study of

adults with classic CAH, the incidence of adrenal crisis was 1.6% in patients treated with crinecerfont (Crenessity) and 0% in patients treated with placebo. In the placebo-controlled clinical study of pediatric patients with classic CAH, there were no events of adrenal crisis.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E25.0	Congenital adrenogenital disorders associated with enzyme deficiency

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

REFERENCES:

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4. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2025. URL http://www.dynamed.com. Accessed 1/31/25.
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2026 [cited 2025 Jan 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline: Crinecerfont (Crenessity) as adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia.
03/15/26	Review and revision to guideline consisting of updating the billing/coding and references.