PDL DRUG REVIEW

Proprietary Name: Crenessity®
Common Name: crinecerfont
PDL Category: Endocrine Metabolic Agents

Comparable Products	Preferred Drug List Status
Corticosteroids	Preferred

Pharmacology/Usage: Crinecerfont, the active ingredient of Crenessity®, is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist. Crinecerfont blocks the binding of CRF to CRF type 1 receptors in the pituitary but not CRF type 2 receptors. Crinecerfont binding to CRF type 1 receptors inhibits adrenocorticotropic hormone (ACTH) secretion from the pituitary, thus reducing ACTH-mediated adrenal androgen production.

Indication: 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).

There is no pregnancy category for this medication; however, the risk summary indicates that available data from reports of pregnancy in clinical trials are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. If Crenessity® is administered during pregnancy, or if a patient becomes pregnant while receiving Crenessity®, health care providers should report exposure to Crenessity® by calling 1-855-CRNSITY. The safety and efficacy of use in the pediatric population less than 4 years of age have not been established.

Dosage Form: Available as:

- Capsules: 25mg, 50mg, and 100mg. (Swallow whole with liquid)
- Oral Solution: 50mg/ml. (Discard any unused solution after 30 days of first opening the bottle.)

Recommended Dosage: Patients receiving Crenessity® should continue glucocorticoid replacement therapy for the adrenal insufficiency associated with congenital adrenal hyperplasia.

Androstenedione levels can be assessed beginning four weeks after Crenessity® initiation to inform reduction in glucocorticoid dosage as clinically indicated. Do not reduce the glucocorticoid dosage below that required for replacement therapy.

The recommended dosage for adults is 100mg PO BID with a meal in the morning and evening. The recommended dosage for pediatric patients 4 years of age and older is weight-based and administered PO BID with a meal in the morning and evening. Refer to the table below, which was adapted from the prescribing information.

Weight	Dosage Regimen with a meal
10kg to less than 20kg	25mg PO BID
20kg to less than 55kg	50mg PO BID

Weight	Dosage Regimen with a meal
Greater than or equal to 55kg	100mg PO BID

If a dose or doses are missed, advise the patient to take one dose as soon as possible (even if it is soon before the next scheduled dose) and then to resume the regular dosing schedule.

Crenessity® is not recommended in patients with severe renal impairment or end-stage renal disease.

Drug Interactions: Crenessity® is a CYP3A4 substrate. Concomitant use of Crenessity® with a strong or moderate CYP3A4 inducer decreases crinecerfont exposure, which may reduce Crenessity® efficacy.

Increase Crenessity® morning and evening dosages 2-fold when Crenessity® is used concomitantly with a strong CYP3A4 inducer. Refer to the prescribing information for additional information.

Increase Crenessity® evening dosage 2-fold when Crenessity® is used concomitantly with a moderate CYP3A4 inducer. Do not increase the morning dosage. Refer to the prescribing information for additional information.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Crenessity®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included fatigue (10%), headache (1%), dizziness (5%), arthralgia (7%), back pain (3%), decreased appetite (2%), and myalgia (1%).

Study 1 excluded subjects with active suicidal ideation with intent or plan within the six months prior to screening and those with a history of suicidal behavior within the past year, based on the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at screening. Three of 122 Crenessity®-treated subjects (2.5%) reported suicidal ideation without method, intent or plan on the C-SSRS during the 24-week double-blind treatment period compared to 1 of 59 placebo-treated patients (1.7%). One of the three subjects receiving Crenessity® and the placebo-treated subject reported a lifetime history of suicidal ideation. One Crenessity®-treated subject without a history of suicidal ideation or behavior attempted suicide during the open-label period after 320 days of treatment.

A hypersensitivity reaction occurred in a subject after 3 days of Crenessity® treatment. If a clinically significant hypersensitivity reaction occurs, start appropriate therapy and discontinue Crenessity®.

Continue glucocorticoids upon initiation of and during Crenessity® treatment. Do not reduce the glucocorticoid dose below the dose required for cortisol replacement. Acute adrenal insufficiency or adrenal crisis can occur in patients with underlying adrenal insufficiency who are on inadequate daily glucocorticoid doses, especially in situations associated with increased cortisol need. Any adjustment of daily glucocorticoid dosage after starting Crenessity® should be performed under the supervision of a healthcare provider. Use glucocorticoid stress doses in case of increased cortisol need.

Contraindications: In patients with hypersensitivity to crinecerfont or any excipients of the product.

Manufacturer: Neurocrine Biosciences, Inc.

Analysis: The efficacy of Crenessity® to reduce androgen levels and enable a reduced glucocorticoid dose while maintaining androgen control in adults with classic CAH was assessed in a randomized, double-blind, placebo-controlled study that enrolled adults (N=182) 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.

Subjects were randomized to Crenessity® or placebo for 24 weeks; during the first 4 weeks of Crenessity® treatment, subjects maintained a stable glucocorticoid regimen except for stress dosing as needed. During weeks 4 to 12,

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 10mg/m^2/day in hydrocortisone dose equivalents adjusted for body surface area by week 12. From weeks 12 to 20, the glucocorticoid dose was further adjusted, if needed, to achieve androstenedione control by week 24. The included patients had a mean age of 31 years (range 18 to 58), while 51% were male and 90% were white. At baseline, the mean glucocorticoid total daily dose in hydrocortisone equivalents was 32mg/day, with mean androstenedione levels of 620ng/dL prior to the morning glucocorticoid dose.

The efficacy of Crenessity® was assessed by the least-squares (LS) mean 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 statistically significantly greater in the Crenessity® group at -27% compared to -10% in the placebo group (placebo-subtracted LS mean difference of -17%; p<0.0001).

At week 24, there was a statistically significantly greater percentage of subjects achieving a reduction to a physiologic glucocorticoid daily dose (≤11mg/m^2/day hydrocortisone equivalents) while androstenedione was controlled (≤120% of baseline or ≤ULN) with 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 Crenessity® group was statistically significantly different at -299ng/dL compared to the LS mean increase from baseline in the placebo group of 46ng/dL (placebo-subtracted LS mean difference -345 ng/dL; p<0.0001).

Pediatric study: The efficacy of Crenessity® to improve androgen control and enable a reduced glucocorticoid dose while maintaining androgen control in pediatric patients with classic CAH was assessed in a phase 3 randomized, double-blind, placebo-controlled study that enrolled pediatric patients 4 to 17 years of age (N=103) with classic CAH due to 21-hydroxylase deficiency and inadequate androgen control on supraphysiological glucocorticoid doses.

Subjects were randomized to Crenessity® or placebo for 28 weeks, using weight-based dosing. During the first 4 weeks of Crenessity® treatment, subjects were maintained on a stable glucocorticoid regimen except for stress dosing, as needed. The mean age of included patients was 12 years (range 4 to 17), while 41% were Tanner Stage 1 or 2, 52% were male and 63% were white. With respect to concurrent glucocorticoid use at baseline, 92% were receiving hydrocortisone alone and 8% were receiving prednisone [or equivalent] (with or without hydrocortisone). At baseline, subjects were receiving a mean glucocorticoid total daily dose in hydrocortisone equivalents of 16mg/m^2/day and had a mean androstenedione level of 431ng/dL and mean serum 17-hydroxyprogesterone level of 8682ng/dL prior to the morning glucocorticoid dose.

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 10mg/m^2/day (hydrocortisone dose equivalents adjusted for body surface area) by week 28 while maintaining androstenedione control. Results suggested that at week 4, following a treatment period at a stable glucocorticoid dose regimen, the LS mean reduction from baseline in serum androstenedione in the Crenessity® group was statistically significantly different at -197ng/dL compared to the increase of 71ng/dL in the placebo group (placebo-subtracted LS mean difference -268ng/dL; p=0.0002).

At week 4, following a treatment period at a stable glucocorticoid regimen, the LS mean reduction from baseline in serum 17-hydroxyprogesterone in the Crenessity® group was statistically significantly different at -5865 ng/dL compared to the increase of 556ng/dL in the placebo group (LS mean treatment difference -6421, 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 Crenessity® group was statistically significantly different at -18% compared to the increase of 6% in the placebo group (placebo-subtracted LS mean difference -24%, p<0.0001).

Place in Therapy: 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). Patients receiving Crenessity® should continue glucocorticoid replacement therapy for the adrenal insufficiency associated with congenital adrenal hyperplasia. In addition, androstenedione levels can be assessed beginning four weeks after Crenessity® initiation to inform reduction in glucocorticoid dosage as clinically indicated. Do not reduce the glucocorticoid dosage below that required for replacement therapy. The safety and efficacy of use were assessed in both adult and pediatric patients, in randomized, double-blind, placebo-controlled studies. The LS mean percent change from baseline in daily glucocorticoid dose for adults (primary outcome) was statistically significantly greater in the Crenessity® group than placebo ($p<0.0001$). At week 4 in the pediatric study, following a treatment period at a stable glucocorticoid dose regimen, the LS mean reduction from baseline in serum androstenedione (primary outcome) in the Crenessity® group was statistically significantly different as compared to placebo ($p=0.0002$). Crenessity® is the first FDA-approved treatment for patients with classic CAH, approved as adjunctive treatment to control androgens. Hydrocortisone is suggested as first line treatment for adults with classic CAH.[2]

Summary

There is no evidence at this time to support that Crenessity® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Crenessity® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Crenessity® [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; 2024.

[2] UpToDate. Treatment of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults. Accessed February 2025.

Prepared By: Iowa Medicaid Date: 02/17/2025