Crenessity™ (crinecerfont) – New orphan drug approval

- On December 13, 2024, the FDA announced the approval of Neurocrine Biosciences' Crenessity (crinecerfont), 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).**

- **Classic CAH is a rare genetic condition** affecting the adrenal glands, which produce hormones such as cortisol and androgens. Patients with classic CAH do not produce enough cortisol and produce too many androgens. These patients require high doses of glucocorticoids (more than is typically needed to replace the deficient cortisol) because the glucocorticoids also help to reduce the excess levels of androgens.

- Crenessity works by reducing excessive adrenal androgen production, which helps reduce the amount of glucocorticoid treatment needed.

- The efficacy of Crenessity was established in a randomized, double-blind, placebo-controlled study in 182 **adults 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 Crenessity or placebo for 24 weeks. After the first four weeks, the glucocorticoid dose was reduced to replacement levels, then adjusted based on levels of androstenedione, an androgen hormone. The primary endpoint was the least-squares (LS) mean percent change from baseline in the total glucocorticoid daily dose while androstenedione was controlled after 24 weeks.

    — The LS mean percent change from baseline in daily glucocorticoid dose was greater in the Crenessity group at -27% compared to -10% in the placebo group (placebo-subtracted LS mean difference -17, 95% CI: -24, -10 $p < 0.0001$).

- The efficacy of Crenessity was also established in a randomized, double-blind, placebo-controlled study in 103 **pediatric 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 Crenessity or placebo for 28 weeks. The primary endpoint was the change from baseline in serum androstenedione at week 4.

    — 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 -197 ng/dL compared to the increase of 71 ng/dL in the placebo group (placebo-subtracted LS mean difference -268, 95% CI: -403, -132; $p = 0.0002$).

- Warnings and precautions for Crenessity include **hypersensitivity reactions and risk of acute adrenal insufficiency or adrenal crisis** with inadequate concomitant glucocorticoid therapy.

- The most common adverse reactions (≥ 4% and greater than placebo) with Crenessity use in **adults** were **fatigue, headache, dizziness, arthralgia, back pain, decreased appetite, and myalgia**.

- The most common adverse reactions (≥ 4% and greater than placebo) with Crenessity use in **pediatric** patients were **headache, abdominal pain, fatigue, nasal congestion, and epistaxis**.

- The recommended dose of Crenessity in adults is 100 mg orally, **twice daily** with a meal in the morning and evening.

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- The recommended dose of Crenessity in pediatric patients is weight-based (25 mg to 100 mg) and administered orally, twice daily with a meal in the morning and evening.
- Neurocrine Biosciences plans to launch Crenessity about a week after approval. Crenessity will be available as a capsule (5 mg, 50 mg, and 100 mg) and an oral solution (50 mg/mL).

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