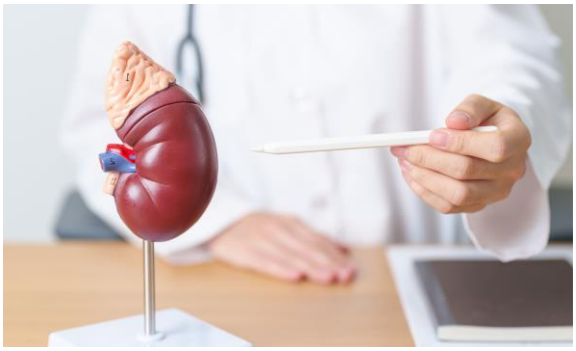
FDA Approves Crinecerfont for Adult, Pediatric Patients with Congenital Adrenal Hyperplasia

The decision is based on positive results from the CAHtalyst trials, which both met their primary and secondary end points.

Crinecerfont (Crenessity; Neurocrine Biosciences) received FDA approval for use with glucocorticoids to control androgen levels in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH). This decision marks crinecerfont as the first new treatment option for these patients in 70 years.[1]

CAH is a rare genetic disorder characterized by an enzyme deficiency, altering the production of adrenal steroid hormones including cortisol, aldosterone and adrenal androgens. There are 2 types of CAH: classic, which is diagnosed at birth or in early infancy, and nonclassic, which may not be symptomatic until childhood or adulthood.[1,2]



Adrenal gland model

Approximately 95% of classic CAH cases are caused by a deficiency in the enzyme protein 21-hydroxylase (21-OH), which is needed to produce proper amounts of adrenal hormones. Patients with CAH typically produce too many androgens and not enough cortisol, leading to an increased risk of metabolic diseases, early or rapid puberty, abnormal bone growth, and fertility issues. If left untreated, it can result in salt wasting, dehydration, and mortality.[1]

Many patients with CAH are treated with exogenous glucocorticoids (GCs) to reduce excess levels of androgens; however, doses are typically higher than needed to replace deficient cortisol. High doses of GCs have been linked insignificant complications of steroid excess, weight gain, diabetes, cardiovascular disease, and osteoporosis. There are also cognitive and psychological impacts associated with long-term use of GCs that can cause changes to mood and memory.[1,2]

Crinecerfont is a potent and selective oral corticotropin-releasing factor type 1 receptor (CRF1) antagonist that reduces excessive adrenal androgen production, which may help reduce the amount of GC treatment needed. Its safety and efficacy were observed in the CAHtalyst Pediatric

(NCT04806451) and CAHtalyst Adult (NCT04490915) studies where it was well tolerated with few treatment-related adverse events (TEAEs).[1,3,4]

"The clinical results across both CAHtalyst studies support the efficacy and safety profile of CRENESSITY and its ability to reduce the overproduction of adrenal androgens, allowing for a meaningful reduction in glucocorticoid dosage, while maintaining or enhancing control of these androgens," Richard Auchus, MD, PhD, professor at the University of Michigan Health, said in a news release. "Chronic treatment with supraphysiologic glucocorticoids can cause a number of short- and long-term health consequences, such as obesity, hypertension and osteoporosis, so the ability for patients with CAH to lower their glucocorticoid dose to a more physiologic level can have profound benefits."[1]

In the CAHtalyst Pediatric study, investigators randomized 103 participants to receive either crinecerfont (n=69) or placebo (n=34). At week 4, crinecerfont met its primary end point, demonstrating significant reductions in androstenedione levels from baseline (−197 ng per deciliter [−6.9 nmol/liter]) compared with placebo, which showed substantial increases in their levels (71 ng per deciliter [2.5 nmol/liter]). At week 28, the secondary end point was met, showing that pediatric patients receiving crinecerfont were able to reduce their GC doses and maintain androgen levels.[1,3]

Additional findings demonstrated that crinecerfont also resulted in a 4 times greater steroid dose reduction compared with placebo, as well as a 12 times greater reduction in 17-hydroxyprogesterone (17-OHP) in pediatric patients.[1,3]

The CAHtalyst Adult trial, 182 patients were randomly assigned to receive either crinecerfont (n=122) or placebo (n=60). At week 24, crinecerfont met its primary end point of significant GC dose reductions while maintaining or improving baseline androstenedione levels, as well as its secondary end point of decreased androstenedione levels at Week 4. According to the study results, 63% of patients receiving crinecerfont achieved a GC dose in the physiologic range while androstenedione was maintained or improved compared with patients taking placebo (18%).[1,4]

In adults, treatment with crinecerfont was associated with 2 times greater steroid dose reductions, a 6 times greater decrease in androstenedione, and a 37 times greater reduction in 17-OHP compared with those taking placebo.[1,4]

The most common TEAEs were temporary and mild to moderate in severity. The most common adverse effects headache, abdominal pain, fatigue, nasal congestion and nosebleeds in pediatric patients; and fatigue, headache, dizziness, joint pain, back pain, decreased appetite and muscle pain in adult patients.[1]

"Today's approval provides an important advance for patients with classic congenital adrenal hyperplasia and highlights the FDA's continued commitment to advancing effective and safe treatments for rare diseases," Theresa Kehoe, MD, director of the Division of General Endocrinology in the FDA's Center for Drug Evaluation and Research, said in a news release. "The FDA will continue working with patients, drug companies and health care providers to address the unmet medical needs of the rare disease community."[1]

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