CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218808Orig1s000, 218820Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	218808 (soft gel capsule) and 218820 (oral solution)
PDUFA Goal Date	December 30, 2024
Nexus TTT #	2024-9302 and 2024-9305
Reviewer Name(s)	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Laura Zendel, PharmD
Review Completion Date	December 12, 2024
Subject	Evaluation of Need for a REMS
Established Name	Crinecerfont
Trade Name	Crenessity
Name of Applicant	Neurocrine Biosciences, Inc.
Therapeutic Class	Selective corticotropin releasing factor-1 (CRF1) receptor antagonist
Formulation(s)	soft gelatin capsules (25, 50, and 100 mg) and oral solution (50 mg/ml)
Dosing Regimen	Adults: 100 mg orally twice daily with morning and evening meals Pediatric patients 4 years and older: dosage is weight-based

Pediatric Patients 4 years and Older Age and Body Weight and administered orally twice daily with the morning and evening meals	**Dosage Regimen**
Pediatric patients weighing ≥ 55 kg	100 mg orally twice daily
Pediatric patients weighing 20 kg to <55 kg	50 mg orally twice daily
Pediatric patients weighing 10 kg to <20 kg	25 mg orally twice daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Crenessity (crinecerfont) is necessary to ensure the benefits outweigh its risks. Neurocrine Biosciences Inc. submitted New Drug Applications (NDAs) 218808 and 218820 for Crenessity with the proposed indication (b) (4) . The indication was updated to " (b) (4) (b) (4) (b) (4) . Two adequate and well controlled clinical trials in the CAH population (Trial 3006 in adults and Trial 2006 in pediatric patients) demonstrated substantial evidence of effectiveness for Crenessity in decreasing androstenedione levels compared with placebo at 4 weeks in the setting of stable glucocorticoid dose and allow for adrenal androgen control with decreasing doses of glucocorticoids. The risks associated with Crenessity include adrenal insufficiency, neutropenia, and suicidal ideation and behavior. Cases of adrenal insufficiency and crisis reported in the clinical development program for CAH were likely due to inadequate glucocorticoid dosing during stress conditions such as acute illness while on Crenessity. Neutropenia was observed in participants on Crenessity; however, the clinical significance is unclear. Adverse event incidences for Infection and infestation were higher in the placebo group than in crinecerfont group in Trail 3003 (adults) and lower in the placebo group than in the crinecerfont group in Trial 2006 (pediatrics). Changes to the absolute white blood cells (WBCs) were small and remain within the normal range. Though one suicide attempt was reported in the adult trial, the results based on the Columbia Suicide Severity Rating Scale (C-SSRS) above baseline in both trials were confounding as CAH patients have background risk for psychiatric disorder and glucocorticoids, commonly used to treat CAH, have been associated with neuropsychiatric effects. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of General Endocrinology (DGE) determined a REMS is not needed to ensure the benefits of Crenessity outweigh its risks. Endocrinologists, who are the likely primary providers, would be closely monitoring for adverse events and adjusting glucocorticoid dosing in patients with CAH. The indication statement will be updated to reinforce Crenessity as an adjunctive treatment to glucocorticoid replacement and labeling in warnings and precautions also reinforces that healthcare providers monitor adrenal hormone levels to ensure adequate glucocorticoid dosage, especially in stressful situations to mitigate the risk of adrenal insufficiency after initiation of Crenessity. Due to the uncertainties in the data for neutropenia and suicidal ideation and behavior with Crenessity, these risks will be addressed as adverse events (Section 6) in labeling and further evaluated with enhanced pharmacovigilance surveillance.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Crenessity (crinecerfont) is necessary to

ensure the benefits outweigh its risks. Neurocrine Biosciences, Inc. submitted New Drug Applications (NDAs) 218808 and 218820 for crinecerfont soft gelatin capsules and crinecerfont oral solution, respectively, for the proposed indication (b) (4) This application is under review in the Division of General Endocrinology (DGE). The risks associated with Crenessity include acute adrenal insufficiency, neutropenia, and neuropsychiatric safety concern of suicidal ideation and behavior. The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Crenessity (crinecerfont), a new molecular entity (NME)[a], is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist which inhibits adrenocorticotropic hormone (ACTH) secretion from the pituitary gland, thereby reducing excessive adrenal androgen production. The proposed indication is (b) (4) The Applicant's proposed presentations of Crenessity are as oral soft gel capsules (25 mg, 50 mg, and 100 mg) under NDA 218808 and as an oral solution (50 mg/ ml) under NDA 218820. The drug is for chronic use[b] and is to be taken with food. For adults (18 years and older), the proposed dose is 100 mg twice daily and for pediatric patients, the dosages are based on body weight. For pediatric patients weighing 55 kg or greater, the recommended dose is 100 mg twice daily; those weighing 20 kg to less than 55 kg, the recommended dose is 50 mg twice daily; and for those weighing 10 kg to less than 20 kg, the recommended dose is 25 mg twice daily.

Crinecerfont was granted Orphan Drug designation on March 15, 2019, Fast Track designation on June 15, 2021, and Breakthrough Therapy designation on December 1, 2023, for the treatment of children and adults ages 4 years and older with classic CAH. Crinecerfont is not marketed in other countries.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218808 and NDA 218820 relevant to this review:

- 3/15/2019: Orphan Drug designation granted for crinecerfont the treatment of CAH
- 6/15/2021: Fast track designation granted for crinecerfont for the treatment of CAH
- 12/1/2023: Breakthrough Therapy designation granted for crinecerfont for the treatment of CAH

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 4/29/2024: The Agency received NDA 218808 and NDA 218820 submissions for Crenessity (crinecerfont) (b) (4)

- 8/23/2024: Mid-Cycle Communication issued to the Applicant indicated that there were no major safety concerns or risk management issues identified at this time

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Classic Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired synthesis of cortisol, adrenal insufficiency and excess adrenal androgen. The most common form of CAH is due to 21-hydroxylase deficiency (21OHD)) caused by mutations in cytochrome P450 (CYP)21A2 and accounts for approximately 95% of cases.[1] Based on worldwide neonatal screening, the prevalence of CAH is approximately 1 in 15,000 livebirths. In the United States (US), the prevalence is lower in Black Americans than in White Americans (1 in 42,000 versus 1 in 15,500, respectively).[2c]

The defective conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol in patients due to 21OHD results in decreased cortisol synthesis, loss of negative feedback, and increased corticotropin secretion which leads to increased production of adrenal-derived androgens and a variable degree of aldosterone deficiency. Excess adrenal androgen production manifests in the following conditions: virilization of external female genitalia, hirsutism, acne, negative impact growth and development, infertility in females and males, and testicular adrenal rest tumors in males. CAH can be a life-threatening condition due to adrenal crisis.[d]

3.2. Description of Current Treatment Options

The goal of pharmacologic treatment of CAH is to lower the production of androgens and replace hormones deficiencies. People with classic CAH can manage the condition by taking hormone replacement therapies throughout their lives.

Current standard of care therapies for CAH include glucocorticoid (e.g., hydrocortisone) and mineralocorticoid (fludrocortisone) replacement, and salt supplementation (in infants).[3] Serum 17OHP and androstenedione (A4) are traditional indicators of the adequacy of glucocorticoid (GC) treatment in CAH.

Under standard of care treatment, supraphysiologic doses of GC are often necessary to suppress the high ACTH levels and control adrenal androgen production in patients with CAH, creating the clinical

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

management challenge of balancing disease control (by normalizing adrenal androgen levels) with avoiding iatrogenic Cushing's syndrome (due to excess GC exposure). Consequences of chronic supraphysiologic GC exposure include growth suppression, osteoporosis, and serious metabolic comorbidities such as obesity, hypertension, and insulin resistance, as well as increased overall cardiovascular risk. Currently there are no alternatives to supraphysiologic GC treatment available to manage androgen excess in CAH, therefore, there is an unmet need in this patient population.

4. Benefit Assessment

The efficacy and safety of crinecerfont was demonstrated in two pivotal Phase 3 studies, NBI-74788-CAH3003 (Trial 3003), NCT 04490915, which enrolled adult patients (aged ≥ 18 years), and NBI-74788-CAH2006 (Trial 2006), NCT 04806451, which enrolled pediatric patients (aged 4 to 17 years of age). These two studies were designed similarly, consisting of a 24-week double-blind, placebo-controlled period (Trial 3003, adults) and 28-week (Trial 2006, pediatrics), followed by 52 weeks (Trial 3003, adults) and 24 weeks (Trial 2006, pediatrics) of open-label treatment with crinecerfont. Participants were also required to be on a stable supraphysiologic GC dose regimen[e]. A total of 182 adult subjects (122 crinecerfont, 60 placebo) and 103 pediatric patients (69 crinecerfont, 34 placebo) with CAH were randomized to receive crinecerfont at the proposed commercial dose or placebo. In both studies, participants were eligible to continue into an open-label extension period. Demographics were generally similar between the treatment groups for both trials with approximately equal number of males to females. In Trial 3003 (adults), the mean age of randomized participants was 31 years (range: 18 to 58 years), 90% White, and 38% of participants were from the United States (US). In Trial 2006 (pediatrics), the mean age of the randomized participants was 12 years (range: 4 to 17 years), 63% White, and 56% of participants were from the US.

The primary endpoint for Trial 3003 (adults), the least square mean (LSM) percent change from baseline (CFB) in GC daily dose at Week 24 while androstenedione (A4) was controlled (≤ 120% of baseline or ≤ULN), was met with the LSM difference (crinecerfont – placebo) of -17% (95% confidence interval [CI]: -24, -10], $p < 0.0001$). Two key secondary endpoints were met: (1) proportion of reduction in GC daily dose to ≤11 mg/m^2/day at Week 24 while A4 controlled was 45% (63% [crinecerfont] vs 18% [placebo], $p < 0.0001$), and (2) change from baseline in serum A4 level at Week 4 (on usual GC dose) with LSM difference (crinecerfont – placebo) of -344 ng/dl (95% CI: -457, -232, $p < 0.0001$). Other secondary endpoints such as change in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), weight (%), and total fat mass at Week 24 were not statistically significant.

For Trial 2006 (pediatrics), the primary endpoint, the LSM difference from baseline in serum A4 at Week 4 (on usual GC daily dose), was met with LSM difference of -268 ng/dl (95% CI: -403, -132, $p = 0.0002$). Key secondary endpoints were met: (1) the LSM treatment difference (crinecerfont - placebo) in GC daily dose at Week 28 while A4 controlled (≤120% of baseline or ≤ULN) was -24% (95% CI: -30, -17, p <

[e] Supraphysiologic glucocorticoid is defined in Trial 3003 (adults) as total daily dosage >13 mg/m^2/day in hydrocortisone dose equivalents and in Trial 2006 (pediatrics) as total daily dosage >12 mg/m^2/day hydrocortisone equivalents.

0.0001), and (2) the LSM difference in serum 17-OHP level at Week 4 was -6421 ng/dL (95% CI: -8387, -4454), p < 0.0001). Further, an additional secondary endpoint finding of reduction in GC daily dose to physiologic level (≤11 mg/m2/day) while maintaining A4 control at Week 28 was 30% vs 0% (crinecerfont vs placebo), p = 0.0009.

Although no pediatric participants weighing 10 to < 20 kg were enrolled in Trial 2006, the clinical reviewer concluded population pharmacokinetic (popPK) modeling and simulation would support the proposed 25 mg BID dosing regimen for the 10 to <20 kg pediatric subgroup and is expected to produce similar exposures to those of 50 mg BID for the 20 to <55 kg pediatric subgroup.

Based on the results of Trial 3003 and Trial 2006, the clinical reviewer concluded there were substantial evidence of efficacy of crinecerfont for CAH treatment. Crinecerfont significantly lowered adrenal androgen levels at Week 4 while GC dosage remained stable, and allowed for a significant decrease in GC daily dosage while androgen levels were controlled. [f] Additionally, the review team determined the difference in crinecerfont exposure between the oral solution and capsule is not considered clinically meaningful and the formulations can be switched based on patient preference.

5. Risk Assessment & Safe-Use Conditions

The two Phase 3 Trials, 3003 (adults), and 2006 (pediatrics) were used to support the safety review of crinecerfont for CAH. A total of 179 participants were exposed to crinecerfont for ≥ 46 weeks in the two trials combined. Total exposure to crinecerfont was 216 person-years in Trial 3003 (134 person-years) and Trial 2006 (82 person-years) combined. Total exposure to crinecerfont in both trials was 216 person-years, with 134 person-years in Trial 3003 and 82 person-years in Trial 2006.

No deaths occurred in either Trial 3003 or Trial 2006 during the one-year study period. In the Trial 3003 extended open-label period, there was one death (at Month 12) for a participant on study drug due to adrenal crisis from an acute infectious illness that was not adequately treated with stress dose of steroid. The clinical reviewer concluded the death was not likely related to study drug.

The overall percentage of participants experiencing any adverse event (AEs) during the double-blind periods were similar in the crinecerfont group compared to the placebo group in Trial 3003 (83% and 81%, respectively) and Trial 2006 (84.% and 82.%, respectively). The most common AEs that are likely drug related in Trial 3003 are fatigue, dizziness, arthralgia, back pain, and decreased appetite, whereas, in Trial 2006, the most common AEs were headache, abdominal pain, and fatigue. The overall rate of serious treatment-emergent adverse events (TEAEs) during the double-blind treatment period in the crinecerfont group was 3.3% (4 subjects) vs 0% in placebo group in Trial 3003 and 1.4% (1 subject) in Trial 2006. Similar trends in serious adverse events (SAEs) were seen in the open-label periods for both trials. The overall rate of study drug discontinuation was similar in both trials, 3003 (3.3% in crinecerfont group vs 0% in placebo group) and 2006 (3% in crinecerfont group vs 0% in placebo group), during the double-blind treatment period. The clinical reviewer determined most of the serious TEAEs in the

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

double period of both trials was not likely study drug related. There was one serious adverse event of suicide attempt that led to discontinuation of crinecerfont (see further description in section 5.3 below).

There were no hypersensitivity-related events in the pivotal Phase 3 trials of crinecerfont for the treatment of CAH that were clearly drug-related. However, one patient experienced throat tightness, perioral edema, and generalized rash three days after treatment with crinecerfont in a Phase 1 study. Labeling will include the risk of hypersensitivity in Warnings and Precautions.

5.1. Adrenal Insufficiency

The SAE of acute adrenal insufficiency was observed in both trials. Group query of AEs preferred terms for adrenal insufficiency during the double-blind treatment period in Trial 3003 (adults) found greater incidences in the crinecerfont group (43%) vs placebo group (27%), whereas, in Trial 2006 (pediatrics), there were greater incidences in the placebo group (42%) compared to the crinecerfont group (36%). The pattern of time to onset is similar between crinecerfont and placebo groups in both trials, making adrenal insufficiency less likely to be drug-related and more likely due to disease state. All participants in Trial 3003 (8 participants) and Trial 2006 (2 participants) experiencing an adrenal crisis were secondary to acute illnesses coupled with lack of adequate stress dose of steroid. The clinical reviewer recommends updating the indication statement to address the role of crinecerfont as an adjunctive therapy to physiologic GC replacement. In addition, the label will include recommendations to not decrease the GC dose below physiologic replacement levels, that stress dose GCs continue to be necessary during acute illnesses or other situations of increased need, and for supervision by healthcare provider in monitoring A4 levels and adjusting GC dose after initiation of crinecerfont.

5.2. Neutropenia

The clinical significance of decreases in neutrophil counts is unclear. Decreased neutrophil counts (<2 x 10^3 cells/uL) occurred more frequently in study participants treated with crinecerfont compared to placebo during the double-blind treatment periods of both Trial 3003 (14% versus 5%) and Trial 2006 (37% versus 16%). Adverse event coding to FDA Medical Query (FMQ) for Infections and Infestations system organ class (SOC) showed the incidence of bacterial infection and purulent material in Trial 3003 (adults) was greater in the placebo group than in the crinecerfont group, whereas in Trial 2006 (pediatrics) there was a greater incidence in the crinecerfont group than in the placebo group. The absolute white blood cell (WBC) values decreased slightly but stayed in the normal range in patients on crinecerfont and stabilized over the study period. Reduced GC dose observed with crinecerfont may factor into the decreased WBC. No study participant in either trial discontinued study drug because of neutropenia. The clinical reviewer recommends including neutropenia as an adverse reaction (Section 6) in labeling to inform prescribers of this observation and enhanced pharmacovigilance surveillance to further evaluate this risk.

5.3. Suicidal Ideation and Behavior

Crinecerfont acts centrally in the pituitary gland and was previously investigated for the treatment of major depression. Additionally, patients with CAH have background risk for neuropsychiatric disorder.[4,5]

Further, GCs, commonly used in the management of CAH patients are associated with neuropsychiatric effects (e.g., suicide, suicide attempt, psychosis, mania, depression, panic disorder, and delirium, confusion, or disorientation).[6] Per the 2018 clinical practice guidelines for CAH, clinicians should be aware that individuals with CAH may be at risk of developing mental health problems and should have a low threshold for referral to psychological or psychiatric treatment.[3]

In the clinical trials, patients with active suicidal ideation within six months prior to screening or lifetime history of suicidal behavior, based on the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at screening were excluded. However, as noted above, there was one suicide attempt reported In Trial 3003. The case involved a 29-year-old female who was hospitalized for taking 19 tramadol tablets and thiocodin as well as a self-inflicted arm injury[g]. This incident occurred after a 7-year relationship break-up. Crinecerfont was discontinued on day 320. The investigator considered the suicide attempt to be unrelated to study treatment.

More participants in the crinecerfont group had a numeric increase on their C-SSRS compared to placebo in both trials.[h] In Trial 3003, 3 participants (3/120 = 2.5%) in the crinecerfont group had a C-SSRS score shift from 0 to a maximum of 2 (non-specific active suicidal thoughts) versus 1 participant (1/58 or 1.7%) in the placebo group during the 24-week double-blind treatment period. No participants in Trial 3003 had an increase in their C-SSRS score during the open-label treatment period. In Trial 2006, a total of 4 participants (4/67 or 6%) in the crinecerfont group versus none (0/31) in the placebo group had a C-SSRS score shift from 0 at baseline to a maximum above 0 during the 28-week double-blind treatment period. During the open-label treatment period, one participant shifted their C-SSRS score from 0 at baseline to 3 (active suicidal ideation with any methods [not plan] without intent to act). Results of the narrow FMQ for psychiatric SOC were mixed. During the double-blind period of the trials, psychiatric SOC for Trial 3003 was 20.3% in the placebo group vs 12.3% in crinecerfont group and for Trial 2006, placebo group was 3% vs crinecerfont group was 7.2%.

The Division of Psychiatry (DP) was consulted to provide guidance on labeling with regards to the higher incidence of suicidal ideation and behavior observed in patients receiving crinecerfont vs placebo. Given the rare incidence of neuropsychiatric and suicidal ideation and behavior-related events and the uncertainty observed in available clinical trial data, DP recommended describing the risk in adverse reactions (Section 6).[7] Further, a Boxed Warning or Warning and Precaution is not warranted at this time. The clinical reviewer concurs with DP's recommendation. Additionally, the clinical reviewer recommends further evaluation of this risk with enhanced pharmacovigilance surveillance.

6. Expected Postmarket Use

[g] Thiocodin: codeine phosphate hemihydrate is available as an over-the-counter product in Poland for dry, persistent cough (https://www.drugs.com/international/thiocodin.html).

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6.1. Healthcare Setting

Endocrinologists are the primary specialists involved in the care of patients with CAH. Since most patients are likely to be on GCs for treatment of CAH, endocrinologists would be knowledgeable on monitoring for adrenal hormone levels, adverse events, and managing the GC dosage to maintain physiologic GC levels.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Crenessity beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of Crenessity on the basis of the efficacy and safety information currently available. CAH is a rare disease with significant morbidity and adverse effects on quality of life. Current treatment for CAH is challenging, often having to balance supratherapeutic GC dosage to normalize adrenal androgen levels while avoiding iatrogenic Cushing syndrome from excess GC exposure. There are currently no non-hormonal treatments for CAH that may help reduce adverse effects from excessive GC treatment.

Both pivotal trials (Trial 3003 in adults and Trial 2006 in pediatrics) in CAH patients demonstrated statistically significant differences favoring the effectiveness of crinecerfont vs placebo treated participants on change from baseline (CFB) in GC daily dose, reduction in GC daily dose, and change in serum A4. Additionally, the pediatric study, also demonstrated improvement in the difference in serum 17-OHP and reduction in GC daily dose to physiologic levels between crinecerfont vs placebo treated participants. Crinecerfont was generally well tolerated. However, three serious risks of adrenal insufficiency, neutropenia, and suicidal ideation and behavior were identified in the clinical development program.

The clinical reviewer noted that acute adrenal insufficiency was likely due to disease process and inadequate adjustment of GC therapy that may result in adrenal crisis during treatment with crinecerfont. This risk will be addressed by updating the indication statement to emphasize the role of crinecerfont in the treatment of CAH. The indication statement is changed from "(b) (4) " to "(b) (4) (b) (4)." Acute adrenal insufficiency will also be included in Warnings and Precautions (Section 5) to reinforce that healthcare providers should monitor and adjust GC dosages after initiation of crinecerfont and during situations of increased corticoid needs to maintain physiologic GC levels.

The significance of neutropenia observed in the clinical trials is unclear with lower incidence in the crinecerfont group than in placebo group in the adult trial (Trial 3003), whereas there was a higher incidence in the crinecerfont group than in the placebo group for the pediatric trial (Trial 2006). The

absolute changes in WBC were small and remained within the normal range for both trials. This risk will be communicated as an adverse event (section 6) in labeling and further evaluated with enhanced pharmacovigilance surveillance.

Similarly, there is uncertainty in the data surrounding suicidal ideation and behavior risk observed in the clinical trials. Though there was one report of suicidal attempt in a study participant taking crinecerfont (Trial 3003) and there was a greater proportion of participants on crinecerfont vs placebo in both trials that reported numeric increase on their C-SSRS above zero, the number of cases reported are small and the results are confounding due to background psychiatric disorders in CAH patients and associated neuropsychiatric events with GCs. This risk will be included in labeling as an adverse reaction (Section 6) and further evaluated with enhanced pharmacovigilance surveillance.

DRM and DUOG determined a REMS is not necessary for Crenessity; these risks can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The risks of adrenal insufficiency, neutropenia, and suicidal ideation and behavior can be adequately mitigated through labeling. In general, healthcare providers who treat CAH are specialists who are aware to routinely monitor their patients closely for adverse events and to adjust GC dosages, when needed.

Should DGE have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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/s/

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