CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212801Orig1s000

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	212801
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 11, 2020.
Subject	Review to determine if a REMS is necessary
Established Name	osilodrostat
Trade Name	Isturisa
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	cortisol synthesis inhibitor
Formulation(s)	1mg, 5mg and 10 mg tablets
Dosing Regimen	The recommended starting dose is 2 mg orally twice daily.

Reference ID: 4559552

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity osilodrostat (Isturisa) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a New Drug Application (NDA) 212801 for osilodrostat with the proposed indication for the treatment of Cushing's disease. The serious risks associated with the use of osilodrostat are hypocortisolism, QTc prolongation and potential effects of elevated levels of adrenal hormone precursors. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

Division of Risk Management (DRM) and Division of Metabolism and Endocrinology Products (DMEP) have determined that if approved, a REMS is not necessary to ensure the benefits of osilodrostat outweigh its risks. Cushing's disease is a severe disease associated with increased mortality, mainly related to cardiovascular and infectious diseases, and a serious burden, mostly due to metabolic complications and psychiatric disorders that significantly impair the health-related quality of life. The clinical presentation of patients with Cushing's disease can be broad and establishing the diagnosis can be difficult. To decrease morbidity and mortality in these patients, early recognition and rapid control of hypercortisolemia is necessary. Surgery remains the optimal treatment in all forms of Cushing's syndrome, but may not be curative. Individualized medical treatment and a multidisciplinary approach are needed for optimal control of hypercortisolemia and management of comorbidities. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies. In the clinical trial, osilodrostat appeared efficacious in both its primary and secondary outcomes. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of osilodrostat for the treatment of Cushing's disease. The most concerning adverse reactions observed with the use of osilodrostat are hypocortisolism, QTc prolongation and potential effects of elevated levels of adrenal hormone precursors. If osilodrostat is approved, labeling, which will include Warnings and Precautions, Patient Counseling Information to be included in section 17, and in the PPI will be used to communicate the safety issues and management of toxicities associated with osilodrostat.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) osilodrostat is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a New Drug Application (NDA) 212801 for osilodrostat with the proposed indication for the treatment of Cushing's disease.[1] The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information and a Patient Package Insert (patient labeling or PPI).

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2 Background

2.1 PRODUCT INFORMATION

Osilodrostat is a NME NDA type 505(b)(1) pathway application.[a] It is a cortisol synthesis inhibitor, which potently inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.[1] Osilodrostat will be supplied as 1 mg, 5 mg, and 10 mg tablets. The recommended starting dose is 2 mg orally twice daily. The dose should be gradually titrated (initially by increments of 1 mg or 2 mg twice daily) based on individual response and tolerability, with the goal of achieving normal cortisol levels.[b] The maximum recommended dose of osilodrostat is 30 mg twice daily. Osilodrostat was granted orphan drug designation on September 13, 2013. Osilodrostat is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for osilodrostat (NDA 212801) relevant to this review:

- 05/30/2013: Investigation New Drug IND 117489 submission for osilodrostat (LCI699) was received.
- 09/13/2013: Orphan Drug designation granted
- 03/07/2019: NDA 212801 submission for osilodrostat with the proposed indication for the treatment of Cushing's disease, received.
- 08/28/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for osilodrostat.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cushing's disease (CD) and Cushing's syndrome (CS), are rare diseases characterized by high cortisol blood levels and impairment of circadian oscillation. CD derives from pathologic adrenocorticotropic hormone (ACTH) secretion usually triggered by micro- or macroadenoma of the pituitary gland, which is considered as a form of secondary hypercortisolism. In contrast, CS describes the complexity of clinical consequences triggered by excessive cortisol blood levels over extended periods of time irrespective of their origin.[2] Cushing's syndrome (CS) is a rare disorder resulting from prolonged exposure to excess glucocorticoids. The hallmark of CS is a chronic hypercortisolemic state which is associated with multiple co-morbidities that ultimately increase the risk of mortality.[3] Clinical manifestations of chronic hypercortisolism include metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidemia, and hypercoaguable state. Other clinical signs and symptoms of CS include: supraclavicular and dorsal fat pads; proximal muscle weakness; osteoporosis with increased risk of

[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.*

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fractures; skin changes (wide purple striae, hirsutism, acne); impaired immune function with increased risk of infection; neuropsychiatric disorders (depression, mood changes, and cognitive impairment), hypogonadism, and menstrual disorders in women.[4] The incidence of CS is estimated to be equal to 1–3 cases per million inhabitants per year, whereas its prevalence is close to 40 cases per million inhabitants.[5,c] Cushing's Disease is a severe disease associated with increased mortality, mainly related to cardiovascular and infectious diseases, and a serious burden, mostly due to metabolic complications and psychiatric disorders that significantly impair the health-related quality of life.[6,d] Clinical manifestation of CS, apart from corticotropin-releasing hormone (CRH-), ACTH-, and cortisol-producing (malign and benign) tumors may also be by exogenous glucocorticoid intake. Patient presentation and clinical symptoms substantially vary depending on duration and plasma levels of cortisol. In 80% of cases CS is ACTH-dependent and in 20% of cases is ACTH-independent, respectively.[2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The primary lines of therapy in CD consists of trans-sphenoidal surgery (TSS) of the pituitary adenoma (in case of ACTH-producing tumors) and in patients not amenable for surgery radiotherapy remains an option. The surgical effectiveness varies depending on expertise in pituitary surgery and the size and extension of the anatomic mass. Post-surgical remission rates of 60-90% of microadenomas have been reported in CD, and up to 50-70% for macroadenomas.[5] Hypopituitarism is common after TSS with a range between 13 and 81%. In case of immediate surgical failure or late recurrence, several therapeutic modalities are available: second pituitary surgery, medical treatments, radiation techniques, or bilateral adrenalectomy. The main disadvantages of radiotherapy are that normalization of ACTH secretion may take extended periods of time (eventually years) to occur demanding for medication while success of radiation is awaited, and that patients may develop generalized anterior pituitary insufficiency. If damage to the surrounding normal pituitary tissue occurs during surgery, the patient may require lifelong pituitary hormone replacement. However, an examination of remission and recurrence rates in long-term follow-up studies reveals that potentially up to 40% to 50% of patients could require additional medical treatment.[2] Medical control of hypercortisolemia may be needed in occult cases, while awaiting surgery, when surgery is contraindicated or unsuccessful, and while awaiting the effect of radiation treatment. Medical treatments for hypercortisolemia include agents that inhibit steroidogenesis (ketoconazole, metyrapone, mitotane, and etomidate), modulate ACTH release (somatostatin and dopamine agonists) or block glucocorticoid action at its receptor (mifepristone). A major concern with all medical therapies is the risk of overtreatment and adrenal insufficiency. Medical control of hypercortisolemia can be achieved in two ways: either by blocking cortisol production to achieve normal levels, or by blocking cortisol secretion completely along with glucocorticoid replacement (block and replace). Regardless of the strategy, all patients on medical therapy should be educated about the symptoms of adrenal insufficiency and the emergency use of glucocorticoids. Ketoconazole has been used off label for medical control of hypercortisolism in the US.[3] However, ketoconazole has a boxed warning for the serious hepatotoxicity including cases with a fatal outcome or requiring liver transplantation and QT prolongation and drug interactions leading to QT prolongation.[7] . In 2016, the Agency advised against its use for to treat skin and nail fungal infections.[8] The European

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[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.*

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Medicines Agency (EMA) has recently withdrawn ketoconazole from the market because of hepatic dyscrasia in patients treated for fungal infections.[9] Both ketoconazole and metyrapone have been associated with an increase in ACTH secretion and loss of control of hypercortisolism over time in CD. It is important to note that cortisol and ACTH levels remain unchanged or increase with the use of mifepristone and cannot be used to gauge treatment success or to diagnose adrenal insufficiency. Moreover, increases in ACTH and cortisol levels can lead to (worsening of) mineralocorticoid effects (hypertension, edema, hypokalemia), and women can develop endometrial thickening during prolonged treatment. Overall, medical treatment in CS needs to be individualized according to patient characteristics, potential side effects, and other pharmacological properties of the drugs.[3]

In conclusion the clinical presentation can be broad and establishing the diagnosis can be difficult. To decrease morbidity and mortality in these patients, early recognition and rapid control of hypercortisolemia is necessary. Surgery remains the optimal treatment in all forms of CS; but may not be curative. Individualized medical treatment and a multidisciplinary approach are needed for optimal control of hypercortisolemia and management of comorbidities. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies.

4 Benefit Assessment

The efficacy and safety of osilodrostat was evaluated in adult patients with CD in a phase III, multicenter, double blind, randomized withdrawal study following a 24-week, single arm, open-label dose titration period (Study C2301; NCT02180217). Patients with CD with persistent or recurrent disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery and baseline 24-uring free cortisol (UFC) greater than 1.5 ULN derived from three 24-hour urine collections received a starting dose of 2 mg osilodrostat twice daily that could be gradually increased up to a maximum of 30 mg twice daily at least every 2 weeks during an initial 12-week period (Study Period 1). The dose could be reduced at any time during the study for intolerability. Patients who did not require further dose increase and tolerated the drug during the subsequent 12-week period (Weeks 13 to 24: Study Period 2) and had mUFC ≤ ULN at Week 24, entered 8-week Randomization Withdrawal period and were randomized to receive blind treatment with osilodrostat or placebo. Patients who completed RW period and those who were withdrawn from RW period preliminary continued treatment with osilodrostat in 14-week open-label treatment period 4. Patients who were not eligible for the randomization at Week 24 continued open-label treatment with osilodrostat in the study; the dose was allowed to be increased for efficacy and decreased for intolerably. The eligibility criteria included a mean UFC value [mean urinary free cortisol (mUFC),] greater than 1.5 times the [upper limit of normal (ULN) = 138 nmol/24h) at screening, and a confirmation of the pituitary source of excess Adrenocorticotropic Hormone (ACTH). A total of 137 patients were enrolled in this study. At Week 26, 71 patients were randomized in a 1:1 ratio to continue receiving osilodrostat (n = 36) or to switch to placebo (n = 35) for 8 weeks (Weeks 26 to 34) (double-blind, randomized withdrawal (RW) Phase), followed by open-label osilodrostat for the remainder of the study. Patients who were not eligible for randomization (n = 47) continued on open-label osilodrostat treatment. Nineteen patients discontinued prior to Week 26.

The primary objective of the study was to compare the proportion of complete responders at the end of the 8-week RW period between patients randomized to continue on osilodrostat and the ones switched to placebo. A complete response for the primary endpoint was defined as a patient who had mUFC ≤ upper limit of normal (ULN) based on central laboratory result at the end of the 8-week RW period (Week 34), and who neither discontinued nor had any dose increase above their Week 26 dose level

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during the RW period of the study. Patients who discontinued the randomized treatment or discontinued the study during the RW period were considered non-responders. At randomization (Week 26) patients were stratified according to the actual dose of osilodrostat (≤ 5 mg twice daily vs > 5 mg twice daily) at Week 24 and history of pituitary irradiation. The key secondary objective was to assess the complete response rate at Week 24. Complete response for the key secondary endpoint was defined as a patient with mUFC ≤ ULN at Week 24 and the dose of osilodrostat during Study Period 2 (Weeks 13 to 24) was not increased above the level established at the end of Study Period 1 (Week 12). Patients who were missing mUFC assessment at Week 24 were counted as non-responders for the key secondary endpoint.

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for osilodrostat. At Week 8 of RW period, the percentage of responders for the primary endpoint was 86% and 30% in osilodrostat and placebo groups, respectively. The primary efficacy endpoint [proportion of complete responders at the end of the 8-week RW period (at Week 34)] was statistically significantly different between osilodrostat and placebo as shown in Table 1.[1,10,11,e]

Table 1: Results of the Primary Endpoint – Phase III Study (C2301)[1,10,11,e]

Primary Endpoint	Osilodrostat (N = 36) n (%)	Placebo (N = 34) n (%)	Response Rate Difference (odds ratio)
Complete response rate at the end of the 8-week randomized withdrawal (RW) period (Week 34) (95% CI)	31 (86) (71, 95)	10 (29) (15, 48)	osilodrostat vs. placebo 57 (38, 76) 2-sided p-value < 0.001
Abbreviation: CI, Confidence Interval.			

The key secondary endpoint, complete response rate after 24 weeks of treatment with osilodrostat in the initial single-arm treatment period, without any dose increase between Week 13 and 24 of the open-label period of the study was achieved by 72/137 (52.6%) with 95% 2-sided CI of (43.9, 61.1). The lower bound of this 95% CI exceeded 30%, the pre-specified threshold for statistical significance and minimum threshold for clinical benefit. Overall, mUFC consistently decreased during treatment with osilodrostat. Median mUFC was reduced from 476.4 nmol/24h (3.5 x ULN) at baseline to 62.5 nmol/24h (0.45 x ULN; change from baseline -84.1%) at Week 12 to 75.5 nmol/24h (0.55 x ULN; change from baseline -82.3%) at Week 24 and to 63.3 nmol/24h (0.46 x ULN; change from baseline -87.9%) at Week 48. The effects of osilodrostat on the reduction of mUFC were rapid. Median time to first normal mUFC was 41 days. Patients had a 75.4% and 92.7% probability to achieve normal mUFC by Days 56 and 84 respectively.[1,10,11,e]

[e] 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.*

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5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for osilodrostat. The safety analysis of osilodrostat primarily focuses in 137 CD patients who have been exposed to osilodrostat in the Study C2301 (NCT02180217). The safety of osilodrostat was evaluated in adult patients with CD in a phase III, multicenter, double blind, randomized withdrawal study following a 24-week, single arm, open-label dose titration period (see Section 4: Benefit Assessment).[1]

The most common adverse reactions (incidence ≥20%) noted in the pivotal Phase III study (C2301) with osilodrostat were adrenal insufficiency (51%), fatigue (44%), edema (21%), vomiting (22%), nausea (42%), and headache (34%).[1,11]

Deaths
One death was observed in Study C2301. The patient committed suicide during the Extension Period on Day 551. The patient had a long pre-existing psychiatric history and it was not suspected to be related to study drug.[1,11,12,13]

Serious Adverse Events (SAE)
Over one-third (36.5%; 50/137) of patients had at least one SAE, of which 15% (21/137) had an SAE suspected to be related to study drug. The most common SAEs, reported in >2% of patients, regardless of relation to drug, were adrenal insufficiency (which included the preferred terms adrenal insufficiency, adrenal insufficiency acute, cortisol deficiency) occurred in 13 of 137 patients (9.5%), pituitary tumor (5/137; 3.6%), and gastroenteritis (3/137; 2.2%). Adverse events leading to study discontinuation were reported in 18 patients (13%; n=137). Most common AEs leading to study discontinuation were adrenal insufficiency (3%) and pituitary tumor (3%). Dosage interruptions/adjustment due to an adverse reaction occurred in 106 of patients (77%; n=137). Most common AEs leading to study dose interruption/adjustment were adrenal insufficiency (25%) followed by nausea (18%), fatigue (17%), asthenia (13%).[1,11, 12,13]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 HYPOCORTISOLISM

In Study C2301 (n=137), 70 (51.1%) patients had hypocortisolism related AEs. The most commonly reported hypocortisolism related AEs were adrenal insufficiency (27.7%; n=38/137) and glucocorticoid deficiency (21.2%; n=29/137), cortisol free urine decreased (6.6%; n=9/137), cortisol decreased (1.5%; n=2/137), adrenocortical insufficiency acute (2.2%; n=3/137) and steroid withdrawal syndrome (1.5%; n=2/137). One-third (34%) of adrenal insufficiency (AI) events occurred within the first 12 weeks (Period 1) and 50% of AI events occurred by day 147 (week 21, Period 2). The earliest AI event occurred on Day 2. AI events were observed in 47%, 28% and 25% of patients in non-randomized patients, osilodrostat and placebo patients, respectively. Osilodrostat can lower cortisol levels and lead to hypocortisolism. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, dizziness, Significant lowering of serum cortisol may result in severe life-threatening adrenal insufficiency that may be manifested by hypotension, abnormal electrolyte levels and hypoglycemia. (b) (4)

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(b) (4)

. Labeling also instructs to evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc.). Osilodrostat dose reduction or discontinuation and temporary exogeneous glucocorticoid replacement therapy may be necessary. Factors considered in deciding on the duration of temporary dose decrease/interruption and glucocorticoid treatment should include the longer than half-life of osilodrostat cortisol suppression after the drug discontinuation. Treatment with osilodrostat may be resumed after resolution of symptoms at a lower dose. Labeling also recommends to educate patients on the symptoms associated with hypocortisolism and advise them to contact a healthcare provider if they occur. If approved, the risk of hypocortisolism will likely be communicated with in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with osilodrostat will be included in both Warnings and Precautions and the Dosage and Administration sections of the label.[1]

5.2 QTc Prolongation

Osilodrostat is associated with a dose-dependent QT interval prolongation (maximum mean estimated QTcF increase of up to 5.27 ms at 30 mg), which may cause cardiac arrhythmias.[1] In Study C2301 (n=137), 5 (3.6%) patients had electrocardiogram QT prolonged AEs, and in one patient out of 137 (0.7%) the AE was reported as grade 3; all five events were reported as non-serious. Electrocardiogram QT prolonged AEs required osilodrostat dose adjustment or interruption in three patients (2.2%), and one patient (0.7%) discontinued the study drug (AE resolved after 22 days).12 Labeling instructs to perform an electrocardiogram (ECG) prior to the start of osilodrostat treatment, (b) (4)

Labeling also instructs to correct hypokalemia or hypomagnesemia prior to osilodrostat administration and levels should be monitored periodically during treatment with osilodrostat. Labeling advises caution and recommends more frequent ECG monitoring in patients with risk factors for QT prolongation, (such as congenital long QT syndrome, congestive heart failure, bradyarrythmias, uncorrected electrolyte abnormalities, and concomitant medications known to prolong the QT interval). If approved, the risk of QTc prolongation will likely be communicated with in the Warnings and Precautions section of the label. Monitoring and for toxicities to address the safety issues with osilodrostat will be included in both Warnings and Precautions and the Dosage and Administration sections of the label.[1]

5.3 (b) (4) Adrenal Hormone Precursors[f]

Based on its mechanism of action, osilodrostat blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors (11- deoxy cortisol and 11-deoxycorticosterone,) and androgens. The elevated 11- deoxycorticosterone levels may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Accumulation of androgen precursors and testosterone may lead to hirsutism, hypertrichosis and acne (in females). Labeling recommends to inform patients of the symptoms associated with hyperandrogenism and advise them to contact a healthcare provider if they occur. If approved, the risk of adrenal hormone precursor accumulation related AEs will likely be communicated with in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with osilodrostat will be included in both Warnings and Precautions and the Dosage and Administration sections of the label.[1]

[f] Labeling negotiations were ongoing at the time of completion of this review. The draft label includes this warning.

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6 Expected Postmarket Use

According to the current proposed indication, if approved, osilodrostat is an oral medication that will be used in both inpatient and outpatient settings, and will be prescribed by various types of healthcare providers such as endocrinologists, neurosurgeons and otolaryngological (ENT) surgeons.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for osilodrostat beyond routine pharmacovigilance and labeling. The applicant proposed a PI that includes Warnings and Precautions to address the risks of hypocortisolism, QTc prolongation and potential effects of elevated levels of adrenal hormone precursors, as well as a PPI.

8 Discussion of Need for a REMS

Osilodrostat is a cortisol synthesis inhibitor, with the proposed indication for the treatment of CD.[1] When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for osilodrostat, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for osilodrostat will be various types of healthcare providers such as endocrinologists, neurosurgeons and otolaryngological (ENT) surgeons. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can management without additional risk mitigation measures.

At the time of this review, labeling negotiations were still ongoing with the Applicant. Cushing's disease is a severe disease associated with increased mortality, mainly related to cardiovascular and infectious diseases, and a serious burden, mostly due to metabolic complications and psychiatric disorders that significantly impair the health-related quality of life. Surgery remains the optimal treatment in all forms of Cushing's syndrome, but may not be curative. Therefore, new alternative modalities of medical treatment with improved long-term safety and efficacy are still needed beyond the existing medical therapies. Osilodrostat appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.[13]

DRM and DMEP have determined that if approved, a REMS is not necessary to ensure the benefits of osilodrostat outweigh its risks. The most concerning adverse reactions observed with the use of osilodrostat are hypocortisolism, QTc prolongation and potential effects of elevated levels of adrenal hormone precursors. If osilodrostat is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with osilodrostat, as well as information to be included in section 17, Patient Counseling Information and in the PPI to inform patients. At this time, none of these risks will receive a boxed warning in the label. Additionally, the applicant will be required to complete the ongoing Phase 3, multi-center, randomized, double-blind, 48 week study with an initial 12 week placebo-controlled period as the post-marketing required (PMR) study to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease (Clinical Trial C2302). Safety evaluations include but are not limited to the occurrence of hypocortisolism and adrenal insufficiency.

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9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of osilodrostat. The management of the risks associated with osilodrostat treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Draft Prescribing Information for osilodrostat as currently edited by the FDA, last updated January 30, 2020.

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[11] El-Maouche. Clinical Presentation. Mid-Cycle Meeting, dated August 05, 2019.

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[13] El-Maouche. Clinical Review for NDA 212801 osilodrostat, dated January 14, 2020.

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