CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212801Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/2/2020
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 212801
Applicant	Novartis
Date of Submission	3/7/2019
PDUFA Goal Date	3/7/2020
Proprietary Name	Isturisa
Established or Proper Name	Osilodrostat
Dosage Form(s)	film-coated tablets for oral use
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with Cushing's disease
Applicant Proposed Dosing Regimen(s)	2 mg-30 mg to be administered orally twice a day
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Cushing's Disease (CD) is a rare disease caused by an ACTH-secreting pituitary adenoma, which results in excess cor
associated with increased morbidity and mortality. CD is the most common cause of endogenous Cushing's syndrome
approximately 70% of cases of endogenous CS. Because of the significant morbidity associated with CD, early therap
resection of the adenoma is first-line therapy and the treatment of choice. Surgery is successful in 60-80% patients wit
microadenoma (less than 1 cm in diameter). However, even in patients who respond to surgery, up to 25% will experi
years. Second-line therapy of CD includes pituitary radiation, medical therapy to reduce serum cortisol concentrations
and bilateral adrenalectomy. Although not curative, medical therapy plays an important role in the management of CD
employed in patients with persistence or recurrence of CD despite having undergone surgery, in patients with CD who
control hypercortisolemia until the results of radiotherapy become effective, and in patients who are not candidates for
poor health. Lifelong medical treatment to suppress cortisol levels may be required if the primary cause of Cushing's s
treated successfully with surgery and/or radiation.

The U.S.-approved drugs indicated to treat one or more manifestations of CS/CD are: two injectable formulations of p
analog (Signifor, NDA 200677 and Signifor LAR, NDA 203255, Novartis), and mifepristone, a glucocorticoid recepto
NDA 202107, Corcept Therapeutics). Pasireotide is approved for the treatment of patients with CD for whom surgery
been curative. Mifepristone is approved for the control of hyperglycemia in adult patients with endogenous CS with ty
(T2DM) or glucose intolerance who have failed surgery or are not candidates for surgery. These drugs are associated w
including QT interval prolongation, gastrointestinal adverse reactions, and adrenal insufficiency. For pasireotide, the
affect compliance or acceptability of the treatment. Registration trials have shown that pasireotide normalized or decr
in □ 40% of patients. As already mentioned, mifepristone is approved only for a subgroup of CS patients - patients w
glucose metabolism - which include about 50-60% of all CS patients. Therefore, there is an unmet need for additional
CS/CD.

Current guidelines from professional societies list several unapproved drugs as part of the medical management of pat
According to these guidelines, steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane and etomidate) are reco
widely used agents in the treatment of CS of any etiology; these drugs are effective in 75- 80% of patients[3]. Treatment

[1] Biller BM, Grossman AB, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol M
[2] Nieman LK, Biller BM, et al. Endocrine Society Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin
Aug;100(8):2807-31.
[3] Feelders RA, Hofland LJ, de Herder WW. Medical treatment of Cushing's syndrome: adrenal-blocking drugs and ketaconazole. Neuroendocrin

associated with such adverse reactions as gastrointestinal adverse effects, adrenal insufficiency, liver toxicity (ketocon hypertension and hirsutism (metyrapone), etc. Thus, extensive clinical monitoring is required which may limit their us Overall, therapeutic options for treatment of CS remain limited and many patients with CS remain undertreated.

The Applicant has demonstrated in a single, multi-center, double-blind, randomized withdrawal (RW) study of osilodr single arm, open-label dose titration period (study C2301) that treatment with osilodrostat in patients with non-surgica effective in reducing mean 24-hour urinary free cortisol (mUFC) levels from baseline. In this study, 137 patients were osilodrostat for 24 weeks in a dose titration open-label single arm period. The starting dose was 2 mg BID; the dose w levels every 2 weeks to maximum dose 30 mg bid to achieve normalization of mUFC. The prespecified titration sched mg, 15 mg, 20 mg and 30 mg; however, some subjects were titrated more slowly than was prespecified or had doses d because of drug tolerability and adverse events including adrenal insufficiency. After the first 24 weeks of treatment, 7 responders at week 24 (defined as patients who had normal mUFC and did not require a dose increase during the previ randomized to receive osilodrostat or placebo in the RW period. Those who were not eligible for randomization contin label osilodrostat.

The primary endpoint was the proportion of patients whose mUFCs remained in the normal range after withdrawal of osilodrostat and placebo groups. The key secondary efficacy endpoint was the proportion of complete responders in th period. To be considered successful, the lower bound of the 95% CI for the proportion of patients who had normalizat was to exclude 30%, representing the minimum threshold demonstrating a clinically significant response to therapy in without any insight as to whether the patient will be a responder to osilodrostat or not (i.e. how the drug will be used i primary analysis demonstrated that osilodrostat was superior to placebo at Week 34, the end of the RW period: 86.1% patients in the osilodrostat group maintained normal mUFC without dose change compared to 29.4% (95% CI: 15.1, 4 placebo group. The response rate was not affected by the dose or history of pituitary radiation and ranged from 83.9% randomization stratification factor (dose at week 24 -> 5 mg bid and ≤5 mg bid and history of pituitary radiation). The confirmed that the UFC lowering effect was attributable to the drug itself and not to the other factors such as inactive demonstrated by significant difference in the proportion of responders in active drug versus placebo groups). The key endpoint achieved the pre-specified goal: 72 of 137 (52.6%; 95% CI: 43.9, 61.1) of patients met the definition for com lower bound excludes 30%.

The most common adverse events (AE) in the 48-week Core Phase of the pivotal study C2301 were hypocortisolism r (37%), headache (30%), insomnia (26.3%) fatigue (24%), vomiting (19.7%), nasopharyngitis (19.7%). The high rate o AEs was most likely overestimated due to poor definition of the term of 'adrenal insufficiency (AI)' in the protocol th specific signs and symptoms (nausea, fatigue, etc.) of the condition without concurrent serum cortisol levels. As such, tolerated rapidly decreasing cortisol levels were defined as having adrenal insufficiency; however, their cortisol levels range. There was no death due to AI in the study, and all events improved/resolved with osilodrostat dose adjustment glucocorticoids. Overall, hypocortisolism-related AEs are expected events based on the mechanism of action of osilo

dose adjustment/interruption and treatment with glucocorticoids will be recommended in the WARNING and PRECA
USPI to mitigate this risk. In addition, the pre-specified titration schedule used in the clinical study may also account f
recommend a more conservative approach to titration in the postmarketing setting. Thus, the risk will be further mitiga
recommendations which will advise not to increase the dose more frequently than every 2 weeks, to consider using sm
to base the decision of whether to increase the dose not only on absolute cortisol values, but also on the rate of cortisol
patient signs and symptoms.

Other potential safety issues associated with the use of osilodrostat include the risk of QT prolongation and
accumulation-related adverse reactions (hypertension, hypokalemia, hirsutism, acne). All these risks will be mitigat
which will include recommendations on appropriate patient selection, on monitoring for occurrence of these reacti
address these reactions including but not limited to osilodrostat dose adjustment and/or temporary interruption. A WAI
section discussing these safety concern will be included in labeling to ensure prescribers recognize that osilodrostat m
risks and can take appropriate precautions in patients at risk.

In conclusion, safety and efficacy data from the single, double blind randomized withdrawal phase 3 study conducted
osilodrostat for the treatment of recurrent or non-surgical Cushing's disease have demonstrated that the benefits outwe
population. Thus, I recommend approval of osilodrostat for the treatment of adult patients with CD. However, I recom
indication to adult patients with CD for whom pituitary surgery is not an option or has not been curative reflecting the
evaluated in the clinical program.
All identified safety issues can be mitigated by communicating risks in the product label and recommending appropria
monitoring and dose adjustment if required.

The following postmarketing requirements should be issued to further characterize the safety profile of osilodrostat.

- To complete the ongoing Phase 3 multi-center, randomized, double-blind, 48-week study with an initial 12-we
  period (study C2302). This study will evaluate the safety profile of osilodrostat, including rate of hypocortisoli
  dosing regimen that dose titration every 3 weeks)

These safety issues may be assessed postmarketing because they do not adversely impact the overall benefit risk asses

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