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APPLICATION NUMBER:

211150Orig2s000

OTHER ACTION LETTER(S)

NDA 211150/Original 2

COMPLETE RESPONSE

Bioprojet Pharma
c/o Harmony Biosciences, LLC
Attention: Michele A. Roy, RN, MS
VP, Regulatory Affairs
630 W Germantown Pike, Suite 215
Plymouth Meeting, PA 19462

Dear Ms. Roy:

Please refer to your new drug application (NDA) dated December 14, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Wakix (pitolisant) 4.45 mg and 17.8 mg tablets.

NDA 211150 provides for the use of Wakix (pitolisant) tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 211150/Original 1 – Treatment of excessive daytime sleepiness in adult patients with narcolepsy
- NDA 211150/Original 2 – Treatment of cataplexy in adult patients with narcolepsy

The subject of this action letter is NDA 211150/Original 2. A separate action letter will be issued for NDA 211150/Original 1.

All future submissions to NDA 211150/Original 1 and NDA 211150/Original 2 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 211150/Original 2, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

FDA has concluded that your NDA submission does not provide substantial evidence of effectiveness to support the approval of pitolisant for treatment of cataplexy in adult patients with narcolepsy. Substantial evidence typically consists of at least two adequate and well-controlled trials, each convincing on its own. To support the cataplexy claim, you submitted results from: 1) analyses on HARMONY I on the daily

rate of cataplexy (DRC) in a subgroup of patients with a history of cataplexy; and 2) HARMONY CTP.

The analyses of HARMONY I have a number of inadequacies, and we do not regard the study as an adequate and well-controlled trial for the cataplexy endpoint:

1) Cataplexy was a secondary endpoint in HARMONY I. There was no prospective plan to control the Type-I error rate for secondary endpoints in this study.

2) The subgroup of interest was defined post hoc based on event(s) that occurred post-randomization, which violates the randomization principle and could lead to invalid conclusions.

3) The statistically significant finding for cataplexy in HARMONY I was dependent on how missing values were handled (i.e., missing or zero values were assigned a value of 0.5; if they were excluded from the analysis, the treatment effect was no longer statistically significant).

The Agency has required two positive studies in other narcolepsy development programs (e.g., sodium oxybate, modafinil), as was explained to you during development.

Under some circumstances, FDA can consider approval based on a single study with confirmatory evidence (see FDA's 1998 "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products"). Although we view HARMONY CTP as a positive study, it had significant weaknesses, and is not the type of study that could, by itself, provide evidence of effectiveness. This was a small study (n=105), conducted exclusively in Eastern Europe. Race and ethnicity were not reported, and <10% of the subjects were elderly. We also have concerns regarding the generalizability of the study results to the to-be-marketed population in the U.S.

Path Forward

A second trial, substantiating the results of HARMONY CTP, will be required to obtain the cataplexy indication. The substantiating study should be a randomized, double-blind, placebo-controlled, fixed-dose trial of pitolisant for cataplexy that enrolls a meaningful fraction of U.S. patients. We hope that you will choose to pursue this path, and we will be glad to provide additional guidance on the study.

LABELING

We reserve comment on the proposed labeling until NDA 211150/Original 2 is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before NDA 211150/Original 2 may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.[2]

If you have any questions, contact LT Brendan Muoio, Senior Regulatory Project Manager, at (240) 402-4518 or brendan.muoio@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
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