NDA 220265

COMPLETE RESPONSE

Chiesi Farmaceutici S.p.A
c/o Chiesi USA, Inc.
Attention: Matt Medlin PhD, RAC
Sr. Director, Americas Regulatory Affairs, Global Rare Diseases
175 Regency Woods Place, Suite 600
Cary, NC 27518

Dear Shannon Sears:

Please refer to your new drug application (NDA) dated (b) (4) for idebenone tablets.

We have completed our review of this application 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/ STATISTICAL

(1) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

There was inadequate evidence to support the efficacy of idebenone (IDE) to (b) (4). The RHODOS study (SNT-II-003) failed to meet its primary endpoint for effectiveness. The LEROS study (SNT-IV-005) in combination with an externally controlled natural history (NH) cohort from two case record surveys (SNT-IR-006 and SNT-CRS-002) demonstrated weak efficacy evidence of idebenone to treat patients with LHON, as there were substantial issues and limitations in the study design:

- The LEROS study's dates of disease onset ranged from December 2011 to March 2019, whereas the NH cohort onset dates were from August 1959 to February 2016. This difference could imply differences in standard of care, patient population changes, and changes in reporting standards.
- Roughly half of the health seeking (taking idebenone) patients were excluded from the would-be NH cohort but not from the treatment cohort, with no propensity score analysis to model this treatment assignment. This would induce selection bias in the likely event that there are fundamental differences between the users and non-users of idebenone in the NH cohort.

- There were a large proportion of patients who dropped out of the LEROS study by year 1. Of the patients included in the primary analysis, 19% had no data at year 1 in the LEROS study; 54% had no data at year 1 in the NH cohort. Although a missing data analysis was done to account for missingness, various assumptions used in this analysis were unverifiable. Missing/lost follow-up data this prevalent are a serious potential source of bias.
- The NH cohort appeared to primarily use the Snellen method for the primary endpoint whereas the LEROS study used the more sensitive ETDRS method.

In addition to these potential sources of bias, there are pre-specification concerns: Echoing FDA's concerns in the (b) (4), Advice letter, the NH comparator was collected concurrently with LEROS trial. For this reason, FDA cautioned the Sponsor that LEROS was unlikely to be considered as an adequate and well-controlled efficacy trial .

We recommend that you conduct adequate and well controlled (AWC) clinical investigations in accordance with in § 314.126 that successfully demonstrate the safety and effectiveness of idebenone tablets in the (b) (4).

(b) (4)

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

NONCLINICAL

(b) (4)

(b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4), this name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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 product under consideration regardless of indication, dosage form, or dose level.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application 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*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4) .

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

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/

(b) (4)

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