



NDA 209531/S-016

COMPLETE RESPONSE

Biogen, Inc.
Attention: Charlene Wheeler, MSHS
Director, Global Regulatory Sciences
225 Binney Street
Cambridge, MA 02142

Dear Charlene Wheeler:

Please refer to your supplemental new drug application (sNDA) [REDACTED] (b) (4)

[REDACTED] for Spinraza (nusinersen) injection.

This "Prior Approval" efficacy supplement to your application proposes revisions throughout the Prescribing Information (PI) regarding a completed clinical study [Study 4 (NCT04089566)] to provide support for inclusion of an additional higher dosing regimen. Two corresponding additional strength presentations [28 mg/5 mL (5.6 mg/mL) and 50 mg/5 mL (10 mg/mL)] were proposed for administration of the new dosing regimen. This sNDA also proposes revisions to the Pediatric Use subsection (8.4) of the PI to include results from a combined 6- and 13-week toxicity study in juvenile monkeys.

We have completed our review of this application, 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.

NONCLINICAL AND PRODUCT QUALITY

Your response to our [REDACTED] (b) (4), information request regarding [REDACTED] (b) (4) product specifications [REDACTED] (b) (4)

(b) (4)

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated [REDACTED] (b) (4), which may be a resubmission of your draft labeling provided in an electronic response communication also dated [REDACTED] (b) (4).

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.¹

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources² and Pregnancy and Lactation Labeling Final Rule³ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

³ <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on your carton and container labeling submission dated [REDACTED] ^{(b)(4)}.

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 in the original submission.
 - Present tabulations of the new safety data combined with the supplemental application data.
 - Include tables that compare frequencies of adverse events in the supplemental application 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 subject 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 supplemental application 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.

ADDITIONAL COMMENTS

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

Upon our review of your Form 356h, we noticed that it does not contain all the facilities listed in Module 3. In your resubmission, ensure that Form 356h includes all relevant facilities. Additionally, we recommend that you include FEI numbers in Module 3 to facilitate our review process. Furthermore, please also confirm if

(b) (4) conducts microbiological and/or sterility tests because these tests have been included in the release testing for the drug product, but the facility's role in performing these specific tests is unclear from Section 3.2.P.3.1. If these tests are not performed at (b) (4), indicate it clearly in Module 3 Section 3.2.P.3.1. For additional guidance on Agency expectations regarding facility information that should be included in an application, refer to FDA guidance document titled *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*.⁴

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 314.65. You may also request an extension of time in which to resubmit the application.

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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*.

If you have any questions, contact [REDACTED] (b) (4)

[REDACTED]

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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