



NDA 218223

COMPLETE RESPONSE

Mapi Pharma Ltd.
c/o ProPharma Group
Attention: Sarah Waleszczak, MS
Senior Consultant, Regulatory Program Management
1129 Twentieth St. NW, Suite 600
Washington, DC 20036

Dear Sarah Waleszczak:

Please refer to your new drug application (NDA) (b) (4)
[REDACTED] for glatiramer acetate (GA) Depot.

We also acknowledge receipt of your amendments dated (b) (4)
[REDACTED], which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

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.

PRODUCT QUALITY

(b) (4)

[REDACTED]

(b) (4)



(b) (4)



Drug Product

(b) (4)



Process

(b) (4)



(b) (4)



(b) (4)



(b) (4)



Microbiology

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



CLINICAL/STATISTICAL

- 1) In addition to and independent of the deficiencies related to the lack of an adequate scientific bridge described in Biopharmaceutics comment #1 above, your Phase 3 trial (Study Mapi GA Depot Phase III – 001) did not provide interpretable or persuasive findings of efficacy for GA Depot as a treatment for relapsing forms of multiple sclerosis (RMS), and therefore does not meet the evidentiary standard for substantial evidence of effectiveness when considered independent of the failure to establish the scientific bridge to Copaxone

necessary for reliance on findings of safety and effectiveness of Copaxone in the context of a 505(b)(2) NDA.

Though the Phase 3 study achieved a statistically significant finding in its primary efficacy endpoint, there are substantial concerns regarding the quality and integrity of relapse data upon which the primary endpoint was based, many of which were conveyed in the Study May Proceed Letter for (b) (4), dated (b) (4). These concerns would need to be addressed in a new adequate and well-controlled study demonstrating a significant treatment effect on a rigorously measured primary outcome. We strongly recommend that you seek the Division's feedback on any protocol for a future study intended to provide substantial evidence of effectiveness.

The reasons for our determination that the primary efficacy outcome data are not interpretable are as follows:

- a) The multiple sclerosis (MS) relapse determination methodology was not acceptable for a primary efficacy outcome measure.
 - i) The Phase 3 study protocol and other materials submitted with your NDA did not include documentation of the process used for relapse confirmation. Only investigator-determined (i.e., protocol-defined and non-protocol-defined), not suspected, relapses were recorded, as you confirmed in your (b) (4), response to IR. As stated in the Study May Proceed Letter for (b) (4), dated (b) (4), "there should be a process for documentation of the disposition of all potential relapses including the dates of the initial clinical assessment and all related assessments, identification of the assessor(s), and a final determination of whether the event was considered a relapse... This entire process should be auditable."

Therefore, the Division was unable to audit the process you utilized for relapse evaluation and could not determine how relapses were confirmed. Because of the lack of accounting of suspected or unconfirmed relapses, we cannot conduct sensitivity analyses to evaluate the robustness of your relapse outcome. Due to an inability to determine how relapses were defined and confirmed, we cannot consider your primary efficacy outcome to be interpretable.

- ii) The window for subject evaluation for potential relapse assessment following symptom onset (2 weeks) was unacceptably prolonged. As stated in the Study May Proceed Letter for (b) (4), dated (b) (4), "all subject reports of a possible relapse should be assessed within no more than 48 hours of receipt by the site staff. All related assessments should be completed within no more than 72 hours." A duration of 2 weeks

between symptom onset and relapse assessment could potentially lead to recall bias by the subject. A delay in relapse assessment could also yield an uninterpretable Expanded Disability Status Scale (EDSS) score if the subject had an examination that took place after spontaneous recovery had occurred or a subject was treated prior to the Treating Investigator's assessment. Our analysis indicates that 25% of subjects in the GA Depot and placebo groups who had investigator-determined relapses (as identified in the ADPRIM dataset) were evaluated by the Treating Investigator more than 48 hours after symptoms were reported, with a maximum time to evaluation of 11 days.

- iii) The Treating Investigator was not blinded to the EDSS rater's assessments, which was a potential source of a systematic confirmation bias. Though we acknowledge that, per the protocol, disclosure of the EDSS score to the Treating Investigator was necessary to determine whether a relapse was protocol-defined, this disclosure is not an acceptable approach in clinical trial relapse assessment. The Treating Investigator and EDSS rater should be blinded to each other's assessments for integrity and interpretability of efficacy data.
- iv) The protocol did not include an independent Relapse Adjudication Committee. Though an independent assessment is not a requirement for an adequate and well-controlled study, inclusion of an independent Relapse Adjudication Committee is strongly recommended to increase the objectivity of the relapse determination process when there is ambiguity in a per-protocol relapse assessment. Therefore, in the setting of the other concerns enumerated in this letter, the lack of such a committee in your trial means there is no objective verification of protocol-defined relapses and results in the inability to resolve the deficiencies in the relapse determination process identified during review.
- v) Magnetic resonance imaging (MRI) was not included as a standard component of the relapse evaluation, which also raises concerns over the adequacy of the relapse evaluation and relapse definition processes. MRI evaluation is considered standard of care for MS relapse assessment and is an objective means of verifying relapse occurrence.
- b) The high number of major protocol deviations pertaining to missed study drug doses reported in Study Mapi GA Depot Phase III – 001, although generally balanced between the groups, is concerning and further limits study interpretability, particularly in the setting of an assessment of a monthly depot injection.
- c) Data were not collected after treatment discontinuation, which could have provided necessary context for interpreting the primary efficacy outcome data.

Since the reason for study discontinuation may be related to the treatment assignment (i.e., perceived lack of efficacy or an adverse event) or the primary endpoint (i.e., a relapse), the loss of these data may lead to bias in the estimated treatment effect. Collection of post-discontinuation efficacy (in addition to safety) data via a final study visit is an expectation in an adequate and well-controlled clinical trial.

- d) During the review of this application, the Division noted errors in datasets and the Clinical Study Report, which were acknowledged via IRs. In the setting of the interpretability concerns due to the relapse evaluation and definition process discussed in Clinical/Statistical comment #1a, the noted errors and omissions in your application raised concerns regarding the quality and reliability of all the data submitted in support of this application. The IR responses you provided in some cases could not provide necessary clarity regarding the apparently erroneous data. Examples of such irreconcilable errors include, but are not limited to, the following:
- i) There was an error in the study period end date (Last Patient Last Visit) in the Clinical Study Report. Your response to IR received on (b) (4), stated that "June 17 was a typo; as per the data collected it should have been June 15, 2022."

We were unable to replicate the study period end date with the data submitted. Your response to IR received on (b) (4), did not adequately explain the definition of the date of treatment completion submitted with the study data and its relation to the study period end date from the Clinical Study Report.

- ii) Several issues related to coding of protocol deviations for Study Mapi GA Depot Phase III – 001 were identified during this review cycle. Despite IRs sent on (b) (4), the coding of deviations and subject numbers you provided in summary tables and line listings submitted in response to these IRs remained inconsistent with those included in the ADDV dataset.
- iii) In your response to IR received on (b) (4), you stated that you discovered that 2 different guidances were used to code and evaluate protocol deviations in the dataset included with the original NDA submission. It remains unclear whether the protocol deviations that were reported represent an accurate account of all deviations that occurred.
- 2) In addition to the data quality and interpretability issues discussed in Clinical/Statistical comment #1, the secondary MRI-related endpoints yielded discordant results regarding a potential treatment effect of GA Depot, both within

your Phase 3 study and compared to previously completed placebo-controlled studies for Copaxone.

Your Phase 3 study failed to demonstrate a statistically or clinically significant effect on new or enlarging T2 hyperintense MRI lesions compared to placebo. Additionally, though there was a statistically significant effect of GA Depot on the frequency of new T1 gadolinium-enhancing MRI lesions compared to placebo, we are concerned that these results may not be robust due to assumptions about the behavior of missing data. The prespecified sensitivity analysis for this endpoint assumed no treatment effect after attributable early discontinuation, and the results of this sensitivity analysis were not statistically significant. This observed inconsistency among key secondary endpoints in your Phase 3 study is not indicative of a robust, clinically meaningful, or interpretable treatment effect of GA Depot, and does not align with previous placebo-controlled data for Copaxone or other therapies approved for RMS.

Moreover, in the absence of an adequate scientific bridge, the observed inconsistencies in MRI endpoints are concerning for important differences between GA Depot and Copaxone that would further preclude reliance on the listed drug for safety and efficacy data.

- 3) The safety data submitted in your application are inadequate to inform a comprehensive safety evaluation. There is an absence of routine safety laboratory assessments, including detailed urinalysis data, serum immunoglobulins, pancreatic enzymes, and certain electrolytes (chloride, bicarbonate, calcium, magnesium, and phosphorus). The submitted electrocardiogram (ECG) data were also considered inadequate.
- 4) Study Mapi GA Depot Phase III – 001, the Phase 3 study intended to demonstrate similarity of the safety profile between GA Depot and Copaxone, raised new safety concerns for GA Depot and suggested important differences in the safety profiles of GA Depot and Copaxone. Particularly in the absence of an adequate scientific bridge, the observed differences in the safety profile of GA Depot and that of the listed drug are concerning for important differences between the products that would further preclude a reliance on the listed drug for safety and efficacy data.
 - a) Treatment with GA Depot was associated with severe injection site reactions, including injection site abscess. Though injection site abscess is reported as an infrequent adverse reaction (i.e., occurring in 1/100 to 1/1,000 patients) in current approved labeling for Copaxone, the frequency of injection site abscesses in Study Mapi GA Depot Phase III – 001 (estimated via Division analysis to be 4.3% of GA Depot-treated subjects compared to 0% of placebo-treated subjects, based on pooling of the Preferred Terms abscess limb, abscess, and injection site abscess, with review of the associated

verbatim terms to confirm location) greatly exceeded the established experience with Copaxone.

- b) The Division's analysis indicated that treatment with GA Depot was associated with systemic injection-related reactions manifesting as influenza-like illness and pyrexia. These systemic injection-related reactions did not appear to be consistent with the known phenomenon of immediate post-injection reaction discussed in current approved labeling for Copaxone and are generally not expected with the listed drug (Copaxone). There is no precedent for glatiramer acetate to be associated with this type of reaction, which is typically associated with interferon beta products approved for the treatment of RMS.
- c) Additionally, cases of erythema nodosum were reported at a higher frequency in the Phase 3 study when compared to controlled studies of Copaxone. Erythema nodosum is a painful inflammatory panniculitis which can be disfiguring or lead to treatment discontinuation. If present at a higher frequency in association with GA Depot, this adverse event could indicate reduced safety in the RMS population relative to Copaxone and could reduce treatment compliance.

CLINICAL PHARMACOLOGY

- 1) Your immunogenicity analysis was based on a random subset of the total subjects (109 out of 508) from the treatment arm in Study Mapi GA Depot Phase III-001, which is not acceptable. The immunogenicity analysis should include all subjects from the treatment arm, providing a comprehensive assessment of the incidence of anti-drug antibodies (ADAs) and their potential impact on safety and efficacy outcomes.

NONCLINICAL

(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 Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected

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>

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

Refer to 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. Resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

FACILITY INSPECTIONS

Facility Deficiency

Following pre-approval inspection (PAI) of the (b) (4) (b) (4) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.

Facility Comments

1)

(b) (4)

2)

3)

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 original application data.
 - Include tables that compare frequencies of adverse events in the original 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 original 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:

Human Factors

- 1) Based on our review of the use-related risk analysis (URRA) and justification, we have determined that you do not need to submit human factors (HF) validation study data with the proposed GA Depot NDA 218223, as you currently propose the product be supplied as a convenience kit and administered by healthcare professionals only. However, it will be necessary for you to consider how any revisions to your proposed product to address the deficiencies outlined above will impact your user interface. If your user interface is revised in response to this Complete Response Letter, additional HF considerations may apply.

- 2) In your response to the IR dated (b) (4), you stated that you plan to

(b) (4)

Combination Product

Combination products are subject to the CGMP requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210 and 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements.

³ 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>

⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

We acknowledge that your application includes information intending to demonstrate compliance with the device QS regulation. However, this information has not been reviewed at this time because, based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection rather than reviewed as part of the quality assessment of your application. Therefore, this information must be available upon inspection, and assessment of this information has been deferred for possible review during inspection to demonstrate your compliance with 21 CFR part 4. Ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

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.

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* (September 2023).

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)

03/08/2024 12:31:13 PM