



NDA 217338

COMPLETE RESPONSE

RB Health (US) LLC
Attention: Ebru Unver Kulak
Senior Regulatory Manager
399 Interpace Parkway
Parsippany, NJ 07054

Dear Ebru Unver Kulak:

Please refer to your new drug application (NDA) [REDACTED]

(b) (4)

[REDACTED] t for naproxen sodium [REDACTED], dextromethorphan hydrobromide [REDACTED], guaifenesin [REDACTED] extended-release (ER) tablet.

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.

CLINICAL

You have not provided sufficient evidence to support the proposed 12-hour duration of action and dosing regimen for your proposed ER product. The submitted pharmacokinetic (PK) data demonstrate that each component of the proposed fixed-dose combination product is bioequivalent (BE) with that from approved listed drugs, Mucinex DM (guaifenesin 600 mg; dextromethorphan hydrobromide 30 mg ER tablet [NDA 021620]) and Aleve (naproxen sodium tablet [NDA 020204]). However, Aleve has a dosing direction that instructs consumers to take 1 tablet (i.e., 220 mg naproxen sodium) every 8 to 12 hours while symptoms last and allows consumers to take 2 tablets within the first hour for the first dose. Demonstration of BE of the naproxen component from your drug to Aleve is not adequate to support the modification of the dosing interval to the proposed 12-hour dosing interval.

[REDACTED], you submitted scientific literature in attempt to support that naproxen's PK profile is "independent of combination pharmaceutical products, formats, or co-administration." Additionally, you proposed to rely on FDA's finding for a third listed drug, Aleve-D Sinus and Cold (naproxen sodium 220 mg; pseudoephedrine HCl 120 mg extended-release tablet [NDA 021076]), to support efficacy of a 12-hour dosing interval for the naproxen component, for which you provided an indirect PK bridge. However, the submitted literature did not provide sufficient evidence for the proposed

product because different naproxen-containing products and formulations were used in the literature reports. Furthermore, the data underpinning the indirect bridge to Aleve-D Sinus and Cold (naproxen sodium 220 mg; pseudoephedrine HCl 120 mg extended-release tablet [NDA 021076]) were based on data retrieved from FDA reviews, which are not considered an appropriate source of information to rely on for approval from a regulatory perspective. See e.g., 21 CFR 314.430(e)(2).

Therefore, we conclude that the submitted material do not provide substantial evidence of efficacy to support the proposed 12-hour duration of action and dosing regimen. We remain concerned about the potential for waning or loss of analgesic and antipyretic effects of naproxen before the next dose of the proposed product.

To address these concerns, you may consider the following approaches among others:

- (1) Provide clinical efficacy data to support a 12-hour duration of use when studied in a relevant patient population, or
- (2) Conduct a relative bioavailability study to establish a scientific bridge between the proposed product and Aleve-D Sinus and Cold (naproxen sodium 220 mg; pseudoephedrine HCl 120 mg extended-release tablet [NDA 021076]).

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please 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. 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) 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 product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

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