CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

OTHER ACTION LETTERS

NDA 215320

COMPLETE RESPONSE

AFT Pharmaceuticals Ltd.
c/o Chesapeake Regulatory Group, Inc.
6574 River Clyde Drive
Highland, MD 20777

Attention: David Zuchero, MS, JD
US Agent for AFT Pharmaceuticals, Ltd.

Dear Mr. Zuchero:

Please refer to your new drug application (NDA) dated and received August 31, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Combogesic (acetaminophen/ibuprofen) solution for injection.

We also acknowledge receipt of your amendment dated June 20, 2022, and received June 21, 2022, which was not reviewed for this action. You may incorporate applicable sections of the amendment 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.

NONCLINICAL

You have not provided adequate toxicological risk assessments for leachables over the 5 mcg/day qualification threshold. We acknowledge your original approach in utilizing a toxicological threshold of concern of 120 mcg/day as recommended in ICH M7. However, this approach only addresses the genotoxicity aspects of a compound and is not acceptable to address the general toxicity of any given leachable compound. In addition, we acknowledge receipt of the June 21, 2022 submission containing a toxicological risk assessment for tentatively identified compounds detected above the analytical evaluation threshold; however, this submission was not formally reviewed because, as noted in your cover letter of the submission, the compounds have only been tentatively identified to date and method validation is still ongoing. Our assessment of the safety of leachables to support a marketing application should be based on confirmed compounds quantified using validated methods.

Information needed to address the deficiency

Submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold. Submit documentation that the structural identification of the compounds has been confirmed and quantification has been completed using validated methods. The risk assessment should be based on the maximum level of each leachable expected to be present in the drug product based upon the analysis of the data from your long-term stability samples. The approach for toxicological evaluation of the safety of leachables should be based on good scientific principles. Include copies of all referenced studies upon which a safety assessment is based. In addition, consider the following points as you prepare your toxicological risk assessments:

a. If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

b. Published literature submitted to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, [e.g., BIBRA Toxicology Advice & Consulting (BIBRA), Cosmetic Ingredient Review (CIR), Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA)], although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports should be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study should be discussed and justification should be provided to support your assertion that these data are adequate to support the safety of your container closure system.

c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.

PRESCRIBING INFORMATION

Draft labeling will be provided in a separate communication. Upon resubmission of your application, submit draft labeling that is responsive to that communication. Do not submit prior to your official resubmission date.

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 Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] 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
- 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

Draft carton and container labeling will be provided in a separate communication. Upon resubmission of your application, submit draft carton and container labeling that is responsive to that communication. Do not submit prior to your official resubmission date.

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[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

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

PROPRIETARY NAME

Please refer to correspondence dated, November 29, 2021, which addresses the proposed proprietary name, Combogesic IV. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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.

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*.

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

If you have any questions, call LCDR Mavis Y. Darkwah, PharmD, GWCPM, RAC-US, Regulatory Project Manager, at (240) 402-3158.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
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/

RIGOBERTO A ROCA
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