CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209471Orig1s000

OTHER ACTION LETTERS

NDA 209471

COMPLETE RESPONSE

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

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

Dear Mr. Zuchero:

Please refer to your new drug application (NDA) dated and received March 1, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Combogesic (acetaminophen and ibuprofen) tablets.

We acknowledge receipt of your amendment dated May 7, 2020, which constituted a complete response to our December 22, 2017, action 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 reason for this action below.

FACILITY INSPECTIONS

1. An inspection of the (b) (4) facility is required before this application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel to (b) (4) we were unable to conduct an inspection of the (b) (4) facility during the current review cycle for your application. Currently, the need for a facility inspection, and an assessment of the findings, is the only deficiency with your application. If approval of your application will continue to rely upon (b) (4) facility, we request that you do not respond to this Complete Response letter until after the travel restrictions are lifted so that the Agency can work with you to plan and conduct the required inspection.

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 PLR

Requirements for Prescribing Information[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.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

A. Container ((b) (4) Label and Carton Labeling

1. It is unclear if the placeholders, “barcode space” on the container label or the “Space for BARCODE” on the carton labeling, are intended to be linear barcodes. The drug linear barcode is often used as an additional verification; therefore, it is an important safety feature that should be part of the label whenever possible. Revise the container label and carton labeling to include the graphical representation of the linear barcode. Furthermore, ensure that the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the linear barcode in accordance with 21 CFR 201.25(c)(i).

2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We also recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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

(b) (4)

C. Carton Labeling

1. The carton labeling includes the following statement (b) (4) This statement is not consistent with the Prescribing Information. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information for full dosage information."

2. The carton labeling does not include product identifiers. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[a] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

PROPRIETARY NAME

Please refer to correspondence dated, August 5, 2020, which addresses the proposed proprietary name, Combogesic. 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 patient 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 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 Sandy Truong, PharmD, Regulatory Project Manager, at 301-796-5719.

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
11/06/2020 02:46:46 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209471

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 March 1, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for COMBOGESIC (ibuprofen 97.5 mg/acetaminophen 325 mg) Film-Coated Tablets.

We also acknowledge receipt of your amendment dated November 22, 2017, 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.

CLINICAL

1. You have not adequately described the exposure to your product.

   To address this deficiency, provide specific and accurate exposure information in terms of distribution of number of patients exposed versus number of doses exposed, including exposure during the open-label extension stage in any of the multiple-dose studies. Clarify exposure per treatment arm for the single-dose pharmacokinetic studies MX-9, 10, 11, 13b, 14a and 14b. Provide information on number of patients exposed per number of doses for Study MX-1. Summarize the exposure during the open-label extension stage of the two 24-hour studies.

STATISTICAL

2. The datasets you provided for Study AFT-MX-6 were not of sufficient quality to allow for a thorough review of efficacy. We were not able to confirm your primary and secondary analyses and, therefore, we were not able to conclude that this study provided

sufficient evidence of efficacy. These concerns were conveyed on April 20, June 7, and July 12, 2017.

In a response from you dated June 13, 2017, you acknowledged the derivation of these datasets were generated manually within Microsoft Excel, which produced errors in the datasets submitted to the NDA. To address this concern, you proposed the following:

1. *The sponsor will contract a third party to produce SAS programs to reproduce the primary and secondary analyses from the submitted ADaM domains.*

2. *As an extra level of confirmation, for complete traceability, the sponsor will contract a third party to produce SAS programs for the derivation of new ADaM datasets as well as primary and secondary endpoint analyses from the submitted SDTM domains.*

However, your amendment dated November 22, 2017, was not reviewed for this action. Incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

NONCLINICAL

3. You have not provided adequate justification for the proposed drug substance specification for (b) (4). Because (b) (4) has been reported to produce chromosomal aberrations in human lymphocytes, reduce the drug substance specification for (b) (4) to as low as technically feasible.

4. Your application does not address the potential presence of elemental impurities in your drug product in accordance with ICH guidance document: *Q3D Elemental Impurities*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf.

   To address this deficiency, analyze the final drug product for elemental impurities as per the above guidance taking into consideration the maximum daily dose of 12 tablets per day. Provide safety justification for any elemental impurity that exceeds the ICH permissible daily exposures for the oral route of administration.

PRODUCT QUALITY

Drug Product

5. The chromatograms example included in the analytical procedure document are illegible and cannot be used to assess the methods.

To address this deficiency, provide a copy of the full drug product analytical method(s) with legible representative chromatograms.

6. The total impurity results observed at release and over stability studies do not support the proposed acceptance limit of NMT (b) (4)%.

   To address this deficiency, tighten your total impurity specifications for release and stability based on the data you have provided in the NDA.

7. The drug product regulatory specifications which include all required quality attributes and their corresponding acceptance limits have not been provided.

   To address this deficiency, provide the final regulatory acceptance limits and tests for the release and stability of the drug product.

8. You have not provided a certification to demonstrate that the lactose used as an excipient complies to the BSE/TSE regulations.

   To address this deficiency, provide a certification to demonstrate that the lactose used as an excipient in the drug product complies to the BSE/TSE regulations. See "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use," located at: www.fda.gov/RegulatoryInformation/Guidances/ucm125182.htm

Process

9. (b) (4)

10

11. In Section 3.2.P.3.5, you have referred to the four exhibit batches as validation batches, all of which are smaller than your proposed commercial batch size.

    To address this deficiency, confirm that process validation will be performed in three commercial-scale ((b) (4)) validation batches using the approved commercial process, per current FDA Guidance "Process Validation: General Principles and Practices." https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

FACILITY INSPECTIONS

12. During a recent inspection of (b) (4), product/process controls, lab controls, and QA functions for the facility were found unacceptable for this NDA. Our field investigator observed issues at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

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 patient 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.

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 *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows when you resubmit your application:

A. Carton Labeling

1. Display the established name with the dosage form.[1]

2. We note the lot number is absent from the carton labeling; however, there are placeholders for several other numbers (BN, GTIN, Sr. No.) instead. We recommend you add the lot number to the carton labeling in accordance with 21 CFR 201.10(i)(1) and relocate the other numbers (BN, GTIN, and Sr. No) away from the lot number to avoid confusing the lot number with these other numbers.[2]

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[2] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

3. Submit revised carton labeling with the actual NDC number instead of the placeholder.

(b) (4)

2. See A.2

MEDICATION GUIDE

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

PROPRIETARY NAME

Refer to the Agency's correspondence dated, May 18, 2107, which addresses the proposed proprietary name, COMBOGESIC. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

ADDITIONAL COMMENTS

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

Pediatrics

1. We note in your agreed pediatric study plan (PSP) that you plan to conduct a pharmacokinetic, safety, and efficacy study in (b) (4). However, the Pediatric Research Equity Act (PREA) requires a pediatric assessment for indications for which sponsors are receiving or seeking approval in adults, unless the requirement was waived or deferred. As you are seeking an acute pain indication, a (b) (4) is not acceptable for fulfilling the requirements under PREA for your product. Submit an updated PSP with your resubmission to conduct the study in this age group in an appropriate acute pain population.

Labeling

2. During our review of your submitted labeling submitted on February 28, 2017, we found that you did not provide a review and summary of the available clinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of COMBOGESIC labeling.

Submit the following information when you respond to the Complete Response Letter. If you believe the information is not applicable, provide justification.

- a review and summary of all available published literature regarding acetaminophen and ibuprofen use in pregnant and lactating women and the effects of acetaminophen and ibuprofen on male and female fertility (include search parameters and a copy of each reference publication),

- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

and use the Selected Requirements for Prescribing Information checklist, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm373025.pdf.

Clinical efficacy

3. Provide time-specific pain intensity difference (PID) data and curves for the initial dose. Note: time-specific PID data need to be summarized in terms of mean (standard deviation, SD), including values from missing data management and the actual number of patients providing data points (not counting the ones affected by missing data management) at each scheduled time point. The entire ITT population should be included in data analyses incorporating missing data management. In cases of dosing time error and/or delayed pain measurements the hours for pain measurements should be counted based on the actual time interval after dosing.

4. Provide results of analyses of treatment differences between each active treatment and placebo for the primary endpoint in addition to comparing treatment differences between the drug combination and each of the other three treatments.

5. Provide time-specific PID data and curves covering the entire 48-hour evaluation period similar to the request above.

6. Provide a summary for single-dose onset in terms of median time to perceptible pain relief (PR) confirmed by meaningful PR. For patients who had perceptible PR within the first six hours not followed by meaningful PR any time afterwards within the first six hours, time to onset should be censored to six hours and the entire ITT population should be included in data analyses.

7. Provide a summary for single-dose duration in terms of median time to rescue and/or remedication (second dose of study medication) by the end of the first dosing interval, including censored data and covering the entire ITT population. The number and proportion rescued in the initial dosing interval should also be included in the summary of rescue information.

8. Provide subpopulation analyses to compare the US study population to the study population in New Zealand with respect to all the clinical efficacy items described above.

9. Clarify the number and proportion of patients of African and/or Hispanic descent per treatment group.

Clinical safety

10. Provide summary shift tables that include information on the number of cases with normal baseline lab tests changed to abnormal at follow-up and abnormal baseline lab tests worsened at follow-up, the severity of changes in terms of multiples of change (1.5x, 3x, 5x, 10x, etc.), their occurrence with respect to treatment and doses received during double-blind and open-label stages, clinical relevance of the findings, and outcomes of the abnormalities with or without treatments.

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 FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

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 Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Ellen Fields, MD, MPH
Deputy Director
Division of Anesthesia, Analgesia,
And Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLEN W FIELDS
12/22/2017