CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209471Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

CDTL and Division Director Summary Review for Regulatory Action

Date	March 1, 2023
NDA Number	209471
Applicant Name	AFT Pharmaceuticals
Date of Original Submission	March 1, 2017 Complete Response Letter issued December 22, 2017
Date of First Complete Response Submission	May 7, 2020 Complete Response Letter issued November 6, 2020
Date of Second Complete Response Submission	July 27, 2021
PDUFA Goal Date	January 27, 2022
Established (USAN) Name	Ibuprofen 97.5mg/acetaminophen 325 mg
Proposed Trade Name	Combogesic
Dosage Forms / Strength	Film-coated tablets
Proposed Indication	For the short-term management of mild to moderate acute pain
Action	Approval

Material Reviewed/Consulted OND Action Package, including reviews by:	
Clinical	Christina Fang, MD
Pharmacology Toxicology	Carlic Huynh, PhD / Newton Woo, PhD
OPQ/ONDP	Application Team Leader: Valerie Amspacher, PhD o Drug Substance: Jeff Medwid, PhD / Donna Christner, PhD o Drug Product: Renish Delvadia, PhD /Julia Pinto, PhD o Manufacturing: Yeung Chan, PhD / Jingbo Xiao, PhD o Biopharmaceutics: Leah Falade, PhD / Hansong Chen, PharmD, PhD o Environmental: Renish Delvadia, PhD / Julia Pinto, PhD o Regulatory Business Process Manager: Anika Lalmansingh
OCP/DCP II	Wei Qiu PhD; Yun Xu, PhD
OSE/OMEPRM/DMEPA	Cameron Clark, PharmD / Valerie S. Vaughan, PharmD / Mishale Mistry, PharmD, MPH
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DNDSI/OSIS	James Lumalcuri
Project Management Staff	Sandy Truong, PharmD / Swati Patwardhan, MS, RAC

DCP II = Division of Clinical Pharmacology II
DMEPA = Division of Medication Error Prevention and Analysis
DNDSI = Division of New Drug Study Integrity
OCP = Office of Clinical Pharmacology
OMEPRM = Office of Medication Error Prevention and Risk Management
ONDP = Office of New Drug Products
OPDP = Office of Prescription Drug Promotion
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology
OSIS = Office of Study Integrity and Surveillance

1. Benefit-Risk Assessment

The benefit-risk assessment has not changed from the assessment that Dr. Hu documented in her review of November 6, 2020. The following table is reproduced from that review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is associated with a variety of injuries and illnesses and impacts millions of Americans' lives each year • Acute pain is generally self-limited and typically requires treatment for no more than a few weeks • Untreated acute pain leads not only to short-term suffering, morbidity, and negative impact on quality of life but may also progress to chronic pain.	• Acute pain is common in a variety of medical and surgical settings • While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important regardless of the etiology.
Current Treatment Options	• Non-pharmacologic management of acute pain includes rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, and relaxation techniques. • Two major pharmacologic classes of analgesics for treating acute pain include opioid and non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. • Combination analgesics include opioid and non-opioid drug classes and combinations of two non-opioid drugs of different drug classes.	• A multi-modal approach that includes medications, nerve blocks, physical therapy and other modalities should be considered for the management of acute pain conditions. • Prescription analgesic remains an important component of acute pain management. • There are multiple current pharmacologic treatment options available for patients with acute pain.
Benefit	• The efficacy of Combogesic was supported by the pivotal phase 3 Study AFT-MX-6. • AFT-MX-6 enrolled patients with acute postoperative dental pain ≥ 40mm on a 100mm VAS scale. The study demonstrated statistically significant superiority of Combogesic to acetaminophen, ibuprofen, and placebo based on primary endpoint SPID48. • Additional analyses on time specific pain intensity difference (PIDs), the time to meaningful pain relief (two-stopwatch method), and rescue medication use are supportive of Combogesic as an acute analgesic and each component contributes to the claimed effect. • The study was limited in that none of the secondary efficacy endpoints testing were adjusted to control multiplicity. • The use of an opioid rescue in a non-opioid acute pain trial would confound the assessment of true treatment effect. However, since all four treatment arms received opioid rescue medication, it is still possible to compare rescue medication use in the Combogesic arm to other treatment arms.	• There is sufficient evidence in Study AFT-MX-6 to support the efficacy of Combogesic and the combination rule is fulfilled in treating mild to moderate acute pain.
Risk and Risk Management	• Exposure to Combogesic included any exposure in about 600 subjects and cumulative exposure to ≥4 doses in 350 subjects and to ≥8 doses in about 250 subjects. • Short-term exposure of up to eight doses of did not show increased risks for total AEs or common individual AEs with use of Combogesic as compared with each of the active treatments (Combogesic, ibuprofen, and acetaminophen). • No new safety signals were identified when acetaminophen and ibuprofen were used in combination. Common (>2%) AEs in the Combogesic group were mild in nature and included nausea (15%), vomiting (7%), headache (5%), and dizziness (3%).	• Safety evaluation of acetaminophen and ibuprofen relies on the Agency's previous finding of safety for the reference products. • The safety database for this new combination is adequate to support the safety of acetaminophen and ibuprofen when used in combination. • The safety data from the clinical studies did not reveal any unanticipated adverse effects with Combogesic. • Although the safety evaluation is limited to a few days, additive toxicity is not anticipated because interaction between acetaminophen and ibuprofen is unlikely based on an in vitro human enzyme study and pharmacokinetic studies.

2. Background

The Applicant, AFT Pharmaceuticals, has submitted a 505(b)(2) application on March 1, 2017, for Combogesic, a fixed-dose combination tablet containing acetaminophen (325 mg) and ibuprofen (97.5 mg) for short-term management of mild-to-moderate acute pain in adults.

The listed drugs on which the Applicant is relying on the Agency's previous findings of safety and efficacy are Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123), and Motrin tablets (ibuprofen 300 mg, 400 mg, 600 mg, 800 mg; NDA 17463) for the ibuprofen component. Dr. Hu noted in her review that the marketing status for Motrin is classified as "discontinued"; however, it was not discontinued or withdrawn for reasons of safety or efficacy.

This is the third review cycle for this application. During the first review cycle, several deficiencies were identified in several areas, including clinical, statistical, nonclinical, and product quality. The details about these deficiencies are described in the Complete Response (CR) letter issued on December 22, 2017.

At the end of the second review cycle, the Applicant was issued a second CR letter on November 06, 2020, because of the need to inspect the manufacturing facility. The CR letter stated the following:

> 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.

The Applicant has chosen to address this deficiency by reformulating their product and replacing their original formulation, manufactured by (b) (4), with a tablet manufactured by Mayne Pharma Inc., Greenville, NC, USA.

3. Product Quality

As noted above, the Applicant has submitted information on a new formulation, with new drug substance and drug product manufacturers, as well as new analytical methods and stability data. The overall recommendation from the OPQ review team is for approval of this application.

Specifically, for the drug substance, the team noted:

> "For this resubmission both drug substances DMF suppliers for this NDA were changed from the first two submissions. Both DMFs have been recently reviewed as Adequate. As a result, there are no approvability issues for the drug substance portion of this application and there are no deficiencies that need to be reported to the Applicant with respect to the drug substance portion of this application. The data is adequate to support the use of Acetaminophen and Ibuprofen in the manufacture of Combogesic (b) (4) (Acetaminophen/Ibuprofen) tablet drug product."

For the drug product, the team noted:

> "In the current resubmission package, the Applicant has replaced their previous formulation of Combogesic tablets manufactured by (b) (4) with a reformulated Combogesic tablet manufactured by Mayne Pharma Inc., Greenville, NC, USA. The reformulated Combogesic tablets (acetaminophen 325 mg/Ibuprofen 97.5 mg) are developed as white, biconvex, capsule-shaped, film-coated tablets. The proposed reformulated Combogesic tablet manufacturing process involves (b) (4) . Adequate data has been submitted in the resubmission package and subsequent IR responses to support the proposed re-test period of (b) (4) No novel excipients are used in the proposed formulation. The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substances. The tablets are packaged in a 250 mL HDPE bottle with one white, round (b) (4) cap and (b) (4) desiccant (b) (4) to package 250 tablets. The Applicant has provided 36 months of long-term and 6 months accelerated stability data for three registration batches; no significant stability trends are observed. The stability data supports the proposed shelf-life of 36 months."

From a biopharmaceutics standpoint:

> "The Applicant has resubmitted the NDA and reformulated its proposed drug product to be manufactured in Greenville, NC. As per SUPAC-IR, the changes in formulation and manufacturing site are considered Level 3 changes. The reformulated product is manufactured using (b) (4) . A new dissolution method has been developed with the goal of (b) (4) . A BE study has been conducted to compare the original formulation vs. the reformulated drug product, which is assessed by the Office of Clinical Pharmacology (OCP).
> The Applicant's proposed dissolution method is acceptable. The dissolution method is not discriminatory to changes in manufacturing processes or excipients for ibuprofen. However, due to the new manufacturing process that (b) (4) ."

Lastly, with respect to manufacturing facilities:

> "The drug product is Acetaminophen/ibuprofen tablet with strength of 325 mg Acetaminophen and 97.5 mg Ibuprofen. The manufacturing process includes (b) (4)
>
> Process review was deemed adequate at the end of review cycle #2.* However, both drug product formulation and commercial manufacturing facilities have changed for the third review cycle and they have been withdrawn from the current submission. During third cycle review, (b) (4) have been identified as high risk unit operations. (b) (4)
>
> .
>
> The drug product manufacturing facility has experience manufacturing similar immediate release tablets formulations. The firm is currently cGMP compliant and is deemed approvable at this time. Similarly, drug substance manufacturing facilities have experience manufacturing other API and intermediates by chemical synthesis and are currently cGMP compliant and are also deemed approvable at this time."

For additional details, please refer to the OPQ review.

I concur with the conclusions reached by the product quality reviewers that, from a product quality perspective, the application can be approved at this time.

4. Nonclinical Pharmacology/Toxicology

Drs. Carlic Huynh and Newton Woo, in their summary of the nonclinical findings, noted the following:

> No new toxicology studies were submitted to support this NDA resubmission (see previous nonclinical reviews). The Applicant submitted a new formulation, elemental impurities evaluation, and new drug substance and drug product specifications that were reviewed by the Pharmacology Toxicology review team. The new formulation does not contain any novel excipients. The drug substance specifications for acetaminophen and ibuprofen, drug product specifications for Combogesic®, and elemental impurities evaluations were reviewed and deemed acceptable.

For additional details, please refer to the pharmacology/toxicology review.

I concur with the review team that the application can be approved at this time.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted two bioequivalence studies, ACIB-T0218-16 and ACIB-T0218-17, to demonstrate that the reformulated Combogesic tablets were bioequivalent to the original formulation of Combogesic under fasting and fed conditions.
Study ACIB-T0218-16 was a randomized, single-dose, 2-way crossover, open label study to evaluate and compare acetaminophen and ibuprofen PK parameters of three reformulated Combogesic tablets and three original formulation Combogesic tablets in 30 healthy volunteers under fasting condition.

Study ACIB-T0218-17: a randomized, single-dose, 2-way crossover, open label study to evaluate and compare acetaminophen and ibuprofen PK parameters of three reformulated Combogesic tablets and three original formulation Combogesic tablets in 30 healthy volunteers under high fat fed condition.

The review team described the results of the studies in their review as follows:

> Study ACIB-T0218-16:
>
> "Median (min, max) Tmax values for acetaminophen were similar: 0.75 (0.25, 2.00) h for reformulation and 0.50 (0.25, 2.00) h for original formulation. Median (min, max) Tmax values for ibuprofen were similar: 1.25 (0.25, 3.00) h for reformulation and 1.25 (0.50, 6.00) h for original formulation. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf values following a single dose administration of three reformulated Combogesic tablets are bioequivalent to that for a single dose administration of three original formulation Combogesic tablets under fasting condition because the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence limits under fasting condition. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for acetaminophen Cmax, AUC0-t, and AUC0-inf were 99.37% (87.89 – 112.34%), 101.19 (98.51 – 103.95%), and 101.17% (98.38 – 104.04%), respectively. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for ibuprofen Cmax, AUC0-t, and AUC0-inf were 112.34% (101.82 – 123.95%), 104.28 (100.98 – 107.70%), and 104.33% (101.25 – 107.51%), respectively."
>
> Study ACIB-T0218-17:
>
> "Median (min, max) Tmax values for acetaminophen were similar: 1.25 (0.5, 6.00) h for the reformulation and 1.25 (0.5, 3.00) h for original formulation. Median (min, max) Tmax values for ibuprofen were similar: 1.25 (0.75, 6.00) h for reformulation and 1.38 (0.75, 6.00) h for original formulation. Acetaminophen and ibuprofen Cmax, AUC0-t, and AUC0-inf values following a single dose administration of three reformulated Combogesic tablets are bioequivalent to that for a single dose administration of three original formulation Combogesic tablets under high-fat fed condition because the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf for both acetaminophen and ibuprofen fell within the 80-125% bioequivalence limits under high-fat fed condition. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for acetaminophen Cmax, AUC0-t, and AUC0-inf were 107.63% (101.17 – 114.50%), 103.11 (100.01 – 106.31%), and 103.07% (100.17 – 106.06%), respectively. The point estimates (90% CIs) of the geometric mean ratios (reformulation/original formulation) for ibuprofen Cmax, AUC0-t, and AUC0-inf were 113.14% (106.23 – 120.49%), 103.32 (99.79 – 106.98%), and 103.31% (99.89 – 106.84%), respectively."

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted. The rationale provided was the Office of Regulatory Affairs (ORA) inspected the clinical site in October 2018, and OSIS

inspected the analytical site in [redacted] (b) (4), both of which fall within the surveillance interval. The final classification for both inspections was No Action Indicated (NAI).

Drs. Qui and Xu, in a making their final assessment that, from a clinical pharmacology perspective the information submitted in the application was acceptable, noted the following in their review:

> Bioequivalence between the reformulated Combogesic tablets within this resubmission and the original formulation Combogesic tablets included in the original NDA submission was demonstrated under both fasting and high-fat fed conditions in two bioequivalence studies (ACIB-T0218-16 under fasting condition and ACIB-T0218-17 under high-fat fed condition). The 90% confidence intervals (90% CI) for geometric mean ratios of Cmax, AUC0-t, and AUC0-inf for both acetaminophen and ibuprofen between these two formulation Combogesic tablets fell within the 80-125% bioequivalence limits under both fasting and fed states.

For additional details, please refer to the clinical pharmacology review.

I concur with the review team that the Applicant has provided sufficient clinical pharmacology information to support their application.

6. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant was not required to, and did not submit, any additional efficacy data.

8. Safety

The Applicant submitted a safety information on the combination formulations, including foreign marketing history and post-marketing regulatory actions on the oral formulations of the combination of acetaminophen and ibuprofen at 1000/300 mg dose levels.

Dr. Fang noted that the Applicant provided a list of countries in which the combination products at the specified dose levels had been approved for marketing. Of the two formulations used in the NDA studies the original formulation at acetaminophen/ibuprofen 500/150 mg taken as a 2-tablet dose is currently available in 50 foreign countries since its first approval in New Zealand in 2009. Its marketing status includes Rx only in 15 countries, OTC (OTC-pharmacy only and/or OTC general sale) in 33 countries, and both Rx and OTC in two countries.

Regarding the new low-dose formulation developed for the US market, acetaminophen/ibuprofen 325/97.5 mg taken as a 3-tablet dose, it was approved for marketing in Canada in 2019 with OTC-pharmacy only status.

Neither formulation has received any post-marketing regulatory action from any country since the market approval of the formulation.

Dr. Fang also noted that the post-marketing safety information on the acetaminophen/ibuprofen 500/150 mg formulation based on the most recently compiled worldwide Periodic Safety Update Report (PSUR) dated March 2021 is limited to 54 Individual Case Safety Reports over 406 million tablets distributed worldwide in 12 years, including 20 serious cases of which four cases were intentional overdose and all were known adverse reactions associated with the components. The details about the cases were not provided for review. The PSUR has not been prepared for the new acetaminophen/ibuprofen 325/97.5 mg formulation since its launch in Canada in December 2020 and no adverse reaction reports had been received by the Applicant during the first six months of marketing in Canada.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

There were several discussions between the Division, the Pediatric Review Committee (PeRC), and the Applicant throughout the product's drug development program. PeRC agreed that a partial waiver of studies in patients in the age group from birth to less than 6 months was appropriate due to safety concerns. PeRC also concurred that post-marketing requirements should be imposed for studies in patients in the age group of six months to less than 17 years of age.

11. Other Relevant Regulatory Issues

CDER has made a determination that there are "meaningful differences" between Combogesic (NDA 209471) proposed to be marketed as a prescription (Rx) drug product and the currently marketed OTC product Advil Dual Action with Acetaminophen oral tablets (ADAwA) (NDA 211733), such that both Combogesic and ADAwA may be simultaneously marketed without violating section 503(b) of the FD&C Act. Under the Agency's longstanding interpretation of relevant provisions of section 503(b) of the FD&C Act and its implementing regulations, the same active ingredient (or combination of active ingredients) cannot be simultaneously marketed in both a Rx drug product and an OTC drug product unless a meaningful difference exists between the two that makes the Rx product safe only under the supervision of a licensed practitioner.[1] Generally, when considering whether an Rx drug product differs from an OTC

[1] The distinction between prescription and nonprescription drugs was codified by the Durham-Humphrey Amendments to the Federal Food & Drug Act (FD&C Act) in 1951, which were enacted in order to address the marketplace confusion that arose from the simultaneous marketing of identical or nearly identical drugs on a prescription and OTC basis for identical or equivalent uses (Public Law 82–215, 65 Stat. 648 (1951). See, e.g., H.R. Rep. No. 82–700, at 5 (1951); see also 70 Fed. Reg. 52050 at 52051, Sep. 1, 2005). Prescription drugs are defined

drug in some meaningful way, the Agency considers factors such as the indication, strength, route of administration, dosage form, or patient population.

ADAwA (125 mg ibuprofen (IBU) / 250 mg acetaminophen (APAP)) was approved for nonprescription use on February 28, 2020, for the temporary relief of minor aches and pains due to . . . headache, toothache, backache, menstrual cramps, muscular aches, and minor pain of arthritis in adults and children 12 years of age and older to be taken at a dosing regimen of 2 tablets every 8 hours (up to a daily maximum of 6 tablets) for a maximum daily dosage of 750 mg IBU and 1500 mg APAP. Combogesic (97.5 mg IBU / 325 mg APAP) is proposed for "the short-term management of mild to moderate acute pain" in adults 18 years of age and older with a proposed dosing regimen of 3 tablets every 6 hours as needed for pain relief (up to a daily maximum of 12 tablets) for a maximum daily dosage of 1170 mg IBU and 3900 mg APAP.

The approved indication for ADAwA– "the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4), muscular aches, minor pain of arthritis" is an acute pain indication within the context of general OTC analgesic medications. According to the instructions for use and warnings on the label, the duration of treatment for the approved use of ADAwA is limited to < 10 days. In contrast, Combogesic is proposed for the treatment of mild to moderate acute pain, and although there may be some overlap in the indications for ADAwA and Combogesic with respect to the treatment of mild pain, Combogesic is being proposed for the treatment of acute pain with no restrictions on duration of treatment. We note that there may be many clinical situations in which treatment of acute pain (either mild or moderate) is necessary for more than 10 days, necessitating a licensed healthcare professional's consideration and supervision.

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as those which because of their toxicity or other potentiality for harmful effect, or the method of use, or the collateral measures necessary to their use, are not safe for use except under the supervision of a practitioner licensed by law to administer such drugs, or those drugs which are limited by an approved application under section 505 of the FD&C Act to use under the professional supervision of a practitioner licensed to administer such drugs (see section 503(b)(1) of the FD&C act). A drug that does not meet this definition is nonprescription drug. Under section 503(b)(4)(B) of the FD&C Act, a drug to which the prescription provisions of the act do not apply (i.e., a nonprescription drug) shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the ''Rx only'' symbol. Likewise, under the FD&C Act at 503(b)(4)(A), drugs that are subject to the prescription dispensing provisions of section 503(b)(1) must bear the "Rx only" symbol; if not, they would be misbranded. FDA has long interpreted these provisions to mean that section 503(b) of the FD&C Act does not permit the same active ingredient to be simultaneously marketed in both a prescription and nonprescription drug product, except as described below

Given this dichotomy between prescription and nonprescription drugs, questions have arisen over the years about whether there are any conditions under which an active ingredient may be simultaneously marketed in both a prescription drug product and a nonprescription drug product. FDA has interpreted the language in 503(b)(1) of the FD&C Act to allow marketing of the same active ingredient, or combination of active ingredients, in products that are both prescription and nonprescription, assuming some meaningful difference exists between the two that makes the prescription product safe only under the supervision of a practitioner licensed by law to administer such drugs (70 Fed. Reg. 52050 at 52051, Sep. 1, 2005). The Agency has used the terms "licensed practitioner" (Id.) and "licensed healthcare professional" (see Opportunity for Hearing on a Proposal to Withdraw Approval of Prescription Polyethylene Glycol 3350 Abbreviated New Drug Applications, Notice, 73 Fed. Reg. 63491, Oct. 24, 2008) to mean "a practitioner licensed to administer such drugs" in this context. In this document, these terms will be used interchangeably.

Therefore, the differences between the indications and duration of use constitute meaningful differences between both drug products that makes Combogesic safe only under the supervision of a licensed healthcare professional.

The respective strengths and dosing regimens of ADAwA and Combogesic also constitute meaningful differences in this context, especially as related to the daily doses of APAP under the dosing regimens for each product.[2] At present, prescription APAP unit doses are limited to no more than 325 mg per unit based on safety concerns related to severe liver damage. In addition, all prescription drug products that contain APAP carry a Boxed Warning highlighting the potential for severe liver injury. Moreover, dosing instructions for APAP in the 1988 Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (IAAA TFM)[3] recommends that daily APAP use (dosing of 325 to 1000 mg) not exceed 4000 mg in 24 hours, and that use be limited while symptoms last up to 10 days for pain, and 3 days for fever.

As noted above, ADAwA (125 mg IBU / 250 mg APAP) tablets are approved for a dosing regimen of 2 tablets every 8 hours (up to a daily maximum of 6 tablets) for a maximum daily dosage of 750 mg IBU and 1500 mg APAP. The proposed dosing regimen for Combogesic (97.5 mg IBU / 325 mg APAP) is 3 tablets every 6 hours (up to a daily maximum of 12 tablets) for a maximum daily dosage of 1170 mg IBU and 3900 mg APAP.

With respect to IBU-APAP products, Combogesic, unlike ADAwA, presents a need for a licensed healthcare professional's supervision because of the proposed APAP dose in Combogesic of up to nearly 4000 mg/day, combined with the lack of restricted duration of use. In particular, these factors make Combogesic unsuitable for use without the oversight and guidance of licensed healthcare professional because of the potential for severe liver injury. Notably, should a consumer inadvertently consume a dose of ADAwA greater than what is stated in the labeling, the consumed amount of APAP would still be below the maximum daily amount of 4000 mg recommended by the IAAA TFM, whereas consumption of an extra dose of Combogesic would exceed the maximum IAAA TFM recommended daily amount of 4000 mg potentially putting the patient at a risk of severe liver injury. Therefore, the approved respective strengths and dosing regimens of ADAwA and Combogesic constitute meaningful differences because they impact the overall benefit-risk assessment regarding the maximum available therapeutic dose of APAP for the treatment of acute pain. Such an assessment should be made by a licensed healthcare professional who can monitor the safety of such treatment.

12. Labeling

Consultation was obtained from the Division of Medication Error Prevention and Analysis (DMEPA), Office of Prescription Drug Promotion, Division of Medical Policy Programs

[2] The maximum daily doses of IBU for ADAwA and Combogesic, 750 and 1170 mg, respectively, do not raise significant safety concerns in this context, and do not constitute meaningful differences requiring the intervention of a licensed healthcare professional because both doses fall within approved nonprescription daily dosages of 1200 mg.

[3] 53 Fed. Reg. 46204 (November 16, 1988). The 4000 mg maximum daily dose is very close to the safety margin for liver failure which is approximately 5400 mg over 24 hours.

(DMPP), and the Division of Pediatrics and Maternal Health (during the second review cycle). Their recommendations were incorporated in the labeling discussions with the Applicant.

13. Post-Marketing

As noted above, upon approval of this application, several post-marketing requirements will be imposed regarding pediatric studies. These are as follows:

4401-1 Conduct a study of the efficacy, safety, and pharmacokinetics of Combogesic in patients aged 12 to less than 17 years of age with mild to moderate acute pain.

Draft Protocol Submission:	09/2023
Final Protocol Submission:	12/2023
Study Completion:	03/2025
Final Report Submission:	08/2025

4401-2 Conduct a study of the efficacy, safety, and pharmacokinetics of Combogesic Oral Suspension in patients aged 2 to less than 12 years of age with mild to moderate acute pain.

Draft Protocol Submission:	01/2026
Final Protocol Submission:	04/2026
Study Completion:	07/2027
Final Report Submission:	12/2027

4401-3 Conduct a study of the efficacy, safety, and pharmacokinetics of Combogesic Oral Suspension in infants from 6 months to less than 2 years of age with mild to moderate acute pain.

Draft Protocol Submission:	05/2028
Final Protocol Submission:	08/2028
Study Completion:	11/2029
Final Report Submission:	04/2030

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
03/01/2023 11:19:51 AM

Cross-Discipline Team Leader and Division Director Summary Review

Date	(electronic stamp)
From	Ning Hu, MD MS, Cross-Discipline Team Leader, Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Rigoberto A Roca, MD. Division Director, DAAP
NDA#	209471
Applicant	AFT Pharmaceuticals, Inc
Date of Submission	May 7, 2020
PDUFA Goal Date	November 6, 2020
Proprietary Name	Combogesic
Established or Proper Name	Ibuprofen 97.5mg/acetaminophen 325 mg
Dosage Form(s)	film-coated tablets
Applicant Proposed Indication(s)/Population(s)	For the short-term management of mild to moderate acute pain
Applicant Proposed Dosing Regimen(s)	Three tablets every six hours up to four times a day and not to exceed 12 tablets during a 24-hour period
Recommendation on Regulatory Action	Complete Response

Table of Contents

Material Reviewed/Consulted

OND Action Package, including:			
Cross-Discipline Team Leader	Ning Hu, MD, MS		
Pharmacology Toxicology Review	Carlic Huynh, PhD, Jay Chang, PhD, R. Daniel Mellon, PhD		
Statistical Review	John Lawrence, PhD, Jinglin Zhong, PhD, Jim Hung, PhD		
OPQ Review	Discipline	Primary Assessment	Secondary Assessment
	Drug Substance	Jeff Medwid	Donna Christner
	Drug Product	Stephanie Emory	Julia Pinto, PhD
	Manufacturing	Shujun Chen	Chengjiu Hu
	Microbiology	Shujun Chen	Chengjiu Hu
	Biopharmaceutics	N/A	N/A
	Regulatory Business Process Manager	Anika Lalmansingh	
	Application Technical Lead	Valerie Amspacher	
	Environmental	Stephanie Emory	Julia Pinto
Clinical Pharmacology Review	Qiu Wei, PhD; Yun Xu, PhD		
OSE/DPV	Helen Lee		

OND=Office of New Drugs; CDTL=Cross-Discipline Team Leader; OPQ=Office of Pharmaceutical Quality; CDRH=Center for Device and Radiological Health; OSE=Office of Surveillance and Epidemiology; DMEPA=Division of Medication Errors Prevention; CDR=Commander; BCPS=Board Certified Pharmacotherapy Specialist

1. Benefit-Risk Assessment Framework

The proposed fixed-dose combination product, Combogesic contains acetaminophen (325 mg) and ibuprofen (97.5 mg) for short-term management of mild-to-moderate acute pain in adults. The proposed dosing regimen is three tablets every six hours as needed for pain relief, up to a maximum of 12 tablets per day.

Acute pain can be caused by a variety of different conditions. A multi-modal approach should be considered for the management of acute pain conditions. Prescription analgesic remans an important component of acute pain management. There have been numerous analgesic products approved for the treatment of acute pain including products containing acetaminophen or ibuprofen.

The application is supported by referencing the Agency's previous findings of efficacy and safety for Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123) for the acetaminophen component and Motrin tablets (ibuprofen 300 mg, 400 mg, 600 mg, 800 mg; NDA 17463) for the ibuprofen component.

The efficacy evaluation is be based on the results of the pivotal phase 3 Study AFT-MX-6. The study demonstrated statistically significantly superiority of Combogesic to acetaminophen, ibuprofen, and placebo based on the time-weighted summed pain intensity difference from baseline over 48 hours (SPID 48). Additional analyses on time specific pain intensity difference (PIDs), the time to meaningful pain relief (two-stopwatch method), and rescue medication use are supportive of Combogesic as an acute analgesic and each component contributes to the claimed effect. The study was limited in that none of the secondary efficacy endpoints testing were adjusted to control multiplicity. The use of an opioid rescue in a non-opioid acute pain trial would confound the assessment of true treatment effect, however, since all four treatment arms received opioid rescue medication, it is still possible to compare rescue medication use in the Combogesic arm to other treatment arms.

The safety evaluation of acetaminophen and ibuprofen relies on the Agency's previous findings of safety for the reference products. The safety database for this new combination is adequate to support the safety of acetaminophen and ibuprofen when used in combination. The safety data from the clinical studies did not reveal any unanticipated adverse effects with this combination. Although the evaluation of safety is limited to a few days, additive toxicity is not anticipated because interaction between acetaminophen and ibuprofen is unlikely based on an in vitro human enzyme study and pharmacokinetic studies.

In conclusion, there is sufficient evidence in Study AFT-MX-6 to support the efficacy of Combogesic and the combination rule is fulfilled in treating mild to moderate acute pain. The safety profile is generally consistent with the safety profile of acetaminophen and ibuprofen. The

overall benefit/risk of Combogesic is favorable for short-term management of mild-to-moderate acute pain in adults. The Office of Product Quality recommends a Complete Response because of a withhold due to a facility deficiency.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pain is associated with a variety of injuries and illnesses and impacts millions of Americans' lives each year • Acute pain is generally self-limited and typically requires treatment for no more than a few weeks • Untreated acute pain leads not only to short-term suffering, morbidity, and negative impact on quality of life but may also progress to chronic pain.	• Acute pain is common in a variety of medical and surgical settings • While there is heterogeneity in the types and causes of acute pain, adequate control of acute pain is important regardless of the etiology.
Current Treatment Options	• Non-pharmacologic management of acute pain includes rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, and relaxation techniques. • Two major pharmacologic classes of analgesics for treating acute pain include opioid and non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. • Combination analgesics include opioid and non-opioid drug classes and combinations of two non-opioid drugs of different drug classes.	• A multi-modal approach that includes medications, nerve blocks, physical therapy and other modalities should be considered for the management of acute pain conditions. • Prescription analgesic remains an important component of acute pain management. • There are multiple current pharmacologic treatment options available for patients with acute pain.
Benefit	• The efficacy of Combogesic was supported by the pivotal phase 3 Study AFT-MX-6. • AFT-MX-6 enrolled patients with acute postoperative dental pain ≥ 40mm on a 100mm VAS scale. The study demonstrated statistically significant superiority of Combogesic to acetaminophen, ibuprofen, and placebo based on primary endpoint SPID48.	• There is sufficient evidence in Study AFT-MX-6 to support the efficacy of Combogesic and the combination rule is fulfilled in treating mild to moderate acute pain.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Additional analyses on time specific pain intensity difference (PIDs), the time to meaningful pain relief (two-stopwatch method), and rescue medication use are supportive of Combogesic as an acute analgesic and each component contributes to the claimed effect. • The study was limited in that none of the secondary efficacy endpoints testing were adjusted to control multiplicity. • The use of an opioid rescue in a non-opioid acute pain trial would confound the assessment of true treatment effect. However, since all four treatment arms received opioid rescue medication, it is still possible to compare rescue medication use in the Combogesic arm to other treatment arms.	
Risk and Risk Management	• Exposure to Combogesic included any exposure in about 600 subjects and cumulative exposure to ≥4 doses in 350 subjects and to ≥8 doses in about 250 subjects. • Short-term exposure of up to eight doses of did not show increased risks for total AEs or common individual AEs with use of Combogesic as compared with each of the active treatments (Combogesic, ibuprofen, and acetaminophen). • No new safety signals were identified when acetaminophen and ibuprofen were used in combination. Common (>2%) AEs in the Combogesic group were mild in nature and included nausea (15%), vomiting (7%), headache (5%), and dizziness (3%).	• Safety evaluation of acetaminophen and ibuprofen relies on the Agency's previous finding of safety for the reference products. • The safety database for this new combination is adequate to support the safety of acetaminophen and ibuprofen when used in combination. • The safety data from the clinical studies did not reveal any unanticipated adverse effects with Combogesic. • Although the safety evaluation is limited to a few days, additive toxicity is not anticipated because interaction between acetaminophen and ibuprofen is unlikely based on an in vitro human enzyme study and pharmacokinetic studies.

2. Introduction and Background

The Applicant has submitted a complete response to the complete response (CR) action taken on December 22, 2017 for the NDA for Combogesic, a fixed-dose combination tablet containing acetaminophen (325 mg) and ibuprofen (97.5 mg) for short-term management of mild-to-moderate acute pain in adults. The proposed dosing regimen is three tablets every six hours as needed for pain relief, up to a maximum of 12 tablets per day.

The original NDA was submitted on March 1, 2017, as a 505(b)(2) application referencing the Agency's previous findings of efficacy and safety for Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123) for the acetaminophen component and Motrin tablets (ibuprofen 300 mg, 400 mg, 600 mg, 800 mg; NDA 17463) for the ibuprofen component. The marketing status for Motrin is discontinued; however, it was not discontinued or withdrawn for reasons of safety or efficacy.

In the review of the original NDA review, numerous deficiencies were identified by reviewers from multiple disciplines including clinical, statistical, nonclinical, and product quality. These deficiencies were outlined in the CR letter issued on December 22, 2017.

The deficiencies from nonclinical and product quality review teams and the adequacy of the response to resolve the deficiencies will be discussed in the relevant sections of this review.

There were two clinical deficiencies outlined in the CR letter. The first was inadequate description of the overall exposure to the proposed product. This limited the interpretation of the safety data and the ability to conduct a full review. To address this deficiency, the Applicant was asked to provide specific and accurate exposure information. The second clinical deficiency was associated with the pivotal efficacy trial (Study AFT-MX-6). The statistical review team found the datasets for Study AFT-MX-6 were of insufficient quality to allow a thorough review of efficacy. The Applicant attempted to address the dataset issues one month before the action date of the original NDA and this data could not be reviewed due to insufficient time. In addition, the clinical reviewer, Dr. Fang determined that additional efficacy information from study AFT-MX-6 may be helpful to understand the complete efficacy profile of the proposed product. The additional requirements were conveyed to the Applicant in the CR letter.

The Applicant resubmitted the NDA on August 2, 2018. This submission was determined as an incomplete response due to outstanding unresolved manufacturing facility issues. Refer to the incomplete response letter dated August 27, 2018 for details. A follow-up type C meeting was held to discuss the unresolved issues as detailed in meeting minutes dated February 15, 2019.

3. Product Quality

The manufacturing process/facilities review team in the Office of Pharmaceutical Quality (OPQ) recommends a CR because of a withhold due to a facility deficiency. The drug product and drug substance were deemed adequate to support the approval. Biopharm and microbiology remain adequate from the original review cycle. See the CDTL/Division Director review from the original NDA submission for details regarding the product quality considerations.

Combogesic tablets are white, capsule-shaped, film-coated, and embossed with the letters (b) (4) on one side. Each tablet contains 325 mg of acetaminophen and 97.5 mg of ibuprofen. The final drug product is enclosed in (b) (4) packaging. A shelf life of 36 months is acceptable when the product is stored at or below 20°–25°C (68°–77°F).

During the first review cycle, the chemistry, manufacturing, and controls (CMC) review team identified the deficiencies regarding drug product, and facilities/manufacturing process.

Drug Substance

The drug master files (DMFs) for acetaminophen (b) (4) and ibuprofen have been recently reviewed as adequate. There are no approvability issues for the drug substance portion of this application.

Drug Product

Several deficiencies were identified during the previous review cycle. This review focuses on the Applicant's responses to the quality deficiencies communicated in the CR letter dated December 12, 2017, as well as additional stability data. There are no issues for the drug product portion of this application to preclude the approval.

The most significant deficiencies were an incomplete drug product specification and a total impurities limit not supported by stability data. The Applicant has submitted a complete specification with clearly delineated release and shelf-life acceptance criteria and agreed to further lower the limits for total impurities. The final proposed drug product specification aligns with all applicable ICH guidances, except that the second internal diameter (ID) test is performed by thin layer chromatography (TLC), in which separation is based on the same principle as the first ID test, high performance liquid chromatography (HPLC). The Applicant's commitment to develop a second ID test, as described in ICH guidance Q6A section 3.2.2.b, prior to the release of commercial batches, is considered adequate. The proposed limit of no more than (NMT) (b) (4)% for (b) (4) is significantly higher than release and stability values for the registration batches. However, since the manufacturing variability is not yet known and the affected critical parameters are controlled, the Applicant's commitment to tighten the acceptance criteria for (b) (4) as appropriate, based in additional batch data as it becomes available in the future, is considered adequate. Risk assessments have been provided for elemental impurities and (b) (4). Based on the stability data for 4 batches up to 60 months at long-term conditions and 6 months at accelerated, the proposed 36-month shelf-life is granted.

Manufacturing

The manufacturing process is acceptable. The Office of Pharmaceutical Manufacturing Assessment (OPMA) recommends a CR because of a withhold due to facility deficiency:

> *During a recent inspection of* (b) (4)*, drug product manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.*

In this review cycle, the Applicant revised the (b) (4) per Agency recommendation and (b) (4)

(b) (4) They provided clarification that full process validation will be performed on the first three commercial-scale batches ((b) (4)).

Biopharmaceutics

Biopharmaceutics remains adequate from the first cycle review.

Microbiology

Microbiology remains adequate from the first cycle review.

I concur with the conclusions of OPQ.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review team concludes all nonclinical concerns have been addressed and adequately resolved. The nonclinical Pharmacology/Toxicology data are adequate to support the approval. See the CDTL/Division Director review from the original NDA submission for details regarding the Nonclinical Pharmacology/Toxicology considerations.

The non-clinical deficiencies listed in the CR letter are summarized as follows:

- Reduce the drug substance specification for (b) (4) in acetaminophen component of Combogesic to as low as technically feasible
- Analyze the final drug product for elemental impurities in 12 oral tablets against daily exposure limit by ICH Q3D guidance

In this NDA resubmission, the Applicant adequately addressed both deficiencies by tightening the drug substance (DS) specification for (b) (4) to NMT (b) (4) %, the lowest technically feasible level, and performing an elemental impurity assessment to show the levels of the elemental impurities meet the limits of ICH Q3D.

I concur with the conclusions reached by the nonclinical review team that there are no nonclinical issues to preclude approval.

5. Clinical Pharmacology

See the CDTL/Division Director review from the original NDA submission for details regarding the clinical pharmacology considerations. The clinical pharmacology review team concluded that the pharmacokinetic (PK) information submitted to support the application is acceptable. No new clinical pharmacology or biopharmaceutics data were submitted in support of this application.

The clinical pharmacology findings from the original submission are summarized as follows:

- The bioavailability of acetaminophen and ibuprofen from Combogesic is similar to their respective reference products.
- Fed versus fasted pharmacokinetic findings are not of clinical significance. The product may be taken without regard to food.

- Dose proportionality was demonstrated over the range of one to three tablets of Combogesic.
- A drug interaction between acetaminophen and ibuprofen was not identified in an in vitro human enzyme study and two pharmacokinetic studies.
- The Applicant submitted results from two additional phase 3 studies (AFT-MX-6E and AFT-MX-3) and one phase 2 dose-ranging study (AFT- MX-1) using the Maxigesic product (2 tablets of acetaminophen/ibuprofen 500 mg/150 mg). The overall dosing regimens are comparable between Maxigesic and Combogesic.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Overview of Efficacy studies

The Applicant submitted the results of one pivotal Phase 3, randomized, double-blind, placebo-controlled, parallel-group, full factorial study evaluating the analgesic effect of Combogesic in an acute dental pain population. In addition, the Applicant submitted results from two additional Phase 3 studies (AFT-MX-6E and AFT-MX-1) and one Phase 2 dose-ranging study (AFT-MX-3). Study AFT-MX-6 is a pivotal phase 3 study of the to-be-marketed formulation. The three additional phase 3 studies used a different product, Maxigesic (acetaminophen/ ibuprofen 500 mg/150 mg, approved for use in other countries). The clinical pharmacology review team determined that the exposures of Maxigesic were similar enough to provide reasonable justification for use of these data to support the Combogesic application.

The Division informed the Applicant that one adequate and well-controlled, full factorial study in patients with acute pain would be required to support an acute pain indication for Combogesic. The Applicant originally submitted a request for special protocol assessment (SPA) for the pivotal phase 3 Study (AFT-MX-6). Although agreement was reached on overall trial design, no agreement was reached on the SPA, primarily due to statistical concerns on the proposed imputation model. (Refer to special protocol no agreement letter dated on April 25, 2012.) The study was further discussed at the pre-NDA meeting and the Division agreed that the study appeared adequate to support the submission of an NDA for an acute pain indication. However, during the original NDA review, clinical and statistical review teams identified deficiencies as detailed in the CR letter. The statistical deficiencies in the CR letter were dataset related issues as detailed below and are not relevant to the statistical concerns on the SPA

Study AFT-MX-6E was another controlled full factorial study to evaluate the efficacy in the postoperative (arthroscopy) knee pain population. The datasets submitted for this study were of poor quality and important information was missing from the study report. The Applicant reported a statistically significant treatment difference between Maxigesic (Combogesic equivalent) and placebo based on the primary endpoint of SPID24. However, analysis by Dr. Ren, the statistical reviewer for the original NDA, showed that Combogesic was not statistically significantly superior in analgesia compare with placebo. Dr. Ren's analyses were consistent with the Applicant's in that the study did not demonstrate that each component (acetaminophen and ibuprofen) contributed to the effect. The nonsignificant findings are likely due to the low baseline pain score and high placebo effect in the study population. Studies AFT-MX-1 and AFT-MX-3 were not adequately designed to support the efficacy. The three additional studies are not considered further to support the efficacy. See the Dr.

Fang's Primary Clinical Review dated December 14, 2017 and combined CDTL/Division-Director Review dated December 22, from the original submission for details of these studies.

Summary of efficacy review of Study AFT-MX-6 in original NDA

Study AFT-MX-6 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a full factorial design to compare the combination of acetaminophen 1000 mg and ibuprofen 300 mg (3-tablet regimen of acetaminophen/ibuprofen 325/97.5 strength) to each of the active ingredients and placebo in patients with post-operative dental pain. Eligible patients had undergone the extraction of at least two impacted third molar teeth and with dental pain of ≥ 40mm on a 100mm VAS scale within six hours after the completion of surgery. Patients (N=408) were randomly assigned to one of the four treatment groups at a ratio of 3:3:3:2 to receive Combogesic (a combination of acetaminophen 1000 mg and ibuprofen 300 mg), acetaminophen 1000 mg, ibuprofen 300 mg, or matching placebo, to be dosed every six hours for a total of eight doses. Rescue medication, oxycodone 5-10 mg PRN q4-6 hours, was allowed if the patient requested additional medication for pain beyond the use of the study medication.

The primary efficacy endpoint was time-weighted summed pain intensity difference from baseline to 48 hours (SPID48). The proposed secondary efficacy endpoints include:

- Time to onset of perceptible and meaningful pain relief recorded by two-stopwatch method
- Time to request rescue
- Percentage using rescue
- Amount of rescue
- Maximum VAS pain intensity score
- Time to peak reduction in VAS pain intensity score
- Percentage of responders
- Categorical Global Pain Rating

In the original submission, the Applicant reported statistically significant treatment differences in the SPID48 when comparing Combogesic to each component arm and to placebo in Study AFT-MX-6. The statistical review team noted that the datasets submitted by the Applicant were not of sufficient quality to confirm the Applicant's analyses. The Applicant acknowledged that the derivation of these datasets was generated manually within Microsoft Excel, which produced errors in the datasets submitted to the NDA. The Applicant submitted revised datasets about one month before the action date of the 1st review cycle. These could not be reviewed due to insufficient time. The following deficiency was outlined in the CR letter:

> *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.

In addition, the clinical reviewer determined that additional efficacy analysis may be helpful to understand the complete efficacy profile of the proposed product. The following information requests were conveyed to the Applicant in the CR letter:

- *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.*
- *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.*
- *Provide time-specific PID data and curves covering the entire 48-hour evaluation period similar to the request above.*
- *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.*
- *Provide a summary for single-dose duration in terms of median time to rescue and/or remediation (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.*
- *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.*
- *Clarify the number and proportion of patients of African and/or Hispanic descent per treatment group.*

The current NDA resubmission provides information requested. However, two additional information requests were sent to the Applicant to obtain the following information.

- Exposure details in pharmacokinetic (PK) studies
- Exposure details during the open-label extension phase of in Study AFT-MX-6E or any other study
- Pairwise comparisons between individual components and placebo to be added to the PID summary table for Study AFT-MX-6
- Shift tables to adequately summarize changes in laboratory test results
- Classification of race-ethnicity categories according to the classifications by the US Census Bureau

- Time-specific pain intensity (PI) score per treatment group during the 48-hour evaluation period in Study AFT-MX-6

Summary of efficacy review of Study AFT-MX-6 in resubmission:

The study design features and important elements including patient disposition, protocol deviations, and major demographic information were detailed in Dr. Fang's original NDA review.

Statistical reviewer, Dr. John Lawrence stated that the quality of the data and the analysis in the resubmission are good. Dr. Fang conducted a thorough review of the updated datasets. I concur with the data Dr. Fang presented, however, I have different interpretations of the primary analysis and some of the additional analyses.

Summed pain intensity difference from start of first dose until 48 hours: SPID48

Study AFT-MX-6 demonstrated statistically significantly superiority of Combogesic to acetaminophen, ibuprofen, and placebo based on the time-weighted summed pain intensity difference from baseline over 48 hours (SPID 48) (Table 1). Refer to statistical review by Dr. John Lawrence dated September 30, 2020 for additional details. I consider the combination rule is fulfilled based on SPID48.

Table 1. Primary Efficacy Endpoint, SPID 48

Study MX-6 SPID48 (PI by VAS)	**Combogesic** N=110	**Ibuprofen** N=112	**Acetaminophen** N=111	**Placebo** N=75
Mean Estimate (SE)	31.56 (1.94)	23.18 (1.89)	17.71 (1.89)	14.86 (2.26)
95% Confidence Interval (CI)	27.76; 35.37	19.47; 26.89	14.00; 21.43	10.43; 19.30
		Combo >Ibu	**Combo >APAP**	**Combo >Pla**
		<0.001	<0.001	<0.001

Source: Adapted from Dr. Fang's clinical review. Revised from Table 23 on page 79 of the revised study report in resubmission.

Time specific pain intensity difference: PIDs

The SPID is a time-weighted average of the change in pain scores at time intervals after the start of study treatment. This measure reflects the analgesic effect over the entire assessment period (48 hours) and has been accepted as a primary endpoint in acute pain trials. However, the calculated SPID is not inherently clinically meaningful, because it is not a direct measure of how a patient feels pain, but rather depends on other factors, such as the number and time of assessments collected. Therefore, although a SPID may be an acceptable primary endpoint, it will need to be supported by consistent time-specific pain intensity differences (PID) over the treatment period. The time specific PID demonstrated consistent separation (Table 2) between Combogesic to ibuprofen, acetaminophen during the first dose interval (Figure 1) and over 48 hours (Figure 2). One of the challenges in analgesic studies is the small/inconsistent PID effect size across different analgesic trials. Pain is a subjective phenomenon and varies widely under different investigational conditions. Dr. Fang noted the PID effect size in this study is smaller compare to other NSAIDs or similar drugs studied in dental pain models. The smaller effect size is likely the result of the low assay sensitivity because of the low entry pain scores in this study.

Table 2. Time-Specific PID (PI measured by 100 mm VAS)

	Combo N=110	Ibu N=112	APAP N=111	Pla N=75	Pairwise comparison								
Hours	Mean*				Combo >Ibu	Ibu>Pla	C>I>P		Combo >APAP	APAP>Pla	C>A>P		Combo >Pla
							≥5	≥10			≥5	≥10	
.25	10.1	7.6	7.5	4.1	2.6	3.5			2.7	3.4			6.1
.5	18.8	13.1	15.9	3.5	5.7	9.6	x		3.0	12.3			15.3
.75	25.8	17.1	19.6	3.0	8.7	14.1	x		6.2	16.6	x		22.8
1	31.6	20.9	23.1	-0.5	10.7	21.4	x	x	8.5	23.6	x		32.1
1.5	35.8	27.5	25.7	1.8	8.3	25.7	x		10.1	23.9	x	x	34.0
2	38.2	31.9	27.0	6.8	6.3	25.1	x		11.2	20.2	x	x	31.4
3	38.1	33.6	25.5	14.9	4.5	18.8			12.6	10.7	x	x	23.3
4	38.0	33.3	25.2	19.9	4.7	13.5			12.9	5.3	x		18.2
5	34.3	29.5	21.1	19.8	4.8	9.7			13.2	1.3			14.5
6	29.6	22.7	17.0	18.4	6.9	4.4			12.6	-1.4			11.2
7	39.3	34.7	31.4	22.4	4.6	12.3			8.0	9.0	x		16.9
8	39.8	37.1	30.4	20.8	2.7	16.3			9.3	9.7	x		19.0
12	36.3	28.2	21.3	23.0	8.0	5.3	x		15.0	-1.7			13.3
14	39.2	33.6	29.9	25.6	5.6	8.0	x		9.3	4.3			13.6
18	37.7	29.4	26.0	23.1	8.4	6.3	x		11.8	2.9			14.6
20	42.4	35.9	33.6	27.7	6.5	8.2	x		8.8	5.9	x		14.7
24	36.7	30.5	28.6	27.8	6.2	2.7			8.1	0.8			8.9
26	43.1	38.3	35.2	27.3	4.8	11.0			7.9	8.0	x		15.9
30	35.9	24.8	25.3	26.1	11.1	-1.2			10.5	-0.7			9.8
32	41.3	33.4	33.2	26.9	7.9	6.5	x		8.1	6.3	x		14.4
36	37.1	28.4	25.6	27.4	8.7	1.0			11.5	-1.8			9.7
38	40.3	33.8	32.0	31.2	6.5	2.7			8.3	0.8			9.1
42	38.1	30.7	28.7	31.3	7.4	-0.6			9.4	-2.6			6.7
44	43.7	37.8	37.0	32.8	5.9	5.0	x		6.8	4.2			10.9

*Mean estimate
Source: adapted from Dr. Fang's clinic review; Table 34 on pages 101-105 of the revised study report submitted on July 9, 2020.

Figure 1 Single-Dose PID Curve Over First Six Hours

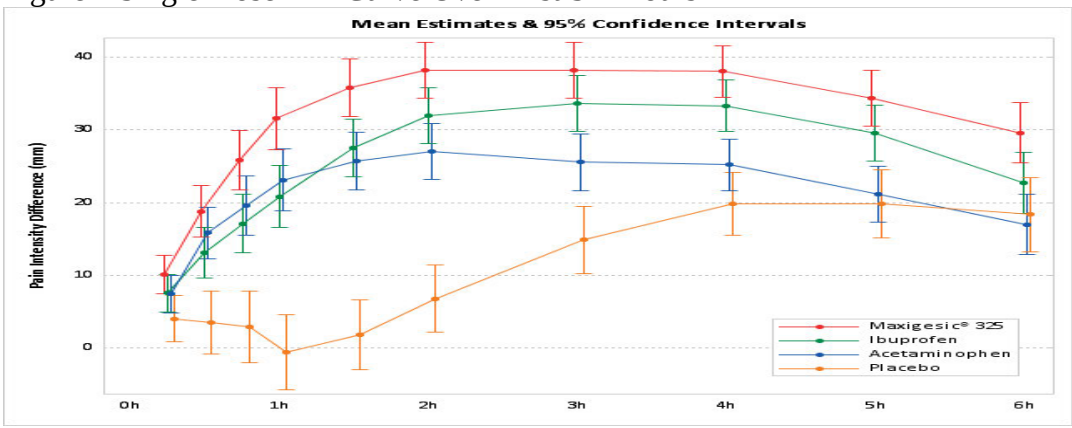
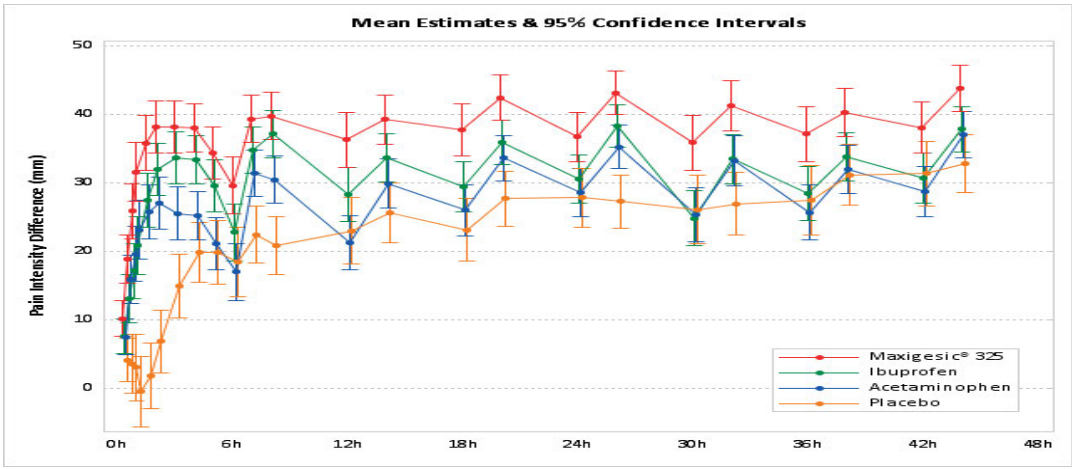


Figure 2 Multiple-Dose PID Curve Over 48 Hours



Secondary endpoints and additional analysis:

None of the Applicant's proposed secondary endpoints testing were adjusted for multiplicity and are considered exploratory in nature. Refer to Dr. John Lawrence's review for proposed secondary analysis and Dr. Fang's review for details on additional analysis.

Time to onset of perceptible and meaningful pain relief recorded by the two-stopwatch method was proposed as the key secondary endpoint. Onset of analgesia was defined by the median time to meaningful pain relief. Median time to meaningful pain relief was shortest for the Combogesic (42.98 min), followed by acetaminophen (48.62 min), and ibuprofen (61.86 min) groups (see details in Dr. John Lawrence's statistical review). This result suggests the component contribution; however, the clinical significance of the contribution is not clear.

Rescue medication use has been critical in assessing efficacy in analgesic trials. Several secondary endpoints regarding the consumption of rescue medication were proposed. However, the rescue medication used in this study is oxycodone 5-10 mg PRN q4-6 hours. As Dr. Fang mentioned, in the current multiple-dose study, use of rescue would not be considered as treatment failure and patients will be kept in the study to maintain the sample size. The use of an opioid rescue in a non-opioid acute pain trial would confound the assessment of true treatment effect. However, since all four treatment arms received opioid rescue medication, it is still possible to compare rescue medication use in the Combogesic arm to other treatment arms.

Although limited, the percentage of patients who used rescue medication supports each component's contribution. The percentage of subjects who took at least one dose of rescue medication was lowest in the Combogesic group (23.9 %), followed by the ibuprofen group (43.2 %), acetaminophen group (53.2%) and highest in placebo group (81.3%). Patients who used the first rescue medication within the first dosing interval was similarly lowest in the Combogesic group (16.5%), followed by the ibuprofen group (30.6%), acetaminophen group (44.1%) and highest in placebo group (70.7%). Median time to initial rescue within the first dosing interval has been used to measure duration of analgesia, however, such an evaluation was not feasible because fewer than 50% of patients used first-interval rescue medication, which on the other hand suggests that Combogesic and each individual component provide analgesia during the initial dose interval.

Summary of efficacy:

The efficacy evaluation will be based on the results of the pivotal phase 3 Study AFT-MX-6.

Study AFT-MX-6 demonstrated statistically significantly superiority of Combogesic to acetaminophen, ibuprofen, and placebo based on the time-weighted summed pain intensity difference from baseline over 48 hours (SPID 48) (Table 1). Additional analyses on time specific pain intensity difference (PIDs), the time to meaningful pain relief (two-stopwatch method), and rescue medication use are supportive of Combogesic as an acute analgesic and each component contributes to the claimed effect. The study was limited in that none of the secondary efficacy endpoints testing were adjusted to control multiplicity. The use of an opioid rescue in a non-opioid acute pain trial would confound the assessment of true treatment effect. However, since all four treatment arms received opioid rescue medication, it is still possible to compare rescue medication use in the Combogesic arm to other treatment arms.

In conclusion, there is sufficient evidence in Study AFT-MX-6 to support the efficacy of Combogesic and the combination rule is fulfilled in treating mild to moderate acute pain.

8. Safety

As a 505(b)(2) application, adequate scientific bridge was established based on bioavailability studies to rely on the Agency's previous finding of safety to support the individual components contained in Combogesic.

The Applicant submitted safety data from the three phase 3 efficacy and safety studies (AFT-MX-6, AFT-MX-6E, and AFT-MX-1), one phase 2 study (AFT-MX-3), and the clinical pharmacology studies. Refer to Dr. Fang's original NDA review for details. The safety population was characterized by healthy volunteers in all the single-dose PK studies, young and healthy adults undergoing third-molar extraction in five of the four multiple-dose studies. Only the study of knee pain (MX-6E) had patients up to the age of 75 years.

Dr. Fang conducted a thorough original review of the safety of Combogesic and noted that the Applicant did not provide sufficient information to determine the overall exposure. The following clinical deficiency was listed in the CR letter at the conclusion of the original NDA review.

> *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.*

In the resubmission, the Applicant submitted clarified exposure information. New safety data from one pediatric study of oral suspension formulation and one adult phase 3 study of an IV formulation are included by the Applicant in the current NDA resubmission as safety updates. The safety data from different formulations are not reviewed to support this NDA.

Overall exposure to Combogesic was reported in 708 subjects including 605 subjects exposed to any full dose and 133 subjects to any partial dose (30 were exposed to both full and partial doses). Of 605 subjects exposed to a full dose of Combogesic 367 (61%) subjects were exposed to at least four doses, 253 (42%) subjects exposed to at least eight doses, and 50 (8%) exposed to at least 12 doses. The safety exposure appears adequate.

Dr. Fang summarized safety findings based on the review of the original NDA and updated information in resubmission

- Of 605 subjects exposed to a full dose of Combogesic, 367 (61%) subjects were exposed to at least four doses, 253 (42%) subjects exposed to at least eight doses, and 50 (8%) exposed to at least 12 doses.

- One case of death from gunshot wound (homicide) was reported in a patient about two weeks after the last dose of Combogesic and was considered unlikely to be related to the study medication.

- Of a total of eight cases of serious adverse events (SAEs) reported in the NDA, two were in the Combogesic group, including one case of deep vein thrombosis occurring two days after the last dose of Combogesic treatment, thought to be due to immobility after the surgery, and one case of post-operative buccal infection reported four days after the last dose of Combogesic at quarter dose level. Both resolved with treatment and were considered unlikely to be related to the study medication.

- Only two patients discontinued the study due to AEs (vomiting and stomach cramps); both received Combogesic.

- About one third of the study population reported AEs and the proportions reporting any AEs and common individual AEs were similar across treatment groups, including the placebo group. The most commonly reported AEs in the Combogesic group included nausea (15%), vomiting (7%), headache (5%), dizziness (3%), somnolence (2%), post-procedure hemorrhage (2%), and swelling face (2%).

- Dose response in AEs could not be adequately assessed due to small sample size of 30 to 50 patients per group in the dose-response Study MX-3.

- Safety monitoring in one multiple-dose study with follow-up laboratory tests scheduled a week after two different treatments administered sequentially in majority of patients before testing could not provide adequate dataset for treatment comparison. Laboratory testing in single-dose studies was of limited value and did not identify clinically meaningful shifts from baseline in PK studies.

- A short duration of exposure of 1 to 2 days is not expected to provide valuable safety information because AE in general were not only related to the level of exposure but also to the duration of exposure. However, safety assessments in acute analgesic studies are limited to a few days due to the nature of the pain studied.

I concur with Dr. Fang's summary of safety findings based on the review of the original NDA and updated information in resubmission

Summary of safety

Safety evaluation of acetaminophen and ibuprofen relies on the Agency's previous finding of safety for the reference products. The safety database for this new combination is adequate to support the safety of acetaminophen and ibuprofen when used in combination. The safety data from the clinical studies did not reveal any unanticipated adverse effects with this combination. Although the safety evaluation is limited to a few days,

additive toxicity is not anticipated because interaction between acetaminophen and ibuprofen is unlikely based on an in vitro human enzyme study and pharmacokinetic studies.

9. Advisory Committee Meeting

There was no advisory committee meeting held for this drug product.

10. Pediatrics

See the CDTL/Division Director review from the original NDA submission for details regarding pediatric use considerations.

Efficacy may be extrapolated from adults to pediatric patients two years of age and older provided that the exposures between adults and those pediatric age groups are similar. If the Applicant is able to address the deficiencies, the following deferred studies will be required:

- A multiple-dose adequate and well-controlled pharmacokinetic, safety, and efficacy study in pediatric patients (b) (4) to <2 years of age with acute pain requiring a combination acetaminophen ibuprofen product
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 2 to <12 years of age with acute pain requiring a combination acetaminophen ibuprofen product
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 12 to <17 years of age with acute pain requiring a combination acetaminophen ibuprofen product

In the resubmission, the Applicant submitted an updated PSP with the results of Study MX-12 in the age group of 2 to 12 years and proposed new timelines for <2 years of age and for 12 to 17 years of age. The revised PSP is not reviewed due to a CR action.

11. Other Relevant Regulatory Issues

See the CDTL/Division Director review from the original NDA submission for details regarding other regulatory issues.

The following section was taken from Dr. Fang's clinical review regarding the Division of Pharmacovigilance (DPV) review on the post marketing safety data in the resubmission. I concur with her summary.

> *The Division of Pharmacovigilance (DPV) reviewed post-marketing safety data to update information on association between acetaminophen use and serious cutaneous adverse events and reported data consistency in support of inclusion of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) in the OTC monograph for acetaminophen products (refer to DPV Review dated October 19, 2020 for detail).*

12. Labeling/DMEPA Review

A comprehensive labeling review was not conducted because of deficiencies that preclude approval.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategy (REMS)

A REMS is not recommended at this time.

Postmarketing Requirements and Commitments (PMRs)

No postmarketing requirements or commitments are recommended at this time.

14. Recommended Comments to the Applicant

CMC provide the following comments:

FACILITY INSPECTIONS

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)*, 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.*

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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RIGOBERTO A ROCA
11/06/2020 02:34:06 PM

Combined Cross-Discipline Team Leader Review And Summary Review for Regulatory Action

Date	(electronic stamp)
Cross-Discipline Team Leader	Joshua M. Lloyd, MD
Deputy Division Director	Ellen Fields, MD, MPH
Subject	Combined Cross-Discipline Team Leader Review And Summary Review for Regulatory Action
NDA	209471
Applicant	AFT Pharmaceuticals
Date of Submission	March 1, 2017
PDUFA Goal Date	January 1, 2018
Proprietary Name / Established (USAN) names	Combogesic / Acetaminophen and Ibuprofen
Dosage forms / Strength	Oral tablets 325 mg/97.5 mg
Proposed Dosing Regimen	Three tablets every six hours with a maximum of 12 tablets per day
Proposed Indication(s)	Short-term management of mild-to-moderate acute pain
Recommended:	Complete Response

1. Introduction

Combogesic is a novel fixed-dose combination drug product containing acetaminophen and ibuprofen. AFT Pharmaceuticals ("Applicant") submitted a 505(b)(2) new drug application (NDA) for Combogesic for the short-term management of mild-to-moderate acute pain referencing the approved products Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123) for the acetaminophen component and Motrin tablets (ibuprofen 300 mg, 400 mg, 600 mg, 800 mg; NDA 17463) for the ibuprofen component. The marketing status for Motrin is discontinued; however, it was not discontinued or withdrawn for reasons of safety or efficacy.

2. Background

Combogesic was developed under IND 107435 and consists of a combination of acetaminophen and the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, both of which are analgesics with a long clinical history of use. Although this combination has never been approved in the U.S., a similar product, Maxigesic, that contains 500 mg of acetaminophen and 150 mg of ibuprofen is approved for use in other countries. The Applicant developed Combogesic as a formulation specific to the U.S. market to address the maximum allowed acetaminophen content for an individual dosage form (i.e., 325 mg). The product was

initially being developed for both acute pain (b) (4); however, the current NDA is for an acute pain indication only. To fulfill the "combination rule" (21 CFR 300.50), which requires that "…each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug," the Division informed the Applicant that one adequate and well-controlled, full factorial study in patients with acute pain would be required to support an acute pain indication for Combogesic. The Division met with the Applicant and provided advice during clinical development, which included a Pre-NDA meeting, where agreement was reached on the data needed to support an NDA for an acute analgesic indication, including the need for a 48-hour full factorial study. The Applicant also submitted a request for special protocol assessment (SPA) for the pivotal acute pain study. Although agreement was reached on overall trial design, no agreement was reached on the SPA, primarily due to statistical concerns surrounding the approach to missing data.

3. CMC/Biopharmaceutics

CMC

Combogesic tablets are white, capsule-shaped, film-coated, and embossed with the letters "(b) (4)" on one side, and each tablet contains 325 mg of acetaminophen and 97.5 mg of ibuprofen. The final drug product is enclosed in (b) (4) packaging. Of note, the product is the (b) (4). DMF (b) (4) for the acetaminophen drug substance and DMF (b) (4) for the ibuprofen drug substance were found to be adequate.

The drug product review identified analytical method and drug product specification deficiencies. Additionally, the process review identified deficiencies related to (b) (4) as well as the description of commercial process validation.

Long-term and accelerated stability data support granting the proposed three-year expiry pending resolution of the CMC deficiencies, and the Applicant included a post-approval stability protocol and commitment testing stability on the commercial batches. The request for a categorical exclusion from the requirement to prepare an environmental assessment was determined to be acceptable.

Although the drug substance manufacturing facilities for this application were found to be acceptable, the facilities review team is recommending withhold based on inspection of the drug product manufacturing facility.

Biopharmaceutics

The proposed dissolution method is based on USP monographs. The biopharmaceutics team found the initially proposed acceptance criterion to be too permissive; however, the Applicant accepted a revised criterion, which was found to be adequate.

CMC recommends a complete response based on the facilities, drug product, and process deficiencies, and I concur with their assessment and conclusions. The CMC review team recommends that the Applicant address the following issues (verbatim) prior to approval:

Facilities

- During a recent inspection of (b) (4), product/process controls, lab controls, and QA functions for the facility was 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.

Drug Product

- The example chromatograms 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.

- 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.

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

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

- A certification is required 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

- (b) (4)
-

- In Section 3.2.P.3.5, you have referred to the 4 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 3 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

4. Nonclinical Pharmacology/Toxicology

No new toxicology studies were required to support this NDA submission, and the existing nonclinical data are sufficient to support the safety of Combogesic for the proposed indication and dosing regimen. The Applicant conducted two non-standard toxicology studies to address findings from several publications, which suggested enhanced gastrointestinal (GI) and/or renal toxicity in rats that received both ibuprofen and acetaminophen. The nonclinical review team noted that these studies had several limitations but there was no increase in GI or renal toxicity or any new safety issues identified for the combination.

The nonclinical review team further noted that there are no safety concerns with the formulation, the ibuprofen drug substance specifications, or the drug product specifications. However, the acetaminophen drug substance specification for (b) (4) needs to be tightened due to the potential for genotoxicity. Additionally, the nonclinical review noted that "the Applicant did not address the potential for elemental impurities to be present in the final drug product." Based on these concerns, the nonclinical review team recommends a complete response, and I concur with their conclusions. The nonclinical review team recommends that the Applicant address the following issues (verbatim) prior to approval:

Nonclinical

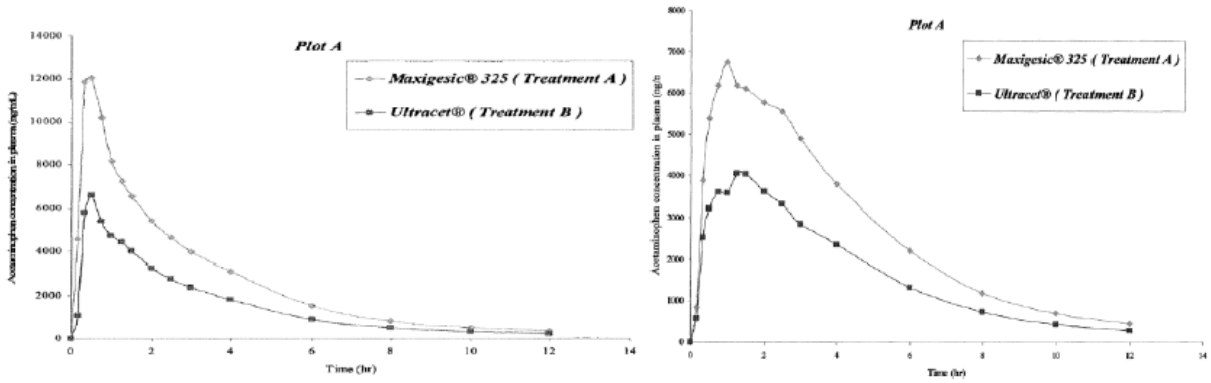
1. You have not provided adequate justification for the proposed drug substance specification for (b) (4). Because (b) (4) has been reported to product chromosomal aberrations in human lymphocytes, reduce the drug substance specification for (b) (4) to as low as technically feasible.

2. 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 pills per day. Provide safety justification for any elemental impurity that exceeds the ICH permissible daily exposures for the oral route of administration.

5. Clinical Pharmacology

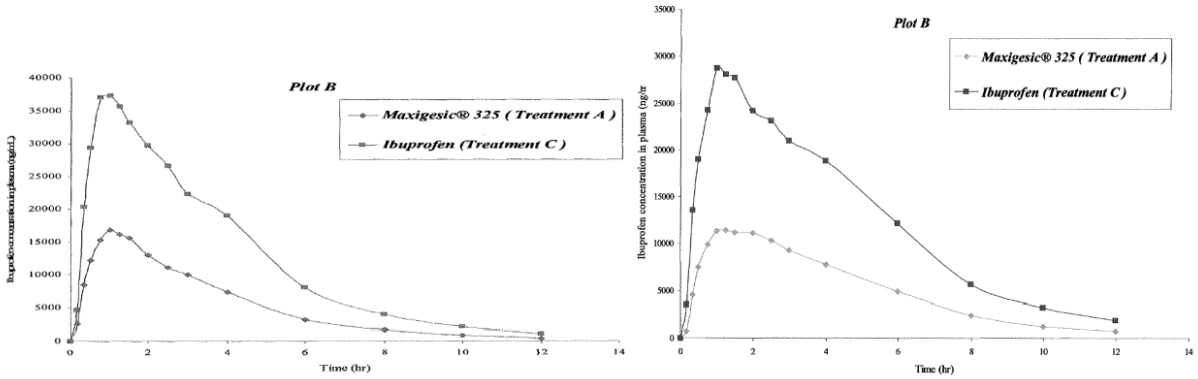
The Applicant conducted two relative bioavailability studies under the fasting and fed states to establish a scientific bridge to the agency's prior findings for the reference products. Studies AFT-MX-13a and AFT-MX-13b were randomized, open-label, single-dose, three-period, crossover studies conducted in 30 healthy volunteers in the fasting and fed states, respectively. Treatments consisted of three Combogesic tablets (total dose of 975 mg acetaminophen and 292.5 mg ibuprofen), two tramadol/acetaminophen tablets (total dose of 650 mg acetaminophen), and one 800 mg tablet of ibuprofen. The results of these studies (summarized in the tables and figures below) demonstrated that Combogesic had higher acetaminophen Cmax and AUC values and lower ibuprofen Cmax and AUC values as compared to the reference products due to differences in dose. However, the dose-normalized AUC values for both acetaminophen and ibuprofen met bioequivalence (BE) criteria in the fasted and fed states. Although the dose-normalized Cmax values met BE criteria in the fed state, the dose-normalized Cmax was 29% greater for acetaminophen and 19% greater for ibuprofen in the fasted state as compared to the reference products. The clinical pharmacology review team concluded that these pharmacokinetic results suggest that the bioavailability of acetaminophen and ibuprofen from Combogesic is similar to their respective reference products.

Figure 1. Mean Acetaminophen Plasma Concentration Versus Time for Combogesic (total acetaminophen dose 975 mg; labeled as Maxigesic 325 in the figure) and tramadol/acetaminophen (total acetaminophen dose 650 mg) under Fasting Condition (Left Panel; Study AFT-MX-13a) and Fed Conditions (Right Panel; Study AFT-MX-13b)



Source: Dr. Qiu's review, pg. 14

Figure 2. Mean Ibuprofen Plasma Concentration Versus Time for Combogesic (total ibuprofen dose 292.5 mg; labeled as Maxigesic 325 in the figure) and ibuprofen (total ibuprofen dose 800 mg) under Fasting Condition (Left Panel; Study AFT-MX-13a) and Fed Conditions (Right Panel; Study AFT-MX-13b)



Source: Dr. Qiu's review, pg. 15

Table 1. Mean (SD) Acetaminophen Pharmacokinetic Parameters for A Single Dose of Combogesic (Treatment A) and a Single Dose of Ultracet (Acetaminophen 325 mg/tramadol HCl 37.5 mg; Treatment B) in Healthy Subjects Under Fasting Condition (Study AFT-MX-13a) and Fed Condition (Study AFT-MX-13b) with and Statistical Analysis of Dose Normalized Cmax and AUCs

PK parameter	**Study AFT-MX-13a** (Fasting)		**Study AFT-MX-13b** (Fed)	
	3 x FDC 325/97.5 tablets (Treatment A) (N = 30)	2 x Ultracet tablets (acetaminophen 325 mg/tramadol HCl 37.5 mg) (Treatment B) (N = 30)	3 x FDC 325/97.5 tablets (Treatment A) (N = 29)	2 x Ultracet tablets (acetaminophen 325 mg/tramadol HCl 37.5 mg) (Treatment B) (N = 29)
Cmax (ng/mL)	16248 (8132)	8334 (3972)	9334 (3452)	6228 (3114)
Tmax (h)*	0.50 (0.17, 2.50)	0.50 (0.33, 2.50)	1.00 (0.33, 3.00)	1.25 (0.17, 6.00)
AUCt (ng.h/mL)	32760 (8872)	18850 (5018)	32662 (9253)	19929 (5688)
AUCinf (ng.h/mL)	34418 (9516)	19890 (5350)	34612 (10189)	21190 (6292)
T1/2 (h)	3.14 (0.57)	3.33 (0.81)	2.94 (0.54)	2.96 (0.59)
	Geometric Mean Ratio(A/B) % (90% CI)			
Cmax/Dose	129.25% (113.42 – 147.30%)		103.77% (91.93 – 117.13%)	
AUCt/Dose	115.58% (111.68 – 119.62%)		109.31% (107.12 – 111.55%)	
AUCinf/Dose	114.57% (110.74 – 118.54%)		108.99% (106.89 – 111.13%)	

*median (min, max)

Source: Dr. Qiu's review, pg. 4

Table 2. Mean (SD) Ibuprofen Pharmacokinetic Parameters for A Single Dose of Combogesic (Treatment A) and a Single Dose of Ibuprofen (Treatment C) in Healthy Subjects Under Fasting Condition (Study AFT-MX-13a) and Fed Condition (Study AFT-MX-13b) with Statistical Analysis of Dose Normalized Cmax and AUCs

PK parameter	**Study AFT-MX-13a** (Fasting)		**Study AFT-MX-13b** (Fed)	
	3 x FDC 325/97.5 tablets (Treatment A) (N = 30)	1 x 800 mg Ibuprofen tablet (Treatment C) (N = 30)	3 x FDC 325/97.5 tablets (Treatment A) (N = 29)	1 x 800 mg Ibuprofen tablet (Treatment C) (N = 29)
Cmax (ng/mL)	19943 (5827)	45278 (9744)	16086 (3840)	43574 (14040)
Tmax (h)*	1.00 (0.33, 4.00)	1.00 (0.50, 4.00)	1.25 (0.50, 4.00)	1.25 (0.50, 6.00)
AUCt (ng.h/mL)	64672 (23026)	152720 (48064)	62074 (12964)	148896 (33744)
AUCinf (ng.h/mL)	66280 (24278)	156480 (50872)	64446 (14212)	156216 (40368)
T1/2 (h)	2.22 (0.29)	2.20 (0.33)	2.24 (0.27)	2.44 (0.42)
	Geometric Mean Ratio(A/C/) % (90% CI)			
Cmax/Dose	118.70% (110.41 – 127.62%)		104.05% (93.91 – 115.29%)	
AUCt/Dose	115.02% (110.73 – 119.47%)		114.20% (110.44 – 118.09%)	
AUCinf/Dose	115.03% (110.81 – 119.41%)		113.33% (109.68 – 117.09%)	

*median (min, max)

Source: Dr. Qiu;s review, pg. 4

Food effect and dose proportionality were evaluated in study AFT-MX-10. This study demonstrated that a high fat meal resulted in an approximately 30% decrease in acetaminophen Cmax, whereas it had no effect on acetaminophen AUCs or ibuprofen AUCs or Cmax. Median Tmax values for both acetaminophen and ibuprofen were slightly prolonged under fed conditions, from 0.5 hours to 1 hour (0.50, 3.00) for acetaminophen and 1 hour (0.50, 12.00) to 1.25 hours (0.50, 3.00) for ibuprofen. The clinical pharmacology review team

determined that the fed versus fasted pharmacokinetic findings are not of clinical significance and that the product may be taken without regard to food. Dose proportionality was demonstrated over the range of one to three tablets of Combogesic.

The potential for drug-drug interactions between the two components of the combination was evaluated in an in vitro human enzyme study and in two pharmacokinetic studies using the combination of 500 mg acetaminophen and 150 mg ibuprofen, none of which identified a drug interaction between acetaminophen and ibuprofen.

All clinical studies that evaluated Combogesic were conducted using the same formulation, which only differed slightly from the to-be-marketed formulation in that the test product was plain on both sides and the commercial product is embossed on one side. The biopharmaceutics review team found that the in vitro comparative dissolution data that the Applicant submitted was adequate to bridge these two formulations.

In addition to the Phase 3 pivotal study, the Applicant submitted results from two additional Phase 3 studies and one Phase 2 dose-ranging study using the Maxigesic product (acetaminophen/ibuprofen 500 mg/150 mg), which, although similar, is formulated to a higher weight to achieve higher doses in individual dosage forms. However, the overall dosing regimens are comparable between Maxigesic and Combogesic. To support the applicability of data using a different formulation, the Applicant submitted results from two relative bioavailability studies (AFT-MX-14a and AFT-MX-14b) that compared three tablets of Combogesic (975 mg acetaminophen and 292.5 mg ibuprofen in total) to two tablets of Maxigesic (1,000 mg acetaminophen and 300 mg ibuprofen in total) as well as to two other formulations in the fasted and fed conditions, respectively. Both studies were randomized, open-label, single-dose, four-way crossover studies conducted in healthy volunteers. The acetaminophen Cmax was 19% greater for Combogesic compared to Maxigesic in the fasted condition, while it met BE criteria in the fed condition. The AUC values for both acetaminophen and ibuprofen, as well as the ibuprofen Cmax, for Combogesic and Maxigesic met BE criteria in both the fed and fasted conditions. The clinical pharmacology review team concluded that similarity in acetaminophen and ibuprofen exposures from three tablets of Combogesic and two tablets of Maxigesic in both the fed and fasted conditions provide reasonable justification for the use of data obtained using two tablets of Maxigesic as supportive for the Combogesic application.

The clinical pharmacology review team found the application approvable from their perspective, and I concur with their conclusions.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The Applicant submitted the results of one pivotal Phase 3, randomized, double-blind, placebo-controlled, parallel-group, full factorial study evaluating the analgesic effect of Combogesic in an acute dental pain population. Dr. Fang and Dr. Ren conducted a full review of this study, as it is the pivotal trial intended to demonstrate analgesic efficacy in acute pain for Combogesic. I will review the salient study design features and describe the significant issues that were encountered during the review of this study.

The Applicant also submitted the results from three additional studies that evaluated the analgesic efficacy of the combination of acetaminophen and ibuprofen, including two Phase 3 studies and one Phase 2 dose-ranging study. Although these studies were conducted using a different formulation (i.e., two tablets of Maxigesic, each of which contain 500 mg acetaminophen and 150 mg ibuprofen), the overall amounts of acetaminophen and ibuprofen are comparable to the proposed dose for Combogesic and the clinical pharmacology review team determined that the exposures were similar enough to provide reasonable justification for use of these data to support the Combogesic application (refer to Section 5 Clinical Pharmacology in this review).

Study AFT-MX-6

Primary objective: To investigate the clinical efficacy and safety of Combogesic compared to its individual components and placebo

Duration of treatment: 48 hours

Population: Adult patients undergoing dental surgery for the extraction of at least two impacted third molar teeth with postoperative dental pain of ≥40 mm on a 100 mm visual analog scale (VAS) within 6 hours after completion of surgery

Treatment: Patients were randomized in a 3:3:3:2 fashion to receive one of the following treatments every 6 hours for a total of 8 doses:

- Combogesic (acetaminophen 975 mg and ibuprofen 292.5 mg per dose)
- Acetaminophen, 975 mg per dose
- Ibuprofen, 292.5 mg per dose
- Placebo

Rescue medication: Oxycodone 5 to 10 mg, every 4 to 6 hours as needed

Design: The study was a multicenter (conducted at four sites, one in the U.S. and three in New Zealand), randomized, double-blind, placebo-controlled, parallel-group, full factorial trial

that include a screening period, dental surgery, a double-blind treatment period, and post-treatment follow-up.

Primary efficacy endpoint: Time-adjusted summation of pain intensity difference up to 48 hours (SPID48) based on pain intensity measurements using a 100 mm VAS

Secondary efficacy endpoints:

- Time to onset of perceptible and meaningful pain relief as recorded by the double stopwatch method
- Time to request rescue
- Percentage using rescue
- Amount of rescue
- Maximum VAS pain intensity score
- Time to peak reduction in VAS pain intensity score
- Percentage of responders
- Categorical Global Pain Rating

The Applicant reported statistically significant primary efficacy results on the SPID48 for study AFT-MX-6. Similarly, the Applicant's results on the secondary analyses were generally supportive of Combogesic as an acute analgesic; however, Dr. Fang (clinical reviewer) noted additional information would be required to complete the assessment (e.g., analyses of single- and multiple-dose effects). Dr. Ren (statistical reviewer) noted that the datasets submitted by the Applicant were not of sufficient quality to confirm the Applicant's primary and secondary efficacy analyses to determine if the results provided established substantial evidence of efficacy. Additionally, because of this, Dr. Ren was not able to evaluate the impact of missing data on the primary and secondary analyses. The Applicant was unable to provide the programs used to derive the primary and secondary analyses because all pre-processing and derivations of the clinical endpoints were performed manually in Microsoft Excel. Therefore, the Applicant contracted a third party to produce SAS programs to reproduce the analyses and for the derivation of analysis datasets. Revised datasets were submitted on November 22, 2017, and could not be reviewed in the context of this review cycle due to insufficient time.

The Applicant also submitted results from two additional Phase 3 studies and one Phase 2 dose-ranging study using the Maxigesic product (acetaminophen/ ibuprofen 500 mg/150 mg) to support this application for Combogesic.

Study AFT-MX-6E was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, full factorial study that was conducted in patients with postoperative (arthroscopy) knee pain. Treatment groups consisted of Maxigesic (1,000 mg acetaminophen and 300 mg ibuprofen in total), acetaminophen (1,000 mg), ibuprofen (300 mg), or placebo given every 6 hours for 24 hours followed by an open-label extension of up to 4 days. The primary endpoint was a SPID24. Although the Applicant reported a statistically significant difference between Maxigesic and placebo on the primary endpoint, the Applicant's results for Maxigesic compared to either acetaminophen alone or ibuprofen alone were not statistically

significant. Dr. Ren's analyses using the Applicant's datasets were not consistent with the Applicant's. Dr. Ren's analysis demonstrated that Maxigesic was not significantly different from placebo, acetaminophen, or ibuprofen, and she concluded that the results from this study do not support efficacy.

An additional Phase 3 randomized, double-blind, parallel-group study (AFT-MX-1) was conducted in a dental pain population; however, this study only compared Maxigesic to each of the individual components without a placebo group (partial factorial design). Additionally, based on the design of this study, Dr. Fang considered it exploratory in nature.

Study AFT-MX-3 was a Phase 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study that was conducted in patients with postoperative dental pain after removal of between two and four impacted third molars. Treatment groups consisted of Maxigesic at a full dose (1000 mg acetaminophen and 300 mg ibuprofen), Maxigesic at a half dose (500 mg acetaminophen and 150 mg ibuprofen), Maxigesic at a quarter dose (250 mg acetaminophen and 75 mg ibuprofen), or placebo given every 6 hours for up to 24 hours followed by an open-label extension of up to 4 days. This study did not evaluate the combination against the individual components and will not be considered further.

Both Drs. Fang and Ren recommended a complete response for this application, and I concur with their conclusions.

Dr. Fang recommend that the Applicant address the following clinical efficacy issues (verbatim) prior to approval:

- Provide time-specific 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.

- 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.

- Provide time-specific PID data and curves covering the entire 48-hour evaluation period in a similar way as stated above.

- Provide 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.

- Provide 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.

- Provide subpopulation analyses for study population in US and sample population in New Zealand, respectively, for all the items described above.

- Clarify the number and proportion of patients of African in origin and Hispanic in ethnicity per treatment group.

The statistical review team recommends that the Applicant address the following statistical efficacy issues (verbatim, as entered into the Complete Response Letter by statistics) prior to approval:

- 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.

  In a response from you dated June 13, 2017 you acknowledged the derivation of these datasets were generated manually within Microsoft Excel and 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.

  We 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.

8. Safety

Extensive clinical experience exists with the individual components of Combogesic as standalone analgesics as well as when used concomitantly. The maximum daily dose of acetaminophen with Combogesic is 3,900 mg, which is within the maximum allowed daily dose of 4,000 mg for acetaminophen. Additionally, the ibuprofen dose that will be administered with Combogesic is within the dose of 400 mg every 4 to 6 hours as needed for mild to moderate pain, as described in the reference ibuprofen product labeling. The exposure to acetaminophen and ibuprofen following dosing with Combogesic is similar to their respective reference products, based on relative bioavailability data, and the intended patient population is the same. Therefore, there is an adequate scientific bridge to rely on the agency's previous finding of safety for the reference products to support the safety of the individual components contained in Combogesic.

The Applicant submitted safety data from the pivotal Phase 3 efficacy and safety study[1], the clinical pharmacology studies, as well as the additional supportive Phase 2[2] and 3[3] studies conducted using Maxigesic to support the safety of acetaminophen and ibuprofen when used in combination.

Dr. Fang reviewed the safety of Combogesic and noted that the Applicant did not provide sufficient information to determine the overall exposure; however, she estimates that at least 106 subjects received 8 doses, at least 284 subjects received 4 doses, and at least 536 subjects were exposed to any dose. Much of the safety population consisted of otherwise healthy adults, with only study AFT-MX-6E (conducted in a post-knee arthroscopy pain population) including patients up to 75 years of age.

One death was reported in study AFT-MX-6, which was in a 26-year old female who was reported to have died from a gunshot wound (homicide) approximately two weeks after the last dose of study medication. As such, this death is unlikely to be related to study medication. Eight non-fatal serious adverse events (SAEs) were reported, including seven in study AFT-MX-6E and one in study AFT-MX-3. The SAEs in study AFT-MX-6E consisted of four events in three placebo patients (palpitation, hemarthrosis, and hemarthrosis followed by pulmonary embolism), one event in the acetaminophen group (hernia repair one day after treatment), one event in the ibuprofen group (hemarthrosis), and one event in the Maxigesic group (deep vein thrombosis). The SAE reported in study AFT-MX-3 was a case of buccal infection that was reported four days after the last dose of Maxigesic, given at the quarter dose level.

Two patients discontinued due to an adverse event. One involved a discontinuation due to vomiting after the second dose of Combogesic in study AFT-MX-6, and the second involved

[1] AFT-MX-6
[2] AFT-MX-3
[3] AFT-MX-6E and AFT-MX-1

discontinuation due to stomach cramps after the second dose of Maxigesic given at the quarter dose level in study AFT-MX-3.

Based on safety data pooled across the four multiple-dose Phase 2 and 3 studies, Dr. Fang notes that "the individual [adverse events] most frequently reported in patients treated with the combination drug acetaminophen/ibuprofen 1000 [mg]/300 [mg] included nausea (15%), vomiting (7%), headache (5%), dizziness (3%), swelling face (2%), post-procedure hemorrhage (2%), and somnolence (2%). These [adverse event] rates were not substantially different from the ones reported in the treatment groups of individual components and the placebo groups."

Although the clinical safety review did not identify any unexpected adverse events associated with the combination of acetaminophen and ibuprofen at the proposed dose level in the clinical studies, Dr. Fang noted several deficiencies that limited interpretation of the safety data and the ability to conduct a full review.

Dr. Fang recommend that the Applicant address the following clinical safety issues (verbatim) prior to approval:

- 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. For example, exposure per treatment needs to be clarified in the single-dose PK studies MX-9, 10, 11, 13b, 14a and 14b. Information on number of patients exposed per number of doses should be provided for Study MX-1. Exposure to more than four doses during the open-label extension stage of the two 24-hour studies should be summarized.

- Provide summary shift table including 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 changes (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.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

10. Pediatrics

Data from the pediatric population were not included in this application. The agency agreed with the Applicant's pediatric study plan (PSP) on February 6, 2017. The PSP includes a request for deferral of all assessments of the safety and effectiveness of Combogesic in all

pediatric populations. The agreed PSP includes an ongoing pharmacokinetic (PK) and safety study in pediatric patients ages 2 to 12 with acute pain after undergoing tonsillectomy with or without adenoidectomy and a proposed PK and safety study in pediatric patients between 12 and 17 years of age in a yet-to-be-decided acute pain model. (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. Therefore, (b) (4) is not acceptable for fulfilling the requirements under PREA, and the Applicant will need to conduct the study in this age group in an appropriate acute pain population. In consultation with the Pediatric Review Committee (PeRC), we will request the Applicant to submit an updated PSP with their resubmission reflecting the proper study population. Other details of the proposed protocols will need to be worked out during the protocol review stage.

If the Applicant is able to address the deficiencies, the following deferred studies will be required:

- A multiple-dose adequate and well-controlled pharmacokinetic, safety, and efficacy study in pediatric patients (b) (4) to <2 years of age with acute pain requiring a combination acetaminophen ibuprofen product
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 2 to <12 years of age with acute pain requiring a combination acetaminophen ibuprofen product
- An open-label, multiple-dose, pharmacokinetic and safety study in pediatric patients 12 to <17 years of age with acute pain requiring a combination acetaminophen ibuprofen product

Efficacy may be extrapolated from adults to pediatric patients two years of age and older provided that the exposures between adults and those pediatric age groups are similar.

11. Other Relevant Regulatory Issues

Good Clinical Practice (GCP)

Damon Green, MD, MS, from the Office of Scientific Investigations (OSI) completed the Clinical Inspection Summary for this application. Study AFT-MX-6 is the pivotal efficacy study submitted in support of this application. This study involved four centers, one in the United States and three in New Zealand. The one site in the U.S. (Dr. Stephen E. Daniels) was selected for audit. OSI found that "the final classification of this inspection was NAI [no deviation from regulations]. Based on the results of the clinical investigator inspection, the study appears to have been conducted adequately, and the data generated by this site appears acceptable in support of the respective application. The raw data used to generate the calculated primary endpoint were verifiable."

Financial Disclosures
The Applicant provided certification that there were no financial interests or arrangements to disclose.

505(b)(2) Committee
This application was presented at a meeting of the 505(b)(2) committee on December 4, 2017, and it was cleared for action from their perspective.

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the Applicant's request for review of the proposed proprietary name Combogesic and found it to be conditionally acceptable. DMEPA also reviewed and provided comments on the proposed labels and labeling and prescribing information. Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed labeling and recommended that the Applicant provide a literature review with their resubmission to support pregnancy, lactation, and fertility labeling. Otherwise, labeling will be addressed in a resubmission.

DPMH recommends that the Applicant provide the following information (verbatim, as communicated over email) prior to approval:

> 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.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response

- Risk Benefit Assessment

  Combogesic is a novel fixed-dose combination product that consists of 325 mg of acetaminophen and 97.5 mg of ibuprofen in each tablet with a proposed dosing regimen of 3 tablets given by mouth every 6 hours (maximum of 12 tablets per day). The acetaminophen and ibuprofen exposures from Combogesic are similar to their respective reference products and the total daily doses and dosing regimen are within the accepted ranges for the individual components. The safety evaluation did not reveal any unanticipated adverse effects with this combination.

  Although the safety profile has been well-characterized, the Applicant was required to conduct one full factorial adequate and well-controlled clinical trial to fulfill the combination rule and establish that each component contributes to the claimed effect. The Applicant's results in the pivotal Phase 3 study intended to establish this could not be replicated due to significant statistical concerns that could not be addressed during this review cycle. The Applicant's additional supportive studies using a different formulation were similarly unable to provide substantial evidence of effectiveness and fulfill the combination rule. Therefore, this application cannot be approved until these deficiencies are addressed.

  Additionally, numerous other deficiencies have been identified in the application, including a withhold recommendation from the CMC facilities review team, that preclude approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  If the deficiencies can be adequately addressed, pediatric studies based on the requirements of the Pediatric Research Equity Act will be required

- Recommended Comments to Applicant

Refer to Sections 3 (CMC), 4 (nonclinical pharmacology/toxicology), 7 (clinical/statistical-efficacy), 8 (safety), and 11 (labeling) for the recommended comments from these individual disciplines, as well as the Complete Response Letter for the final version of these comments.

I have the following additional recommended clinical comment in regard to the Applicant's pediatric study plan:

- We note in your agreed pediatric study plan (PSP) that you plan to conduct a pharmacokinetic, safety, and efficacy study in pediatric patients (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, (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.

Deputy Division Director

I agree with Dr. Lloyd's conclusions that this application receive a complete response for the reasons stated.

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

/s/

JOSHUA M LLOYD
12/22/2017

ELLEN W FIELDS
12/22/2017