CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

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

Cross-Discipline Team Leader and Division Director Summary Review

Date	October 6, 2023
From	Timothy Jiang, MD, PhD; Clinical Reviewer Alla Bazini, MD; Associate Director for Therapeutic Review, Anesthesiology Rigoberto Roca, MD; Division Director
NDA#	215320
Applicant	AFT Pharmaceuticals
Date of Original Submission	August 31, 2021 Complete Response Letter issued June 30, 2022
Date of Complete Response Submission	April 17, 2023
PDUFA Goal Date	October 17, 2023
Proprietary Name	Combogesic IV
Established or Proper Name	Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg in 100 mL
Dosage Form	Injection
Applicant Proposed Indication	Relief of mild to moderate pain, and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Applicant Proposed Dosing Regimen	Acetaminophen 1000 mg /Ibuprofen 300 mg every 6 hours as needed
Regulatory Action	Approval

OND Action Package included reviews by the following:	
Medical Officer	Timothy Jiang, MD, PhD
Clinical Pharmacology Review Team	Wei Qiu, PhD.; Yun Xu, PhD
Pharmacology-Toxicology Review Team	Carlic Huynh, PhD.; Newton Woo, PhD.; R. Daniel Mellon, PhD
Office of Product Quality Review Team Drug Substance Drug Product Microbiology	Team Leader - Valerie Amspacher, PhD Katie Duncan, PhD.; Gaetan Ladouceur, PhD Renish Delvadia, PhD.; Julia Pinto, PhD Eric Adeeku, PhD.; Elizabeth Bearr, PhD
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Susan Hakeem, Pharm D; Valerie Vaugham, PhD

1. Benefit-Risk Assessment

This is the second review cycle for NDA 215320 that was the subject of one prior Complete Response (CR) action. Refer to Section 4, Nonclinical Pharmacology/Toxicology, of CDTL memo by Dr. Roca dated June 30, 2022, for additional information regarding the Complete Response Letter (CRL) issued during the first review cycle.
Nonclinical deficiencies including inadequate data from leachable studies have been adequately addressed in this review cycle (see details in Section 4).

We concur with the clinical benefit-risk assessment in Dr. Brescia-Oddo's primary review of the first review cycle dated June 30, 2023. Pain, particularly if inadequately treated is a serious condition with the potential for significant morbidity. A multimodal strategy including drug-drug combinations of marketed drug products with well characterized safety profiles may be useful compared to administration of the individual drugs as monotherapy. The clinical development program of this NDA demonstrated efficacy of primary endpoint. The overall safety experience is consistent with that of the monotherapies, acetaminophen and ibuprofen, when administered over a short duration of time (five days or less).

The Division concludes that the benefits of Combogesic IV outweigh the risks.

2. Background

This document will serve as the Cross-Discipline Team Leader and the Division Director Summary Review of NDA 215320 for the decision on regulatory action for the proposed product, Combogesic IV.

The Applicant submitted NDA 215320 on August 31, 2021, through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for Ultracet tablets (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg; NDA 21123), and Ibuprofen tablets (Ibuprofen 800 mg; NDA 75682).

On June 30, 2022, CR action was taken due to nonclinical deficiencies including inadequate data from leachable studies. The reasons for the action and recommendation to address these issues in the CRL is provided as follows:

NONCLINICAL
You have not provided adequate toxicological risk assessments for leachables over the 5 mcg/day qualification threshold. We acknowledge your original approach in utilizing a toxicological threshold of concern of 120 mcg/day as recommended in ICH M7. However, this approach only addresses the genotoxicity aspects of a compound and is not acceptable to address the general toxicity of any given leachable compound. In addition, we acknowledge receipt of the June 21, 2022 submission containing a toxicological risk assessment for tentatively identified compounds detected above the analytical evaluation threshold; however, this submission was not formally reviewed because, as noted in your cover letter of the submission, the compounds have only

been tentatively identified to date and method validation is still ongoing. Our assessment of the safety of leachables to support a marketing application should be based on confirmed compounds quantified using validated methods.

Information needed to address the deficiency
Submit a revised toxicological risk assessment for all leachable compounds detected above the 5 mcg/day threshold. Submit documentation that the structural identification of the compounds has been confirmed and quantification has been completed using validated methods. The risk assessment should be based on the maximum level of each leachable expected to be present in the drug product based upon the analysis of the data from your long-term stability samples. The approach for toxicological evaluation of the safety of leachables should be based on good scientific principles. Include copies of all referenced studies upon which a safety assessment is based. In addition, consider the following points as you prepare your toxicological risk assessments:
a. If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.
b. Published literature submitted to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, [e.g., BIBRA Toxicology Advice & Consulting (BIBRA), Cosmetic Ingredient Review (CIR), Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA)], although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports should be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study should be discussed and justification should be provided to support your assertion that these data are adequate to support the safety of your container closure system.
c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.

On April 17, 2023, the Applicant resubmitted this NDA as a Class 2 Complete Response.

3. Product Quality

No new chemistry/manufacturing/controls data were submitted. The Office of Product Quality recommended approval at the time of the first CR Action.

4. Nonclinical Pharmacology/Toxicology

Drs. Huynh, Woo and Mellon provided the Brief Discussion of Nonclinical Findings as follows:

In this second cycle submission, there were no new toxicology studies submitted. In response to the deficiency, the Applicant submitted a revised toxicological risk assessment based on the 5 mcg/day threshold. The maximum amount of leachables detected are qualified by either being below the 5 mcg/day threshold, having an adequate PDE calculated for the leachable, within levels in the Inactive Ingredient Database (IID), or within dietary intake levels. As such, the exposures to the leachables via the proposed product are qualified and do not represent a safety concern at their detected levels. Therefore, the nonclinical deficiency is adequately addressed.

The Nonclinical pharmacology and toxicology team recommends that *From a nonclinical pharmacology toxicology perspective, NDA 215320 for Combogesic® IV may be approved with the postmarketing requirement listed below.*

We concur that there are no outstanding nonclinical issues that would prevent approval. Please see Dr. Huynh's review dated October 5, 2023, for details and pre-clinical postmarketing requirement in Section 10.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted. Clinical Pharmacology team recommended approval at the time of the first CR Action.

6. Clinical Microbiology

No new clinical microbiology data were submitted. Clinical Microbiology team recommended approval at the time of the first CR Action.

7. Clinical/Statistical- Efficacy

No new clinical data were submitted. Drs. Tanya Brescia-Oddo and Rigoberto Roca did not identify approvability issues in efficacy at the time of the first CR Action.

8. Safety

No new clinical data were submitted. Drs. Tanya Brescia-Oddo and Rigoberto Roca did not identify approvability issues in safety at the time of the first CR Action.

In addition, no subject has been exposed to study drug since the original submission. An updated Periodic Safety Update Report (PSUR; dated 14th April 2023) detailing the

worldwide post-marketing safety surveillance did not reveal new safety signal for acetaminophen, ibuprofen or the combination.

9. Advisory Committee Meeting

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

10. Pediatrics

This product is the subject of an approved Pediatric Study Plan (PSP). As noted in Dr. Brescia-Oddo's review, the Applicant requested, and was granted a deferral for studies in all the pediatric age groups. The studies in pediatric patients less than 2 years of age are to be deferred until the completion of a juvenile animal study.

Given that the landmark dates were negotiated prior to the last CR action, the Applicant has updated the PSP with new deadlines after additional input from the Division in this review cycle. The post-marketing requirements with the revised timelines are agreed upon by the Division and PeRC on September 19, 2023.

The following post-marketing requirements will be issued upon approval of the application:

Non-Clinical:

(b) (4)

2) A juvenile animal study to address the safety of acetaminophen and ibuprofen on the development of potential target organs such as the liver, kidney, lung, and testes before initiation of a clinical study of Combogesic® IV in neonates/infants from birth to 2 years of age.

    a. Submission of protocol for Juvenile Animal Study to FDA: December 2024
    b. Initiation of Juvenile Animal Study: March 2025
    c. Completion of Juvenile Animal Study: September 2025
    d. Final report date: December 2025

Clinical:

1) A pharmacokinetic and safety study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in pediatric patients aged 2 to less than 17 years for the short-term management of mild to moderate acute pain.

    a. Submission of protocol: January 2024

b. Initiation of study: September 2024
c. Completion of study: June 2025
d. Submission of final report: September 2025

2) An efficacy, safety, and pharmacokinetic study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in infants from birth to less than 2 years of age for the short-term management of mild to moderate acute pain.

a. Submission of protocol: March 2026
b. Initiation of study: June 2026
c. Completion of study: September 2027
d. Submission of final report: December 2027

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Consultation was obtained from the Division of Medication Error Prevention and Analysis (DMEPA) and see Drs. Hakeem and Vaughan's Label and Labelling Review dated July 19, 2023, for details.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The benefits of Combogesic IV outweigh the potential risks.

Postmarketing Requirements
As noted above, upon approval of this application, several post-marketing requirements will be issued regarding non-clinical and pediatric studies.

14. Recommended Comments to the Applicant

None.

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/

TIMOTHY T JIANG
10/11/2023 07:56:17 PM

ALLA T BAZINI
10/11/2023 08:01:48 PM

RIGOBERTO A ROCA
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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
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CDTL and Division Director Summary Review for Regulatory Action

Date	June 30, 2022
From	Rigoberto Roca, MD
NDA Number	215320
Applicant Name	AFT Pharmaceuticals
Date of Submission	August 31, 2021
PDUFA Goal Date	June 30, 2022
Established (USAN) Name	Acetaminophen 1000 mg/Ibuprofen (as sodium dihydrate) 300 mg in 100 mL
Proposed Trade Name	Combogesic
Dosage Forms / Strength	Injection
Proposed Indication	relief of mild to moderate pain, and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Action	Complete Response

Material Reviewed/Consulted OND Action Package, including reviews by:	
Medical Officer	Tanya Brescia-Oddo, MD
Pharmacology Toxicology	Carlic Huynh, PhD / Nikunj Patel, PhD / Newton Woo, PhD / Dan Mellon, PhD
OPQ/ONDP	Application Team Leader: Valerie Amspacher o Drug Substance: Katie Duncan / Gaetan Ladouceur o Drug Product: Renish Delvadia /Julia Pinto o Process/Facilities: Yuesheng Ye / Tianhong (Tim) Zhou o Microbiology: Eric Adeeku / Paul Dexter o Environmental: Renish Delvadia / Julia Pinto
OCP/DCP II	Wei Qiu PhD; Yun Xu, PhD
OSE/OMEPRM/DMEPA	Cameron Clark, PharmD / Valerie S. Vaughan, PharmD
OTS/OB/DB I	Jing Han, PhD / Katherine Meaker, MS /Sue-Jane Wang, PhD
Project Management Staff	Mavis Darkwah, PharmD / Swati Patwardhan

DB I = Division of Biometric I
DCP II = Division of Clinical Pharmacology II
DMEPA = Division of Medication Error Prevention and Analysis
OB = Office of Biostatistics
OCP = Office of Clinical Pharmacology
OMEPRM = Office of Medication Error Prevention and Risk Management
ONDP = Office of New Drug Products
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology
OTS = Office of Translational Science

1. Benefit-Risk Assessment

I concur with the points raised in the benefit-risk assessment in Dr. Brescia-Oddo's review. Pain, particularly if inadequately treated is a serious condition with the potential for significant morbidity, which are well described in her review.

The following table is reproduced from Dr. Brescia-Oddo's review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is commonly associated with tissue injury, inflammation, surgical procedures, childbirth, or a brief disease process • Post-surgical pain is a major form of acute pain • Clinical symptoms of acute pain often include increased heart rate, blood pressure, and respiratory rate, shallow respirations, agitation or restlessness, facial grimacing, or splinting • Symptoms can last hours, days, or weeks	Effective postsurgical analgesia is an essential component in the care of the surgical patient Inadequate acute pain control can result in increased morbidity, prolonged hospitalization time, and decreased patient satisfaction
Current Treatment Options	• Current treatments for acute postoperative pain include opioids, acetaminophen (APAP), and NSAIDs	A multimodal strategy including drug-drug combinations of marketed drug products with well-characterized safety profiles may be useful compared to administering the individual drugs as monotherapy
Benefit	• The Phase 3 clinical efficacy study (AFT-MXIX-07) won the primary endpoint of SPID48 ○ Combogesic IV provides superior analgesia compared to the same doses of ibuprofen or acetaminophen as monotherapy • Clinically meaningful benefit to patients ○ Convenience of two intravenous analgesic drugs in one infusion allowing for improved post-operative pain control and less drug infusion time	Demonstrated efficacy of primary endpoint through several sensitivity analyses Clinically meaningful benefit to patients in the form of improved post-operative analgesia and convenience
Risk and Risk Management	• Ofirmev (IV acetaminophen) has been approved since 1951 • Caldolor (IV ibuprofen) has been approved since 1974 • No drug-drug interactions between acetaminophen and ibuprofen • No overlapping toxicities observed in	Size of the safety database was adequate to characterize the safety profile as agreed on in the pre-NDA meeting The overall safety experience is consistent with that of the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clinical studies (liver transaminases) • No SAEs attributed to Combogesic IV • Infusion site pain occurred at a higher rate in the Combogesic IV treatment arm; severity mostly mild • Incidence of common AEs was comparable or improved compared to monotherapies and/or placebo	monotherapies, acetaminophen and ibuprofen, when administered over a short duration of time (5 days or less) No serious safety signals were observed in the safety population

2. Background

The Applicant, AFT Pharmaceuticals, has submitted a 505(b)(2) application for Combogesic (Acetaminophen 1000 mg/Ibuprofen 300 mg in 100 mL) for the following indication:

> For the relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary. Combogesic IV is indicated for short-term use of five days or less.

The listed drugs being used by the Applicant and 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 Ibuprofen tablets (Ibuprofen 800 mg; NDA 75682).

The regulatory history for this application is well-summarized in Dr. Brescia-Oddo's review, and will only be briefly touched upon here:

- November 2014 – Pre-IND Interaction, IND 124213 (Written Responses Only). It was conveyed that the proposed factorial study appeared to meet the FDA's requirements for one adequate and well-controlled, full factorial study in patients with acute post-operative pain. Of note, the Applicant did not seek any additional input from the Division and submitted the protocol for the factorial study in September 2016.

- January 2018 – Pre-NDA meeting. As captured in Dr. Brescia-Oddo's review, the following were the major points discussed during that meeting:

  - Addition of the indication of moderate-to-severe pain, consistent with the approved labeling for IV formulations of the individual components, acetaminophen and ibuprofen; remove proposed indication of (b) (4)
  - The Division did not agree with (b) (4)

- The Division recommended pooling safety data across patients with single-dose exposures (Studies 01, 06, and 12) and then patients with multiple-dose exposures (Studies 07 and 11)
- Safety data from studies of the Combogesic oral formulation are not directly supportive of the IV formulation due to PK; data from Combogesic tablets may be submitted and cross-referenced if the relevance is clearly stated
- Required safety data: exposure of at least 300 patients with multiple-dose exposures and at least 50 of those patients exposed for at least 5 days (required because of higher Cmax and more rapid rise in concentrations with the IV formulation compared to the oral formulations of RLDs)
- Conduct a bridging study for Combogesic IV to rely on the Agency's previous findings for Ultracet and ibuprofen; must use the absolute PK for comparison

Dr. Brescia-Oddo also noted in her review, the Applicant noted their decision to refer to Ultracet and Motrin as the listed drug products, instead of Ofirmev and Caldolor.

3. Product Quality

The overall recommendation from the OPQ review team was for approval of the application.

Specifically, for the drug substance, the team noted:

> "The CMC information for the acetaminophen drug substance is cross- referenced to DMF (b) (4) This DMF was last reviewed by Friedrich Burnett, Ph.D. in support of NDA (b) (4) on 20-Jul-20 and found to be adequate. The retest period is (b) (4) when stored at (b) (4)
>
> The CMC information for ibuprofen sodium dihydrate is cross-referenced to DMF (b) (4) DMF (b) (4) was reviewed by Katharine Duncan, Ph.D. in support of this NDA on 29-Mar-22 and found to be adequate. The retest period is (b) (4) when stored at (b) (4) .
> The NDA is recommended for approval from the perspective of drug substance quality."

For the drug product, the team noted:

> "All the excipients used in the proposed formulation are of USP/NF grade. The excipients are within the inactive ingredient database (IID) limit for the intravenous route of administration (calculated based on maximum daily dose of 400 mL per the proposed label). 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 proposed container closures are routinely used for the storage of intravenous solution
>
> The extractable and leachables analytical methods and studies are adequate from the CMC perspective. The Applicant has provided 36 months of long-term and intermediate

For adult patients weighing greater than or equal to 50 kg (actual body weight): The recommended dosage of COMBOGESIC IV is one vial (100 mL; acetaminophen 1,000 mg/ibuprofen 300 mg) administered as a 15-minute infusion every 6 hours, as necessary.

For adult patients weighing less than 50 kg (actual body weight): The recommended dosage is 15 mg/kg acetaminophen and 4.5 mg/kg ibuprofen, administered as a 15-minute infusion every 6 hours, as necessary. This equates to a maximum single dose of 750 mg acetaminophen and 225 mg ibuprofen (discard remaining medicine in vial), and a total daily dose of 3,000 mg (3 g) acetaminophen and 900 mg ibuprofen."

stability data for three registration stability batches, and 24 months of long-term and intermediate stability data for two registration stability batches; 6 months of accelerated stability data are provided for all five registration batches. The Applicant has adequately justified the proposed drug product specification and validated respective analytical methods. Overall, the stability data supports the proposed shelf-life of 24 months."

And for product microbiology:

(b) (4)

The submission is recommended for approval."

Lastly, with respect to manufacturing deficiencies:

(b) (4)

The proposed commercial manufacturing facilities include: 1) Two manufacturers for the two drug substances, 2) One drug product manufacturing, primary packaging, finish product release and stability testing, and 3) no contract testing lab. They are all acceptable for the proposed function."

For additional details, please refer to the OPQ review.

Outstanding or Unresolved Issues

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, Nikunj Patel, Newton Woo, and Dan Mellon completed the primary nonclinical pharmacology and toxicology review of NDA 215320. In their summary of the nonclinical findings, they noted the following:

There are no novel excipients in the proposed product and all excipients are in the FDA Inactive Ingredients Database for coverage at the dose and duration of the proposed product. The acetaminophen drug substance specifications (including (b) (4)), ibuprofen drug substance specifications, and the drug product specifications (including (b) (4)) are acceptable. The elemental impurities assessment is acceptable per ICH Q3D.

To support the safety of the proposed container closure system, which is a glass vial and a grey (b) (4) stopper, the Applicant submitted an extractables and leachables evaluation. The analytical evaluation threshold (AET) was reviewed and deemed acceptable. Leachables data were evaluated from: three batches stored at 0 months under normal storage conditions, one batch stored at 6- and 12 months under normal

storage conditions as well as one batch stored at 3 months under accelerated conditions. The initial summary tables indicated that all identified extraction compounds were not observed as leachable compounds at any time point tested. After several Information Requests from CMC and PT, the Applicant disclosed that there were errors in the reported levels of the leachable data and that the actual levels were 100-fold higher. It was communicated that a toxicological risk assessment should be submitted for any compound above 5 mcg/day. In response, the Applicant submitted toxicological risk assessments based on a Toxicologic Threshold of Concern (TTC) of 120 mcg/day per ICH M7. Although the TTC of 120 mcg/day addresses the genotoxicity aspect of a compound, this approach does not account for general toxicity concerns. A revised toxicological risk assessment should be submitted for any leachable compounds detected above the 5 mcg/day threshold for general toxicity concerns.

In support of this marketing application, the Applicant has submitted a 3-day IV toxicity study in rats that is non-GLP (Study N2716), a 14-day IV toxicity study in rats (Study AFTMXIV-13), and a 4-cycle IV toxicity study with 2 weeks recovery in rats (Study G11395). The 3-day toxicity study in rats was a dose-range finding study used to inform the doses for the definitive 14-day toxicity study in rats. The 4-cycle IV toxicity study was conducted as an initial study but the Applicant was informed that this study did not mimic the clinical dosing regimen and was recommended to conduct a 14-day repeat-dose toxicity study that mimics the clinical dosing regimen.

In the pivotal 14-day IV toxicity study, rats were dosed with vehicle control, Acetaminophen IV control (100 mg/kg/day), Ibuprofen IV control (30 mg/kg/day), Combogesic® IV (25/7.5 mg/kg/day APAP/Ibu), Combogesic® IV (50/15 mg/kg/day APAP/Ibu), or Combogesic® IV (100/30 mg/kg/day APAP/Ibu) via a 15-minute infusion, 4-times a day for 14 consecutive days. Macroscopic findings were in the jejunum in the ibuprofen IV control and Combogesic® IV high dose groups (nodules and adhesions of mucosa of jejunum) that were not worse than ibuprofen alone and in the spleen in the Combogesic® IV mid- and high dose groups (adhesions) with no microscopic correlate. Microscopic findings in the gastrointestinal tract included the stomach (mucosal necrosis and mixed cell infiltration of the submucosa), jejunum (ulceration, mixed cell infiltration, and neovascularization), and cecum (mixed cell infiltration). The findings with the Combogesic® IV formulation were not worse than either Acetaminophen or Ibuprofen alone and were expected effects of NSAIDs (acetaminophen) and cyclooxygenase inhibitors (ibuprofen).

The Applicant submitted blood compatibility studies as well as an IV local tolerance study in male rabbits in support of the proposed drug product in support of the proposed drug product. Combogesic® IV did not cause hemolysis and did not cause additional plasma protein flocculation/precipitation or platelet aggregation as compared to acetaminophen IV or ibuprofen IV alone.

In the IV local tolerance study, the effects of a single intravenous or perivenous dose of the negative control (vehicle), Combogesic® IV (3.0 mg APAP + 0.9 mg ibuprofen), Acetaminophen IV solution (3.0 mg), or Ibuprofen IV solution (0.9 mg) via a slow bolus injection into the marginal ear vein was evaluated. Combogesic® IV administration resulted in local irritation but was not different than the acetaminophen IV or ibuprofen IV control groups.

Taken together the nonclinical studies conducted by the Applicant demonstrate that the toxicity profile of Combogesic® IV was comparable and not worse than the toxicity profiles of the individual drug components acetaminophen and ibuprofen at the same doses. However, the Applicant did not submit an adequate leachables evaluation to

> adequately qualify the safety of the container closure system, which is the glass vial and rubber stopper. Notably, adequate toxicological risk assessments for leachables above the 5 mcg/day qualification threshold have not been submitted.

The team's recommendation regarding approvability of the application is noted below:

> From the nonclinical pharmacology toxicology perspective, the Applicant did not provide an adequate extractables/leachables assessment to qualify the safety of the container closure system and therefore, the proposed drug product is not recommended for approval at this time.

Outstanding or Unresolved Issues

Of note, the Applicant submitted an amendment on June 21, 2022, containing a toxicological risk assessment for tentatively identified compounds detected above the analytical evaluation threshold. However, the cover letter of the submission indicated that the compounds have only been tentatively identified to date, and method validation were still ongoing. That submission was not reviewed during this review cycle because our assessment of the safety of leachables to support an marketing application should be based on confirmed compounds quantified using validated methods.

I concur with the review team that the Applicant did not provide an adequate extractables/leachables assessment to qualify the safety of the container closure system and therefore, the application cannot be approved at this time.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted three pharmacokinetic Studies AFT-MXIV-01, AFTMXIV-06, and AFT-MXIV-12, described below, and an in vitro drug interaction study. The review team described the studies in their review as follows:

1. Study AFT-MXIV-01: Single-center, single-dose, open-label, randomized, five-way crossover study to evaluate the pharmacokinetic parameters of Maxigesic IV (intravenous paracetamol + intravenous ibuprofen), intravenous paracetamol, intravenous ibuprofen, and Maxigesic tablets, in healthy volunteers
2. Study AFT-MXIV-06: Single-center, single-dose, open-label, randomized, four-way crossover study to evaluate and compare the pharmacokinetic parameters of Maxigesic IV (intravenous acetaminophen + intravenous ibuprofen), Ofirmev (intravenous acetaminophen), Caldolor (intravenous ibuprofen), and Maxigesic 325 tablets, in healthy volunteers
3. Study AFT-MXIV-12: Randomized, Single Dose, Three-way Crossover Open Label Pharmacokinetic Parameters Study of AFT Pharmaceuticals LTD Maxigesic IV (1000 mg Acetaminophen + 300 mg Ibuprofen/100 mL Solution For Infusion), Infusion Over 15 minutes (One Dose Only), Janssen Pharmaceuticals, Inc. Ultracet (325 mg Acetaminophen + 37.5 mg Tramadol Hydrochloride Per Film Coated Tablet) Two Tablets and Dr. Reddy's Laboratories, Inc. IBU Ibuprofen Tablets, USP 800 mg (800 mg Ibuprofen per Film Coated Tablet) One Tablet, After an Oral Administration to 30 Healthy Adults Under Fasting Conditions

Drs. Qui and Xu noted the following in the Summary of Clinical Pharmacology Assessment in their review:

> (1) Comparative Bioavailability of Combogesic IV in Comparison to Ultracet (NDA 21123) and IBU tablets (ANDA 75682): Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen, intravenous infusion over 15 minutes) exhibited 3.1-fold greater acetaminophen Cmax and 2-fold greater AUC0-t and

AUC0-inf values than 2 x Ultracet tablets (acetaminophen 325 mg/37.5 mg tramadol per tablet). Combogesic IV exhibited similar ibuprofen Cmax and 55% lower ibuprofen AUC0-t and AUC0-inf values than 1 x IBU tablet (ibuprofen 800 mg per tablet), a generic product of Motrin (ibuprofen) tablet (NDA 017463).

The dose normalized Cmax values (Cmax/dose) of acetaminophen and ibuprofen for Combogesic IV were 2-fold and 2.4-fold greater than Ultracet and IBU, respectively. The dose normalized AUC0-t, and AUC0-inf values (AUC0-t/dose and AUC0-inf/dose) of acetaminophen for Combogesic IV were 30% and 28% greater than those for Ultracet. The dose normalized AUC0-t values of ibuprofen for Combogesic IV were 21% greater than those for IBU, while dose normalized AUC0-inf values of ibuprofen were comparable to that for IBU. The differences in dose normalized Cmax and AUC values were mainly due to routes of administration.

(2) Comparative Bioavailability of Combogesic IV in Comparison to FDC 500/150 Tablet (acetaminophen 500 mg/ibuprofen 150 mg) and Combogesic Tablet (acetaminophen 325 mg/ibuprofen 97.5 mg, review pending under NDA 209471 as date of May 23, 2022): Combogesic IV (1000 mg acetaminophen and 300 mg ibuprofen, intravenous infusion over 15 minutes) exhibited approximately 2-fold greater Cmax while similar AUC0-t and AUC0-inf values for both acetaminophen and ibuprofen in comparison to either 2 x FDC 500/150 tablets or 3 x Combogesic tablets. Both FDC 500/150 (acetaminophen 500 mg/ibuprofen 150 mg) tablet and Combogesic tablet (acetaminophen 325 mg/ibuprofen 97.5 mg) are developed by the same Sponsor of Combogesic IV.

(3) Dose Proportionality between Combogesic IV Full Dose vs Combogesic Half Dose:
Acetaminophen and ibuprofen Cmax, AUC0-t and AUC0-inf values were dose proportional between Combogesic IV full dose and Combogesic IV half dose.

(4) No PK Drug Interaction between Intravenous Acetaminophen and Intravenous Ibuprofen in Combogesic IV: Acetaminophen and ibuprofen Cmax, AUC0-t and AUC0-inf values for Combogesic IV (acetaminophen 1000 mg and ibuprofen 300 mg) were bioequivalent to 1000 mg intravenous acetaminophen and 300 mg intravenous ibuprofen given alone, respectively.

Of note, Maxigesic is the same product as Combogesic, owned by the Applicant and sold in overseas markets. For additional details, please refer to the clinical pharmacology review.

Outstanding or Unresolved Issues
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 drug development program consisted of several studies, summarized in the table below (adapted from Dr. Brescia-Oddo's review):

Protocol #	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
AFT-MXIV-07	Randomized, Double-blind, Placebo-controlled, multiple-dose, parallel-group, full factorial	Combogesic IV APAP1000 Ibuprofen300 Placebo Q6 hours for 48 hours	1^{o} SPID48 2^{o} SPID 6/12/24 VAS PID Time to/total rescue	48 hours / 5 to 9 days after surgery	276	Bunionectomy	2 sites in United States
Studies to Support Safety							
AFT-MXIV-11	open-label, single-arm	Combogesic IV Q6 hours for 48 hours and extension phase of 50 subjects Q6 hours for 5 days (total 20 doses)	1^{o} incidence of TEAEs 2^{o} Time course of TEAEs / TRAE / TEAEs of interest / Changes in VS, labs / Global	48 hours and extension phase of 50 subjects for 5 days; follow-up 7 days post-discharge	233	Orthopedic, general or plastic surgery	4 sites (2 in United States and 2 in New Zealand)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
AFT-MXIV-01	Single-dose, open-label, randomized, five-way crossover, BA/BE PK	Maxigesic IV IV paracetamol IV ibuprofen Maxigesic tabs	PK sampling		29	Healthy adults	
AFT-MXIV-06	single-dose, open-label, randomized, four-way crossover, BA/BE PK	Maxigesic IV Ofirmev Caldolor Maxigesic 325 tabs	PK sampling		30	Healthy adults	
AFT-MXIV-12	Single-dose, open-label, randomized, three-way crossover, BA/BE PK	Maxigesic IV Ultracet IBU	PK sampling		30	Healthy adults	

The design of the controlled study intended to support efficacy and safety, Study AFT-MXIV-07, is well described in Dr. Brescia-Oddo's review, and in the review by the statistical team. The following table, reproduced from the Applicant's submission, summarizes the design (Source: Clinical Study Report Version 3 (Dated October 5, 2018), Table 3, page 31/183):

Screening Period		Study Day 0: Surgery	Study Days 1-3				Study Day 7 Follow-up Phone Call
Consent	Screening Assessments		Day 1: Post-surgery Qualification*	Day 1: Randomisation to Study Drug**	Day 1-3: Study Drug** administration	Day 3: Discharge	
Participants provided with information about the study	After consent, eligibility is checked	Standard distal first metatarsal bunionectomy procedure using a standardized regimen of regional anesthesia	Participants must be experiencing moderate to severe pain (≥ 40 mm on VAS) post-operatively to be randomized	Maxigesic® IV Acetaminophen Ibuprofen Placebo	Study drugs administered q6h for a total of 8 doses in 48 hours	Additional Post-operative pain medication prescribed	Follow up safety data

*within 9 hours discontinuation of the post-surgical anesthetic block
**100 mL solution for intravenous infusion

The primary efficacy endpoint was the time-adjusted Summed Pain Intensity Difference (SPID) from baseline over 48 hours (TASPID48): TASPID48(mm) = SPID (mm*hr) / time interval from baseline to the final VAS used in the SPID (hr). As noted in Dr. Han's review, the Applicant's calculation of the primary endpoint was incorrect in that the Applicant calculated a TASPIDpre-rescue instead of the concurred SPID48. Sensitivity analyses were conducted by the Applicant in order to utilize all the assessments over 48 hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), using rescue observation carried forward (ROCF) at 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours.

The statistical team's re-analysis of the primary endpoint are summarized in the following table, reproduced from Dr. Han's review:

	Maxigesic® N=75	Ibuprofen N=76	Acetaminophen N=75	Placebo N=50
N	75	76	75	50
Mean (SE)	37.26 (2.56)	24.99 (2.68)	18.32 (2.00)	17.47 (2.59)
Median	41.14	23.93	16.88	20.09
Min ; Max	-23.21 ; 78.58	-21.09 ; 81.17	-30.03 ; 69.84	-16.91 ; 57.80
Mean Estimate (SE)	36.68 (2.22)	24.57 (2.21)	19.32 (2.22)	17.49 (2.72)
95% Confidence Interval	32.31 ; 41.05	20.23 ; 28.91	14.94 ; 23.70	12.14 ; 22.84
Difference Estimate (SE)	-	12.11 (3.13)	17.36 (3.15)	19.19 (3.51)
95% Confidence Interval	-	5.95 ; 18.27	11.17 ; 23.56	12.28 ; 26.10
p-value	-	<0.001	<0.001	<0.001

Model TASPID = Treatment + Baseline Pain

The review team also conducted exploratory subgroup analyses to assess consistency across subgroups with respect to the primary endpoint and noted that there were no important differences in the results within these subgroups compared to the overall analysis.

The summary statement in the statistical review was as follows:

> The main concern is the Applicant's calculation of the primary endpoint. The Applicant calculated the TASPID48 using VAS scores until the first pre-rescue VAS score (inclusive), which is not acceptable because what the Applicant calculated is the TASPID from baseline to the first pre-rescue instead of from baseline over 48 hours. To utilize all the assessments over 48

hours and correspond to the half-life of the rescue medications (oxycodone 5 or 10 mg every 4-6 hours and a secondary rescue analgesia 2-4 mg intravenous morphine sulphate every 4 hours), the Applicant conducted a sensitivity analysis using ROCF 4 hours. The statistical team also requested a reanalysis using ROCF 2 hours. The results from both ROCF 4 hours and ROCF 2 hours analyses support the conclusion that Combogesic® IV is superior to the other three arms (P<0.001).

The conclusion of the statistical review team was that the efficacy of the combination had been established.

Outstanding or Unresolved Issues

I concur with the review team that adequate information has been submitted to support the efficacy of Combogesic.

8. Safety

The safety population of 307 patients included patients who were exposed to at least one dose of Combogesic IV in the multiple-dose studies, AFT-MXIV-07 and AFT-MXIV-11

Dr. Brescia-Oddo's strategy to evaluate the safety database is well-documented in her review; please refer to the review for additional details. The safety findings were noted as follows: there were no deaths in any clinical trials conducted with Combogesic, and no serious adverse events (SAE) reported in Study AFT-MXIV-07. There were two SAEs report in Study AFT-MXIV-11, an episode of hypotension, and an episode of intestinal obstruction. These were deemed to be unlikely to be related to study drug.

An SAE reported in one of the Phase 1 studies (AFT-MXIV-01), consisting of bilateral ankle fractures from a fall while hiking was also considered to be unrelated to study drug, as it occurred during the washout period of the study 4 days after having received a half-dose of Combogesic IV.

The most common treatment-emergent adverse events in Study AFT-MXIV-07 are summarized in the table below, reproduced from Dr. Brescia-Oddo's review:

SOC/PT	Combogesic IV (n=75)	Ibuprofen (n=76)	APAP (n=75)	Placebo (n=50)	Total (n=276)
Any Class, Any Term	69.3%	76.3%	60%	78%	70.3%
Nausea	29.3%	34.2%	33.3%	32%	32.2%
Vomiting	**21.3%**	6.6%	**14.7%**	2%	12%
Dizziness	17.3%	9.2%	9.3%	16%	12.7%
General disorders/administration site conditions	20%	22.4%	10.7%	26%	19.2%
Skin and SQ tissue disorders	14.7%	19.7%	13.3%	14%	15.6%

It was noted that vomiting occurred at a higher incidence than the ibuprofen and placebo groups. The reason is not entirely clear, but Dr. Brescia-Oddo noted that vomiting was not classified as a common TEAE in Study AFT-MXIV-11, and that vomiting occurred at a frequency that was less than the monotherapies in the safety population (pooled data from multiple-dose studies).

The most common treatment-emergent adverse events for the uncontrolled Study AFT-MXIV-11 are summarized in the table below (reproduced from the Applicant's submission):

Preferred Term	Combogesic® IV N=232	
	Patients	Events
Infusion site pain	44 (19.0%)	49
Nausea	28 (12.1%)	32
Infusion site extravasation	18 (7.8%)	19
Constipation	18 (7.8%)	19
Headache	13 (5.6%)	13
Dizziness	9 (3.9%)	12
Polyuria	9 (3.9%)	9
Procedural nausea	8 (3.4%)	8
Somnolence	7 (3.0%)	7
Diarrhoea	5 (2.2%)	5
Alanine aminotransferase increased	5 (2.2%)	5

Dr. Brescia-Oddo's summary of her evaluation of the safety information submitted in the NDA is as follows:

> Combogesic IV (acetaminophen 1000 mg/ibuprofen 300 mg) is a drug-drug combination product consisting of two marketed drug products of an approved formulation and route of administration, Ofirmev (IV acetaminophen) and Caldolor (IV ibuprofen), at maximum total daily doses less than (ibuprofen) or equal (acetaminophen) to doses in approved labeling. The proposed maximum total daily dose of Combogesic IV is 4000 mg acetaminophen and 1200 mg ibuprofen in 24 hours. Additionally, there are no drug-drug interactions between acetaminophen and ibuprofen.
>
> The clinical development program generated safety data from 307 patients treated with Combogesic IV from two Phase 3 multiple-dose studies (AFT-MXIV-07 and AFT-MXIV-11), including 50 subjects exposed for 5 days. Safety data were also generated from 89 subjects exposed to single doses of Combogesic IV from three Phase 1 single-dose studies.
>
> The safety data generated from the two Phase 3 multiple-dose studies did not show any serious safety signals including no strong evidence of overlapping toxicities between acetaminophen and ibuprofen when dosed for 48 hours or 5 days.
>
> Infusion site pain occurred at a higher rate in the Combogesic IV treatment arm compared to the comparator arms among the safety population.
>
> From the clinical standpoint, there were no serious safety concerns identified in the course of this review.

Outstanding or Unresolved Issues

I concur with Dr. Brescia-Oddo that the date from the two multiple-dose studies did not identify any serious safety signal that would preclude approval of this application.

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

As noted in Dr. Brescia-Oddo's review, the Applicant requested, and was granted a deferral for studies in all the pediatric age groups. The studies in pediatric patients less than 2 years of age are to be deferred until the completion of a juvenile animal study. The following post-marketing requirements will be imposed upon approval of the application (the dates may need to be adjusted, depending on the date of approval):

Nonclinical:

(b) (4)

2. A juvenile animal study to address the safety of acetaminophen and ibuprofen on the development of potential target organs such as the liver, kidney, lung, and testes before initiation of a clinical study of Combogesic® IV in neonates/infants from birth to 2 years of age.

    a. Submission of protocol for Juvenile Animal Study to FDA: December 2022
    b. Initiation of Juvenile Animal Study: March 2023
    c. Completion of Juvenile Animal Study: September 2023
    d. Final report date: December 2023

Clinical:

1. A pharmacokinetic and safety study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in pediatric patients aged 2 to less than 17 years for the short-term management of mild to moderate acute pain.

    a. Submission of protocol: Q3 2022
    b. Initiation of study: Q4 2022
    c. Completion of study: Q3 2023
    d. Submission of final report: Q4 2023

2. An efficacy, safety, and pharmacokinetic study of Combogesic® IV (acetaminophen 1000 mg + ibuprofen 300 mg, per 100 mL solution for intravenous infusion) in infants from birth to less than 2 years of age for the short-term management of mild to moderate acute pain.

    a. Submission of protocol: March 2023
    b. Initiation of study: June 2023
    c. Completion of study: September 2025
    d. Submission of final report: December 2025

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues.

12. Labeling

Consultation was obtained from the Division of Medication Error Prevention and Analysis (DMEPA). However, significant deficiencies in the application precluded any labeling discussions with the Applicant. Any discussions with the Applicant regarding the text of the labeling will be conducted during the next review cycle. Comments from the review team in DMEPA will be conveyed during that review cycle.

13. Post-Marketing

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

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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