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APPLICATION NUMBER:

209471Orig1s000

CLINICAL REVIEW(S)

Clinical Review

Date	(electronic stamp)
From	Christina Fang, MD, MPH, Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Ning Hu, MD, MS, Clinical Team Leader, DAAP
Subject	Clinical review
NDA/BLA #	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 97.5 mg/acetaminophen 325 mg
Dosage Form(s)	Tablet
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 over a 24-hour period
Recommendation on Regulatory Action	Complete Response

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Material Reviewed/Consulted

OND Action Package, including:			
Clinical Review/CDTL	Christina Fang, MD, MPH, Ning Hu, MD, MS		
Statistical Review	John Lawrence, PhD, Jinglin Zhong, PhD, Jim Hung, PhD		
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD		
OPQ Review	Discipline	Primary Assessment	Secondary Assessment
	Drug Substance	Jeff Medwid	Donna Christner
	Drug Product	Stephanie Emory	Julia Pinto
	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	None for resubmission		
OSE/DMEPA	DPV review of skin safety across multiple NDAs filed by Helen Lee in DARRTS		

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader
 OPQ=Office of Pharmaceutical Quality
 OSE=Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Errors Prevention
 DPV= Division of Pharmacovigilance
 NDA= new drug application
 DARRTS= Document Archiving Reporting and Regulatory Tracking System

Glossary

AC	advisory committee
AE	adverse event
AGEP	acute generalized exanthematous pustulosis
APAP	acetaminophen
AUC	area under the curve measurement of concentration for total exposure with time
BRF	Benefit Risk Framework
(b) (4)	(b) (4)
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
C _{max}	maximum concentration
CMC	chemistry, manufacturing, and controls
Combo	Combogesic
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRT	clinical review template
CSR	clinical study report
(b) (4)	(b) (4)
DAAP	Division of Anesthesiology, Addiction Medicine and Pain Medicine
DARRTS	Document Archiving Reporting and Regulatory Tracking System
DMEPA	Division of Medication Errors Prevention
DMF	drug master files
DPV	Division of Pharmacovigilance
DS	drug substance
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
HPLC	high-performance liquid chromatography

Ibu	ibuprofen
ICH	International Council for Harmonisation
ID	internal diameter
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
IR	immediate-release
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
Lab	laboratory
NDA	new drug application
NME	new molecular entity
NMT	no more than
NSAID	nonsteroidal anti-inflammatory drug
OND	Office of New Drug
OPMA	Office of Pharmaceutical Manufacturing Assessment
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over the counter
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	pain intensity
PID	pain intensity difference
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PPPM	parents' postoperative pain measure

Clinical Review
Resubmission for NDA 209471 Combogesic

PR	pain relief
PREA	Pediatric Research Equity Act
PRN	taken as needed
PRO	patient reported outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update report
PWR	Pediatric Written Request
REMS	risk evaluation and mitigation strategy
RICE	rest, ice, compression, and elevation
Rx	prescription
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens-Johnson Syndrome
SPID	summed pain intensity difference
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
Tmax	time to reach the maximum concentration
TLC	thin-layer chromatography
VAS	visual analogue scale

1. **Benefit-Risk Assessment Framework**

Acute pain needs effective treatments. Combination analgesics are anticipated to provide improved efficacy and/or reduced risks associated with the individual components used at the same dose levels.

The combination analgesic studied under NDA 209471 is Combogesic oral tablets composed of ibuprofen/acetaminophen 97.5 mg/325 mg to be administered as a single dose at 300 mg/1000 mg and a daily dose at 1200 mg/4000 mg.

The Applicant uses the results from the pivotal Study AFT-MX-6 (which will be abbreviated as MX-6 in this review) as support for efficacy and safety data from all studies included in the NDA submission as support of safety in addition to relying on the Agency's previous findings of efficacy and safety related to the individual components in the combination using a 505(b)(2) pathway.

Based on the results of pairwise comparison between Combogesic and placebo in Study MX-6, acute analgesic effects of Combogesic were shown in primary statistical analysis and were supported by clinically meaningful treatment differences in time-specific pain intensity difference (PID) measurement during the initial and repeated dosing intervals.

In addition to demonstrating effects by direct comparison to placebo, component contribution to the effects of a combination product needs to be supported by statistically significant and clinically meaningful treatment differences by comparing the drug combination to each component and comparing each component to placebo. Component contributions from ibuprofen and acetaminophen to analgesic effects of Combogesic have not been fully demonstrated in Study MX-6 because the treatment difference between acetaminophen and placebo in summed pain intensity difference over 48 hours (SPID 48) was not statistically significant and because the effect size separating the combination product to each component was not shown to be clinically meaningful and could not be linked to the effect size commonly seen in dental studies of the approved oral formulations of NSAIDs using ibuprofen and acetaminophen as active controls or the dental studies of Ultracet, the reference list product for acetaminophen in this NDA.

The results of Study MX-6 have not provided substantial evidence in support of component contribution to the analgesic effects of Combogesic to show benefit of having both components in the combination for treating mild-to-moderate pain due to low assay sensitivity of the study. The use of opioid rescue, a much stronger analgesic, to treat milder dental pain further confounded the results and made it more difficult for the component contribution to be demonstrated.

The proposed short-term use of the combination product is considered reasonably safe as suggested by the clinical safety database not showing new safety signals, lack of drug-drug pharmacokinetic interactions, non-overlapping safety profiles of ibuprofen and acetaminophen, and known safety from long marketing history of the components.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Acute pain refers to pain of acute onset and short duration associated with disease, injury, or inflammation. - Untreated acute pain leads to not only short-term suffering, morbidity, and negative impact on quality of life but also a risk of progression to chronic pain.	Acute pain needs effective management to minimize suffering, morbidity and potential long-term negative consequences.
Current Treatment Options	- Non-pharmacologic management of acute pain includes rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, relaxation techniques, etc. - Two major pharmacologic classes of analgesics for treating acute pain include opioid and nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. - Combination analgesics include opioid and nonopioid drug classes and combination of two nonopioid drugs of different drug categories.	- Combining analgesics of different mechanisms of action may potentially improve efficacy at the same or lower doses with respect to approved doses of the components. - Combining analgesics with different safety profiles may potentially maintain safety at the same dose levels as the approved component doses or improve safety at lower than the approved doses of the individual components. - In any case, component contributions to efficacy and safety of the combination product need to be demonstrated.
Benefit	- Treatment differences between Combogesic and placebo were shown as statistically significantly superior performance in SPID 48 and clinically meaningful separation by time-specific PID measurements during both the single-dose and multiple-dose evaluation periods. - Component contribution was shown in statistically significant differences in SPID 48 based on comparisons of Combogesic to ibuprofen and of ibuprofen to placebo and was not supported by clinically meaningful treatment differences in PID. - Component contribution measured by Combogesic compared to acetaminophen and acetaminophen to placebo was not fully	- Acute analgesic effects of Combogesic were supported by statistically significant and clinically meaningful treatment differences based on comparison to placebo in Study MX-6. - Component contributions from ibuprofen and acetaminophen have not been fully supported by results of Study MX-6 in terms of significant and meaningful treatment differences by comparing Combogesic to the individual components and individual components to placebo according to CDER's interpretation of the Combination Rule for fixed combination prescription drugs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	supported based on lack of demonstration of statistical significance in SPID48 comparison between acetaminophen and placebo and not showing clinical meaningful differences in time-specific PID for the entire initial dosing interval in comparing Combogesic to acetaminophen and acetaminophen to placebo. • Component contribution was shown in proportions of patients reporting acute onset with reported difference of 11% more patients in the Combogesic group with acute onset than each of the individual component groups. • Proportion of rescue use was remarkably higher in the Combogesic group than the individual components. The result was compromised by use of opioid rescue in 5-8% of the ITT population or 10-27% of those rescued to treat mild pain and inappropriate use of opioid in treating mild-to-moderate dental pain in general because dental pain does not typically require opioid analgesics.	• The effect size separating the combination product from each component was not shown to be clinically meaningful and could not be linked to the effect size commonly seen in dental studies of the approved oral formulations of NSAIDs and Ultracet using ibuprofen and acetaminophen as active controls. • The results of Study MX-6 have not provided substantial evidence in support of component contribution to the analgesic effects of Combogesic to show benefit of having both components in the combination for treating mild-to-moderate pain due to low assay sensitivity of the study. • The study had assay sensitivity too low to allow adequate assessment of component contribution probably due to low baseline pain intensity. • The use of opioid rescue, a much stronger analgesic, in treating milder dental pain further confounded the results and made it more difficult for the study to detect true treatment differences and for interpretation of findings.
Risk and Risk Management	• Exposure to a full dose of 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. • Safety data collected in 24-hour and 48-hour double-blind studies did not show increased risks in comparison of each of the active treatments (Combogesic, ibuprofen, and acetaminophen) to placebo in total adverse events (AEs) or common individual AEs. • Common ($>2\%$) AEs in the Combogesic group were AEs minor in nature, including nausea (15%), vomiting (7%), headache (5%), and dizziness (3%). • Safety monitoring by laboratory tests was conducted in one multiple-dose study with follow-up tests scheduled a week after completion of sequential treatments with the same or different study drugs and could not provide adequate dataset for treatment comparison. Laboratory testing results from single-dose PK studies	• Safety data suggested no new safety signals or evidence for component contribution to the risks of using Combogesic • Although safety data based on short-term exposure are of limited value, the lack of drug-drug pharmacokinetic interactions coupled with the known basically non-overlapping safety profiles of ibuprofen and acetaminophen and their long marketing history provide some confidence of safe use of the combination product. • Combogesic tablet contains 325 mg acetaminophen which meets the limit of the maximum amount of acetaminophen per dosage unit allowed for prescription combination product containing acetaminophen with its proposed daily dose of 4000 mg not exceeding the currently recommended total daily dose of acetaminophen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	had limited value and did not identify clinically meaningful shifts from baseline. • The NDA safety database is limited to short-term exposures due to naturally short course of acute pain not allowing continued assessments for more than a few days.	

2. Background

The Applicant has submitted a complete response to the complete response (CR) action taken on December 22, 2017 for this 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 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.

The application was originally submitted on March 1, 2017, as a 505(b)(2) NDA 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.

At the conclusion of the original NDA review (refer to the original discipline reviews and combined CDTL/Division-Director Review in DARRTS dated December 22, 2017, for detail), numerous deficiencies were identified from multiple disciplines including clinical, statistical, nonclinical, and product quality. A Complete Response Letter was issued on December 22, 2017 (refer to the Complete Response Letter in DARRTS for detail).

There were two clinical deficiencies outlined in the complete response letter. The first deficiency was inadequate description of the exposure to the proposed product. This deficiency 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 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. The second deficiency involved statistical issues in confirming the results of efficacy data analyses in the pivotal trial (Study MX-6). The statistical review team found the datasets for Study MX-6 were not of sufficient quality to allow for a thorough review of efficacy. The Applicant attempted to address the dataset issues one month before the action date of the original NDA and the data could not be reviewed due to insufficient time. In addition, the clinical review team determined that additional efficacy information from Study MX-6 will be required to understand the complete efficacy profile of the proposed product. The additional requirements were conveyed to the Applicant in the CR letter and detailed under efficacy review.

The first attempt to resubmit the NDA was dated August 2, 2018 and was considered an incomplete response due to outstanding issues with the manufacturing facilities that had been identified in the complete response letter and were not addressed in the resubmission (refer to the Incomplete Response Letter dated August 27, 2018, for detail). A follow-up type C meeting was held to discuss the Applicant's proposal to address the issues (refer to the Meeting Minutes dated February 15, 2019, for detail).

This review will be focused on the Applicant's complete response submission.

3. Product Quality

The manufacturing process/facilities review team in OPQ recommends a Complete Response.

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

In summary, 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. 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 deficiencies in the facilities, drug product, and manufacturing process. The specific deficiencies and the adequacy of the resubmission to address the deficiencies are discussed under each section.

In conclusion, CMC recommends complete response for this application because of a withhold due to a facility deficiency. The Drug product and drug substance were deemed adequate to support the approval. Biopharmaceutics and microbiology remain adequate from the original review cycle.

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 Complete Response Letter dated December 12, 2017, as well as additional stability data. In conclusion, 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 International Council for Harmonisation (ICH) Guidance, except that the second internal diameter (ID) test is performed by TLC, in which separation is based on the same principle as the first ID test, 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 NMT (not more than) (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), based on additional batch data as they become 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 conditions, the proposed 36-month shelf-life is granted.

Manufacturing

The manufacturing process includes (b) (4)

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

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

The manufacturing process is acceptable, there are no review issues with the process. The Office of Pharmaceutical Manufacturing Assessment (OPMA) review issues are limited to facility inspection.

OPMA recommends withhold due to a facility deficiency. The following deficiency will be conveyed to the sponsor,

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.

Biopharmaceutics

Biopharmaceutics remains adequate from the first cycle review.

Microbiology

Microbiology remains adequate from the first cycle review.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review team concludes all nonclinical concerns have been addressed and are considered 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 Complete Response Letter are briefly summarized below.

- Reduce the drug substance (DS) 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 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. There are no additional nonclinical safety concerns.

5. Clinical Pharmacology

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

No new clinical pharmacology or biopharmaceutics data were submitted in support of this application. There are no outstanding issues.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Introduction

Regulatory history up to the submission of the original NDA was summarized in detail in the clinical review of the original NDA and some prior agreements relevant to the current review are repeated here for reference. The Division agreed with the proposed maximum daily doses of acetaminophen 4000 mg and ibuprofen 1200 mg for the drug combination with consideration of the proposed prescription (Rx) pathway and required one adequate and well-controlled, full factorial study in patients with acute pain to support an acute analgesic indication. In response to the Sponsor's question on appropriateness of the product to be handled Rx considering the issues (acetaminophen-related liver toxicity) raised at the recent Advisory Committee Meeting, the Division let the Sponsor choose between Rx and OTC application status (refer to the responses to questions at the end of the initial IND review dated May 24, 2010 for detail).

In the original NDA submission one of the pivotal Phase 3 clinical trials, Study MX-6, investigated the three-tablet dosing of the combination product Combogesic containing acetaminophen/ibuprofen 325 mg/97.6 mg unit strength. The Applicant also submitted results from two additional Phase 3 studies (MX-6E and MX-1) and one Phase 2 dose-ranging study (MX-3) using a product of different tablet strength, Maxigesic (acetaminophen/ibuprofen 500 mg/150 mg, approved for use in other countries) to support this application. The clinical pharmacology review team determined that the exposures were similar enough between the two products to provide reasonable justification for use of these data to support the Combogesic application. It is determined from the original review that Study MX-6E was not able to show treatment difference between the active groups and placebo during the initial dosing interval and therefore the results from this study do not support efficacy. Studies MX-1 and MX-3 were not adequately designed or powered to support the efficacy of the proposed product and will not be considered further. See the Primary Clinical Review dated December 14, 2017 and combined CDTL/Division-Director Review dated December 22, from the original submission for a detailed discussion of these studies.

The protocol, key findings, and issues in Study MX-6 are summarized below based on the review of the original NDA. Study MX-6 was a multicenter, randomized, double-blind, placebo-controlled, parallel groups 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 ingredient and placebo in patients with dental pain. Eligible patients had undergone the extraction of at least two impacted third molar teeth and with dental pain intensity of ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS) scale within six hours after the completion of surgery. A total of 408 patients 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 with instructions of not to request rescue for mild pain (<40 mm VAS) and not to request rescue within two hours after the initial dose of the study medication.

The primary efficacy endpoint was time-weighted summed pain intensity difference from baseline over 48 hours (SPID48). The following secondary efficacy endpoints were included in the protocol and analyzed by the Applicant.

- 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 on the SPID48 in comparison of Combogesic to each component arm and comparison of Combogesic to placebo in Study MX-6. However, the results submitted by the Applicant could not be confirmed by the statistical review team due to poor data quality and problematic data analyses. In addition, ibuprofen and acetaminophen were not compared to placebo to assess component contributions by the combination rule that the combination performs better than individual components and individual components perform better than placebo. The key secondary analyses generally required from acute analgesic studies were either missing (time-specific PID required to support and interpret SPID) or analyzed incorrectly (acute analgesic onset and duration).

In response to statistical review team's comments on insufficient data quality to confirm the Applicant's primary and secondary efficacy analyses, the Applicant acknowledged that the datasets were generated manually within Microsoft Excel, which produced errors in the datasets submitted to the NDA. The Applicant submitted the revised datasets about one month before the action date of the first review cycle and the data could not be reviewed due to insufficient time.

The additional clinical efficacy data and analysis required for review of efficacy included the following:

- 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 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 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 by the review Division and results of updated efficacy analyses. Based on the overview of the data and analyses in the resubmission two separate 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 MX-6E or any other study
- Pairwise comparisons between individual components and placebo to be added to the PID summary table for Study 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 MX-6

Clinical review strategy

The review of the resubmission will serve as an addendum to the NDA review of the original submission.

This efficacy review has a focus on evaluation of component contribution to the effects of the combination product based on updated dataset and analyses that had not been included in the original study report for Study MX-6 in the initial NDA submission. The results of pairwise comparison between Combogesic and placebo will be summarized at the end of the efficacy review.

Some key components of Study MX-6 such as protocol summary, patient disposition, protocol deviations, and major demographic and baseline characteristics (pending clarification on race categories) had been reviewed and discussed in the original NDA review and will not be repeated here.

The key findings from the second placebo-controlled full factorial study, Study MX-6E had already been reviewed in detail in the original NDA review. The results of the study suggested no significant and meaningful treatment difference between Combogesic and placebo during the initial dosing interval and thus will not be discussed further in the current review.

Current NDA resubmission

Efficacy analyses, Study MX-6

Component contribution by primary efficacy endpoint

The results of the updated analyses of SPID48 per treatment group and pairwise comparison between treatments are summarized in the table below. The results of statistical analyses were in favor of Combogesic in comparison to each individual component and to placebo and were confirmed by sensitivity analyses conducted by the Applicant and by the statistics reviewer (refer to the Statistical Review by Dr. John Lawrence dated September 30 filed in DARRTS). In comparison of individual components to placebo applying the combination

rule, ibuprofen performed better than placebo statistically. However, acetaminophen did not win over placebo by statistical comparison.

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		
		Pairwise comparison				
		Combo >Ibu	Combo >APAP	Combo >Pla	Ibu>Pla	APAP>Pla
		<0.001	<0.001	<0.001	0.003	0.302

Combo=Combogesic

Ibu=ibuprofen

APAP=acetaminophen

Pla=placebo

Source: Table 23 on page 79 of the revised study report in resubmission.

Subgroup analyses by country

The study enrolled 2/3 of the study population in New Zealand and 1/3 in the U.S. Although the study was not powered to allow adequate statistical comparison, data consistency in numerical trend was shown in subgroup analyses by country.

Exploratory efficacy endpoint SPID6

In exploratory statistical analysis with interpolation of missing VAS scores and/or times, last pre-rescue VAS score carried forward to the end of 6-hour measurements, and no multiple imputation conducted for the 10 early withdrawers in the analysis, the results showed Combogesic>ibuprofen>acetaminophen>placebo sequentially.

Reviewer's comments

According to CDER's interpretation of the Combination Rule for fixed combination prescription drugs codified in 21 CFR 300.50, the statement that "each component should itself be tested at an effective dose, dosing regimen, etc., "may translate to having a placebo arm in the combination product studies where the single ingredient component is statistically superior to placebo, and the combination product is statistically significantly superior to each component." (See reference link provided: <http://inside.fda.gov:9003/downloads/cder/officeofthecenterdirector/regulatorybriefings/ucm197694.pdf>.)

Component contribution by statistical comparison of SPID48 between Combogesic and acetaminophen and between acetaminophen and placebo had not been fully demonstrated because treatment difference between acetaminophen and placebo was not statistically significant.

Subgroup analyses did not suggest data inconsistency between the subpopulations by country as an explanation of the findings.

Results of exploratory analysis suggest component contribution measured by SPID6.

Component contribution by time-specific PID

PID per treatment group and per treatment comparison are summarized in the table below. PID pain curves for the initial dosing interval and for the entire 48-hour evaluation period are shown in the figures following the table below.

Treatment differences in PID between Combogesic and individual components and between individual components and placebo are highlighted in blue if the difference was at least 10 mm and highlighted in yellow if the difference was at least 5 mm in the table. A component contribution will be judged by achieving at least 10 mm effect size in both pairwise comparisons of Combogesic to an individual component and then comparison of an individual component to placebo.

The results revealed that the component contribution was shown only at one time point at Hour 1 for ibuprofen, only from 1.5-3 hours for acetaminophen, and over none of the time intervals for both components.

Using PID differences of at least 5 mm in least two consecutive measurements to evaluate effect sizes of treatment differences during the repeated dosing intervals, the component contribution was shown during Hours 12-20 for ibuprofen, during Hours 7-8 for acetaminophen, and during none of the time intervals for both components.

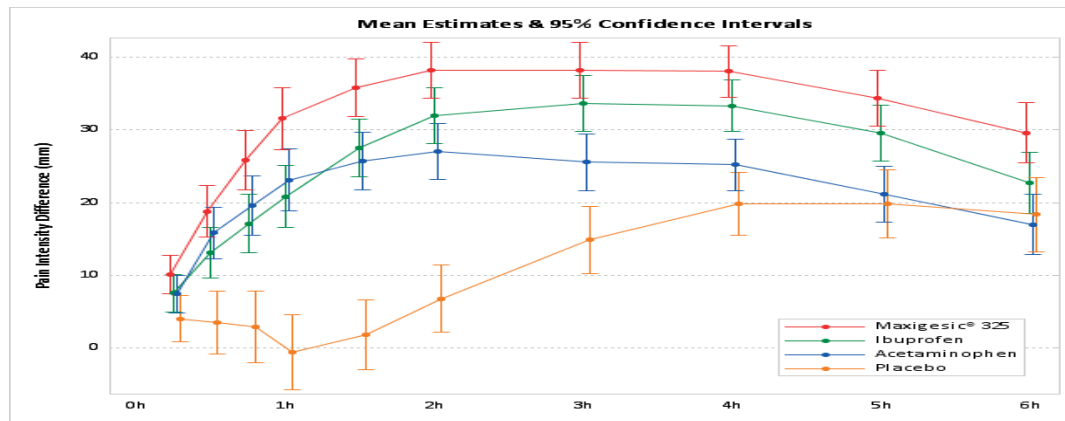
Table 2 Time-Specific PID (PI Measured by 100 mm VAS)

	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

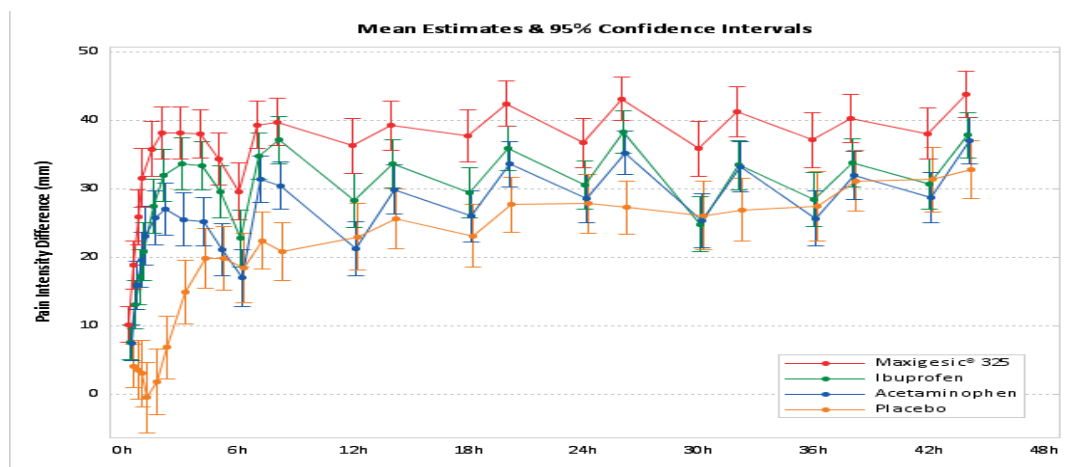
Source: Table 34 on pages 101-105 of the revised study report submitted on July 9, 2020.

Figure 1 Single-Dose PID Curve Over First Six Hours



Source: Figure 14 on page 96 of the revised study report in resubmission.

Figure 2 Multiple-Dose PID Curve Over 48 Hours



Source: Figure 15 on page 99 of the revised study report in resubmission.

Reviewer's comments

CDER's interpretation of the Combination Rule also stated that "the effect size separating the combination product to each component should be clinically meaningful" and "should be linked to the effect size that was the basis for approval of the single ingredient products."

Because of the multi-factorial nature of SPID48, it is not clinically interpretable. The magnitude of SPID has been shown to have high variation and inconsistency across studies or even between similar studies. Effect sizes of treatment differences in time-specific PID will be used to interpret SPID to determine if the statistically significant findings are clinically meaningful.

The pattern of PID curves fluctuating horizontally in parallel and the position of PID curves between the third and the seventh doses suggested that the remaining pain levels were not sufficient to allow demonstration of multiple-dose effects after the third dose and that PID difference maintained in these later dosing intervals could have been due to keeping most patients (96%) to the end of the study regardless of their need for additional analgesics in a study population already recruited with lower baseline PI than a typical dental study. The summation of PID under the parallel PID curves over these later dosing intervals appeared to have a major contribution to the magnitude of SPID 48 and its associated statistical significance showed in primary analysis.

Though component contribution was suggested by exploratory statistical analysis of SPID6, the much smaller and not clinically meaningful treatment differences between Combogesic and ibuprofen relative to effect sizes of treatment differences between ibuprofen and placebo based on PID curves and PID data in the initial dosing interval suggested non-meaningful component contribution from acetaminophen.

A typical dental study with carefully selected sample population is usually associated with higher assay sensitivity than the other known pain models. Large effect size of treatment difference from placebo in PID had been shown consistently in single-dose dental studies of NSAIDs using ibuprofen or acetaminophen as active controls in many prior NDA applications and in dental studies of Ultracet included in the NDA 21123 application (refer to Appendix for examples and explanations).

The effect sizes of treatment differences between ibuprofen and placebo over 0.75-4 hours and differences between acetaminophen and placebo over 0.5-3 hours shown in Study MX-6 would have been expected to sustain during the entire first dosing interval and beyond, and the similar effect sizes would have been expected in comparing Combogesic to each of the individual components during at least the initial dosing interval. Using relatively low borderline criteria of minimum effect sizes of 10 mm during the first dosing interval and 5 mm during the other dosing intervals to measure clinical meaningfulness of effect sizes, component contributions (combination > individual components > placebo) from both ibuprofen and acetaminophen were not shown simultaneously at any scheduled measurement time point during the study.

The low assay sensitivity as suggested by the results of Study MX-6 was probably due to lack of inclusion of patients with bony involvement, lack of involvement of impacted mandibular third molars, and lack of specification on baseline pain to include at least moderate-to-severe intensity as required in most successful dental studies.

Time-specific PI

Time-specific PI scores are listed in the table below. At Hour 7 (the first pain measurement after the second dose) mean PI scored 17, 22, and 25 for the Combogesic, ibuprofen, and acetaminophen treatment group, respectively. Pain measurements from Hour 7 to Hour 44 during the repeated dosing intervals had fluctuation within a roughly constant range per individual active treatment group, i.e., PI in a range of 13-20 mm for Combogesic, 18-32 mm for ibuprofen, and 20-35 mm for acetaminophen and PI mostly below 20 mm for Combogesic and below 30 mm for the individual components.

Table 3 Time-Specific PI

Study MX-6 PI	Combo N=110	Ibu N=112	APAP N=111	Pla N=75
Hours	Mean			
0	56.2	56.1	55.4	58.4
.25	46.1	48.6	48.0	54.2
.5	37.4	43.1	39.9	54.3
.75	30.5	39.1	36.3	54.3
1	24.7	35.4	32.9	57.7
1.5	20.5	28.8	30.4	55.1
2	18.1	24.4	29.2	50.1
3	18.3	22.8	30.8	41.8
4	18.4	23.1	31.2	36.6
5	22.1	26.9	35.3	36.7
6	26.8	33.7	39.3	38.3
7	17.0	21.6	25.0	34.0
8	16.4	19.2	25.7	35.9
12	19.8	28.0	34.9	33.7
14	17.0	22.7	26.3	30.9
18	18.5	26.9	30.3	33.3
20	13.9	20.4	22.8	28.5
24	19.7	25.8	27.8	28.3
26	13.2	18.0	21.1	28.9
30	20.5	31.5	31.1	29.9
32	15.0	22.9	23.1	29.3
36	19.3	27.9	30.8	28.7
38	16.2	22.5	24.5	24.7
42	18.4	25.6	27.8	24.5
44	12.9	18.8	19.7	23.4

Source: Cover letter in the response to information request submitted on August 25, 2020

Reviewer's comments

The time-specific PI profile was similar to PID profile, and the mean PI measurements for each active treatment group fell to a range of low scores leaving not much space for further pain reduction. The low assay sensitivity did not allow adequate evaluation of multiple-dose effects of the individual components or evaluation of component contributions during either single-dose or multiple-dose periods.

Updated analyses of onset data

Onset data from the initial dosing interval are summarized in terms of median time to onset of perceptible pain relief confirmed by meaningful pain relief and the proportion of patients having achieved the onset. The results showed an acute onset of about 20 minutes for Combogesic, 29 minutes for ibuprofen, and 22 minutes for acetaminophen. The treatment differences were 9 and 2 minutes, respectively.

The differences in proportions achieving onset were about 32% between the individual components and placebo and about 11% between Combogesic and the individual components.

Table 4 Onset Data (Initial Dosing Interval)

Study MX-6 Onset	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
Perceptible confirmed by meaningful PR				
N (%) achieved	94 (85.5%)	84 (75.0%)	83 (74.8%)	32 (42.7%)
Combogesic vs component, %		10.5%	10.7%	
Median time to onset of confirmed perceptible PR, minutes	19.69	29.08	22.03	-
95% Confidence Interval, minutes	16.02; 23.28	21.07; 35.33	18.08; 28.83	104.38; -
Combogesic vs component, minutes		-9.39	-2.34	
Median time to onset of meaningful PR, minutes	42.98	61.86	48.62	-
95% Confidence Interval, minutes	34.20; 49.17	51.20; 47.85	38.97; 61.75	
Combogesic vs component, minutes		-18.88	-5.64	

Source: Table 24 on page 81 and Table 35 on page 104 of the revised study report in resubmission.

Reviewer's comments

Each individual component ibuprofen or acetaminophen alone showed an acute analgesic onset of less than 30 minutes based on median time to onset of perceptible relief confirmed by meaningful relief. There is no space for further improvement of onset in a clinically meaningful way. A few minutes (2-9 minutes) of earlier onset in use of Combogesic versus components are not considered clinically meaningful differences. Likewise, 6-19 minutes of differences in median time to onset of meaningful relief are not considered clinically significant in patients already achieving meaningful relief around one hour. The proportions achieving acute onset showed a small component contribution.

Updated analyses of rescue data

Single-dose rescue data in the resubmission are summarized along with 48-hour rescue data from the original submission in the table below. Median time to initial rescue within the first dosing interval was not assessable because less than 50% of patients in all active treatment groups took rescue before the second dose in the study, and thus could not be used to measure single-dose duration or to evaluate component contributions.

The differences in proportions using rescue during the first dosing interval were about 40% between ibuprofen and placebo, 27% between acetaminophen and placebo, 14% between Combogesic and ibuprofen, and 28% between Combogesic and acetaminophen.

Table 5 Rescue Data

Study MX-6 Rescue	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
# patient providing data	109	111	111	75
N (%) taking rescue in the first 6 hours	18 (16.5)	34 (30.6)	49 (44.1)	53 (70.7)
Combogesic vs component, %		-14.1	-27.6	
Median time to rescue, hours	NE	NE	NE	1.75
N (%) taking rescue in 48 hours	26 (23.9)	48 (43.2)	59 (53.2)	61 (81.3)
Combogesic vs component, %		-19.3	-29.3	

NE=not evaluable

Source: Table 28 on page 89 and Tables 36 and 37 on pages 106-107 of the revised study report in resubmission.

Reviewer's comments

Time to the initial request of rescue during the first dosing interval has been used reliably as a measure of single-dose duration in dental studies of NSAIDs in post-operative patients with sufficient baseline PI. In most of these studies, more than 50% patients in each active treatment group rescued within the initial dosing interval. The low proportions requesting rescue in the ibuprofen and acetaminophen groups during first six hours in this study suggested that lower than expected baseline PI could be part of the reason in addition to explanations related to protocol restrictions on rescue use that patients were discouraged from requesting rescue during the first two hours post the initial dose.

Although the protocol instructed patients not to take rescue for mild pain (<40 mm on VAS scale as specified in the protocol) the use of opioid rescue for mild dental pain was reported in 5-8% of the ITT population among treatment groups or 10-27% of those rescued as protocol deviations (refer to the original Clinical Review dated December 14, 2017). The use of opioid rescue for mild-to-moderate dental pain is considered inappropriate because dental pain is less severe in nature and does not typically require analgesics of opioid strength.

In a single-dose dental study, the patients taking initial rescue are considered as treatment failure and their post-rescue pain scores are handled by missing data management. Therefore, the type of rescue medication has no impact on pain measurements after rescue. In a multiple-dose study, however, all pain scores are included in data analysis regardless of the use of rescue to maintain sample size. The use of a stronger opioid analgesic rescue in a study of non-opioid drug with lower analgesic strength would have confounded pain evaluation, especially in cases when patients are enrolled with lower than expected baseline pain intensity. Perhaps a more restrictive use of opioid rescue only for severe or intolerable pain would help to minimize rescue use in multiple-dose studies of non-opioid analgesics.

Summary of efficacy findings based on the review of the original NDA and resubmission

Key findings from Study MX-6:

1. Component contribution from ibuprofen and acetaminophen to the effects of Combogesic

- Component contribution was shown in statistically significant differences in SPID 48 based on comparisons of Combogesic to ibuprofen and ibuprofen to placebo and not supported by clinically meaningful treatment differences in PID according to CDER's interpretation of the Combination Rule for fixed combination prescription drugs. Treatment differences between Combogesic and ibuprofen in PID were too small to show clinically meaningful component contribution from acetaminophen to the analgesic effects of Combogesic.
- Component contribution measured by Combogesic compared to acetaminophen and acetaminophen to placebo was not fully supported based on lack of demonstration of statistical significance in SPID48 comparison between acetaminophen and placebo and not showing clinical meaningful differences in time-specific PID for the entire initial dosing interval in comparing Combogesic to acetaminophen and acetaminophen to placebo.

- Component contribution was shown in proportions of patients reporting acute onset with reported difference of 11% more patients in the Combogesic group with acute onset than each of the individual component groups
- Proportion of rescue use was remarkably higher in the Combogesic group than the individual components. The result was compromised by taking opioid rescue for treating mild pain reported as protocol deviations in 10-27% of patients rescued.
- The study had assay sensitivity too low to allow adequate assessment of component contribution probably due to low baseline pain intensity and perceivably remarkable confounding effects from opioid rescue, which is considered a stronger analgesic with a potential to mask study results.

Table 6 Summary of Component Contribution, Study MX-6

Component contribution	Combo>Ibu>Pla	Combo>APAP>Pla	Comment
Primary, SPID48	Yes	Not fully supported	Acetaminophen>placebo not shown
PID	Not supported	Not supported	Based on effect size ≥ 10 mm in 1 st 6 hours and ≥ 5 mm in Hours 7-48, component contributions from both components not shown at any time point.
Combo vs component	Ibu	APAP	
Median time to onset	Shorter by 9 minutes	Shorter by 2 minutes	Differences not clinically meaningful
% with onset	11% more	11% more	Small additional benefit from Combogesic
Median time to rescue	(< 50% rescued)	(< 50% rescued)	Not able to use the endpoint
% rescued in 6 hours	14% less	28% less	Showed component contribution
% rescued in 48 hours	19% less	29% less	

2. Efficacy summary by comparing Combogesic to placebo

As summarized in the table below in comparison to placebo the analgesic effects of Combogesic were shown as statistically significant treatment difference in SPID supported by meaningful separation in time-specific PID, acute onset, sizable difference of 43% more reporting onset, and sizable difference of 54-57% less of patients using rescue.

Table 7 Efficacy Summary by Comparing Combogesic to Placebo

Endpoints	Effect size in comparison to placebo	P value	Comment
Primary, SPID48		p<0.001	
Time-specific PID	11-34 mm, 1 st dosing interval (DI) 17-19 mm, in 1 st 2 hours after 2 nd dose 13-15 mm, pre-dose & 2-hour post-dose 3 rd - 4 th DI 9-10 mm pre-dose & 14-16 mm 2-hour post-dose, 5 th -6 th DI 9-10 mm pre-dose & 2-hour post-dose, 7 th DI		Treatment differences from placebo were most remarkable in the 1 st dosing interval and up to 2 hours in the 2 nd dosing and gradually decreased during subsequent dosing intervals

Median time to onset	NE, <50% of placebo reported onset in 1 st DI 20 minutes for Combogesic		Acute onset demonstrated
% with onset	42.8% (85.5 vs 42.7%)		Sizable difference
Median time to rescue	NE, <50% of Combogesic group rescued in 1 st DI		
% rescued in 6 hours	-54.2% (16.5 vs 70.7%)		Sizable difference
% rescued in 48 hours	-57.4% (23.9 vs 81.3%)		Sizable difference

Source: All tables above.

Efficacy conclusion

Acute analgesic effects of Combogesic were supported by statistically significant and clinically meaningful treatment differences based on comparison to placebo in Study MX-6.

Component contributions from ibuprofen and acetaminophen have not been fully supported by results of Study MX-6 in terms of significant and meaningful treatment differences by comparing Combogesic to the individual components and individual components to placebo. The difference in SPID 48 between acetaminophen and placebo was not statistically significant. Also, the effect size separating the combination product from each component was not shown to be clinically meaningful and could not be linked to the effect size commonly seen in dental studies of the approved oral formulations of NSAIDs using ibuprofen and acetaminophen as active controls or linked to effect size demonstrated in dental studies of Ultracet.

The results of Study MX-6 have not provided substantial evidence in support of component contribution to the analgesic effects of Combogesic to show benefit of having both components in the combination for treating mild-to-moderate pain due to low assay sensitivity of the study. The use of opioid rescue, a much stronger analgesic, in treating milder dental pain further confounded the results and made it more difficult for the component contribution to be demonstrated.

CDTL comments:

Dr. Fang has provided a thorough review of the updated datasets submitted for study AFT-MX-6 and conducted additional analyses that are necessary to understand the complete efficacy profile of the proposed product. I concur with the data she presented and some of her analysis. However, I have different interpretations of the primary analysis and some of the additional analysis.

Study AFT-MX-6 demonstrated statistically significantly superiority of Combogesic to acetaminophen, ibuprofen, and placebo (Table 1) based on the time-weighted summed pain intensity difference from baseline over 48 hours (SPID 48).

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 result of the low assay sensitivity because of the low entry pain scores in this study.

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.

Additional analyses on time 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.

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

Correction of demographic characterization of the study population by race and ethnicity

The race categories in the original NDA included Caucasian, Maori, Asian/Pacific Islander, and Other (10-20% with no details about the race categories for patients grouped under other) with no mentioning about Black race and Hispanic ethnicity. The resubmission on May 7, 2020 included a long list of incorrect categories under 'other/mixed race' such as European, Italian, South African, Latino, Indian, Chinese, and Taiwanese (refer to Table 14 on pages 70-71 for detail). An Information Request was sent to the Applicant to group all patients by race-ethnicity categories according to classification by the US Census Bureau. The updated information was shown in the table below.

Table 8 Demographics: Race and Ethnicity

Study MX-6 Race/ethnic groups	Combo N=110	Ibu N=112	APAP N=111	Placebo N=75	Total N=408
Non-Hispanic total	102 (92.7)	105 (93.8)	101 (91.0)	66 (88.0)	375 (91.9)
White	93 (84.5)	90 (80.4)	97 (87.4)	57 (76.0)	337 (82.6)
Black	2 (1.8)	3 (2.7)	0.0	5 (6.7)	10 (2.5)
Asian & Pacific Islander (including Maori)	6 (5.5)	9 (8.0)	3 (2.7)	4 (5.3)	22 (5.4)
American Indian & Alaska Native	0	0	1 (0.9)	0	1 (0.2)
Mixed race	1 (0.9)	3 (2.7)	0.0	1 (1.3)	5 (1.2)
Hispanic-Any race	8 (7.3)	7 (6.3)	10 (9.0)	8 (10.7)	33 (8.1)
White	8 (7.3)	6 (5.4)	10 (9.0)	8 (10.7)	32 (7.8)
Black	0	1 (0.9)	0	0	1 (0.2)

Source: Cover letter in the response to IR submitted on August 25, 2020.

Reviewer's comments

Patients of African origin or Hispanic ethnicity were under-represented in this study due to two thirds of the study population being in New Zealand.

Clarification on exposure

Exposure in the single-dose PK studies was clarified and the details are summarized in Table 13 in the Attachment. Exposure information for the multiple-dose efficacy studies was updated to include patients exposed during the open-label extension phase in Study MX-6E. Multiple-dose exposure was summarized by the number of doses exposed in Table 14 and by cumulative number of doses exposed in Table 15 in the Appendix.

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). Multiple-dose exposure to a full dose of Combogesic included 367 patients to at least four doses, 253 patients to at least eight doses, and 50 patients to at least 12 doses.

Table 9 Brief Summary of Exposure to Combogesic

Overall	Full dose	Partial dose	Total
Any dose	605	133	708
≥4 doses	367	76	443
≥8 doses	253		253
≥12 doses	50		50

Source: Table A1-A3 in Appendix.

Clarification on laboratory test results

There was one (Study MX-6E) of the four multiple-dose studies conducted with had laboratory tests. Blood samples for laboratory tests were collected at screening and at follow-up visit on Days 8-10 after both the double-blind treatment in four treatment groups and the subsequent open-label extension treatment in two treatment arms, either Combogesic or acetaminophen as shown in the table below. The end-of-study laboratory tests reflected effects of two different sequential treatments in the majority of patients and could no longer be used for treatment comparison or for evaluation of component contributions to the abnormal laboratory findings.

Table 10 Treatment Sequence Before Follow-up Laboratory Test, Study MX-6E

Double-blind, 4 doses	Combogesic		Ibuprofen		Acetaminophen		Placebo	
Open-label, 1-16 doses	Combo	APAP	Combo	APAP	Combo	APAP	Combo	APAP

In single-dose, crossover, PK studies very few laboratory test results had shifts from normal to abnormal range and none of the shifts in lab test values were considered as clinically significant findings by the Investigators or the Institutional Review Boards (IRB).

Safety updates

There have been no additional clinical studies of the tablet formulation. New safety data from one pediatric study of oral suspension formulation and one adult Phase 3 study of IV formulation are included by the Applicant in the current NDA resubmission as safety updates. The pediatric study is briefly summarized in the

review section 10 below. Safety data from these studies of different formulations will be reviewed in detail when corresponding NDA or NDA supplement is ready for submission and will not be included in the safety review of the tablet formulation here.

Safety summary based on safety review of the original NDA and updated information in resubmission

- Exposure to a full dose (three tablet) of Combogesic was reported in 605 subjects and cumulative exposure included 367 (61%) subjects exposed to at least four doses, 253 (42%) exposed to at least eight doses, and 50 (8%) exposed to at least 12 doses.
- One case of death of 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.
- A total of eight cases of serious adverse events (SAEs) were reported and two of them in the Combogesic group, including one case of deep vein thrombosis that occurred 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 the quarter dose level. Both resolved with treatment and were considered unlikely to be related to the study medication.
- There were only two cases of dropouts due to AEs (vomiting and stomach cramps) and both were reported in patients receiving Combogesic.
- About one third of the study population reported AEs and the proportions reporting any AEs or common individual AEs were similar across the treatment groups, including the placebo group. The most commonly reported AEs reported 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 the small sample size of 30-50 patients per group in the dose-response Study MX-3.
- Safety monitoring by laboratory tests was conducted in one multiple-dose study with follow-up tests scheduled a week after completion of sequential treatments with the same or different study drugs and could not provide adequate dataset for treatment comparison. Laboratory testing results from single-dose PK studies had limited value and did not identify clinically meaningful shifts from baseline.
- Evaluation of component contribution to safety of the combination in the NDA safety database is limited to short-term exposures in 24-hour and 48-hour studies due to the naturally short course of acute pain not allowing continued assessments for more than a few days. Very short duration of exposure of one to two days would not be expected to provide valuable safety information because AEs in general are not only related to the level of exposure but also the duration of exposure.

Brief summary on FDA mandated limit on acetaminophen unit strength and statements about daily dose

FDA required all prescription combination drug products containing acetaminophen to limit the strength of acetaminophen to 325 mg per dosage unit to reduce the risks of severe liver injury from inadvertent acetaminophen overdose leading to liver failure, liver transplant, and death and to reduce risks of unintentional

overdose from concomitant use with other acetaminophen containing products. FDA also required a Boxed Warning highlighting the potential for severe liver injury added to the labeling of all prescription drug products that contain acetaminophen.

Factors contributing to the high incidence of unintentional acetaminophen overdose included that taking a large amount of acetaminophen over a short period of time causes liver injury as agreed by the experts, but a specific threshold dose for toxicity has not been established and may not be the same for all persons based on available information. Additionally, we cannot currently identify all the factors that might increase an individual's risk of acetaminophen toxicity, particularly at doses near the current recommended total daily dose of 4,000 mg per day¹

Safety conclusion

No new safety signals or evidence suggesting component contribution to the risk associated with the use of Combogesic were identified based on the review of safety data and treatment comparisons in double-blind studies of 24-hour and 48-hour in duration.

Although safety data collected in such short time intervals are of limited value, the lack of drug-drug pharmacokinetic interactions coupled with the known basically non-overlapping safety profiles of ibuprofen and acetaminophen and their long marketing history provide some confidence in safe use of the combination product.

The Combogesic tablet contains 325 mg acetaminophen which meets the limit of the maximum amount of acetaminophen per dosage unit allowed for prescription combination product containing acetaminophen with its proposed daily dose of 4000 mg not exceeding the currently recommended total daily dose of acetaminophen.

CDTL comments:

I concur with Dr. Fang's safety review and conclusion.

9. Advisory Committee Meeting

Not planned.

10. Pediatrics

The Division's agreement on the proposed initial Pediatric Study Plan (iPSP) was sent to the Sponsor of IND 107435 on February 6, 2017. The PSP was subsequently transferred to NDA 209471 on March 22, 2018, after the original NDA submission received the Complete Response in December 2017.

The agreed iPSP described the proposed deferral of pediatric studies for all three pediatric age groups of (b) (4) 2-12, and 12 -17 years and the anticipated submission timelines for the studies. The studies in the age groups of (b) (4) and 12-17 years were in planning stage and the study of the age group of 2-12 years (Study MX-12) was ongoing according to the agreed iPSP.

¹ The Federal Notice issued by FDA: <https://www.regulations.gov/document?D=FDA-2011-N-0021-0001>

An updated version of the agreed PSP was submitted with the NDA resubmission and included a summary table describing the key components of the protocol for each pediatric study and reported the major clinical findings in the complete pediatric Study MX-12 of the age group of 2-12 years. It also included a proposal for a new set of timelines. The Applicant had not submitted the study report for Study MX-12.

11. Other Relevant Regulatory Issues

The Division of Pharmacovigilance (DPV) reviewed post-marketing safety data in updating safety information on association between acetaminophen use and serious cutaneous adverse events and found data consistency in support of the regulatory decision to include Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) and Acute Generalized Exanthematous Pustulosis (AGEP) in the OTC monograph for acetaminophen products (refer to the DPV Review dated October 19, 2020 for detail).

12. Labeling/DMEPA Review

Labeling will be reviewed separately and completed in the final review cycle leading to product approval.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategy (REMS)

A REMS is not recommended at this time.

Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended at this time.

14. Recommended Comments to the Applicant

Discussion

The results of Study MX-6 suggest that the dental study conducted did not have sufficient assay sensitivity to allow demonstration of significant and meaningful component contributions measured by SPID 48 and supported by time-specific PID, due to low baseline pain intensity and potential confounding effects introduced by inappropriate use of opioid rescue for treating mostly milder dental pain.

Dental pain is a representative model for studying acute pain not serious in nature and not typically requiring opioid type drugs for pain management. It is considered the most sensitive model for studying acute pain if being carefully planned. Baseline pain needs to be in the moderate-to-severe range to provide assay sensitivity in all acute analgesic studies regardless of whether the proposed indication is for treating mild-to-moderate pain or for moderate-to-severe pain. The use of opioid rescue should probably be reserved mainly for severe or intolerable pain not manageable by the study drugs of non-opioid class. The initial request of rescue should not be instructed to be delayed for the reason of not interfering with the measurement of analgesic duration of the initial dose.

Mild-to-moderate pain is manageable by treatment with ibuprofen 300 mg alone or acetaminophen 1000 mg alone and may not require the combination containing the maximum amount of acetaminophen per dose or per

daily dose. Because of the uncertainty about threshold acetaminophen dose for liver toxicity and the precipitating factors for the increase of individuals' risks to acetaminophen toxicity at near 4000 mg daily dose as stated in the FR notice, Combogesic with the maximum amount of acetaminophen dosing might need to be reserved for use in a more controlled setting. Combogesic at the proposed dose might have a potential benefit in treating a more severe type of post-operative pain when analgesics are switched from IV to oral to help to eliminate the use of opioid and contribute to the current public health effort in dealing with the opioid crisis.

In the primary reviewer's opinion the Applicant has not provided full support of component contribution to analgesic efficacy of Combogesic for treating mild-to-moderate pain due to lack of statistically significant treatment differences between acetaminophen and placebo by primary endpoint SPID 48 and lack of clinically meaningful treatment differences in PID required as key supportive evidence in demonstrating component contribution from either ibuprofen or acetaminophen based on the review of NDA data. It is up to the review Division to decide the clinical recommendation for approval.

15. Appendix

Effect size in single-dose dental studies

Summarized in the table below are historical NDA data from multiple NDAs in seven randomized, active- and placebo-controlled, parallel group, single-dose studies of post-operative dental pain being used to support analgesic indications for treating minor aches and pains at the proposed dosing interval of every 4-6 hours PRN. The studies had sample size limitation of ≤ 50 per treatment group and used 4-point categorical scale of 0-3 (where 0=no pain, 1=mild pain, 2=moderate pain, and 4=severe pain) to measure PI.

The effect size was determined from comparison of mean PID in the active treatment groups to mean PID of the placebo group. The maximum effect size in PID by comparing active treatment to placebo was around two categorical points in a typical dental study and effect size of at least one categorical point difference from placebo in PID was maintained for 4-6 hours in the seven dental studies as shown in the table below.

Table 11 Effect Sizes $\geq$ One Categorical Point in PID Difference from Placebo in Dental Studies of NSAIDs

Dental study	1	2	3	4		5	6	7
Effect size ≥ 1	Time (hours)					Time (hours)		
NSAID #1-HD	0.75-4	0.75-5	0.5-6	0.75-6	NSAID #2-HD	0.5-6		
NSAID #1-LD	0.75-4	2-4	1-3	0.75-6	NSAID #2-LD	0.5-6	0.5-6	0.5-6
Ibuprofen 400	0.75-6	2-4	1-6					
Ibuprofen 200			0.75-6			1-6		0.75-6
APAP 1000				0.75-6				
APAP 650							0.5-6	

Note: HD=high dose; LD=low dose.

Source: Capstone research project with the title “Translation of pain scores and patient counts to effect size and measurement of single-dose duration based on analysis of historical data” presented by Christina Fang at the Annual Capstone Symposium at the Johns Hopkins Bloomberg School of Public Health in 2007.

Comparative PID data from single-dose dental studies of Ultracet in NDA 21123 are summarized below. The effect size of at least one-half of a categorical point treatment difference from placebo in PID was maintained for up to 8 hours for Ultracet (with recommended dosing interval of every 4-6 hours) and ibuprofen 400 mg and for up to 6 hours for acetaminophen 650 mg.

Table 12 Effect Sizes ≥ 0.5 Categorical Point in PID Difference from Placebo in Dental Studies of Ultracet

Dental study number	010	012	013
Effect size ≥ 0.5	Time (hours)		
Tram 75/APAP650	1-5	1-8	0.5-8
APAP 650	1-3	1-4	0.5-6
Ibuprofen 400	1-5	2-8	1-8

Source: NDA 21123.

Exposure in single-dose PK studies

Exposure in single-dose crossover PK studies are summarized in the table below. Of the 203 subjects exposed in the PK studies 179 were exposed to a full dose and 53 exposed to a fraction of the full dose.

Table 13 Exposure in PK Studies

	Strength x #tabs	Number of doses		Number of patients*		
		Full dose	Partial dose	n	Full dose	Partial dose
MX-8	500/150 x 2	1		12	12	
MX-9	325/97.5 x 1		1	23		23
MX-10 (crossover)	325/97.5 x 1		1	27		
	325/97.5 x 2		1	28		28*
	325/97.5 x 3	2		27	27	
MX-11 (crossover)	500/150 x 2	2		26	26	
	500/150 x 1		1	2		2*
MX-13a	325/97.5 x 3	1		30	30	
MX-13b	325/97.5 x 3	1		29	29	
MX-14a (crossover)	325/97.5 x 3	1		26		
	500/150 x 2	1		27	27	
	1000/300 (suspension)	1		27		
	1000/300 (sachet)	1		27		
MX-14b (crossover)	325/97.5 x 3	1		28	28	
	500/150 x 2	1		28		
	1000/300 (suspension)	1		28		
	1000/300 (sachet)	1		28		
Total					179	53

*Same patient was exposed to a single dose in more than one study period with a washout between the periods.
Source: Table 7 on page 13 of safety summary submitted July 9, 2020

Exposure in multiple-dose efficacy studies

Exposure and cumulative exposure in multiple-dose efficacy studies are summarized in the two tables below, with inclusion of updated exposure information during open-phase treatment period in Study MX-6E. Exposure to a full dose of Combogesic included any exposure in 426 patients, to at least four doses in 367 patients, at least eight doses in 253 patients, and at least 12 doses in 50 patients.

Exposure to a partial (a half or a quarter) dose of Combogesic included any exposure in 80 patients and to at least four doses in 76 patients.

Table 14 Exposure in Efficacy Studies

Study	MX-6	MX-6E			MX-1	MX-3		
Strength	325/97.5 x 3	500/150 x 2			500/150 x 2	500/150 x 2	500/150 x 1	500/150 x 0.5
Dose		Total	db± open ext	Open ext only			Half dose	Quarter dose
1	1	20		20	3	2		1

2	2	18		18		1		1
3		12		12			1	1
4		27	14(db only)	13	1	27	33	43
5		20	7	13				
6		16	4	12				
7		16	4	12	7			
8	107	26	8	18	32			
9		12	2	10				
10		15	7	8				
11		11	6	5				
12		13	6	7				
13		4	1	3				
14		5	3	2				
15		4	3	1				
16		16	4	12				
17		3	3					
18		1	1					
19		1	1					
20		3	3					
Total	110	243	77	166	43	30	34	46

Db=double-blind

Ext= extension

Source: Tables 1-4 on pages 8-10 and Table 6 on page 12 of safety summary submitted July 9, 2020

Table 15 Cumulative Exposure in Efficacy Studies

Study	MX-6	MX-6E	MX-1	MX-3	All studies	MX-3		
Strength	325/97.5 x 3	500/150 x 2			N (full dose)	500/150 x 1	500/150 x 0.5	N (partial dose)
Dose	Full dose					Half dose	Quarter dose	
≥1	110	243	43	30	426	34	46	80
≥2	109	223	40	28	400	34	45	79
≥3	107	205	40	27	379	34	44	78
≥4	107	193	40	27	367	33	43	76
≥5	107	166	39		312			
≥6	107	146	39		292			
≥7	107	130	39		276			
≥8	107	114	32		253			
≥9		88			88			
≥10		76			76			
≥11		61			61			
≥12		50			50			
≥13		37			37			
≥14		33			33			
≥15		28			28			
≥16		24			24			
≥17		8			8			
≥18		5			5			
≥19		4			4			
20		3			3			

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/s/

CHRISTINA L FANG
11/05/2020 08:52:34 PM

NING HU
11/05/2020 08:57:56 PM
Refer to CDTL comments in this review and the CDTL/Division Director Summary Review.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209471
Priority or Standard	Standard
Submit Date(s)	March 1, 2017
Received Date(s)	March 1, 2017 (received by the reviewer on June 5, 2017)
PDUFA Goal Date	January 1, 2018 (12/29/17)
Division/Office	Division of Anesthesia, Analgesia, and Addiction Products/ODEII
Reviewer Name(s)	Christina Fang, M.D., M.P.H.
Review Completion Date	December 14, 2017
Established/Proper Name	Acetaminophen/ibuprofen
(Proposed) Trade Name	Combogesic
Applicant	AFT pharmaceuticals
Dosage Form(s)	Tablet
Applicant Proposed Dosing Regimen(s)	Acetaminophen/ibuprofen 325 mg/97.5 mg three tablets every 6 hours up to 4 time a day
Applicant Proposed Indication(s)/Population(s)	For the short term management of mild to moderate acute pain in adults
Recommendation on Regulatory Action	Complete response
Recommended Indication(s)/Population(s) (if applicable)	None

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
APAP	acetaminophen
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
Ibu	ibuprofen
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OA	osteoarthritis
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over the counter
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PI	pain intensity
PID	pain intensity difference
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	pain relief
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SPID	summation of pain intensity difference
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The proposed to-be-marketed drug product in the current NDA is a combination product containing acetaminophen and ibuprofen at 1000 mg and 300 mg levels to be given as three tablets of combination at 325/97.5 formulation strength for acute pain indication. The combination product was originally marketed in New Zealand at formulation strength of 500/150 on a 2-tablet dosing regimen. The lower strength combination of 325/97.5 was developed specifically for the US market in response to the FDA recommendation of limiting amount of acetaminophen to 325 mg per dose in combination analgesic products.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence of effectiveness could not be determined due to unresolved issues with statistical analyses and lack of key information defining single-dose characteristics including pain intensity difference (PID) data and curves and single-dose onset and duration based on analyses of the entire intent-to-treat (ITT) study population, and lack of time-specific PID data and curves characterizing multiple-dose effects to support findings on the primary endpoint, summation of PID (SPID).

1.3. Benefit-Risk Assessment

In addition to the deficiencies in efficacy data analyses and summary, and presentation of findings, there are a number of deficiencies identified in the safety database, especially in terms of incomplete exposure information and inadequate summary of laboratory findings.

Therefore, benefit-risk could not be evaluated adequately until the deficiencies in efficacy and safety data submission are addressed by the Applicant.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	☒ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	☒ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Acute pain is probably one of the most common symptoms associated with all kinds of medical conditions driving people to seek for immediate medical attention or self-medication. Treatment for acute pain should be secondary to the treatment of medical conditions that cause the pain and should be given only as needed at the minimum effective dosage to improve benefit/risk ratio.

2.2. Analysis of Current Treatment Options

There have been many drug products approved for treating acute pain including products containing

acetaminophen or ibuprofen. The two major drug classes for treating acute pain are opioids and non-opioid analgesics such as NSAID, acetaminophen, aspirin, etc.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

None.

3.2. Summary of Presubmission/Submission Regulatory Activity

The original drug development plan aimed at both acute and chronic pain indications and included two acute pain models of post-surgical dental and bunionectomy pain, two chronic pain models, one of which is osteoarthritic pain (second to be identified), and a phase 4 tolerability study. A protocol for a dose ranging, factorial, 24-hour study of dental pain (MX-3) was submitted in the initial IND (#107435). The Division informed the Sponsor about the requirement of a 48-hour full factorial study to support efficacy for acute pain and provided a number of specific comments about study hypothesis, proposed analyses, and exclusion of symptoms related to dental procedures in safety data collection.

In response to the Sponsor's questions on the drug development plan included in the initial IND submission, the Division agreed that it was acceptable to have a maximum daily dose of 4000 mg acetaminophen and 1200 mg ibuprofen with the proposed dosage of acetaminophen/ibuprofen 1000/300 q6 hours for the combination product, exposure in 500-1000 subjects would be acceptable for acute and chronic indications, and 505(b)(2) would be an appropriate pathway. The Division pointed out that a well-controlled full factorial study of 12 weeks in duration would be required to support a chronic pain indication, the proposed dose levels could be for either prescription or OTC products, and planned pediatric formulations should have concentrations meeting US market expectations (refer to clinical review of the initial IND dated May 24, 2010 for detail).

The Sponsor submitted two protocols on June 15, 2011, one for study of dental pain (MX-6) and another for study of OA pain (MX-7) requesting for Special Protocol Assessments. Because of issues related to the proposed statistical analyses the Division sent a 'no agreement' letter (refer to the letter to the Sponsor dated July 29, 2011). Subsequently, the Sponsor and the Division had multiple communications on these statistical issues as indicated by two additional letters of 'no agreement' sent to the Sponsor (refer to the letter dated November 8, 2011 and April 25, 2012 for detail) and a meeting devoted entirely to the discussion of statistical issues before the last 'no agreement' letter was sent (refer to the meeting minutes dated March 1, 2012 for detail). There were no records if these statistical issues had been adequately addressed.

At the pre-NDA meeting held on July 9, 2015 the Division informed the Sponsor about the requirement of factorial study for (b) (4), requirement of efficacy and safety data (b) (4) need to pool safety data across studies in ISS, and need to identify reference products and provide adequate bridging information (refer to the meeting minutes dated August 5, 2015 for detail).

There were multiple communications between the Sponsor and the Division during the period of May 2016 and

February 2017 in attempt to reach an agreement on Pediatric Study Plan. The final agreement on deferring pediatric studies (b) (4) was reached in early 2017 (refer to the letter dated February 6, 2017 for detail).

3.3. Foreign Regulatory Actions and Marketing History

Maxigesic was originally marketed in New Zealand in 2009 and had been subsequently registered in Australia, United Arab Emirates (UAE), Singapore, Malaysia and more than 15 European countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Based on FDA's inspection of the US clinical site, which enrolled 135 patients in Study MX-6, Dr. Damon Green concluded that: "the study appears to have been conducted without violation in data integrity or subject safety and well-being. The data generated by this site appears acceptable in support of this current application." "The raw data used to generate the calculated primary endpoint were verifiable." The three study sites in New Zealand, which jointly enrolled 2/3 of the study population were not inspected.

4.2. Product Quality

Several CMC deficiencies for facilities, process, and drug product were identified (refer to Dr. Ciby Abraham's review for detail).

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There were no nonclinical data in the NDA submission.

4.5. Clinical Pharmacology

Based on clinical pharmacology review, PK findings included the following (refer to Dr. Wei Qiu's review for detail).

- Bioequivalence demonstrated in comparison of dose normalized acetaminophen and ibuprofen in the combination product at 325/97.5 strength to the reference products (with a notice of 29% greater C_{max} for acetaminophen and 19% greater C_{max} for ibuprofen under fast condition in comparison of the combination product to reference products)
- No food effects on the combination at 325/97.5 strength (except about 30% lower C_{max} for acetaminophen)

- Dose proportionality shown over the range of 1, 2, and 3 tablets of the combination at 325/97.5 strength
- No drug interactions between acetaminophen and ibuprofen
- Bioequivalence demonstrated between three tablets at lower strength of 325/97.5 and two tablets at higher strength of 500/150 (with a notice of 19% greater Cmax under fasting for acetaminophen in the lower strength combination)

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 1 Clinical Study Inventory

Protocol #	# Centers/ Countries	Design	Formulation strength	Treatment	#subject	Population	Endpoint	Follow- up
Multiple-dose efficacy and safety								
AFT-MX-6	3 sites in New Zealand 1 site (135 patients) in USA	Randomized Double-blind Placebo- controlled, Parallel Full factorial	APAP/ibu 325/97.5 (given as 3 tablets)	Combogesic Ibuprofen300 APAP1000 Placebo Q6 hours for 48 hours	110 112 111 75	Dental pain	1° SPID48 2° Onset Rescue % & time to PI ↓ by ≥50% Max VAS Global	Hour 48 Day 30
AFT-MX-6E	2 sites in New Zealand	Randomized Double-blind Placebo- controlled, Parallel Full factorial	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic Ibuprofen300 APAP1000 Placebo Q6 hours for 24 hours	77 75 73 75	Knee pain, arthroscopy related	1° SPID24 2° Onset Rescue % & time to PI ↓ by ≥50% SPID6 Max VAS Global	Hour 24 Day 8-10 Day 30
AFT-MX-3	2 sites in New Zealand	Randomized Double-blind Placebo- controlled, Parallel	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic F Maxigesic H Maxigesic Q Placebo Q6 hours for	30 34 46 49	Dental pain	1° SPID24 2° Onset Rescue % & time to PI ↓ by ≥50%	Hour 24 Day 8-10 Day 30

		Full factorial		24 hours			Max VAS Global	
Multiple-dose PK/PD and safety								
AFT-MX-1	2 sites in New Zealand	Randomized Double-blind Parallel factorial (Maxigesic vs each component)	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic Ibuprofen300 APAP1000 Q6 hours for 48 hours	40 39 43	Dental pain	1° SPI 2° Rescue Global pain Nausea rating # vomiting Sleep Global general PK/PD	Hour 24 Day 8-10 Day 30
AFT-MX-PK-1		Single-dose Population PK followed by multidose	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic Ibu APAP q6 hours	14 12 17	Dental pain		
AFT-MX-PD-1		Multiple-dose PD	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic Ibu APAP q6 hours (3-8 doses given)	39 36 37	Dental pain		
Note: Study MX-PK-1 and MX-PD-1 are part of Study MX-1								
Single-dose PK								
AFT-MX-9	1 site in India 2/13	Single-dose Open label 2-period crossover BA/BE	APAP/ibu 325/97.5 (given as 1 tablet)	Combogesic Ibuprofen 97.5 mg	24 in Period 1 19 in Period 2	Healthy adults	PK sampling 0-12 hours	
AFT-MX-10	1 site in Jordan 12/13-1/14	Single-dose Open label 4-period crossover Dose range Food effect	APAP/ibu 325/97.5 (given as 1, 2, or 3 tablets)	1-tab Combo 2-tab Combo 3-tab Combo fasted 3-tab Combo Fed	28 in Period 1 27 in P Periods 2, 3, & 4	Healthy adults, male	PK sampling 0-12 hours	
AFT-MX-13a	1 site in Jordan 3/16-4/16	Single-dose Open label 3-period crossover Comparing to RLDs	APAP/ibu 325/97.5 (given as 3 tablets)	Combogesic Ultracet 2 tab (APAP 650) Ibu 1 tab (Ibuprofen800) Fasted & dose normalization	30	Healthy adults	PK sampling 0-12 hours	
AFT-MX-13b	1 site in Jordan 3/16-4/16	Single-dose Open label 3-period crossover Comparing to RLDs	APAP/ibu 325/97.5 (given as 3 tablets)	Combogesic Ultracet 2 tab (APAP 650) Ibu 1 tab (Ibuprofen 800) Fed & dose normalization	30 in Periods 1 & 2 29 in Period 3	Healthy adults	PK sampling 0-12 hours	

AFT-MX-14a	1 site in Jordan 7/16-8/16	Single-dose Open label 4-period crossover Comparing 2-tab and 3-tab formulations	APAP/ibu 325/97.5 (3 tablets) vs 500/150 (2 tablets), fasting	Combination APAP/Ibu 1000/300 in 4 formulations: Suspension Sachet 2-tablet 3-tablet	30 in Period 1 27 in Period 2, & 26 in Periods 3 & 4	Healthy adults, male	PK sampling 0-12 hours	
AFT-MX-14b	1 site in Jordan 7/16-8/16	Single-dose Open label 4-period crossover Comparing 2-tab and 3-tab formulations	APAP/ibu 325/97.5 (3 tablets) vs 500/150 (2 tablets), fed	Combination APAP/Ibu 1000/300 in 4 formulations: Suspension Sachet 2-tablet 3-tablet	30 in Period 1 28 in Periods 2, 3, & 4	Healthy adults, male	PK sampling 0-12 hours	
AFT-MX-11	1 site in Jordan 1/14-2/14	Single-dose Open label 4-period crossover BA/BE	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic fasted Maxigesic fed Ibuprofen300 APAP1000	28 in Period 1, 27 in P Period 2, 26 in Periods 3 & 4	Healthy adults		
AFT-MX-8	1 site in Jordan 9/12-1/13	Single-dose Open label 2-period crossover Metabolic	APAP/ibu 500/150 (given as 2 tablets)	Maxigesic APAP1000	12	Healthy adults		

Source: individual study reports

5.2. Review Strategy

There were four multiple-dose, controlled efficacy studies, AFT-MX-6, AFT-MX-6E, AFT-MX-3, and AFT-MX-1. The lower formulation strength of 325/97.5 on three-tablet dosing regimen was studied in MX-6 and the higher strength of 500/150 on two-tablet dosing regimen was studied in MX-6E, MX-3, and MX-1. The amounts of acetaminophen/ibuprofen studied were at 1000mg/300mg levels approximately in all trials. The brand name for the higher strength formulation is Maxigesic, which is available on foreign markets. A new brand name Combogesic has been obtained for the lower strength formulation. The two names were used interchangeably in the NDA submission. For the purpose of this review the higher strength formulation will be called Maxigesic and lower strength formulation called Combogesic to distinguish between them.

Study MX-1 was the first efficacy study and was conducted several years earlier than the other three trials. It is considered exploratory in nature by its study design with no placebo control, no requirement of baseline pain level, no fixed schedule for pain data collection (pain to be recorded every 1-2 hours), and no collection of data on acute analgesic onset. Data from Study MX-1 will be used for review of safety and the study will not be discussed under efficacy review.

Study MX-6 (full factorial study of dental pain), MX-6E (full factorial study of knee pain post arthroscopy), and MX-3 (dose response study of dental pain) had very similar study design, efficacy data collection, and efficacy endpoints. Study MX-6 evaluated component contribution using the lower strength formulation on 3-tablet dosing regimen and will be reviewed in detail.

Study MX-6E also studied component contribution but used higher strength formulation on 2-tablet regimen. It was conducted and analyzed in a very similar way as that of Study MX-6 and will be discussed in less detail because of equivocal outcomes suggested by single-dose PID curves.

Study MX-3 was a relatively small dental study not designed to study component contribution. The study was conducted by the same group of Investigators conducting dental Study MX-6 in New Zealand (refer to the last table in Appendix at the end of the review). Data from this study could help us to learn response pattern in patients with dental pain in New Zealand. So the study will be discussed briefly.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study of Dental Pain, #MX-6

6.1.1. Study Design

Overview and Objective

Study MX-6 was planned as a full factorial study of 48 hours in duration for the purpose of studying component contribution to analgesic effects and safety of the combination product containing acetaminophen 1000 mg and ibuprofen 300 mg in patients with dental pain.

Trial Design

Study MX-6 was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel groups 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 ingredient and placebo in patients with dental pain.

Study Population

Eligible patients were to have been adult patients undergoing dental surgery for the extraction of at least two impacted third molar teeth with post-surgical dental pain of ≥ 40 mm on a 100mm VAS scale within six hours after the completion of surgery.

Treatments

Eligible patients were planned to be randomized 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.

The planned rescue medication was oxycodone 5-10 mg PRN q4-6 hours. Patients were to have been encouraged to avoid rescue if having mild pain (<40 mm VAS) and to wait for up to 90 minutes post dose, if possible (the waiting period was changed from 90 minutes in Amendment 4 to two hours in the final version of the protocol).

Efficacy data collection

Efficacy data to be collected were to have included the measurements of pain intensity (PI) on an 100 mm visual analogue scale (VAS) at baseline, at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6 and 7 hours post dose in recovery room, prior to and two hours after each repeated dose after discharge, and before taking rescue medication; onset data based on two stopwatch recording of onset of perceptible and meaningful pain relief within first six hours post dose; rescue data in terms of time to rescue and amount of rescue (number of tablets); patient global pain rating on a 5-point categorical scale (also called Categorical Global Pain Rating, CGPR) at the end of 48-hour evaluation period or prior to use of rescue.

Study Endpoints

The planned primary efficacy endpoint was time-adjusted summation of pain intensity difference up to 48 hours, SPID48. The planned secondary efficacy endpoints included time to onset of perceptible and meaningful pain relief recorded by two-stopwatch method; time to request for rescue, percentage using rescue, and amount of rescue; percentage as responders defined in terms of PI reduction by $\geq 50\%$ from baseline (response rate), maximum PI by VAS, and time to peak PID (PI reduction by $\geq 50\%$ from baseline); Categorical Global Pain Rating (CGPR).

Safety monitoring was planned to involve assessment and recording of adverse events (AEs) at 48-hour and 30-day follow-up contacts by telephone.

Statistical Analysis Plan

Refer to the statistical review.

Protocol Amendments

There were nine versions of the protocol: the original protocol and eight protocol amendments. Major changes in each protocol amendment are summarized with the dates and number of patients enrolled under each protocol version as shown below. A noticeable change was the increase of sample size twice during the study because the results of Study MX-3 showed small effects.

Table 2 Protocol Amendments, Study MX-6

Protocol version	Date	Changes	Submitted in NDA	#patients initiated
Original protocol	7/3/12		x	0
Amendment 1	9/4/12	Addition of a new site; Clarification on exclusion criteria #18, use of rescue, and global rating.	x	0
Amendment 2	12/5/12	Change of site name; Clarification on dosing instruction;	x	0

		Reduction of strata from 4 to 2; Expansion of prohibited medication		
Amendment 3	1/16/13	Increase of study power from 80% to 90%; Increase of sample size from 220 to 275 (to 75 per active treatment and 50 on placebo)	x	0
Amendment 4	5/2/13	Clarification on prohibited medication	x	64?
Amendment 5	9/4/13	Clarification on prohibited medication; Specification of anesthetic technique; Removal of fasting requirement for collecting blood samples	x	67?
Amendment 6	4/1/14	Clarification on use of rescue in terms of avoid use if PI<40mm and wait for up to 2 hours post dose	x	23?
Amendment 7	6/16/14	Addition of a new site	x	51?
Amendment 8	7/30/14	Increase of sample size again from 275 to 352 (to 96 per active treatment and 64 on placebo); Addition of a new site	x	211?

6.1.2. Study Results

Compliance with Good Clinical Practices

Study protocol and protocol amendments, Investigator's Brochure, Patient Information Sheet and Consent Form were all approved by Independent Ethics Committee – Health and Disability Ethics Committee, Ministry of Health and Health Authority Medsafe's SCOTT Committee in New Zealand and protocol amendment 8 and informed consent by IRB at the US site. The Applicant stated that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and in conformance with the ICH GCP guidelines (1997) and regulations of the New Zealand Ministry of Health. The clinical inspection of the study site in the USA concluded of no apparent violation in data integrity or subject safety and well-being.

Financial Disclosure

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators as below, had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The clinical investigators on the list included Dr. (b) (6) and Dr. (b) (6) at the (b) (6) site, Dr. (b) (6) and Dr. (b) (6) at the (b) (6) site, Dr. (b) (6) at the (b) (6) site, and Dr. (b) (6) at the (b) (6) site.

Patient Disposition

Dropout rate was very low, only 4%. Specific reasons for early withdrawal were listed in the table below and involved only up to three cases per treatment arm for any particular reason.

Table 3 Patient Disposition, Safety Population, Study MX-6

Study MX-6 Patient Disposition, N (%)	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75	Total N=408
Prematurely discontinued	4 (3.6)	4 (3.6)	3 (2.7)	7 (9.3)	18 (4.4)
Reasons for withdrawal					
Adverse events	1 (0.9)		3 (2.7)	3 (4.0)	7 (1.7)
Lack of efficacy	1 (0.9)	2 (1.8)		2 (2.7)	5 (1.2)
Taking prohibited medication		1 (0.9)		1 (1.3)	2 (0.5)
Non-compliance (inconsistent record)	1 (0.9)	1 (0.9)			2 (0.5)
Lost to follow-up	1 (0.9)				1 (0.2)
No more pain				1 (1.3)	1 (0.2)

Source Table 13 on page 67 and Appendix 16.2.1 on pages 2-3

Protocol Violations/Deviations

Protocol deviations were not summarized and individual cases were listed in the Appendix. The information is summarized below by the reviewer based on the individual data listing excluding those described as early dropouts. About one quarter of the sample population had one or more protocol deviations. Major deviations were delayed dosing time (8% or 5-12% among treatment groups) and rescued at lower PI (7% or 5-8% among treatment groups).

Reviewer's comments:

The overall proportion and the differential proportions of delayed dosing time might have some impact on study outcomes.

Table 4 Summary of Protocol Deviations, Safety Population, Study MX-6

Study MX-6 Protocol Deviations N (%)	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75	Total N=408
N (%) with ≥ 1 Deviation	27 (24.5)	25 (22.3)	36 (32.4)	20 (26.7)	108 (26.5)
N (%) with ≥ 1 Specific Deviation					
Eligibility criteria					
Dose missing or reduced	0	0	1 (0.9)	0	1 (0.2)
Dosing time error	7 (6.4)	6 (5.4)	13 (11.7)	6 (8.0)	32 (7.8)
Pain scores by VAS missing	1 (0.9)	0	5 (4.5)	2 (2.7)	8 (2.0)
PI by VAS miss-timed	1 (0.9)	0	0	0	1 (0.2)
Global pain rating missing	4 (3.6)	4 (3.6)	3 (2.7)	0	11 (2.7)
Global pain rating miss-timed	3 (2.7)	5 (4.5)	6 (5.4)	3 (4.0)	17 (4.2)
Rescue taken at low PI	7 (6.4)	6 (5.4)	9 (8.1)	6 (8.0)	28 (6.9)
Taking restricted medication					
Lab tests missing	2 (1.8)	1 (0.9)	3 (2.7)	0	6 (1.5)
Lab sampling miss-timed					
Vital signs missing	0	2 (1.8)	0	0	2 (0.5)
Vital signs miss-timed					0
Follow-up visit delayed	5 (4.5)	5 (4.5)	4 (3.6)	4 (5.3)	18 (4.4)
Follow-up visit missing	0	0	0	1 (1.3)	1 (0.2)
Other: diary not returned	1 (0.9)	0	0	0	1 (0.2)
Other: stratification error					

Source Appendix 16.2.2

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are summarized in the table below.

Patients were young as expected for the age group undergoing third molar extractions. Male to female ratio was about 1:2. Most (80-90% overall) patients were Caucasian and the rest were Maori, Pacific Islander, Asian and other race (not specified). Treatment groups were basically balanced in demographic characteristics.

The study had three sites in New Zealand and one site involving 135/408, or 1/3 of patients in the USA.

Mean PI was in mid-fifties on 100 mm VAS scale.

Reviewer's comments

The Applicant needs to clarify which specific race was under race category of 'other.' The sample population represented the racial distribution of population in New Zealand. Comparing to the racial groups of the US population Caucasian and Asian/ Pacific Islander were well represented. Information on enrollment of African American was not given.

The relatively low baseline pain intensities might not allow adequate assessment of acute analgesic effects for even just a single dose of individual active ingredient alone in comparison to patterns observed in typical dental studies.

Table 5 Demographic and Baseline Characteristics, Study MX-6

Study MX-6 Demographic Characteristics	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75	Total N=408
Age (years)					
Mean (SD)					
Median					
Min-Max	16.1-52.5	18.0-50.4	18.1-50.2	18.0-55.4	16.1-55.4
Sex, N (%)					
Male	41 (37.3)	30 (26.8)	35 (31.5)	27 (36.0)	133 (32.6)
Female	69 (62.7)	82 (73.2)	76 (68.5)	48 (64.0)	275 (67.4)
Race, N (%)					
Caucasian	96 (87.3)	91 (81.3)	98 (88.3)	60 (80.0)	345 (84.6)
Maori	5 (4.6)	4 (3.6)	0	2 (2.7)	11 (2.7)
Asian/ Pacific Islander	1 (0.9)	1 (0.9)	0	1 (1.3)	3 (0.7)
Other	11 (10.0)	21 (18.8)	16 (14.4)	15 (20.0)	63 (15.4)
Weight (kg)					
Mean (SD)					
Median					
Min-Max	50.0-113.0	50.0-119.0	50.0-120.0	51.0-105.0	50.0-120.0
Baseline PI VAS					
Mean (SD)	56.2 (13.9)	56.1 (14.3)	55.4 (13.2)	58.4 (15.3)	56.4 (14.0)
Median					
Min-Max	40-98	40-94	40-94	40-100	40-100

Source: Table 14 on page 69, Tables 16 and 17 on page 71, and Table 22 on page 76

Efficacy Results – Primary Endpoint

The Applicant claimed that SPID48 (which was actually SPID44 based on summation of PID up to Hour 44) was analyzed using mainly last observation carried forward (LOCF) for missing data due to rescue in the first six hours and using other imputation methods to manage different types of missing data. Sensitivity analyses were conducted by the Applicant to verify the results of the primary analysis. There were many problems with data quality and data analyses. The results submitted by the Applicant could not be confirmed by the statistical reviewer, Dr. Yi Ren.

Combogesic was compared to each of the other three treatments, the placebo and the two individual active ingredients, ibuprofen and acetaminophen. However, ibuprofen and acetaminophen were not compared to placebo individually.

Reviewer's comments

The results of primary efficacy analyses could not be determined until deficiencies are adequately addressed by the Applicant. Each of the individual active ingredients ibuprofen and acetaminophen should also be compared to placebo.

Table 6 Primary Efficacy Endpoint, SPID 48, Study MX-6

Study MX-6 SPID48, 100 mm VAS	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
Mean (SE)	31.48 (1.93)	22.70 (1.91)	17.46 (1.89)	13.94 (2.27)
Median				
Lower-upper	27.71-35.26	18.96-26.43	13.75-21.17	9.50-18.38
Difference in LS Mean vs placebo (95% CI)				
p-value	<0.001			
vs Combogesic (95% CI)				
p-value		<0.001	<0.001	<0.001

Source: Table 23 on page 78

Data Quality and Integrity

Because of poor data quality and multiple errors in data analyses of primary and secondary efficacy endpoints the Applicant's results could not be confirmed (refer to the review by Dr. Yi Ren for detail).

Reviewer's comments

In addition to the major deficiencies in data quality and analyses as mentioned above, **time-specific PID data and PID curves** were missing in the NDA submission. Data and curves related to time-specific PID are necessary because effect sizes of SPID could not be standardized, reproduced, or interpreted for its clinical meaning, and could be biased against the treatment arm with more early dropouts. The findings on SPID need to be supported by clinically meaningful separation of PID curves during the treatment and evaluation period. Time-specific PID data need to be summarized in terms of mean (standard deviation, SD) including values from missing data management, 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 for the integrity of the dataset. 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.

Efficacy Results – Secondary and other relevant endpoints

The deficiencies and uncertainties about the primary analysis preclude the supportive role of secondary analyses. Nevertheless, the key secondary findings and the major deficiencies in reporting results of secondary endpoints will be discussed for providing a more complete list of deficiencies.

Single-dose onset

The Applicant presented median time to perceptible pain relief (PR) and median time to meaningful PR separately without conducting analyses of time to perceptible PR confirmed by meaningful PR within the initial dosing interval.

Reviewer's comments

Single-dose onset is defined by median time to perceptible PR confirmed by meaningful PR for NSAIDs and similar analgesics. 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.

Table 7 Onset, Study MX-6

Study MX-6 Onset	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
Onset of perceptible PR				
N (%) achieved	102 (92.7%)	94 (84.7%)	97 (86.6%)	48 (64.0%)
Median (SE) time to , minutes	19.27 (1.27)	19.77 (1.75)	23.38 (3.27)	34.22 (8.20)
Lower-Upper, minutes	16.78-21.75	16.34-23.20	16.97-29.79	18.14-50.29
Onset of meaningful PR				
N (%) achieved	94 (85.5%)	83 (74.8%)	84 (75.0%)	31 (41.3%)
Median (SE) time to , minutes	42.83 (3.81)	48.62 (6.17)	61.28 (6.17)	-
Lower-Upper, minutes	35.37-50.30	36.53-60.70	49.20-73.37	-
Time to onset based on censored data in 1st 6 hours, ITT	N=110	N=112	N=111	N=75
Median, minutes				
95% CI				

Source: Table 24 on page 79

Rescue data

The Applicant reported the number of patients and proportions taking rescue during the entire evaluation period of 48 hours. Median time to rescue was reported for the subset rescued in 48 hours.

Reviewer's comments

Single-dose duration is defined by median time to rescue and/or remedication (second dose of study medication) by the end of the first dosing interval. The key information on rescue in terms of the number and

proportion rescued in the initial dosing interval and median time to rescue and/or remedication for the entire ITT population during the first dosing interval were all missing in the NDA submission.

Table 8 Rescue Data, Study MX-6

Study MX-6 Rescue	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
# patient providing data	109	111	111	75
N (%) taking rescue in 48 hours	26 (23.9)	48 (43.2)	59 (53.2)	61 (81.3)
Time to rescue in subset rescued, hours	N=26	N=48	N=59	N=61
Median	2.48	2.14	2.38	1.57
25 th -75 th centile	1.05-9.00	1.00-9.64	1.47-5.03	1.05-2.43
Min-max (Study 6)	0.68-46.75	0.53-44.40	0.50-43.32	0.50-34.33
Amount of rescue, mg				
Mean (SD)	3.90 (9.34)	7.21 (11.55)	11.17 (15.09)	18.33 (19.20)
Median	0	0	5	10
Min-Max	0-55	0-50	0-55	0-100
N (%) taking rescue in 1 st 6 hours				
Time to rescue/remedication in 1 st dosing interval, ITT	N=110	N=112	N=111	N=75
Median, hours				
95% CI				

Source: Table 28 on page 86

Responder Analysis

Responders were defined by the Applicant as patients having PI reduction from baseline by ≥ 50 . The Applicant reported response rate in terms of proportions becoming responders and reported mean time for the responders to achieve PI reduction from baseline by $\geq 50\%$.

Reviewer's comments

These endpoints in terms of proportion of study population achieving at least 50% reduction from baseline PI and time to the event have not been widely used or accepted as key endpoints characterizing acute analgesic effects. Nevertheless, time to an event should be reported in terms of median time and based on the entire ITT population.

Table 9 Responder Analyses, Study MX-6

Study MX-6 Responder	Combogesic N=110	Ibuprofen N=112	Acetaminophen N=111	Placebo N=75
# patient providing data	109	111	111	75
N (%) with $\geq 50\%$ ↓ of baseline pain	83 (76.1)	63 (56.8)	49 (44.1)	13 (17.3)
Time to $\geq 50\%$ ↓ of baseline pain in subset of responders, hours				
Mean (SE)	12.0 (3.9)	20.0 (5.2)	24.0 (3.4)	26.0 (4.6)
Lower –Upper	4.4-19.6	9.9-30.1	17.4-30.6	16.9-35.1
Time to $\geq 50\%$ ↓ of baseline pain, ITT				
Median, hours				

95% CI				
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Source Table 26 on page 83 and Table 27 on page 84

Dose/Dose Response

Dose response was not studied in this trial. The dose studied appeared to be a mismatch to the baseline PI in this dental pain study. Ibuprofen as a single ingredient in the 200-400 mg dose range and acetaminophen alone in the 650-1000 mg dose range had been used as an active control respectively in numerous acute analgesic studies of dental pain showing relatively strong effects. The combination of the two working by different mechanisms would be expected of capable in treating more severe pain than the kind of baseline pain levels reported in the current study. The dose of the combination at the level of acetaminophen 1000 mg/ibuprofen 300 mg seems to would have been beneficial to patients with more severe acute pain with its potential use in settings aimed at reduction of use of opioids.

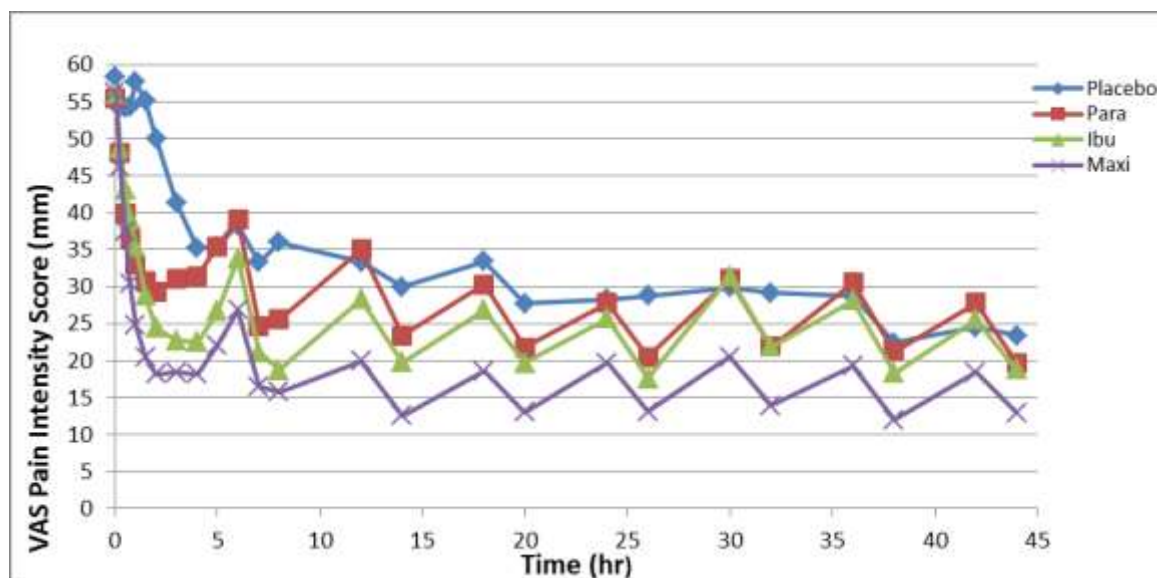
Durability of Response

Single-dose duration could not be adequately evaluated due to lack of information on median time to rescue/remedication in the first dosing interval for the ITT population. Multiple-dose duration could not be adequately evaluated because of lack of time-specific PID data and curves covering the 48-hour evaluation period.

Persistence of Effect

On the average, patients (including those on placebo) responded mainly to the initial dose as estimated from the 44-hour PI curves submitted in the original NDA. After the second dose the pattern consisted of PI curve fluctuation around two horizontal lines defined by pre-dose and 2-hour post-dose PI for each treatment. Placebo curve even crossed acetaminophen curve at multiple time points starting at Hour 5 and crossed ibuprofen curve starting at Hour 30. The patterns of PI curves suggest that the initial PI was not sufficiently high to provide a space for further improvement after the initial doses.

Figure 1 Pain Intensity Curve, 48 hours, Study MX-6



Source: Figure 16 on page 95

Additional Analyses Conducted on the Individual Trial

N/A

6.2. Study of Knee Pain Associated with Arthroscopy, #MX-6E

6.2.1. Study Design

Study MX-6E had a very similar protocol as that of Study MX-6. It was designed to study component contribution to the combination of acetaminophen 1000 mg and ibuprofen 300 mg at higher formulation strength of 500/150 given with 2-tablet dosing regimen to patients with postoperative (arthroscopy) knee pain. Unlike Study MX-6, Study MX-6E was a 24-hour study and had an open-label extension treatment with either Maxigesic or acetaminophen for up to four days following the four doses (one-day) of double-blind treatment. Other distinctive elements of the protocol for Study MX-6E included SPID24 as the primary endpoint, SPID6 as an additional secondary endpoint, and follow-up laboratory tests scheduled for Day 8-10 visit (the only multiple-dose study with follow-up laboratory tests). The major components of the protocol are summarized in the table below.

Table 10 Study Protocol, Study MX-6E

	AFT-MX-6E
Design	Multiple-center, randomized, double-blind, placebo-controlled, parallel groups, full factorial
Pain model	Postoperative (arthroscopy) knee pain
Population	Knee arthroscopy excluding ligament repair or replacement
Stratification	Baseline PI: moderate (40-69) vs severe pain (≥ 70)
Baseline PI	VAS ≥ 40 mm within 6 hours after surgery
Treatment	APAP/Ibuprofen 1000/300, APAP 1000 mg, Ibuprofen 300 mg, Placebo Q6 hours up to 24 hours (4 doses each taken as 2 tablets of APAP 500 mg, ibuprofen 150 mg, or Maxigesic 500/150) followed by Open-label extension with either combo or APAP for up to 4 days
Rescue	Oxycodone 5-10 mg PRN q4-6 hours; patients encouraged to wait for up to 90 minutes post dose
Efficacy data	- PI at 0, .25, .5, .75, 1, 1.5, 2, 3, 4, 5, & 6 hours (in hospital) - PI at 0 & 2 hours (while awake) after each dose - PI before rescue - Time to onset of PR by two stopwatches - Rescue data - Global PR rating (5-point scale) at 24 hours or before rescue
Primary endpoint	SPID24
Secondary efficacy endpoints	- Onset by time to perceptible PR - Onset by time to meaningful PR - SPID6 - Max VAS % with PI $\downarrow$ by $\geq 50\%$ in 1st 6 hours - Time to peak PID - Time to rescue % requiring rescue

	- Amount of rescue - Global pain relief rating
Follow-up	Hour 24 by phone for efficacy and safety data Day 8-10 visit for return of diary and lab tests Day 30 by phone for AE
Safety	- General AEs and - Drug-specific AEs - Clinically significant change of lab test results

Source: Protocol Amendment 7 (original protocol and other protocol amendments were not submitted)

Note: Summary of changes in protocol amendments will not be presented here (refer to pages 23-24 of the study report).

6.2.2. Study results

Patient Disposition, Protocol Deviations, and Demographic and Baseline Characteristics

Dropout rate was very low, only 3% (refer to the patient disposition table below). Close to one third of the sample population had one or more protocol deviations. Major deviation was missing one or more pain measurements in 13-19% patients (refer to the protocol deviation table below), which might have an impact on study outcomes. The study was conducted in New Zealand and had 84% Caucasian and 14% Maori in the sample population and did not mention if there were patients of African in origin (refer to the demographic/baseline characteristic table below).

Moderate baseline pain intensity was reported in an overwhelming majority or 93% of patients (92-95% among the treatment groups). Baseline PI measured by 100 mm VAS scale should be available but not reported.

Reviewer's comments:

The low baseline PI had left not much space for improvement and therefore would not allow adequate assessment of multiple-dose or even single-dose acute analgesic effects.

Table 11 Patient Disposition, Safety Population, Study MX-6E

Study MX-6E Patient Disposition, N (%)	Maxigesic N=77	Ibuprofen N=75	Acetaminophen N=73	Placebo N=75	Total N=300
Prematurely discontinued	1 (1.3)	4 (5.3)		4 (5.3)	9 (3.0)
Reasons for withdrawal					
Adverse events		2 (2.7)		2 (2.7)	4 (1.3)
Taking prohibited medication	1 (1.3)	1 (1.3)			2 (0.7)
Non-compliance (inconsistent record)				1 (1.3)	1 (0.3)
Violation of eligibility criteria				1 (1.3)	
Missing multiple doses		1 (1.3)			1 (0.3)

Source Appendix 16.2.1 on page 2

Table 12 Summary of Protocol Deviations, Safety Population, Study MX-6E

Study MX-6E Protocol Deviations N (%)	Maxigesic N=77	Ibuprofen N=75	Acetaminophen N=73	Placebo N=75	Total N=300
N (%) with ≥ 1 Deviation	23 (29.9)	22 (29.3)	24 (32.9)	24 (32.0)	93 (31.0)

N (%) with ≥ 1 Specific Deviation					
Eligibility criteria					
Dose missing or reduced					
Dosing time error	3 (3.9)	7 (9.3)	1 (1.4)	6 (8.0)	17 (5.7)
Pain scores by VAS missing	10 (13.0)	11 (14.7)	13 (17.8)	14 (18.7)	48 (16.0)
Missing ≥ 1 PI during and after	3 (3.9)	1 (1.3)	6 (8.2)	3 (4.0)	13 (4.3)
Missing ≥ 1 PI during	1 (1.3)	1 (1.3)	1 (1.4)	1 (1.3)	4 (1.3)
Missing ≥ 1 PI after	3 (3.9)	4 (5.3)	4 (5.5)	4 (5.3)	15 (5.0)
Missing pre-rescue PI	3 (3.9)	5 (6.7)	2 (2.7)	6 (8.0)	16 (5.3)
PI by VAS miss-timed					0
Global pain rating missing	1 (1.3)	3 (4.0)	0	2 (2.7)	6 (2.0)
Global pain rating miss-timed					0
Rescue taken at low PI					0
Taking restricted medication	1 (1.3)	1 (1.3)	0	0	2 (0.7)
Lab tests missing	6 (7.8)	7 (9.3)	7 (9.6)	6 (8.0)	26 (8.7)
Lab sampling miss-timed					0
Vital signs missing	5 (6.5)	1 (1.3)	0	1 (1.3)	7 (2.3)
Vital signs miss-timed					0
Follow-up visit delayed	3 (3.9)	8 (10.7)	5 (6.8)	2 (2.7)	18 (6.0)
Follow-up visit missing	1 (1.3)	0	0	0	1 (0.3)
Other: diary not returned					
Other: stratification error					

Source Appendix 16.2.2

Table 13 Demographic and Baseline Characteristics, Study MX-6E

Study MX-6E Demographic Characteristics	Maxigesic N=77	Ibuprofen N=75	Acetaminophen N=73	Placebo N=75	Total N=300
Age (years)					
Mean (SD)	45.6 (12.3)	45.1 (12.7)	47.5 (13.6)	45.6 (14.1)	45.9 (13.1)
Min-Max	17.7-73.9	18.9-75.3	17.8-73.8	16.8-73.9	16.8-75.3
Sex, N (%)					
Male	39 (50.6)	47 (62.7)	50 (68.5)	49 (65.3)	185 (61.7%)
Female	38 (49.4)	28 (37.3)	23 (31.5)	26 (34.7)	115 (38.3%)
Race, N (%)					
Caucasian	62 (80.5)	64 (85.3)	65 (89.0)	61 (81.3)	252 (84.0%)
Maori	15 (19.5)	10 (13.3)	8 (11.0)	10 (13.3)	43 (14.3%)
Asian/ Pacific Islander	0	1 (1.3)	0	0	1 (0.3%)
Other	0	0	0	4 (5.3)	4 (1.3%)
Weight (kg)					
Mean (SD)	85.9 (15.4)	88.0 (14.4)	86.9 (14.3)	86.5 (13.9)	86.8 (14.5)
Min-Max	53.4-119.4	56.4-116.5	57.0-117.0	59.0-119.7	53.4-119.7
Baseline PI cat.					
Moderate, n	71 (92.2)	71 (94.7)	69 (94.5)	69 (92.0)	280 (93.3%)
Severe, n	6 (7.8)	4 (5.3)	4 (5.5)	6 (8.0)	20 (6.7%)
Baseline PI VAS Not reported					

Source: Table 11 on page 64, Table 12 on page 65, and Table 13 on page 66

Efficacy Endpoints

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

This study had the same kind of poor data quality and problematic and non-confirmable data analyses as discovered in Study MX-6.

Primary Efficacy endpoint

The only statistically significant treatment difference in SPID24 was between Maxigesic and placebo per Applicant's analyses. The results of pairwise comparisons were not found statistically significant based on the statistical reviewer, Dr. Ren's analyses using the Applicant's dataset.

Table 14 Primary Efficacy Endpoint, SPID24, Study MX-6E

Study MX-6E Primary efficacy endpoints, SPID24	Maxigesic N=77	Ibuprofen N=75	Acetaminophen N=73	Placebo N=75
Mean (SE)	(b) (4)			
Lower-upper				
Difference vs Maxigesic				
Difference vs placebo				

Note: Data after rescue were not included by the Applicant.

Source: Table 16 on page 70

Reviewer's comments:

The single-dose PID curve shown below suggested that all treatment groups had close to maximum response to the initial dose, which was confirmed by the Applicant's responder analyses that majority of patients in each treatment group reached $\geq 50\%$ reduction of baseline pain and the group mean time to reach such response in the responder subset was around two hours for the three active treatment groups and < 1.5 hours for placebo group (refer to the secondary endpoint table below). The PID curves for ibuprofen, acetaminophen, and placebo were basically overlap and crossing from each other during the first dosing interval. The curve separation of > 5 mm between Maxigesic and placebo was noticeable only in the time interval of Hour 1-2. Small curve separation between Maxigesic and each of the two active components did not appear to suggest meaningful component contribution to analgesic effect of the drug combination.

Multiple-dose PID data and curves were not submitted. Multiple-dose PID curves were predicted to be mostly overlap and fluctuating around low PID levels based on single-dose response and the status of the curves at the end of the initial dosing interval. It would be unnecessary to request reanalysis and submission of multiple-dose PID data and curves.

The results suggest that the study failed to show single-dose effects in comparing Maxigesic to placebo and failed to show component contribution from the individual ingredients to analgesic effects of drug combination. Further discussions of secondary endpoints are considered unnecessary.

Figure 2 Single-Dose PID Curve, Study MX-6E

(b) (4)

Source: Figure 5 on page 72

Secondary Efficacy endpoints

The key secondary endpoints are summarized in the table below as a reference.

Table 15 Summary of Secondary Efficacy Endpoints, Study MX-6E

Study MX-6E Secondary efficacy endpoints	Maxigesic N=77	Ibuprofen N=75	Acetaminophen N=73	Placebo N=75	Source
Onset of pain relief (PR)					
Onset of perceptible PR: N (%) achieved					
Median (SE) time to, minutes	(b) (4)				Table 17, page 73
Lower-Upper, minutes					
Onset of meaningful PR: N (%) achieved					
Median (SE) time to, minutes					Table 17, page 73
Lower-Upper, minutes					
Time to onset, censored, 1st 6 hours, ITT	Key information missing from Study Report				
Median (95% CI), minutes					
Rescue					
N (%) taking rescue in 48 hours	(b) (4)				Table 24, page 80
Time to rescue in subset rescued, hours					Table 22, page 78
Mean (SE)					
95% CI					
Amount of rescue, mg					Table 23, page 79
Mean (SD)					
N (%) taking rescue in 1st 6 hours	Key information missing from Study Report				
Time to rescue/remedication, 1st dosing interval, ITT	Key information missing from Study Report				
Median (95% CI), hours					
Responder analyses					
# patient providing data					

N (%) with $\geq 50\%$ ↓ of baseline pain	(b) (4)				Table 20, page 77
Time to $\geq 50\%$ ↓ of baseline pain in responders, hours					Table 21, page 77
Mean (SE)					
Lower –Upper					
Time to $\geq 50\%$ ↓ of baseline pain, ITT					
Median (95% CI), hours					

6.3. Study of Dental Pain, #MX-3

6.3.1. Study Design

Study MX-3 was a relatively small study of dose response comparing Maxigesic full dose at acetaminophen/ibuprofen 1000/300 mg (Maxigesic-F), half dose at 500/150 (Maxigesic-H), and quarter dose at 250/75 (Maxigesic-Q) to placebo in patients with dental pain. Study MX-3 had an open-label extension treatment with either Maxigesic or acetaminophen for up to four days following the four doses of double-blind treatment and SPID24 as the primary endpoint similar to Study MX-6E. The major components of the protocol are summarized in the table below.

Table 16 Study Protocol, Study MX-3

Design	Multiple-center, randomized, double-blind, placebo-controlled, parallel groups, dose-response
Pain model	Postoperative dental pain
Population	Removal of 2-4 impacted third molar, one of which must have been mandibular and require bone removal
Stratification	Baseline PI: moderate (40-69) vs severe pain (≥ 70) and local vs general anesthesia
Baseline PI	VAS ≥ 40 mm (> 50 mm in the original protocol) within 6 hours after surgery
Treatment	APAP/Ibuprofen 1000/300 (Maxigesic-F), APAP/Ibuprofen 500/150 (Maxigesic-H), APAP/Ibuprofen 250/75 (Maxigesic-Q), or Placebo Q6 hours up to 24 hours (taken as 2 tablets of APAP/ ibuprofen combination at various strengths, 500/150, 250/75, or 125/37.5) Amendment 5 allowed Open-label extension with either combo or APAP for up to 4 days
Rescue	Oxycodone 5-10 mg PRN q4-6 hours; patients encouraged to wait for up to 90 minutes post dose
Efficacy data	- PI at 0, .25, .5, .75, 1, 1.5, 2, 3, 4, 5, & 6 hours (in hospital) - PI q2 hours (while awake) during Hour 8-24 - PI before rescue - Time to onset of PR by two stopwatches - Rescue data - Global pain rating (5-point scale) at 48 hours
Primary endpoint	SPID24
Secondary efficacy endpoints	- Max VAS % with PI ↓ by $\geq 50\%$ in 1st 6 hours - Time to peak PID - Onset by time to perceptible PR confirmed by meaningful PR (with no statistical analysis plan) - Time to rescue % rescued - Amount of rescue

	Global pain rating
Follow-up	Hour 24 by phone for efficacy and safety data, Day 8-10 visit for diary return and vital signs, and Day 30 by phone for AE
Safety	- General AEs and - Drug-specific AEs

Source: Protocol Amendment 3 (initial enrollment) and 5 (final version)

Note: Summary of changes in protocol amendments was not provided in the study report.

6.3.2. Study results

Patient Disposition, Protocol Deviations, and Demographic and Baseline Characteristics

Dropout rate was low (about 8%, 6-13% among the treatment groups), mainly in the categories of lack of efficacy and non-compliance in terms of inconsistent data recording. About one third of the sample population had one or more protocol deviations, most noticeable in the category of missing one or more pain measurements (20% overall, 7% in the full dose group and >20% in the other three groups), which were expected to have an impact on study outcomes. The study was also conducted in New Zealand by the same group of investigators as in Study MX-6 and MX-6E and had same (slightly worse) major problem of insufficient baseline pain intensity.

Table 17 Patient Disposition, Safety Population, Study MX-3

Study MX-3 Patient Disposition, N (%)	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49	Total N=159
Prematurely discontinued	4 (13.3)	2 (5.9)	3 (6.5)	4 (8.2)	13 (8.2)
Reasons for withdrawal					
Lack of efficacy	3 (10.0)			3 (6.1)	6 (3.8)
Non-compliance (inconsistent record)	1 (3.3)	2 (5.9)	1 (2.2)		4 (2.5)
Adverse events			1 (2.2)		1 (0.6)
Violation of eligibility criteria			1 (2.2)		1 (0.6)
Withdrawn consent				1 (2.0)	1 (0.6)

Source Appendix 16.2.1 on page 2

Table 18 Summary of Protocol Deviations, Safety Population, Study MX-3

Study MX-3 Protocol Deviations N (%)	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49	Total N=159
N (%) with ≥ 1 Deviation	5 (16.7)	14 (41.2)	20 (43.5)	15 (30.6)	54 (34.0)
N (%) with ≥ 1 Specific Deviation					
Dose missing or reduced	0	1 (2.9)	1 (2.2)	0	2 (1.3)
Dosing time error	1 (3.3)	0	3 (6.5)	0	4 (2.5)
Pain scores by VAS missing	2 (6.7)	8 (23.5)	10 (21.7)	11 (22.4)	31 (19.5)
Missing pre-rescue PI	1 (3.3)	1 (2.9)	2 (4.3)	1 (2.0)	5 (3.1)
Taking restricted medication	0	3 (8.8)	1 (2.2)	1 (2.0)	5 (3.1)
Vital signs missing	0	0	2 (4.3)	1 (2.0)	3 (1.9)
Vital signs miss-timed	0	0	0	1 (2.0)	1 (0.6)
Follow-up visit delayed	0	0	2 (4.3)	1 (2.0)	3 (1.9)
Follow-up visit missing	0	1 (2.9)	0	0	1 (0.6)
Other: stratification error			1 (2.2)		1 (0.6)

Source Appendix 16.2.2

Table 19 Demographic and Baseline Characteristics, Study MX-3

Study MX-3 Demographic Characteristics	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49	Total N=159
Age (years)					
Mean (SD)	24.5 (8.7)	22.3 (4.2)	23.8 (5.7)	24.2 (8.4)	
Min-Max	17.2 - 58.3	16.6 - 38.0	16.0 - 43.4	16.9 - 55.5	16.0-58.3
Sex, N (%)					
Male	10 (33.3%)	16 (47.1%)	22 (47.8%)	21 (42.9%)	69 (43.4%)
Female	20 (66.7%)	18 (52.9%)	24 (52.2%)	28 (57.1%)	90 (56.6%)
Race, N (%)					
Caucasian	29 (96.7)	26 (76.5)	40 (87.0)	46 (93.9)	141 (88.7)
Maori	1 (3.3)	5 (14.7)	3 (6.5)	2 (4.1)	11 (6.9)
Asian/ Pacific Islander	0	3 (8.8)	3 (6.5)	1 (2.0)	7 (4.4)
Weight (kg)					
Mean (SD)	74.7 (17.8)	75.2 (14.1)	73.2 (11.8)	74.3 (16.6)	
Min-Max	56.0-120.0	51.4-104.6	56.3-107.0	50.6-114.7	50.6 - 120.0
Baseline PI cat.					
Moderate, n	30 (100)	30 (88.2)	44 (95.7)	46 (93.9)	150 (94.3)
Severe, n	0	4 (11.8)	2 (4.3)	3 (6.1)	9 (5.7)
Baseline PI VAS					
Mean (SD)	47.6 (7.0)	53.1 (11.4)	52.1 (8.0)	51.6 (9.1)	
Min-Max	40 - 66	40 - 89	41 - 75	40 - 81	40 – 89

Source Table 9 on page 59, Table 10 on pages 59-60, Table 11 on page 61, Table 12 on pages 61-62

Primary Efficacy endpoint

Table 20 Primary Efficacy Endpoint, SPID24, Study MX-3

Study MX-3 Primary efficacy endpoints, SPID24	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49
Mean (SD)	20.12 (18.01)	20.44 (20.78)	19.25 (19.99)	6.63 (19.79)
Min, Max	(b) (4)			
Difference vs placebo				

Note: Data after rescue were not included by the Applicant.

Source: Table 16 on pages 65-66

Reviewer's comments:

Poor data quality and data analyses were probably more problematic in this study, which had a relatively small sample size and was conducted less rigorously than the other two studies. Even though the p values from the Applicant's analyses showed significant separation in SPID24 between placebo and each of the three active treatments at different dose levels, a remarkable treatment difference between placebo and any active treatment was shown only in the time interval of 0.5-2.5 hours as illustrated by the single-dose PID curves (refer to the figure below). Starting at Hour 3 placebo PID curve crossed all the curves of the active treatments, indicating treatment failures. Such rapid increase in placebo response during the second half of the first 6-hour dosing interval is very unusual in dental studies (placebo response is maintained at low level as a feature of dental pain model).

The study failed to show single-dose effects and results could not be used to support either the analgesic effects of the drug combination at any dose level or show dose response between different dose levels of the combination. Further discussions of secondary endpoints are considered unnecessary.

Figure 3 Single-Dose PID Curve, Study MX-3



Source: Figure 4 on page 66

Secondary Efficacy endpoints

The key secondary endpoints are summarized in the table below as a reference.

Table 21 Summary of Secondary Efficacy Endpoints, Study MX-3

Study MX-3 Secondary efficacy endpoints	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49	Source
Onset of pain relief (PR)					
Onset of perceptible PR: N (%) achieved					
Median (SE) time to, minutes	(b) (4)				Table 20, page 69
Lower-Upper, minutes					
Onset of meaningful PR: N (%) achieved					
Median (SE) time to, minutes					Table 20, page 69
Lower-Upper, minutes					
Time to onset, censored, 1st 6 hours, ITT	Key information missing from Study Report				
Median (95% CI), minutes					
Rescue					
N (%) taking rescue in 48 hours	(b) (4)				Table 22, page 71
Time to rescue in subset rescued, hours					Table 21, page 70
Mean (SE)					
95% CI					
Amount of rescue (doses per subject or per group?)					Table 23, page 71
Mean (SD)					
N (%) taking rescue in 1st 6 hours					Table 25, page 73
Time to rescue/remedication, 1st dosing	Key information missing from Study Report				

interval, ITT					
Median (95% CI), hours					
Responder analyses					
# patient providing data					
N (%) with $\geq 50\%$ ↓ of baseline pain	(b) (4)				Table 18, page 68
Time to $\geq 50\%$ ↓ of baseline pain in responders, hours					Table 19, page 68
Mean (SE)					
Lower –Upper					
Time to $\geq 50\%$ ↓ of baseline pain, ITT					
Median (95% CI), hours					

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

Of the three efficacy studies designed to evaluate acute analgesic effects two (Study MX-6E and MX-3) failed to show single-dose effects. Response to the initial dose has been shown to be the most robust portion of response curve capable of differentiating treatment effects of acute analgesia in many clinical trials conducted previously. Study MX-6 could not be adequately reviewed because of deficiencies in data submission, data summary, and data analysis (refer to the Review Section 6 for detail). Therefore, effectiveness of the drug combination could not be integrated.

7.1.1. Primary Endpoints

Refer to the Review Section 6.1.2

7.1.2. Secondary and Other Endpoints

Refer to the Review Section 6.1.2

7.1.3. Subpopulations

Three efficacy studies MX-6, MX-6E, and MX-3 were all initiated at the same two clinical centers in New Zealand and conducted by the same group of four investigators (Note: the other two sites in study MX-6 were added later when the sample size was increased twice during the study). Since Study MX-6E and MX-3 had usually high placebo responses, subpopulation analyses with respect to study populations in the US versus New Zealand would be considered important. The Applicant submitted subpopulation analyses on April 26, 2017 upon request. However, these analyses had the same kind of deficiencies as the analyses in the original NDA submission.

7.1.4. Dose and Dose-Response

Refer to the Review Section 6.1.2

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Refer to the Review Section 6.1.2

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Pending until deficiencies have been addressed

7.2.2. Other Relevant Benefits

Pending until deficiencies have been addressed

7.3. Integrated Assessment of Effectiveness

Analgesic efficacy of the combination product acetaminophen/ibuprofen 1000/300 could not be determined due to unresolved issues with statistical analyses and lack of key information defining single-dose characteristics including pain intensity difference (PID) data and curves and single-dose onset and duration based on analyses of the entire intent-to-treat (ITT) study population, and lack of time-specific PID data and curves characterizing multiple-dose effects to support findings on the primary endpoint, SPID48, in Study MX-6.

Listed below are the deficiencies related to efficacy analyses to be addressed by the Applicant:

- 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.

8. Review of Safety

8.1. Safety Review Approach

The safety profiles of the individual ingredients of the combination product at the proposed dose levels are known from their long marketing history in this country. Safety information from the single-dose, crossover studies are of limited value. The focus of safety review is to see if the use of combination might be associated with changes in adverse event (AE) rates in the areas of known toxicities associated with each component by examining safety data pooled across multiple-dose studies of 24-48 hours in duration.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The exposure data were neither presented accurately nor summarized adequately. The reviewer has to go over all the individual study reports to gather the information in order to construct the exposure table as below. A rough estimate of exposure to the drug combination would include exposures to 8 doses in at least 106 subjects, to 4 doses in at least 284 subjects, and to any dose in at least 536 subjects. Exposure data were not provided for Study MX-1 and exposure over the period of open-label extension were not submitted by the Applicant.

Reviewer's comments:

Exposure could not be described more accurately until the missing information is submitted.

Table 22 Exposure to Acetaminophen/Ibuprofen Combination at All Formulation Strengths

Study	APAP/Ibu x # of tablets	#dose exposed	#subjects exposed	Subject exposure distribution in multiple-dose studies							
				1 dose	2 doses	3 doses	4 doses	5 doses	6 doses	7 doses	8 doses
MX-6	325/97.5 x 3	1-8	110	1	2				1		106
MX-6E	500/150 x 2	4	77				77				
MX-3	500/150 x 2	1-4	30	3		1	26				
	500/150 x 1	3-4	34			2	32				
	500/150 x 0.5	1-4	46	1	1	1	43				
MX-1	500/150 x 2	1-8	44	?	?	?	?	?	?	?	?
MX-9	325/97.5 x 1	1	19-24?								
MX-10 (crossover)	325/97.5 x 1	1	27-28?								
	325/97.5 x 2	1									
	325/97.5 x 3	1									
MX-13a	325/97.5 x 3	1	30								
MX-13b	325/97.5 x 3	1	29-30?								
MX-14a (crossover)	325/97.5 x 3	1	26-30?								
	500/150 x 2	1									

MX-14b	325/97.5 x 3	1	26-30?	
(crossover)	500/150 x 2	1		
MX-11	500/150 x 2	1	26-28?	
MX-8	500/150 x 2	1	12	

Source: Individual study reports.

8.2.2. Relevant characteristics of the safety population:

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 ages of 75 years.

8.2.3. Adequacy of the safety database:

The duration of exposure of up to two days is considered very short for gathering useful safety information. A study population with more severe pain requiring more days of analgesic treatment would be ideal but not practical in acute pain settings.

Key safety areas with regard to data availability based on individual study reports are summarized as shown in the table below.

Table 23 Overall Safety Database

Study	Summary list of Individual AEs	Death	Serious AEs	Dropout due to AE	Follow-up lab tests	Follow-up EKG
MX-6	Yes	One fatal case from gunshot wound	No	1/7 in Combogesic group	Not scheduled	Not scheduled
MX-6E	No (only listed body systems involved)	No	7 cases: 4 on placebo & 1 on each active treatment	0/4 in Maxigesic group	Yes	Not scheduled
MX-3	Yes	No	1 on half dose	1 on quarter dose	Not scheduled	Not scheduled
MX-1	No (only listed body systems involved)	No	No	No	Not scheduled	Not scheduled
MX-9	Reported no AEs				No clinically significant abnormalities	No clinically significant abnormalities
MX-10	Reported no AEs				No discussion or summary of results	Not scheduled
MX-13a	4 AEs in Ultracet group, none in subjects taking Maxigesic	No	No	No	No discussion or summary of results	No discussion or summary of results
MX-13b	3 AEs in Ultracet group, one of which (flank pain) was also thought to be related to Maxigesic	No	No	No	No discussion or summary of results	No discussion or summary of results
MX-14a	1 case of toothache	No	No	No	No discussion or summary of results	No discussion or summary of results
MX-14b	Reported no AEs				No discussion or summary of results	No discussion or summary of results

MX-11	Reported no AEs				No discussion or summary of results	Not scheduled
MX-8	Reported no AEs				No clinically significant abnormalities	Not scheduled

Source: Individual study reports

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission had a poor quality characterized by missing and inaccurate information, inconsistency of data presentation, and lack of adequate summaries.

8.3.2. Categorization of Adverse Events

Common AEs reported by 2% of any treatment groups were summarized across studies by organ systems, symptom severity, and relationship to study drugs. There were no summary lists of individual AEs in two of the four multiple-dose study reports to serve as comparisons.

8.3.3. Routine Clinical Tests

One multiple-dose study of knee pain (MX-6E) had follow-up laboratory tests. Most single-dose studies had follow-up lab tests and/or follow-up EKG. However, no discussions or summaries of the findings were included in most of the study reports.

8.4. Safety Results

8.4.1. Deaths

One case of death was reported in Study MX-6 in a 26-year-old female who was treated with Combogesic for two days and was reported of died of gunshot wound (homicide) about two weeks after the last dose of study medication. The death was unlikely to be related to the study medication.

8.4.2. Serious Adverse Events

Eight cases of SAEs were reported including seven in Study MX-6E and one in Study MX-3. SAEs in Study MX-6E included four events reported in three placebo patients: a case of palpitation, a case of hemarthrosis, and another case of hemarthrosis followed by pulmonary embolism days later; one case of hernia repair a day after treatment with acetaminophen, one case of hemarthrosis two hours after the initial dose of ibuprofen, and one case of deep vein thrombosis leading to emergency room visit in a patient two days after the last dose of Maxigesic treatment. The case of deep vein thrombosis resolved with treatment and was thought to be due to immobility after the surgery. The SAE in Study MX-3 was a case of buccal infection reported four days after the last dose of Maxigesic treatment at quarter dose level. The event resolved with treatment and was classified as post-operative infection unlikely to be related to study medication.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Only two cases of dropouts due to AEs were reported including one case of vomiting after the second dose of Combogesic in Study MX-6 and one case of stomach cramps after the second dose of Maxigesic at quarter dose level in Study MX-3.

8.4.4. Significant Adverse Events

None.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Based on safety data pooled across four multiple-dose studies the AEs were reported in one third of the study population including 79 (30%) patients treated with a full dose of the combination, 87 (38%) patients treated with acetaminophen, 66 (29%) patients treated with ibuprofen, and 74 (37%) patients on placebo. The rates were very similar between the treatment groups. The most commonly reported AEs, accounting 2% in any of the treatment group, are summarized across studies in the table below. The individual AEs most frequently reported in patients treated with the combination drug acetaminophen/ibuprofen 1000/300 included nausea (15%), vomiting (7%), headache (5%), dizziness (3%), swelling face (2%), post-procedure hemorrhage (2%), and somnolence (2%). These AE rates were not substantially different from the ones reported in the treatment groups of individual components and the placebo groups.

Table 24 Treatment-Emergent Common (2%) AEs across Studies

	APAP/Ibu 1000/300 N=261	Acetaminophen N=231	Ibuprofen N=231	Placebo N=199	Total N=922
Total number of AEs	145	142	101	133	521
N (%) with ≥1 AE	79 (30%)	87 (38%)	66 (29%)	74 (37%)	306 (33%)
Gastrointestinal disorders					
Nausea	40 (0.15)	43 (0.19)	27 (0.12)	45 (0.23)	155 (0.17)
Vomiting	18 (0.07)	22 (0.10)	8 (0.03)	20 (0.10)	68 (0.07)
Constipation	2 (0.01)	4 (0.02)	2 (0.01)	1 (0.01)	9 (0.01)
Dyspepsia	1 (0.004)	3 (0.01)	4 (0.02)	1 (0.01)	9 (0.01)
Injury, poisoning and procedural complications					
Post Procedural Hemorrhage	6 (0.02)	1 (0.004)	3 (0.01)	4 (0.02)	14 (0.02)
Nervous system disorders					
Headache	14 (0.05)	14 (0.06)	9 (0.04)	14 (0.07)	51 (0.06)
Dizziness	7 (0.03)	9 (0.04)	9 (0.04)	9 (0.05)	34 (0.04)
Somnolence	5 (0.02)	2 (0.01)	0	1 (0.01)	8 (0.01)
Skin and subcutaneous tissue disorders					
Swelling face	6 (0.02)	10 (0.04)	9 (0.04)	6 (0.03)	31 (0.03)
Pruritus	1 (0.004)	1 (0.004)	1 (0.004)	5 (0.03)	8 (0.01)

Source: Table 7 on page 15 and Table 17 on page 26 of ISS

Of all the treatment emergent AEs about 53% were graded as mild, 40% as moderate, and 7% as severe.

Dose response was investigated in Study MX-3 with common AEs summarized in the table below. The most commonly reported AEs were nausea, vomiting, dizziness, and headache. Data from such a small study were not considered helpful in determining comparative safety profiles between different dose levels.

Table 25 Common AEs (2% in Any Active Treatment Group) in Dose Response Study

Study MX-3	Maxigesic-F N=30	Maxigesic-H N=34	Maxigesic-Q N=46	Placebo N=49
Total number of AEs	29	25	29	44
N (%) with ≥ 1 AE	15 (50%)	14 (41%)	17 (37%)	20 (41%)
Gastrointestinal disorders				
Nausea	5 (16.7)	6 (17.6)	8 (17.4)	11 (22.4)
Vomiting	2 (6.7)	6 (17.6)	5 (10.9)	11 (22.4)
Abdominal pain upper				
Injury, poisoning and procedural complications				
Alveolar osteitis	0	2 (5.9)	0	0
Nervous system disorders				
Headache	2 (6.7)	0	2 (4.3)	8 (16.3)
Dizziness	2 (6.7)	3 (8.8)	2 (4.3)	2 (4.1)

Source: Table 38 on page 85

8.4.6. Laboratory Findings

The Applicant compared the median changes in hemoglobin and mean change in liver enzymes between the two active treatments, Maxigesic and acetaminophen, that were designated as treatment options during the open-label stage and summarized AEs about liver enzyme elevation in terms of which treatments were received during double-blind and open-label stages, the number of doses received, and the time lag between the last dose of study medication and the blood sampling for lab tests. Lists of individual patients' lab results were submitted in response to the Division's request of shift tables. These kinds of information were inadequate to allow a substantial review of laboratory abnormalities.

Reviewer's comments:

Mean and/or median change in values in laboratory parameters are not considered useful information in analyses of safety data collected from relatively small studies. The key information expected from a summary shift table for any diagnostic test in this setting should include the number and proportion 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 (1.5x, 3x, 5x, 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.

8.4.7. Vital Signs

Information on vital signs was not collected in the four multiple-dose studies and findings were not reported from the single-dose studies.

8.4.8. Electrocardiograms (ECGs)

Five out of eight single-dose crossover PK studies had follow-up EKG. Some had follow-up EKG at the end of study after the subjects received different crossover treatments. One report stated that there were no clinically significant abnormalities and the findings were not discussed or summarized in the other four PK study reports.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. [Name Safety Issue]

Submission-specific safety issues such as known liver toxicity associated with acetaminophen and known renal toxicity associated with ibuprofen could not be discussed without adequate data summary on the related laboratory abnormalities.

8.6. Safety Analyses by Demographic Subgroups

Not applicable at this time.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Refer to the labeling for individual ingredients.

8.8.2. Human Reproduction and Pregnancy

Refer to the labeling for individual ingredients.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable at this time.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not for non-opioid analgesics.

8.9. Safety in the Postmarket Setting

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

8.9.1. Safety Concerns Identified Through Postmarket Experience

8.9.2. Expectations on Safety in the Postmarket Setting

8.9.3. Additional Safety Issues From Other Disciplines

8.10. Integrated Assessment of Safety

Integrated assessment of safety could not be completed at this time because of inadequate safety data summaries by the Applicant.

Listed below are the deficiencies related to safety summaries to be addressed by the Applicant:

- 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 and Other External Consultations

Not planned.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

No labeling recommendation at this review cycle.

10.2. Nonprescription Drug Labeling

11. Risk Evaluation and Mitigation Strategies (REMS)

Not required.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study MX-6, MX-6E, MX-3, and MX-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>7</u> (Investigators are listed in the table below)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 26 List of Investigators Covered by Financial Disclosure Form

(b) (6)

Table 27 Investigators Conducted Multiple Studies by Country and Study Site

(b) (6)

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/s/

CHRISTINA L FANG
12/14/2017

JOSHUA M LLOYD
12/14/2017