CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 12, 2023

To: Timothy Jiang, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Rita Joshi, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for COMBOGESIC IV (acetaminophen and ibuprofen) (b) (4) for intravenous use

NDA: NDA 215320

In response to DAAP's consult request dated April 28, 2023, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for COMBOGESIC IV (acetaminophen and ibuprofen) injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on October 3, 2023, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 6, 2023, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LATOYA S TOOMBS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 11, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215320
Product Name, Dosage Form, and Strength:	Combogesic IV (acetaminophen and ibuprofen) Injection, 1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
Applicant/Sponsor Name:	AFT Pharmaceuticals, Ltd
TTT ID #:	2023-4609-1
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA Associate Director of Nomenclature and Labeling:	Idalia E. Rychlick, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 6, 2023 for Combogesic IV. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Combogesic IV (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

[a] Hakeem, S. Label and Labeling Review for Combogesic IV (NDA 215320). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 JUL 19. TTT ID No.: 2023-4609.

2 CONCLUSION

The Applicant implemented all but one of our recommendations. We previously requested the Applicant add graduation marks to the infusion container. In response, the Applicant provided the following rationale for not adding the graduation marks[b]:

- For adult patients weighing greater than or equal to 50 kg, the recommended dosage of COMBOGESIC IV is one vial administered as a 15-minute infusion. From 2015 to 2018, the weight for adults 20 years and older in the U.S. from the 5th to 95th percentile was 49.8 to 119.6 kg for females and 61.7 to 130.3 kg for males.[c] This shows that in 95% of adults, a full vial (100 mL) would be administered.
- For adults less than 50 kg, the dosage is 15 mg/kg acetaminophen and 4.5 mg/kg ibuprofen. This dosage would require a specific volume to be administered. Graduation marks on the drug product vial, however, would not aid the administration for patients less than 50 kg because, as per the package insert, the product must be transferred to a different container.

We considered the Applicant's rationale and do not object to their plan to not include the graduation marks on the container. Thus, we have no additional recommendations at this time.

[b] Response to FDA Information Request, October 3, 2023 (NDA 215320 Combogesic IV). Auckland (NZ): AFT Pharmaceuticals; 2023 OCT 06. Available from: \\CDSESUB1\EVSPROD\nda215320\0030\m1\us\12-cover-letters\cover-letter-0030.pdf.

[c] https://www.cdc.gov/nchs/data/series/sr_03/sr03-046-508.pdf

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/s/

VALERIE S VAUGHAN
10/11/2023 03:00:48 PM

IDALIA E RYCHLIK
10/11/2023 03:09:42 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 19, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215320
Product Name, Dosage Form, and Strength:	Combogesic IV (Acetaminophen and ibuprofen) injection, 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AFT Pharmaceuticals, Ltd
FDA Received Date:	April 17, 2023
TTT ID #:	2023-4609
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Combogesic IV (Acetaminophen and ibuprofen) injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Combogesic IV prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

NDA 215320 is a 505(b)(2) NDA and the listed drug products are Ultracet, NDA 021123 and Motrin, NDA 017463.

AFT Pharmaceuticals submitted their original NDA on August 31, 2021.

DMEPA previously reviewed the proposed prescribing information (PI), container label and carton labeling under the initial NDA submission.[a] However, the application received a Complete Response (CR) letter on June 30, 2022 due to nonclinical deficiencies.

On April 17, 2023, AFT Pharmaceuticals resubmitted NDA 215320 as a Class 2 resubmission to address the deficiencies in the CR letter.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Clark, C. Label and Labeling Review for Combogesic IV (NDA 215320). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 APR 05. RCM No.: 2021-1739.

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for AFT Pharmaceuticals, Ltd.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented in the Dosage and Administration section, the dosage instructions do not specify if ideal body weight or actual body weight should be used for weight-based dosing.	To ensure that the intended dose is calculated correctly to prevent wrong dose errors.	We recommend specifying whether ideal body or actual body weight should be used to calculate the recommended dosage.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosage instructions do not specify if ideal body weight or actual body weight should be used for weight-based dosing.	To ensure that the intended dose is calculated correctly to prevent wrong dose errors.	We recommend specifying whether ideal body or actual body weight should be used to calculate the recommended dosage.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The discard statement "Discard unused portion" is not present next to the package type term "single-dose vial".	Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose.	We recommend revising the statement "Single-Dose Vial" to read as "Single-Dose Vial. Discard Unused Portion". See *Guidance for Industry: Selection of the Appropriate Package Type Terms and*

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018).[b]

5 RECOMMENDATIONS FOR AFT PHARMACEUTICALS, LTD

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The active ingredient section includes the text, "Each 100 mL single-dose vial contains: Acetaminophen 1000 mg…mannitol 3285 mg". The numbers "1000" and "3285" are presented as large numbers and appear without commas to improve readability.	Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".	We recommend revising the numbers "1000" and "3285" to include a comma, for example, to read as 1,000 instead of 1000. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.[c]
2.	The discard statement "Discard unused portion" is not present next to the package type term "single-dose vial" on the	Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose.	We recommend revising the statement "Single-Dose Vial" to read as "Single-Dose Vial. Discard Unused Portion". See *Guidance for Industry: Selection*

[b] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from https://www.fda.gov/media/117883/download.

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	principal display panel of the carton and is embedded between the osmolality and storage information where it can be missed on the container label.		*of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*.[b]
3.	The handling statement "protect from heat" appears separated from other important storage and handling instructions (e.g., Do not refrigerate or freeze).	Additional context for storage and handling could be missed and result in deteriorated drug medication errors.	Relocate the statement "protect from heat" to appear with the full storage and handling information. Additionally, consider bolding or using a different color font to highlight the handling statements. On the container label, consider deleting the duplicate package-type term and discard statement embedded between the osmolality and storage information to allow for additional space for the "protect from heat" statement.
4.	The strength statement lacks prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.).

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.	
Container Label			
1.	As currently presented, the product's proprietary name, established name, and strength are not displayed in an inverted manner on the bottom of the PDP or the side panel.	The product information should be readable and remain legible when the vial is suspended upside down during administration.	We recommend adding the proprietary name, established name, and strength of the product in an inverted manner on the bottom of the PDP or side panel so the product name and strength can be easily read when the container is hanging.
2.	The container label is missing graduation marks on the side of the label.	Having graduation marks on the infusion container can help health care practitioners identify the amount of drug that remains in the infusion container during administration.	We recommend adding graduation marks in milliliters to the infusion container. The graduation marks should be readable when the infusion container is hung upside down for administration.
3.	The terminology within the statement of dosage statement (i.e., (b) (4) [redacted] is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Recommended Dosage: see Prescribing Information."
Carton Labeling			

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals, Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The terminology within the statement of dosage (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information."
2.	As currently presented, the following (b) (4) appearing in close proximity to the net quantity contributes to label clutter. (b) (4)	Label clutter can contribute to medication errors. The (b) (4) distract from the net quantity statement.	We recommend removing the (b) (4) on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Combogesic IV that AFT Pharmaceuticals, Ltd submitted on April 17, 2023.

Table 4. Relevant Product Information for Combogesic IV	
Initial Approval Date	N/A
Active Ingredient	Acetaminophen and ibuprofen
Indication	Relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
Dose and Frequency	• Acetaminophen 1,000 mg/ibuprofen 300 mg (as sodium dihydrate) administered as 15-minute infusion every 6 hours, as necessary.
How Supplied	(b) (4)
Storage	Controlled Room Temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 5, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 215320. Our search identified one previous review[d], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C.—N/A

APPENDIX D.—N/A

APPENDIX E.—N/A

[d] Clark, C. Label and Labeling Review for Combogesic IV (NDA 215320). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 APR 05. RCM No.: 2021-1739.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Combogesic IV labels and labeling submitted by AFT Pharmaceuticals, Ltd

- Container label received on April 17, 2023.
- Carton labeling received on April 17, 2023.
- Prescribing Information received on April 17, 2023, available from \\CDSESUB1\EVSPROD\nda215320\0027\m1\us\114-labeling\draft\labeling\draft-labeling-text.pdf.

F.2 Label and Labeling Images

Container label

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 2, 2022

To: Tanya Brescia-Oddo, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Rachel Jang, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for Combogesic (Acetaminophen and Ibuprofen) injection

NDA: NDA 215320

This memo is in response to DAAP's labeling consult request dated October 7, 2021. OPDP defers comment on the proposed labeling at this time, and requests that DAAP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	April 5, 2022
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 215320
Product Name and Strength:	Combogesic IV (acetaminophen and ibuprofen) injection, 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AFT Pharmaceuticals Ltd.
FDA Received Date:	August 31, 2021 and November 24, 2021
OSE RCM #:	2021-1739
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Combogesic IV (acetaminophen and ibuprofen) injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Combogesic IV prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

While reviewing the PI, container label and carton labeling we noted that the package type term was not included. Therefore, we consulted with the Office of Pharmaceutical Quality (OPQ), to confirm the appropriate package type term and discard statement for the product. In their response, OPQ confirmed that this is a "single-dose product because it is for single patient and single occasion, and discard the remaining." Thus, we provide a recommendation in sections 5 and 6 below to include the package type term, single dose, and discard statement to the labels and labeling.

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for AFT Pharmaceuticals Ltd.

5 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Numbers greater than or equal to 1,000 are presented without the use of a comma in the Dosage and Administration section of Highlights and Full Prescribing Information.	Misinterpretation of thousands "1000" as hundreds "100" or ten-thousands "10000" may occur.	Present numbers greater than or equal to 1,000 with a comma.
Highlights of Prescribing Information			
1.	The Dosage and Administration section does not specify that the included dosage is for adult patients weighing greater than or equal to 50 kg. Furthermore, the dosage for adult patients weighing less than 50 kg has been omitted.	Dosages included in the Highlights should be accurate and reflective of all dosages that are included in the Full Prescribing Information.	Revise the dosage and administration section of the highlights to include the following, or similar, recommendations: • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5.2)] • The recommended adult dosage of COMBOGESIC IV for patients weighing greater than or equal to 50 kg is 1,000 mg of acetaminophen and 300 mg of ibuprofen administered as a 15-minute infusion every 6 hours, as necessary (2) • The recommended adult dosage of

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			COMBOGESIC IV for patients weighing less than 50 kg is 15 mg/kg acetaminophen and 4.5 mg/kg ibuprofen administered as a 15-minute infusion every 6 hours, as necessary (2) • Do not exceed a total daily dose of 4,000 mg of acetaminophen from all sources (2)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The dosage does not contain a space between the numerical dose and unit of measurement (i.e. 4000mg and 1200mg).	Missing space between the numerical dose and unit of measurement may decrease readability.[a]	Add a space between the numerical dose and unit of measurement. For example, change 4000mg and 1200mg to 4,000 mg and 1,200 mg, respectively.
2.	The section 2.1 Important Dosage and Administration Instructions contains several units of measurement to describe the total daily dose (i.e. (b) (4) (b) (4) 4000 mg acetaminophen/1200 mg ibuprofen).	The use of multiple units of measurement when describing the dose, may lead to confusion and misinterpretation.	Revise to the following: "Do not exceed the maximum total daily dose of COMBOGESIC IV (4,000 mg acetaminophen and 1,200 mg ibuprofen) in 24 hours."

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 FEB 07]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The weight-based dosages for patients weighing less than 50 kg is displayed as (b) (4). Additionally, the maximum single dose is listed as (b) (4).	Basing dosages on milliliters as opposed to milligrams may lead to overdose or underdose errors if the dose is prescribed in mL but dispensed in milligrams or vice versa.	Revise the weight-based dosing information based on (b) (4)) to weight-based dosing based on milligrams (e.g. 15 mg/kg acetaminophen and 4.5 mg/kg ibuprofen). Revise the maximum single dose statement (b) (4) to "750 mg acetaminophen and 225 mg ibuprofen".
4.	The Dosage and Administration section does not include adequate preparation instructions for doses for patients weighing less than 50 kg where less than the full contents of the vial will be administered.	To reduce the risk of confusion, this section should inform the healthcare provider of the appropriate method to prepare doses that are less than the full contents of the vial.	Add an additional bullet to section 2.4, Instructions for Intravenous Administration, stating "For doses less than 1,000 mg acetaminophen and 300 mg ibuprofen, the appropriate dose must be withdrawn from the container and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (weight-based) from an intact sealed COMBOGESIC IV container and place the measured dose in a separate empty, sterile container (e.g., glass bottle, plastic intravenous container, or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL container of COMBOGESIC IV is not

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			intended for use in patients weighing less than 50 kg. COMBOGESIC is supplied in a single-dose container and the unused portion must be discarded."
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The package type term has been omitted.	The package type term is used to identify how the medication should be safely handled and used.	Add the package type term, "Single-dose vial. Discard unused portion."
2.	The strength presentation is included (b) (4)	The proposed strength presentation does not align with United States Pharmacopeia standards to include the total strength per total volume followed in parentheses by the strength per milliliter.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate strength presentation and convey this to the Applicant. Note, revisions to Section 3 of the FPI will need to be applied to Section 16 as well.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The package type term has been omitted.	The package type term is used to identify how the medication should be safely handled and used. According to the Draft Guidance for Industry on Package Type Terms, a Single-Dose container "is designed for use with a single patient as a single injection/infusion."[b]	Add the package type term: "Single-dose vial. Discard unused portion."

[b] Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The How Supplied/Storage and Handling section includes the statement (b) (4)	This statement promotes an unsafe practice of administration of the contents if the full contents are not needed. If a patient requires a smaller dose, the solution should be transferred to a separate container and the unused portion should be discarded to reduce the risk of accidental overdose.	Revise the statement to the following or a similar statement: "For doses less than 1,000 mg acetaminophen and 300 mg ibuprofen, the appropriate dose must be withdrawn from the container and placed into a separate container prior to administration. Discard unused portion."
(b) (4)			
Container label and Carton labeling			
1.	The strength presentation appears cluttered and incorrect on the principal display panel and includes redundant information with the established name, (b) (4) (b) (4)	The proposed presentation of strength may lead to confusion and dosing errors. Furthermore, the strength does not align with United States Pharmacopeia (USP) standards. Also, the quantity per milliliter for the ibuprofen active ingredient is incorrect. It is presented as (b) (4) instead of 3 mg/mL.	We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriate strength presentation and convey this to the Applicant. We propose that the Applicant removes redundant statements (i.e., (b) (4) and revise to appear as or in similar format to: Acetaminophen and Ibuprofen injection

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
2.	The strength presentation is not prominently displayed, and is preceded by the route of administration statement.	The proposed presentation of strength may lead to confusion.	To increase the prominence of the strength move the strength presentation to directly above the route of administration statement. If OPQ concurs with the strength presentation included in recommendation 1 above, then the route of administration should be preceded by the established name and strength as follows: Acetaminophen and Ibuprofen injection 1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL) For Intravenous Infusion Only

6 RECOMMENDATIONS FOR AFT PHARMACEUTICALS LTD.

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The route of administration is included as an abbreviation, (b) (4)	Presenting the route of administration as an abbreviation may lead to misinterpretation of the correct route of administration.	Revise (b) (4) to the intended meaning, “For intravenous infusion only”.
2.	As currently presented the modifier, “IV”, in the proprietary name, may be misinterpreted as the letter “N”.	The proposed font which presents the letter “I” as slanted towards the letter “V” may lead to confusion	Revise the font to reduce the risk of misinterpretation of the modifier.

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		and misinterpretation of the modifier, "IV".	
3.	The quantity per milliliter for the ibuprofen active ingredient is incorrectly included as (b) (4).	Based on the total quantity of 300 mg and total volume of 100 mL, the quantity per milliliter should be 3 mg/mL which is consistent with the Prescribing Information.	Revise the quantity per milliliter for the ibuprofen active ingredient from (b) (4) to 3 mg/mL.
4.	We note that the proprietary name is printed in two different (b) (4) colors. (b) (4)	We typically reserve highlighting a portion of the name as a strategy to mitigate name confusion.	We recommend you consider presenting the proprietary name in one color.
5.	The package type term has been omitted. Furthermore, the side panel includes the statement (b) (4).	The package type term is used to identify how the medication should be safely handled and used. Also, the statement (b) (4) is not common discard terminology and may lead to confusion.	Add the package type term "Single-dose vial. Discard unused portion." Furthermore, remove the statement (b) (4) from the side panel.
Container Label			
1.	The net quantity, 100 mL, is in close proximity to the strength and has equal prominence.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in	Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.

Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		close proximity to the strength statement.	
Carton Labeling			
1.	(b) (4)		Remove (b) (4) (b) (4)
2.	The human-readable serial number has been omitted from the product identifier statement.	The product identifier should contain the NDC, serial number, lot and expiration date. [c] [c] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2021. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf	Add the location of the human-readable serial number to the product identifier.

[c] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2021. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Combogesic IV that AFT Pharmaceuticals Ltd. submitted on November 24, 2021.

Table 4. Relevant Product Information for Combogesic IV	
Initial Approval Date	N/A
Active Ingredient	Acetaminophen and ibuprofen
Indication	relief of mild to moderate pain and for the management of moderate to severe pain as an adjunct to opioid analgesics, where an intravenous route of administration is considered clinically necessary
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)
Dose and Frequency	• acetaminophen 1,000 mg/ibuprofen 300 mg (as sodium dihydrate) administered as 15-minute infusion every 6 hours, as necessary.
How Supplied	(b) (4) [redacted]
Storage	Controlled Room Temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 26, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, acetaminophen and ibuprofen. Our search did not identify any previous reviews.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Combogesic IV labels and labeling submitted by AFT Pharmaceuticals Ltd.

- Container label(s) received on August 31, 2021
- Carton labeling received on August 31, 2021
- Prescribing Information and Medication Guide (Image not shown) received on August 31, 2021, available from \\CDSESUB1\evsprod\nda215320\0000\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx

F.2 Label and Labeling Images

Container label(s)

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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