# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209471Orig1s000

# OTHER REVIEW(S)

# 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: | January 18, 2022 |
| Requesting Office or Division: | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| Application Type and Number: | NDA 209471 |
| Product Name and Strength: | Combogesic (acetaminophen and ibuprofen) tablet, 325 mg/97.5 mg |
| Applicant/Sponsor Name: | AFT Pharmaceuticals |
| OSE RCM #: | 2018-1703-3 |
| DMEPA 1 Safety Evaluator: | Cameron Clark, PharmD |
| DMEPA 1 Team Leader: | Valerie S. Vaughan, PharmD |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on January 12, 2022 for Combogesic. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label for Combogesic (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

The Applicant implemented our recommendation and we have no additional recommendations at this time.

[a] Clark, C. Label and Labeling Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 JAN 10. RCM No.: 2018-1703-2.



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CAMERON D CLARK
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VALERIE S VAUGHAN
01/18/2022 10:02:32 AM

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

# MEMORANDUM TO FILE

| | |
|---|---|
| **Date of Consult Request**: | August 17, 2021 |
| **From:** | Division of Pediatrics and Maternal Health (DPMH)<br>Kerri-Ann Jennings, MS, BSN, RN<br>Senior Regulatory Project Manager |
| **To:** | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| **NDA Number**: | NDA 209471 |
| **Drug**: | acetaminophen/ibuprofen (Combogesic) |
| **Applicant**: | AFT Pharmaceuticals, Inc. |
| **Indication**: | For the short-term management of mild to moderate acute pain |

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) submitted a consult request to the Division of Pediatrics and Maternal Health (DPMH) on August 17, 2021, requesting the review of the Pregnancy and Lactation Labeling Rule (PLLR) labeling for the above referenced NDA.

DPMH participated in applicable internal team meetings from October 22, 2021 through December 14, 2021 to discuss the application. PLLR recommendations were proposed for the labeling during an internal meeting on December 9, 2021.

DPMH- Maternal Health has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Christos Mastroyannis, MD
DPMH Maternal Health Team Leader- Tamara Johnson, MD, MS
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

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KERRI-ANN JENNINGS
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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: | January 10, 2022 |
| Requesting Office or Division: | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| Application Type and Number: | NDA 209471 |
| Product Name and Strength: | Combogesic (acetaminophen and ibuprofen) tablet, 325 mg/97.5 mg |
| Applicant/Sponsor Name: | AFT Pharmaceuticals |
| OSE RCM #: | 2018-1703-2 |
| DMEPA 1 Safety Evaluator: | Cameron Clark, PharmD |
| DMEPA 1 Associate Director for Nomenclature and Labeling: | Mishale Mistry, PharmD, MPH |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on December 14, 2021 for Combogesic. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label for Combogesic (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

## 2 CONCLUSION

The Applicant implemented all of our recommendations. However, we have identified an additional issue of concern regarding the use of two different colors to display the proprietary name. We provide a recommendation in section 3 below.

[a] Clark, C. Label and Labeling Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 27. RCM No.: 2018-1703-1.

## 3 RECOMMENDATION FOR AFT PHARMACEUTICALS

(b) (4)

We typically reserve highlighting a portion of the name as a strategy to mitigate name confusion. Therefore, we recommend you consider presenting the proprietary name in one color.



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CAMERON D CLARK
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MISHALE P MISTRY
01/11/2022 03:11:26 PM

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

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

# Memorandum

**Date:** December 22, 2021

**To:** Christina Fang, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Sandy Truong, 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) tablets, for oral use

**NDA**: NDA 209471

---

In response to DAAP's consult request dated August 17, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for the original NDA/BLA submission for COMBOGESIC (acetaminophen and ibuprofen) tablets, for oral use.

**Labeling**: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on December 17, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI/IFU were sent under separate cover on December 21, 2021.

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 14, 2021, 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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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | December 21, 2021 |
| To: | Sandy Truong, PharmD<br>Regulatory Project Manager<br>**Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Shawna Hutchins, MPH, BSN, RN<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>LaToya (Shenee) Tombs, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Medication Guide (MG) |
| Drug Name (established name): | COMBOGESIC (acetaminophen and ibuprofen) |
| Dosage Form and Route: | Tablets, for oral use |
| Application Type/Number: | NDA 209471 |
| Applicant: | AFT Pharmaceuticals LTD. |

## 1 INTRODUCTION

On July 27, 2021, AFT Pharmaceuticals LTD., re-submitted for the Agency's review an original New Drug Application (NDA-209471) for COMBOGESIC (acetaminophen and ibuprofen), tablets, for oral use, for the proposed indication of use for the short-term management of mild-to-moderate acute pain.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on December 3, 2021 and August 17, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for COMBOGESIC (acetaminophen and ibuprofen), tablets, for oral use.

## 2 MATERIAL REVIEWED

- Draft COMBOGESIC (acetaminophen and ibuprofen) MG received on July 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 17, 2021.
- Draft COMBOGESIC (acetaminophen and ibuprofen) Prescribing Information (PI) received on July 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 17, 2021.
- Approved DUEXIS (ibuprofen and famotidine) reference labeling dated April 28, 2021.
- NSAID Template dated June 2015.

## 3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHAWNA L HUTCHINS
12/21/2021 08:35:13 AM

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12/21/2021 10:20:36 AM

LASHAWN M GRIFFITHS
12/21/2021 10:53:00 AM

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: | October 27, 2021 |
| Requesting Office or Division: | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| Application Type and Number: | NDA 209471 |
| Product Name and Strength: | Combogesic (acetaminophen and ibuprofen) tablet, 325 mg/97.5 mg |
| Product Type: | Multi-Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | AFT Pharmaceuticals |
| FDA Received Date: | July 27, 2021 |
| OSE RCM #: | 2018-1703-1 |
| 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 (acetaminophen and ibuprofen) tablet, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Combogesic prescribing information (PI) and container label for areas of vulnerability that may lead to medication errors.

## 1.1 REGULATORY HISTORY

NDA 209471 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 March 1, 2017. On December 22, 2017, a Complete Response (CR) Letter was issued for NDA 209471 due to clinical, statistical, nonclinical, drug product and facility inspection deficiencies.[a] On August 6, 2018, AFT Pharmaceuticals resubmitted NDA 209471 as a Class 2 resubmission to address the deficiencies outlined in the CR Letter. However, on August 27, 2018, the resubmission was deemed incomplete and an Acknowledgement of Incomplete Response Letter was issued to AFT Pharmaceuticals.[b] On May 7, 2020 AFT Pharmaceuticals submitted their complete response to the deficiencies included in the CR letter and Acknowledge Incomplete Response letter as a Class 2 resubmission. However, on November 6, 2020, NDA 209471 was issued a second CR letter due to a facility inspection deficiency.[c] On July 27, 2021, AFT Pharmaceuticals resubmitted NDA 209471 as a Class 2 resubmission to address the facility inspection deficiency. In their cover letter, AFT Pharmaceuticals noted that in order to address the facility inspection deficiency they "replaced their previous formulation of Combogesic tablets manufactured by (b) (4) with a reformulated Combogesic tablet manufactured by Mayne Pharma Inc."[d]

(b) (4)

However, due to the change in manufacturing facility/formulation, AFT pharmaceuticals has changed their packaging to a bottle containing 250 tablets per bottle.

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[a] Meyer, A. Complete Response for Combogesic. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2017 DEC 22. NDA 209471.

[b] Meyer, A. Acknowledge Incomplete Response for Combogesic. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 AUG 27. NDA 209471.

[c] Meyer, A. Complete Response for Combogesic. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2020 NOV 06. NDA 209471.

[d] Cover Letter for Resubmission for Combogesic (NDA 209471). Auckland (New Zealand): AFT Pharmaceuticals Ltd; 2021 JUL 27. Available from: \\CDSESUB1\evsprod\nda209471\0036\m1\us\12-cover-letters\cover-letter-0036.pdf

## 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 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information and container label 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.

## 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 |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling | | | |
| 1. | The How Supplied/Storage and Handling section includes (b) (4) [redacted] . | (b) (4) [redacted] | (b) (4) [redacted] For example, |

<table>
<tr><td colspan="4">Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)</td></tr>
<tr><td></td><td>IDENTIFIED ISSUE</td><td>RATIONALE FOR CONCERN</td><td>RECOMMENDATION</td></tr>
<tr><td></td><td>(b) (4)</td><td>(b) (4)</td><td>revise the table to the following:<table><tr><td>NDC 72260-325-01</td><td>1 bottle containing 250 tablets</td></tr></table></td></tr>
<tr><td colspan="4">Medication Guide</td></tr>
<tr><td>1.</td><td>As currently presented, the Medication Guide only includes reference to the nonsteroidal anti-inflammatory drug (NSAID) component of the drug product.</td><td>Only referencing the NSAID component in the Medication Guide may lead to confusion as patients may misinterpret that Combogesic only contains the NSAID active ingredient, ibuprofen, as opposed to both ibuprofen and acetaminophen.</td><td>To reduce the risk of confusion and misinterpretation that this drug product only contains an NSAID, we recommend that the Medication Guide is revised to include information pertinent to the drug product as a whole (i.e. Combogesic (acetaminophen and ibuprofen)).</td></tr>
</table>

## 5 RECOMMENDATIONS FOR AFT PHARMACEUTICALS

| Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Label(s) | | | |
| 1. | As currently presented, the statement “KEEP OUT OF REACH OF CHILDREN” is prominently displayed at the top of the Principal Display Panel (PDP) of the container label. | The prominence of this statement may take user’s attention away from more important information on the PDP such as the proprietary name, established name and strength. | Relocate the statement “KEEP OUT OF REACH OF CHILDREN” to the side panel of the container label . |

| Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 2. | As currently presented, the side panel of the container label includes the statements (b) (4) and "Recommended Dosage". | Inclusion of both the (b) (4) and "Recommended Dosage" statement is redundant. Furthermore, the (b) (4) statement is inconsistent with the Prescribing Information. | To reduce redundancy and ensure consistency with the PI, retain the statement, "Recommended Dosage", and remove the statement, (b) (4), from the side panel of the container label. |

## APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Combogesic that AFT Pharmaceuticals submitted on July 27, 2021.

| Table 4. Relevant Product Information for Combogesic | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | Acetaminophen and ibuprofen |
| Indication | Short term management of mild to moderate acute pain |
| Route of Administration | oral |
| Dosage Form | Tablet |
| Strength | 325 mg/97.5 mg |
| Dose and Frequency | 3 tablets by mouth every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day |
| How Supplied | bottles containing 250 tablets |
| Storage | Store at (b) (4) excursions permitted to 15 – 30°C (59 - 86°F). |
| Container Closure | Bottle |

### APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 24, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, acetaminophen and ibuprofen. Our search identified four previous reviews[e,f,g,h], 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

[e] Shah, M. Label and Labeling Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 07. RCM No.: 2017-417.

[f] Jones, G. Label and Labeling Review for Advil Dual Action with Acetaminophen (NDA 211733). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 15. RCM No.: 2019-331.

[g] Jones, G. Label and Labeling Review Memo for Advil Dual Action with Acetaminophen (NDA 211733). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 27. RCM No.: 2019-331-1.

[h] Johnson, C. Label and Labeling Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 19. RCM No.: 2018-1703.

## 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,[i] along with postmarket medication error data, we reviewed the following Combogesic labels and labeling submitted by AFT Pharmaceuticals.

- Container label(s) received on July 27, 2021
- Prescribing Information (Image not shown) received on July 27, 2021, available from \\CDSESUB1\evsprod\nda209471\0036\m1\us\114-labeling\draft\labeling\spl\draft-labeling-text.docx

### F.2 Label and Labeling Images

(b) (4)

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

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CAMERON D CLARK
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VALERIE S VAUGHAN
10/27/2021 08:57:53 AM

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: 10/4/2021

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 209471

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the site listed below. The rationale for this decision is noted below.

## Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in October 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NON-RESPONSIVE NON-RESPONSIVE

OSIS inspected the analytical site in NON-RESPONSIVE, which falls within the surveillance interval. The inspection was conducted, under the following submission: NON-RESPONSIVE

The final classification for both inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Site

| Facility Type | Facility Name | Facility Address |
|---|---|---|
| Clinical | International Pharmaceutical Research Center (IPRC) | 1 Queen Rania Street, Sport City Circle, Amman, Jordan |
| | | (b) (4) |

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JAMES J LUMALCURI
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**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

# MEMORANDUM TO FILE

| | |
|---|---|
| **Date of Consult Request**: | June 18, 2020 |
| **From:** | Division of Pediatric and Maternal Health (DPMH)<br>Kerri-Ann Jennings, MS, BSN, RN<br>Senior Regulatory Project Manager |
| **To:** | Division of Anesthesiology, Addiction Medicine, and Pain (DAAP) |
| **NDA Number**: | NDA 209471 |
| **Drug**: | Combogesic (acetaminophen/ibuprofen) |
| **Applicant**: | AFT Pharmaceuticals LTD |
| **Indication**: | Treatment for the short-term management of mild to moderate acute pain |

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on June 18, 2020, requesting assistance in reviewing the labeling for compliance with PLLR format and provide recommendations regarding the proposed language, for applicable sections, for the above referenced NDA.

DPMH completed an initial review of NDA 209471 on November 28, 2017. During the initial review cycle, DAAP decided that the application would receive a Complete Response (CR) action. This is the second review cycle for NDA 209471. DPMH participated in applicable internal team meetings from July 6, 2020 through September 14, 2020 to discuss the application. On July 30, 2020, DPMH was notified that labeling discussions will not take place during this review cycle.

DPMH has no further comments at this time, thus, this memorandum will close out the consult request. If labeling discussions resume upon resubmission of the NDA, DPMH may be re-consulted.

DPMH Maternal Health MO Reviewer- Christos Mastroyannis, MD
DPMH Maternal Health Team Leader- Tamara Johnson, MD, MS
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

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KERRI-ANN JENNINGS
10/15/2020 11:02:43 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

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: | August 19, 2020 |
| Requesting Office or Division: | Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) |
| Application Type and Number: | NDA 209471 |
| Product Name and Strength: | Combogesic (acetaminophen and ibuprofen) tablet, 325 mg/97.5 mg |
| Product Type: | Multi-Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | AFT Pharmaceuticals |
| FDA Received Date: | May 7, 2020 |
| OSE RCM #: | 2018-1703 |
| DMEPA Safety Evaluator: | Cameron Johnson, PharmD |
| DMEPA Team Leader: | Otto L. Townsend, PharmD |

## 1 REASON FOR REVIEW

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

## 2 REGULATORY HISTORY

AFT Pharmaceuticals submitted their original NDA on March 1, 2017. On, December 22, 2017 a Complete Response (CR) Letter was issued for NDA 209471 due to clinical, statistical, nonclinical, drug product and facility inspection deficiencies. On August 6, 2018, AFT Pharmaceuticals resubmitted NDA 209471 to address the deficiencies outlined in the CR Letter. However, on August 27, 2018, the resubmission was deemed incomplete and an Acknowledgement of Incomplete Response Letter was issued to AFT Pharmaceuticals. On May 7, 2020 AFT Pharmaceuticals submitted their complete response to the deficiencies included in the CR letter and Acknowledge Incomplete Response letter as a Class 2 resubmission.

## 3 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

## 4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), container ([redacted] (b) (4) label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

| Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) | | | |
|---|---|---|---|
| | **IDENTIFIED ISSUE** | **RATIONALE FOR CONCERN** | **RECOMMENDATION** |
| **Carton Labeling** | | | |
| 1. | The carton labeling contains a graphic design that states (b) (4) on the principal display panel (PDP). | The (b) (4) graphic competes in prominence with the proprietary name and other more important information. In addition, the statement appears promotional. | We defer to the Office of Prescription Drug Promotion (OPDP) to determine the appropriateness of the statement from a promotional perspective. |
| **Full Prescribing Information – Section 16 How Supplied/Storage and Handling** | | | |
| 1. | The How Supplied/Storage and Handling section includes the quantity of tablets (b) (4) | (b) (4) is an ambiguous description of the quantity of tablets (b) (4) and may lead to confusion. | (b) (4) |

| Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | **IDENTIFIED ISSUE** | **RATIONALE FOR CONCERN** | **RECOMMENDATION** |
| **Container ( (b) (4) Label and Carton Labeling** | | | |
| 1. | It is unclear if the "barcode space" on the container label or the "Space for BARCODE" on the carton labeling are intended to be linear barcodes. | The drug linear barcode is often used as an additional verification; therefore, it is an important safety feature that should be part of the label whenever possible. | Revise the container label and carton labeling to include the graphical representation of the linear barcode. Furthermore, ensure that the linear barcode is surrounded by sufficient white space to allow scanners to correctly read the linear barcode in accordance with 21 CFR 201.25(c)(i). |

| Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | **IDENTIFIED ISSUE** | **RATIONALE FOR CONCERN** | **RECOMMENDATION** |
| 2. | As currently presented, the format for the expiration date is not defined. | To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. | FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. |
| **Container ([(b) (4)] Label** | | | |
| 1. | The dosage form is not included on [(b) (4)] . | The dosage form, tablet, should be included either on the same line as the established name or directly below the established name. | Add the dosage form, tablet, to each i[(b) (4)] . |
| 2. | The [(b) (4)] label does not contain the "Rx Only" statement. | The "Rx only" statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. | Add the "Rx Only" statement to [(b) (4)] label. |

| Table 3. Identified Issues and Recommendations for AFT Pharmaceuticals (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Carton Labeling | | | |
| 1. | The carton labeling includes the following statement: (b) (4) | This statement is not consistent with the Prescribing Information. | To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information for full dosage information." |
| 2. | The carton labeling does not include product identifiers. | In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[a] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. | We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. |

## 5 CONCLUSION

Our evaluation of the proposed Combogesic PI, container ( (b) (4) label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the

[a] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Division convey Table 3 in its entirety to AFT Pharmaceuticals so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Combogesic that AFT Pharmaceuticals submitted on May 7, 2020.

| Table 4. Relevant Product Information for Combogesic | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | Acetaminophen and ibuprofen |
| Indication | Short term management of mild to moderate acute pain |
| Route of Administration | oral |
| Dosage Form | tablet |
| Strength | 325 mg acetaminophen and 97.5 mg ibuprofen |
| Dose and Frequency | 3 tablets every 6 hours as needed for pain relief; up to a maximum of 12 tablets per day |
| How Supplied | (b) (4) |
| Storage | Store at (b) (4) excursions permitted to 15 – 30°C (59 - 86°F) |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 13, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Combogesic and 209471. Our search identified one previous review[b], 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

[b] Shah, M. Label and Labeling Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 07. RCM No.: 2017-417.

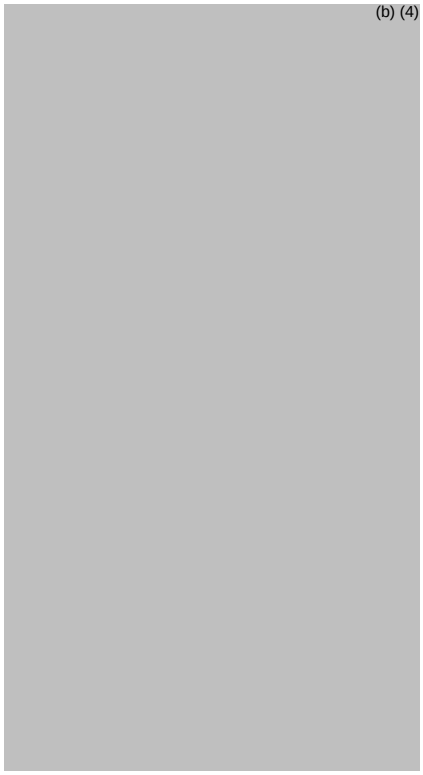
## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Combogesic labels and labeling submitted by AFT Pharmaceuticals received on May 7, 2020.

- Container ( (b) (4) label
- Carton labeling
- Prescribing Information (Image not shown) but can be accessed in EDR via the following link:
    - o \\cdsesub1\evsprod\nda209471\0017\m1\us\114-labeling\draft\labeling\spl\draft-labeling-text.docx

### F.2 Label and Labeling Images




Carton labeling

[c] 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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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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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:** April 10, 2018

**To:** Allison Meyer, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Lisa Basham, Associate Director for Labeling, (DAAAP)

**From:** L. Shenee 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) tablets

**NDA/BLA:** NDA 209471

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This memo is in response to DAAAP's labeling consult request dated April 20, 2017. Reference is made to a Complete Response letter that was issued on December 22, 2017. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DAAAP 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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/s/
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LATOYA S TOOMBS
04/10/2018

**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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# Division of Pediatric and Maternal Health Review

**Date:** November 27, 2017 **Date consulted:** June 26, 2017

**From:** Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

**Through:** Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

**To:** The Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

**NDA:** 209471

**Drug:** COMBOGESIC (acetaminophen 325 mg/ibuprofen 97.5 mg) tablets

**Applicant:** AFT Pharmaceuticals Limited

**Subject:** Pregnancy and Lactation Labeling

**Proposed Indication:** for the short-term management of mild to moderate acute pain

**Materials Reviewed:**

- June 26, 2017, DPMH consult request for NDA 209471, DARRTS Reference ID 4116276
- February 28, 2017, Applicant's submission for NDA 209471 for Combogesic (acetaminophen 325mg/ibuprofen 97.5 mg) tablets
- February 10, 2010, DPMH review of Ofirmev (IV acetaminophen) NDA 22450, Leyla Sahin, MD, DARRTS Reference ID 2740802

- February 9, 2015, DPMH review for IV Acetaminophen NDA 206610, Leyla Sahin, MD., DARRTS Reference ID 3699918
- March 13, 2015, DPMH Non-steroidal anti-inflammatory drugs (NSAID) labeling template of Pregnancy and Lactation Labeling Rule Conversion. Melissa Tassinari, Ph.D, DABT
- October 6, 2015, DPMH review for Caldor (ibuprofen) injection NDA 22348, Miriam Dinatale, D.O., DARRTS Reference ID 3829752
- April 7, 2016, DPMH review for acetaminophen, TSI 1355, Tamara Johnson, M.D., MS., DARRTS Reference ID 4081813
- January 18, 2017, DPMH review for Ofirmev NDA 22450, Tamara Johnson, M.D., MS., DARRTS Reference ID 4043682
- June 23, 2017, DPMH review of Indomethacin NDA 18858, Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID 4116092
- July 7, 2017, DPMH review of multiple NSAID products for NDAs 18147, 22396, 18841, 20776, 20998, 20607, 74802, Christos Mastroyannis, M.D., DARRTS Reference ID 4121882

**Consult Question:** This submission contains the PLLR label. Please review the PLLR.

## INTRODUCTION

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of COMBOGESIC (acetaminophen 325 mg/ibuprofen 97.5 mg) tablets labeling.

## REGULATORY HISTORY

On February 28, 2017, AFT Pharmaceuticals Ltd submitted NDA 209471 for COMBOGESIC (acetaminophen 325 mg/ibuprofen 97.5 mg) tablets. This NDA is a 505(b)(2) application relying on the safety and efficacy of two Reference Listed Drugs, Ultracet (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg), NDA 21123, and IBU (Ibuprofen 800 mg), ANDA 75682.

- Ultracet (acetaminophen 325 mg/tramadol hydrochloride 37.5 mg), NDA 21123, was originally approved on August 15, 2001, and is currently approved for the short-term management of acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
- IBU (Ibuprofen 800 mg), ANDA 75682, was originally approved on November 14, 2001, for relief of mild to moderate pain and the treatment of primary dysmenorrhea.

## BACKGROUND

Drug Characteristics

*COMBOGESIC*

COMBOGENIC is a combination of acetaminophen which is an analgesic and antipyretic, and ibuprofen, which is a non-steroidal anti-inflammatory drug (NSAID).

*Ibuprofen*
Ibuprofen's mechanism of action is not completely understood, but it is thought to be related to prostaglandin synthetase inhibition. Ibuprofen possesses anti-inflammatory, analgesic, and antipyretic activity. Ibuprofen has a molecular weight of 206.28 Daltons, a half-life of 2.22 hours and is >99% protein bound.[1]

*Acetaminophen*
Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent, which has a molecular weight of 151.16 Daltons, a half-life of approximately 2 to 3 hours in adults and is 20% protein bound.[2]

Current State of the Labeling
The current approved labeling for both Reference Listed Drugs (RLDs), IBU (Ibuprofen 800 mg) tablets and ULTRACET (tramadol/acetaminophen) tablets are not in the PLR or PLLR labeling formats. There is no boxed warning in either label on embryofetotoxicity, nor a contraindication for pregnancy or lactation. Additionally, there are no human data related to pregnancy or lactation in either labeling; however, there is non-clinical animal data section that is described in detail below. There are no known drug-drug interactions with hormonal contraception or existing pregnancy testing/contraception recommendations.

**REVIEW**
***PREGNANCY***

Nonclinical Experience
*Ibuprofen*
No clear developmental effects were observed in animal reproduction study in ibuprofen at doses 0.4 times the maximum recommended human dose in the rabbit and 0.5 times the maximum recommended human dose (MRHD) in rats when dosed throughout gestation. In contrast, an increase in membranous ventricular septal defects was reported in rats treated on gestational days 9 and 10 at doses that were 0.8 times the MRHD.

*Acetaminophen*
Treatment of pregnant rats with acetaminophen in equal doses to the maximum human daily dose showed evidence of fetotoxicity and increases in bone variations in fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice and rats treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproductive capacity were reported. In mice, a reduction in number of litters of the parental mating pair was observed as well as retarded growth, abnormal sperm in their offspring and reduced birth weight in the next generation.

The reader is referred to the full Pharmacology/Toxicology review by Carlic Huhnh, Ph.D., DARRTS.

[1] October 6, 2015, DPMH review for Caldor (ibuprofen) injection NDA 22348, Miriam Dinatale, D.O., DARRTS Reference ID 3829752
[2] NDA 209471. Applicant's submission.

Review of Literature
The applicant did not provide a review of published literature.

*Reviewer comment: DPMH notes that the division is taking a Complete Response action on this application and recommends that when the applicant responds to the Complete Response they provide a review of all available published literature regarding acetaminophen and ibuprofen use in pregnant and lactating women and the effects of acetaminophen and ibuprofen on male and female fertility (include search parameters and a copy of each reference publication).*[3]

DPMH has conducted multiple reviews on ibuprofen and acetaminophen containing products with regard to pregnancy exposure. The results of those reviews are summarized below. In addition, DPMH performed a search of published literature using Embase and PubMed using the following search parameters, "ibuprofen and fetal malformations," "ibuprofen and spontaneous abortion and miscarriage," "ibuprofen and embryofetotoxicity," "acetaminophen and fetal malformations," "acetaminophen and spontaneous abortion and miscarriage," "acetaminophen and embryofetotoxicity." The relevant results of this search are summarized below.

*Ibuprofen*
Placental Transfer
According to Micromedex, ibuprofen crosses the placenta.[4] No further information is available.

Spontaneous abortion (SAB)
In a Drug Safety Communication released on January 9, 2015, FDA reviewed the risk of spontaneous abortion (SAB) and NSAID use. FDA noted in that review that these studies all have limitations in study design and that there was too much conflicting information to reach a conclusion.[5]

Patent Ductus Arteriosus (PDA)
Patent Ductus Arteriosus (PDA) is a congenital heart defect present at birth where abnormal blood flow occurs between two of the major arteries connected to the heart (aorta and pulmonary arteries) and is more common in premature infants. It is documented through published literature that the use of NSAIDS, including ibuprofen during the third trimester increases the risk of premature closure of the fetal ductus arteriosus. The NSAID template developed by DAAAP with the assistance of DPMH contains language regarding the risk of premature closure of fetal ductus arteriosus in women exposed to NSAIDs during the third trimester. DPMH

[3] Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).
[4] Ibuprofen. Truven Health Analytics. Micromedex Solutions. http://www.micromedexsolutions.com/micromedex2/librarian/CS/784DE5/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/BA40A2/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Ibuprofen&fromInterSaltBase=true&false=null&false=null&=null#close. Accessed 13 November 2017.
[5] FDA Drug Safety Communication: FDA has reviewed the possible risks of pain medicine use during pregnancy. January 9, 2015.

agrees with the continuation of this language in this labeling based on available published literature regarding NSAID use and the risk of premature closure of fetal ductus arteriosus.[6,7]

Oligohydramnios

DPMH recently added the risk of oligohydramnios starting in the second trimester when exposed to NSAIDS to labeling based on reviews dated June 23, 2017, and July 7, 2017, which included an extensive literature review related to multiple NSAID products.[7,8] Oligohydramnios occurs in 3% to 5% of pregnancies in the United States and 0.4% to 11% of all pregnancies worldwide and it occurs when there is not enough amniotic fluid.[9,10,11] In a case report by Kaplan et al (1994), oligohydramnios and renal failure were reported after the pregnant patient received two days of 200 mg/day indomethacin followed by 2400 mg of ibuprofen daily for 4 weeks. Twins were delivered at 30 weeks by cesarean section with respiratory distress, renal failure and hypothyroidism. One of the twins died 3 week after birth from severe respiratory failure. No further information is available.[12]

In a retrospective observational study published by Jackson, et al. (2014), pregnant patients prescribed ibuprofen for tocolysis before 32 weeks' gestation from January 2011 to September 2013 were reviewed for evidence of oligohydramnios and premature ductus closure. Approximately 84 pregnant women were evaluated for oligohydramnios and 94 fetuses were evaluated for tricuspid regurgitation. The results showed that 8.3% of pregnant patients developed oligohydramnios, 1.1% of fetuses developed tricuspid regurgitation and 9.6% of fetuses developed ductus arteriosus. The authors concluded that ibuprofen had minimal effects on amniotic fluid level or fetal cardiac function. [13]

*Reviewer comment:*
*Although Jackson, et al. concluded that the ibuprofen had minimal effects on amniotic fluid level or fetal cardiac function, the available study details were not available in the publication making the results difficult to analyze. In addition, DPMH disagrees with the authors' conclusions because they appear to support the risks that have been previously identified.*

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[6] March 13, 2015, DPMH Non-steroidal anti-inflammatory drugs (NSAID) labeling template of Pregnancy and Lactation Labeling Rule Conversion. Melissa Tassinari, Ph.D, DABT.
[7] June 23, 2017, DPMH review of Indomethacin NDA 18858, Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID 4116092
[8] July 7, 2017, DPMH review of multiple NSAID products for NDAs 18147, 22396, 18841, 20776, 20998, 20607, 74802, Christos Mastroyannis, M.D., DARRTS Reference ID 4121882
[9] Hill LM, Breckle R, Wolgram KR, et al. Oligohydramnios ultrasound detected incidence and subsequent fetal outcome. Am J Obstet Gynecol 1983;147:407-10.
[10] Alfirevic Z, Luckas M, Walkinshaw SA, et al. A randomized comparison between amniotic fluid index and maximum pool depth in the monitoring of post-term pregnancy. Br J Obstet Gynecol 1997;104:207–11.
[11] Magann E. The amniotic fluid index, single deepest pocket, and two-diameter pocket in normal human pregnancy. Am J Obstet Gynecol 2000;182:1581–8.
[12] Kaplan et al., 1994, Renal failure in the neonate associated with in utero exposure to non-steroidal anti-inflammatory agents, Pediatr Nephrol, 8:700-701.
[13] Jackson J et al., 2014, Safety of ibuprofen tocolysis, Tuesdays Posters, American College of Obstetricians and Gynecologists, 123(5):129S

*Acetaminophen*

Placental Transfer

According to Micromedex, acetaminophen crosses the placenta.[14] In addition, Nitsche, et al. (2017), conducted a study to determine maternal and fetal pharmacokinetic profiles of acetaminophen after administration of a therapeutic oral dose. After a single oral dose of 1,000 mg of acetaminophen upon admission for a scheduled cesarean delivery, maternal venous blood and fetal cord blood were obtained at delivery. Thirty-four patients were enrolled and all delivered beyond 39 weeks' gestation. Fetal acetaminophen pharmacokinetics (PKs) in the fetus were similar to that in the mother and were available as early as 30 minutes after administration indicating rapid placental transfer of the drug.[15]

Overall Major Congenital Malformations

DPMH conducted a review of published literature in 2010[16] and in 2015[17] regarding the use of acetaminophen during pregnancy. The results of a large Danish population-based prospective cohort study were reviewed, which included 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester of pregnancy. The rate of major birth defects in pregnancies exposed to acetaminophen (4.3%) was similar to the rate of major birth defects in the general population in Denmark that was unexposed to acetaminophen (4.28%).[18] A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had a similar rate of major birth defects compared to 4,500 children in the control group.[19] The reader is referred to the full DPMH review for a thorough review of each study.[16]

Overall, previous DPMH reviews have concluded that there is no increased risk in overall major congenital malformations associated with use of acetaminophen during pregnancy when compared to the background rate in the general population and that there are inconsistent data regarding the presence or absence of any one specific malformation.

Attention deficit/hyperactivity disorder (ADHD)

On April 7, 2016, DPMH completed a review memo describing recent findings associating acetaminophen use in pregnancy with attention deficit/hyperactivity disorder (ADHD) as a result of Tracked Safety Issue (TSI) 1355.[20] DPMH concluded that although these studies demonstrate

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[14] Acetaminophen. Truven Health Analytics. Micromedex Solutions. http://www.micromedexsolutions.com/micromedex2/librarian/CS/0428EF/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/21B425/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=acetaminophen&UserSearchTerm=acetaminophen&SearchFilter=filterNone&navitem=searchGlobal# Accessed 13 November 2017.

[15] Nitsche J et al, 2017, Transplacental Passage of Acetaminophen in Term Pregnancy, Am J Perinatol, 34:541-543.

[16] February 9, 2010, DPMH review of Ofirmev (IV acetaminophen) NDA 22450, Leyla Sahin, MD, DARRTS Reference ID

[17] February 9, 2015, DPMH review for IV Acetaminophen NDA 206610, Leyla Sahin, MD., DARRTS Reference ID 3699918

[18] Rebordosa C et al., 2008, Acetaminophen use during pregnancy: effects on risks for congenital abnormalities, Am J Obstet Gynecol, 198:178.e1-178.e.

[19] FEldkamp M et al., 2010, Acetaminophen Use and Risk of Birth Defects, Obstetrics and Gynecology, 115(1):109-115.

[20] April 7, 2016, DPMH review for acetaminophen, TSI 1355, Tamara Johnson, M.D., MS., DARRTS Reference ID 4081813

consistency among the outcomes related to attention problems and general behavior problems, these studies may only be demonstrating a common finding due to common use of the drug in the pregnancy population and are not sufficient to establish a drug-associated risk.

Childhood Wheezing and Asthma

On February 9, 2010, DPMH completed a review of available published studies of wheezing and asthma in children who were exposed to acetaminophen *in utero.* Four prospective studies and one retrospective study were reviewed. All studies were limited by the fact that acetaminophen exposure and respiratory outcomes were self-reported and not confirmed by medical records. DPMH concluded that "While these study findings raise concerns regarding a possible association between prenatal acetaminophen exposure and childhood asthma, it is not possible to make definitive conclusions at the present time due to conflicting results, various confounders, and the complex pathophysiology of asthma."[21,22,23,24,25,26,27] The reader is referred to the full DPMH review for a thorough review of each study.[16]

More recent epidemiologic studies have reported the same results. In a recent publication by Sordillo J, et al. (2015), the investigators looked for an association of antipyretic intake during pregnancy and during the first year of life with asthma-related outcomes before and after controlling for early life respiratory tract infections. Approximately 1490 mother-child pairs from the Project Viva pre-birth cohort study were examined by acetaminophen exposure at the maximum intake of never, 1-9 times or ≥ 10 times in early pregnancy or mid-pregnancy and ibuprofen intake absence or presence in early pregnancy. Unadjusted models showed that prenatal acetaminophen was associated with higher asthma in early childhood but not mid-childhood. However, this study was limited by 1.) not having information on exact dose of acetaminophen, 2.) there was no accounting for common indications for antipyretic use in pregnancy, which could confound associations for prenatal antipyretic exposures, and 3.) the study's inability to determine the relative timing of administration of medication compared with that of respiratory illness and the continued use of antipyretics throughout childhood.[28]

Cryptorchidism

One study in published literature reports the risk of cryptorchidism after exposure to acetaminophen during pregnancy. In a study by Jensen M, et al. (2010), using data from the Danish National Birth Cohort, 47,400 live-born singleton sons of mothers identified from 1996-2002 were identified. Approximately, 980 boys were identified with cryptorchidism, and 565

[21] Shaheen S et al., 2002, Paracetamol use in pregnancy and wheezing in early childhood, Thorax, 57:958-63.
[22] Shaheen S et al., 2005, Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood, 35:18-25.
[23] Rebordosa C et al., 2008, Prenatal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study, Int J Epidemiol, 37(3):583-90.
[24] Persky V et al., 2008, Prenatal exposure to acetaminophen and respiratory symptoms in the first years of life, Ann Allergy Asthma Immunol, 101(3):271-8.
[25] Perzanowski et al., 2009, Prenatal acetaminophen exposure and risk of wheeze at 5 years in an urban, low-income cohort, Thorax. E-pub.
[26] Kang EM et al., 2009, Prenatal exposure to acetaminophen and asthma in children, Obstet Gynecol, 114(6):1295-1306.
[27] Garcia-Marcos L et al., 2009, Is the effect of prenatal paracetamol exposure on wheezing in preschool children modified by asthma in the mother? Int Arch Allergy Immunol, 149:33-37.
[28] Sordillo J et al., 2015, Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children, J Allergy Clin Immunol, 135:441-8.

boys underwent orchiopexy. The study used computer assisted telephone interviews and a self-administered questionnaire to assess the use of acetaminophen, ibuprofen and acetylsalicylic acid during pregnancy. Exposure to acetaminophen during the first and second trimesters of pregnancy was associated with a minor increase in cryptorchidism (HR = 1.33 [95% CI = 1-1.77]). Exposure of acetaminophen, ibuprofen and acetylsalicylic acid at any time during gestational weeks 8 to14 resulted in an HR of 1.38 (1.05-1.85) for cryptorchidism. Exposure within any single trimester alone was extremely weakly associated as was exposure in all 3 trimesters with a HR = 1.17 [CI = 0.94-1.46].[29]

*Reviewers Comment:*
*In the study by Jensen, et al., exposure was defined as self-reported use of acetaminophen, ibuprofen and acetylsalicylic acid just once during the pregnancy and relied on computerized phone interviews and a self-administered questionnaire to determine acetaminophen usage, which may have led to recall bias. Also, there was only a minor increase in the hazard ratio of cryptorchidism in this study which has not been confirmed in any additional studies.*

Overdose

According to published literature, overdose of acetaminophen during pregnancy is common with the majority of cases involving a single large dose of acetaminophen. Pregnancy outcomes are generally good if medical care is sought immediately; however, if medical care is delayed, fetal or maternal death can occur.[30] In a case report by Thornton and Minns (2012), a 22-year-old pregnant female (19 weeks gestation) presented with abdominal pain and hepatotoxicity after ingesting supratherapeutic amounts of acetaminophen to treat dental pain. The patient denied intentional overdose of acetaminophen but admitted to taking 8 to 9 grams of acetaminophen daily for 10 to 14 days. She was also taking acetaminophen with codeine during that time. She required a liver transplant. The fetus remained viable during surgery, however, the fetus died two weeks later.[31]

Summary

*Ibuprofen*

DPMH has completed multiple reviews in the recent years on acetaminophen and ibuprofen-containing products. According to published literature, ibuprofen has been used for tocolysis in the treatment of preterm labor. DPMH recently added the risk of oligohydramnios starting in the second trimester when exposed to NSAIDS to labeling based an extensive literature review related to multiple NSAID products. Also, published literature has consistently concluded that the use of NSAIDS, including ibuprofen, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. The NSAID template developed by DAAAP with the assistance of DPMH contains language regarding the risk of premature closure of fetal ductus arteriosus in women exposed to NSAIDs during the third trimester.

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[29] Jensen M et al., 2010, Maternal Use of Acetaminophen, Ibuprofen, and Acetylsalicylic Acid During Pregnancy and Risk of Cryptorchidism, Epidemiology, 21:779-785.
[30] McElhatton P et al., 1990, Paracetamol Poisoning in Pregnancy: An Analysis of the Outcomes of Cases Referred to the Teratology Information Services of the National Poisons Information Service, Human & Experimental Toxicology, 9:147-153.
[31] Thornton S and A Minns, 2012, Unintentional Chronic Acetaminophen Poisoning During Pregnancy Resulting in Liver Transplantation.

*Acetaminophen*
Overall, there is extensive published literature on the use of acetaminophen exposure during pregnancy. The results from multiple epidemiologic studies indicate that there is no increased risk of congenital malformations compared to a control group of unexposed children. In addition, there are inefficient data regarding acetaminophen exposure during pregnancy and childhood wheezing/asthma, ADHD and other adverse events. The data are inconsistent, self-reported, not verified by medical records and limited by confounders.

***LACTATION***
Nonclinical Experience
There are no available non-clinical data regarding COMBOGESIC and presence in animal milk.

Review of Literature
The applicant did not provide a review of published literature.

DPMH has conducted multiple reviews on ibuprofen and acetaminophen-containing products with regard to lactation. The results of those reviews are summarized below. In addition, DPMH performed a search of published literature using Embase, PubMed, LactMed and *Medication and Mothers' Milk*. No new data were found. Information from previous DPMH reviews for both products is described below.

*Ibuprofen*
In a DPMH review dated October 6, 2015, limited published literature with regard to ibuprofen exposure and human milk were reviewed. In two of the studies reviewed, ibuprofen was not demonstrated in human milk; however, in two additional studies that used more sensitive assays, ibuprofen was found to be present in human milk at relative infant doses (RID) of 0.06% to 0.6% of the maternal weight-adjusted daily dose. Given the low RID (less than 10%) and no adverse effects seen in the breastfeeding infants in each of the studies, DPMH concluded that ibuprofen is considered compatible with breastfeeding.[32,33,34,35,36] Refer to the full DPMH review for more study specifics.[32]

In *Medications and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that ibuprofen enters milk only in very low amounts (0.6% of maternal dose). According to Hale,[43] "ibuprofen is a good choice in analgesics for breastfeeding women due to years of clinical experience for postpartum pain."

According to LactMed,[37] ibuprofen is excreted into breastmilk in small amounts and also has a short half-life; therefore, it is a preferred analgesic. In addition, according to LactMed, there are

[32] October 6, 2015, DPMH review for Caldor (ibuprofen) injection NDA 22348, Miriam Dinatale, D.O., DARRTS Reference ID 3829752
[33] Townsend et al., 1983, Excretion of ibuprofen into breast milk, American Journal of Obstetrics and Gynecology, 149(2):184-186.
[34] Weibert et al., 1982, Lack of ibuprofen secretion into human milk, Clin Pharm, 1(5):457-458.
[35] Walter K et al., 1997, Ibuprofen in human mil, Br J Clin Pharmacol, 44:211-213.
[36] Rigourd et al., 2014, Ibuprofen Concentrations in Human Mature Milk-First Data About Pharmacokinetics Study in Breast Milk with AOR-10127 "Antalait" Study, Ther Drug Monit, 36(5):590-596.
[37] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of

more than 23 published case reports in the literature with infants exposed to ibuprofen through breastfeeding with no adverse effects reported.

*Acetaminophen*

In a DPMH review dated February 9, 2015[15] and February 9, 2010[16], limited published literature with regard to acetaminophen exposure and human milk were reviewed. The review described the presence of oral acetaminophen in human milk with a calculated infant daily dose of 1 to 2% of the maternal dose. The data was calculated from 15 nursing mothers who took a single dose of 650-1000 mg orally of acetaminophen between 2 to 22 months post-partum. No adverse events were reported in the infants. However, in one well-documented report in a breast-fed infant, a maculopapular rash on the upper trunk and face occurred on the infant (2 months old) two days after the mother had taken a 1 gram dose at bedtime that resolved when the mother stopped taking oral acetaminophen and recurred when she resumed oral acetaminophen two weeks later. [38,39,40,41,42]

In *Medications and Mother's Milk*, Dr. Hale[43] describes a study of 11 mothers who received 650 mg of acetaminophen orally with a calculated milk/plasma ratio of 1.08. In another study, three patients received a single dose of 500 mg orally had a reported milk and plasma concentrations of 4.2 mg/L and 5.6 mg/L with a milk/plasma ratio of 0.76. In another lactation study of women on 1000 mg of acetaminophen, milk levels averaged 6.1 mg/L with an average dose of 0.92 mg/kg/day. According to Dr. Hale, the studies reviewed provide a wide variation in milk concentrations; however, the amount an infant could ingest via breast milk is most likely significantly less than the pediatric therapeutic dose.

According to LactMed,[23] acetaminophen is a good for a fever reducer in nursing women as the doses to the infant are much less than doses usually administered to infants. LactMed describes the case of 12 nursing mothers who received a single oral dose of 650 mg of acetaminophen who were 2 to 22 months postpartum. Peak milk levels were 10 to 15 mg/L between 1 and 2 hours after the dose was given. The authors calculated that an infant who ingested 90 mL of breastmilk every 3 hours would have received an average of 0.88 mg of acetaminophen or 0.14% (0.04 to 0.23%) of the mothers dose.[44]

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Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[38] Berlin CM et al., 1980, Disposition of acetaminophen in milk, saliva and plasma of lactating women, Pediatr Pharmacol, 1:135-141.

[39] Berlin CM et al., 1980, Disposition of acetaminophen in milk, saliva and plasma of lactating women, Pediatr Pharmacol, 1:135-41.

[40] Bitzen P-O et al., 1981, Excretion of paracetamol in human breast milk, Eur J Clin Pharmacol, 20-123-5.

[41] Notarianni LJ et al., 1987, Passage of paracetamol into breast milk and its subsequent metabolism by the neornate, Br J Clin Pharmacol, 24:63-7.

[42] Matheson I et al., 1985, Infant rash caused by paracetamol in breast milk? Pediatrics, 76(4):651-652.

[43] Hale, Thomas, Ph.D., Medications and Mother's Milk 2017, Springer Publishing Company.

Summary
DPMH has completed multiple reviews in the recent years on acetaminophen and ibuprofen-containing products with regard to lactation. Based on the available safety and milk data reviewed, both acetaminophen and ibuprofen appear reasonably safe for breastfeeding women. Transfer to breastmilk appears to be low and minimal side effects for the infant have been reported; however, there are no data on the use of both products administered together as a combination product, as in COMBOGESIC. Based on available data, the following statement should be included in the risk summary:

> The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COMBOGESIC and any potential adverse effects on the breastfed infant from COMBOGESIC or from the underlying maternal condition.

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

Nonclinical Experience
Based on animal data, prostaglandins play a role in endometrial vascular permeability, blastocyst implantation and decidualization. Animal studies have shown that administration of prostaglandin synthesis inhibitors result in increased pre- and post-implantation loss. In addition, in animal studies, there was an increased incidence of dystocia and delayed parturition when ibuprofen was used in late pregnancy. The reader is referred to the nonclinical review by Carlic Huynh, PhD. for further details.[1]

Review of Literature
The applicant did not provide a review of published literature with regard to females and males of reproductive potential.

DPMH performed a search of published literature using Embase and PubMed. The relevant results of this search are summarized below.

In a prospective cohort study by McInerney, et al. (2016), data was analyzed from an internet-based prospective cohort of 2573 female pregnancies in the USA and Canada who were enrolled from June 2013 to September 2015 on the use of pain-relieving medications, such as acetaminophen, aspirin, ibuprofen, naproxen and opioids, and time to conception. A dose dependent relationship was observed between naproxen and opioid use and fecundity; however, little evidence or association was seen with regard to acetaminophen, ibuprofen or aspirin.[45]

In addition, based on a recent FDAAA Safety Labeling Change (SLC) letter for NSAIDS, the following standard statement regarding NSAIDS and female infertility is included in section 8.3, Females and Males of Reproductive Potential, Infertility of NSAID labeling:

> Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs,[46] including COMBOGESIC may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have

[45] McInerney K et al., 2017, Preconception use of pain-relievers and time-to-pregnancy: a prospective cohort study, Human Reproduction, 32(1):103-111.
[46] DAAAP Deputy Director for Safety Memorandum. Judith Racoosin, M.D. Spontaneous Abortion, infertility.

shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women taking NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including COMBOGESIC, in women who have difficulties conceiving or who are undergoing investigation of infertility.

The reader is referred to reviews by Melissa Tassinari, PhD, DABT[47]; Jeanine Best MSN, RN, PNP[48,49] and Judith Racoosin, MD, MPH[50] for further details.

Summary

Based on animal data and mechanism of action, NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women taking NSAIDs have also shown a reversible delay in ovulation. The standard statement regarding NSAIDS and female infertility that was developed as part of a FDAAA Safety Labeling Change (SLC) review will appear in section 8.3 Female and Males of Reproductive Potential.

**CONCLUSIONS**

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of TRADENAME labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" subheadings.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," and "Data" subheadings.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" section of labeling was formatted in the PLLR format to include: the "Infertility" subheadings.
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to subsection 8.1 and 8.3 of labeling.

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February 19, 2015. DARRTS Reference ID 3704542.

[47] Feldene Capsules, NDA 18147/S-039. August 22, 2014. Melissa Tassinari, PhD, DABT. DARRTS Reference ID 3614684.

[48] Mobic Tablets and Oral Suspension, NDAs 20938/S-021 and 21530/s-009. Jeanine Best MSN, RN, PNP. December 7, 2011. DARRTS Reference ID 3054635.

[49] Feldene Capsules, NDA 18147/S-039. April 10, 2014. Jeanine Best MSN, RN, PNP. DARRTS Reference ID 3290126.

[50] DAAAP Deputy Director for Safety Memorandum. Spontaneous abortion and infertility. NSAID Class. TSI 1259. September 14, 2012



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

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CARRIE M CERESA
11/27/2017

MIRIAM C DINATALE
11/27/2017

LYNNE P YAO
11/28/2017

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | October 19, 2017 |
| **From** | Damon Green, M.D., M.S., Reviewer<br>Susan Thompson, M.D., Team Leader<br>Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB)<br>Division of Clinical Compliance Evaluation (DCCE)<br>Office of Scientific Investigations (OSI) |
| **To** | Allison Meyer, Sr. Regulatory Project Manager<br>John Hariadi, M.D., Clinical Reviewer<br>Robert Shibuya, M.D., Clinical Team Lead<br>Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| **NDA/#** | 209471 |
| **Applicant** | AFT Pharmaceuticals Ltd. |
| **Drug** | Combogesic (Acetaminophen and Ibuprofen) |
| **NME (Yes/No)** | No |
| **Therapeutic Classification** | Antipyretic and Non-steroidal Anti-inflammatory Drug |
| **Proposed Indication** | Short term management of mild to moderate acute pain |
| **Consultation Request Date** | June 7, 2017 |
| **Summary Goal Date** | October 23, 2017 |
| **Action Goal Date** | December 15, 2017 |
| **PDUFA Date** | January 1, 2018 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Stephen E. Daniels was inspected in support of this NDA. The final classification of this inspection was NAI. Based on the results of the clinical investigator inspection, the study appears to have been conducted adequately, and the data generated by this site appears acceptable in support of the respective application. The raw data used to generate the calculated primary endpoint were verifiable.

# II. BACKGROUND

AFT Pharmaceuticals Ltd., sponsor of NDA 209471, is seeking approval for Combogesic® (Acetaminophen 325 mg/ Ibuprofen 97.5 mg) Tablets, a lower strength formulation of AFT's proprietary MAXIGESIC® product (acetaminophen 500 mg/ibuprofen 150 mg tablets), for the short-term management of mild to moderate acute pain.

Inspections were requested for study **Protocol AFT-MX-6** entitled, "Maxigesic® 325 Acute Dental Pain Study: A multicentre double-blind, placebo controlled, randomized, parallel group comparison of the effects of Maxigesic® 325 versus paracetamol, ibuprofen, and placebo in participants with moderate to severe pain from removal of at least two third molars." The site chosen - Dr. Stephen E. Daniels – had the highest enrollment and no history of previous inspections.

Patients were screened at four study centers: one in the United States, and three in New Zealand. In total, 455 subjects were screened; 408 subjects enrolled. The first patient enrolled on May 28, 2013 and the last patient completed the study on January 14, 2015.

The primary efficacy endpoint is reduction in pain as measured by the change from baseline to Week 12 in the weekly mean of the average daily (24 hour) pain intensity scores (as reported by patients based on the 11-point Numeric Rating Scale (NRS)). The sponsor concluded that Maxigesic® 325 was statistically superior to both acetaminophen and ibuprofen monotherapy and placebo as measured by the primary and secondary efficacy endpoints in AFT-MX-6

# III. RESULTS (by site):

| **Name of CI, Address, Country if non-U.S. or City, State if U.S.** | **Protocol #, Site #, and # of Subjects** | **Inspection Date** | **Classification** |
|---|---|---|---|
| **Stephen E. Daniels, D.O.**<br>Premier Research (site closed)<br>3200 Red River, Suite 301<br>Austin, TX 78705 | Protocol:<br>AFT-MX-6<br>Site: Premier<br>Subjects: 135 | 09/19/2017-<br>09/22/2017 | NAI |

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**1. Dr. Stephen E. Daniels**

Under Protocol AFT-MX-6, 149 subjects were screened, 135 subjects were enrolled, with all 135 completing the study. The number of subject records reviewed during the inspection were 45 in total. The inspection covered a review of all available records as follows: the regulatory binder, 1572, eligibility criteria, test article accountability/disposition, blinding/randomization procedures, site monitoring, adverse events, training, CVs, sponsor communications & approvals, financial disclosures, and delegation of authority with no deficiencies noted. Also reviewed were 100% of the subject's Informed Consent Documents with no deficiencies noted.

The primary efficacy endpoint was not verifiable as per the investigator comments: "I was unable to verify that the primary efficacy endpoints were consistent with the data listings provided in background materials using the source documents and CRFs. The assessment of the primary efficacy was to compare the time-adjusted Summed Pain Intensity Differences (SPIDs) of the Visual Analogue Scale (VAS) pain intensity scores up to 48 hours after the first dose of study medication. I reviewed the data listings against the CRFs and since I did not have the formula to figure out the time adjusted SPID which was the primary endpoint, I verified the numbers that were used to calculate the SPID…I confirmed that the CRF pages were transcribed properly and were correct by checking them against the subject diaries, but the data listings provided by the sponsor did not match…"

*Reviewers Comments: The inspection shows the scores used to calculate the primary endpoint were correctly transcribed to the Case Report Forms from patient diaries. The raw data used to generate the calculated primary endpoint were verifiable.*

In AFT's explanation (Exhibit 4 of the EIR), they state that no discrepancy exists between the dataset (QS dataset) submitted to the FDA and the CRF. They report that "in previous correspondence with the FDA (seq 0010), we acknowledge the difficulties in verifying the SPIDs from the QS domain and Analysis datasets submitted due to the lack of SAS programs, which is a reflection of how the analysis was done (i.e. excel). To reassure the FDA of our findings, we have contracted a third party to re-derive the ADAM datasets and efficacy analysis results from the SDTM domains."

There were no significant observations made during the inspection; therefore, no FDA-483 was issued.

Overall, 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.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader,
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Kassa Ayalew, M.D., M.P.H
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CC:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Shibuya
DAAAP /Project Manager/ Meyer
DAAAP/Medical Officer/Hariadi
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Thompson
OSI/DCCE/GCPAB Reviewer/Green

OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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DAMON C GREEN
10/20/2017

SUSAN D THOMPSON
10/20/2017

KASSA AYALEW
10/20/2017

**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)

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:** | August 7, 2017 |
| **Requesting Office or Division:** | Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) |
| **Application Type and Number:** | NDA 209471 |
| **Product Name and Strength:** | Combogesic (acetaminophen 325 mg/ibuprofen 97.5) tablet |
| **Product Type:** | Multi-ingredient product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | AFT Pharmaceuticals, Ltd. |
| **Submission Date:** | March 1, 2017 |
| **OSE RCM #:** | 2017-417 |
| **DMEPA Primary Reviewer:** | Millie Shah, PharmD, BCPS |
| **DMEPA Team Leader:** | Otto L. Townsend, PharmD |

## 1 REASON FOR REVIEW

This review provides our evaluation of the proposed labels and labeling for Combogesic (acetaminophen/ibuprofen) tablets from a medication error perspective. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested this review as part of their evaluation of the 505(b)(2) NDA submission for Combogesic.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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 |
| Human Factors Study | C-N/A |
| ISMP Newsletters | D-N/A |
| FDA Adverse Event Reporting System (FAERS)* | E-N/A |
| Other | F-N/A |
| Labels and Labeling | G |

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

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed labels and labeling and prescribing information to identify deficiencies that may lead to medication errors and to identify other areas that can be improved.

(b) (4) Label and Carton Labeling

Our review of the carton labeling identified a graphic that states (b) (4) on the principal display panel that competes in prominence with the proprietary name and other more important information. In addition, the statement appears promotional. We defer to the Office of Prescription Drug Promotion (OPDP) to determine the appropriateness of the statement from a promotional perspective.

We identified that the presentation of the established name does not include the dosage form on the (b) (4) label and carton labeling. Additionally, the established name is not presented in parenthesis. Thus, we recommend the Applicant add the approved dosage form to the established name and display the established name and dosage form as determined by the Office of Pharmaceutical Quality (OPQ).

We note the lot number is absent from the carton labeling; however, there are placeholders for several other numbers (BN, GTIN, Sr. No.) instead. Thus, we recommend the Applicant add the lot number to the carton labeling and relocate the other numbers (BN, GTIN, and Sr. No) away from the lot number so that the lot number is not confused with these other numbers.

We determined that the lot number and expiration date are not present on each (b) (4) label. Thus, we recommend the Applicant add the lot number and expiration date to each (b) (4) label to minimize the risk for confusion.

Prescribing Information (PI)

Our review of the prescribing information determined that the dosage form is presented as "tablet", which is inconsistent with the dosage form presented on the carton labeling (film coated tablet). Thus, we recommend ensuring the dosage form throughout the PI is the approved dosage form as determined by OPQ.

(b) (4)

## 4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed (b) (4) label, carton labeling, and prescribing information that can be improved to promote safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

Our review of the *Dosage and Administration* and *How Supplied* sections of the Full Prescribing Information identified the following recommendations for review and consideration by DAAAP.

A. Full Prescribing Information
   1. The dosage form is presented as "tablet," which is inconsistent with the dosage form presented on the carton labeling (film coated tablet). Thus, we recommend ensuring the dosage form throughout the PI is the approved dosage form as determined by the Office of Pharmaceutical Quality (OPQ).
   2. (b) (4)

### 4.2 RECOMMENDATIONS FOR AFT PHARMACEUTICALS, LTD.

We recommend the Applicant implement the following prior to approval of this NDA:

A. Carton Labeling

1. Presentation of the established name does not include the dosage form. Thus, display the established name with the approved dosage form as determined by the Office of Pharmaceutical Quality (OPQ).[a]
2. We note the lot number is absent from the carton labeling; however, there are placeholders for several other numbers (BN, GTIN, Sr. No.) instead. Thus, we recommend you add the lot number to the carton labeling in accordance with 21 CFR 201.10(i)(1) and relocate the other numbers (BN, GTIN, and Sr. No) away from the lot number so that the lot number is not confused with these other numbers.[b]
3. Submit revised carton labeling with the actual NDC number instead of the placeholder.


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

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

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Combogesic that AFT Pharmaceuticals, Ltd. submitted on March 1, 2017, and the listed drugs (LD).

**Table 2. Relevant Product Information for Combogesic and the Listed Drugs**

| **Product Name** | **Combogesic** | **Ultracet** | **Ibuprofen** |
|---|---|---|---|
| **Initial Approval Date** | N/A | August 15, 2001 | November 14, 2001 |
| **Active Ingredient** | Acetaminophen-ibuprofen | Acetaminophen-tramadol HCl | ibuprofen |
| **Indication** | short term management of mild to moderate acute pain | management of acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. | • Relief of signs and symptoms of rheumatoid arthritis and osteoarthritis<br>• Relief of mild to moderate pain<br>• Treatment of primary dysmenorrhea |
| **Route of Administration** | oral | oral | oral |
| **Dosage Form** | Film-coated tablet | tablet | tablet |
| **Strength** | 325 mg/97.5 mg | 37.5 mg/325 mg | 400 mg, 600 mg, 800 mg |
| **Dose and Frequency** | 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day | 2 tablets every 4 to 6 hours as needed for pain relief; maximum of 8 tablets per day | • RA and OA: 1,200 mg to 3,200 mg daily (divided TID or QID)<br>• Mild-Moderate Pain: 400 mg every 4 to 6 hours as needed<br>• Dysmenorrhea: 400 mg every 4 hours as needed |
| **How Supplied/** | (b) (4) | Bottle of 100 tablets | 400 mg: Bottles of |

| | | | |
|---|---|---|---|
| **Container Closure** | | • Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each | (b) (4), 100, or 500 tablets<br>600 mg: Bottles of (b) (4) 100, or 500 tablets<br>800 mg: Bottles of (b) (4), 100, 500 |
| **Storage** | Store at (b) (4) excursions permitted to 15 – 30°C (59 - 86°F). | Store at 20 – 25°C (68 – 77°F); excursions permitted to 15 – 30°C (59 – 86°F). [see USP Controlled Room Temperature]. | Store at room temperature. Avoid excessive heat (40°C (104°F). |

**APPENDIX B. PREVIOUS DMEPA REVIEWS**

**B.1 Methods**

On July 5, 2017, we searched the L:drive and AIMS using the term, Combogesic, to identify reviews previously performed by DMEPA.

**B.2 Results**

Our search did not identify any previous reviews relevant to our current review.

**APPENDIX C. N/A**

**APPENDIX D. N/A**

**APPENDIX E. N/A**

**APPENDIX F. N/A**

**APPENDIX G. LABELS AND LABELING**

**G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Combogesic labels and labeling submitted by AFT Pharmaceuticals, Ltd. on March 1, 2017.

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



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/s/

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MILLIE C BRAHMBHATT
08/07/2017

OTTO L TOWNSEND
08/07/2017