CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215320Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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 13, 2023
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:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AFT Pharmaceuticals, Ltd. (AFT Pharmaceuticals)
PNR ID #:	2023-1044725104
DMEPA 1 Safety Evaluator:	Susan Hakeem, Pharm.D.
DMEPA 1 Team Leader:	Valerie S. Vaughan, Pharm.D.
DMEPA 1 Acting Director:	Irene Chan, Pharm.D., BCPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Combogesic IV, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. AFT Pharmaceuticals did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

AFT Pharmaceuticals previously submitted the proposed proprietary name, Combogesic IV, on August 31, 2021. We found the name, Combogesic IV, conditionally acceptable under NDA 215320 on November 29, 2021.[a] However, NDA 215320 was issued a Complete Response (CR) letter on June 30, 2022.

On April 17, 2023, AFT Pharmaceuticals resubmitted NDA 215320 in response to the deficiencies outlined in the June 30, 2022 CRL and concurrently resubmitted a request for proprietary name review of Combogesic IV as well.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on April 17, 2023.

- Intended Pronunciation: kom-boh-‘jē-zik ī-ˈvē
- Active Ingredient: acetaminophen and ibuprofen
- Indication of Use:
  - the relief of mild to moderate pain (b) (4) (b) (4)
  - the management of moderate to severe pain as an adjunct to opioid analgesics.
- Route of Administration: intravenous
- Dosage Form: injection
- Strength: 1000 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 a 15-minute infusion every 6 hours, as necessary. Do not exceed the maximum total daily dose of four vials (400ml) of COMBOGESIC® IV in 24 hours (equivalent to 4000mg acetaminophen/1200mg ibuprofen).

[a] Clark, C. Proprietary Name Review for Combogesic IV (NDA 215320). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 NOV 29. PNR ID No. 2021-1044724158.

- Adults weighing under 50 kg should be dosed according to their weight, at a dosage of 15 mg/kg acetaminophen and 4.5 mg/kg ibuprofen, administered as a 15-minute infusion every 6 hours, as necessary. This equates to a maximum single dose of 750 mg acetaminophen and 225 mg ibuprofen (discard remaining medicine in vial), and a total daily dose of 3,000 mg (3 g) acetaminophen and 900 mg ibuprofen

- How Supplied: (b) (4) (b) (4)
- Storage: Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not refrigerate or freeze. Store in the original carton in order to protect from light. Protect from heat.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Combogesic IV.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Combogesic IV would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Combogesic IV. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not comment on the findings of OPDP's assessment for Combogesic IV.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Combogesic IV.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[b].

2.2.2 Components of the Proposed Proprietary Name

AFT Pharmaceuticals indicated in their submission that the proposed root proprietary name, Combogesic, is derived from "combination analgesic" and "combination pain reliever". This proprietary name is comprised of a root name, Combogesic, and the modifier, IV. An analysis of the appropriateness of the modifier, IV, is discussed in Section 2.2.9.

We note that Combogesic IV contains the letter strings '-es-', an abbreviation used for 'extra strength'. In some circumstances, the incorporation of medical abbreviations in proprietary names can inadvertently be a source of error. For more information see draft guidance, *Best*

[b] USAN stem search conducted on May 23, 2023.

Practices in Developing Proprietary Names for Human Prescription Drug Products.[c] Although we typically discourage the inclusion of medical abbreviations in proprietary names, we determined that the location of this abbreviation in the infix of the name and its lack of prominence make it unlikely for this abbreviation to be separated from the surrounding letters in a manner that would lead to confusion in this case. Thus, we conclude that in this case, we do not object to the inclusion of the letter string '-es-' in the infix of the proposed proprietary name.

2.2.3 Comments from Other Review Disciplines at Initial Review

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not forward any comments or concerns related to Combogesic IV at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Seventy-eight practitioners participated in DMEPA's prescription studies for Combogesic IV. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[d] identified 56 names with the combined score of ≥55% or individual orthographic or phonetic score of ≥70%. We had identified and evaluated some of the names in our previous proprietary name review. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We note that none of the product characteristics have changed, and we agree with the findings from our previous review for the names evaluated previously. Therefore, we identified 17 names not previously analyzed. These names are included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	1

[c] Guidance for Industry: Best Practices in Developing Proprietary Names for Human Prescription Drug Products. 2020. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[d] POCA search conducted on May 23, 2023 in version 5.2.

Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	16
Low similarity name pair: combined match percentage score ≤54%	0

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 17 names contained in Table 1 determined none of the names will pose a risk for confusion with Combogesic IV as described in Appendices C through H.

2.2.8 Safety Assessment of the use of multiple dosage forms under the same root name

In our previous review, we assessed the appropriateness of using the same root name, Combogesic, for the injection formulation proposed under NDA 215320, which would represent a product line extension given Combogesic tablet (NDA 209471) is already marketed.[a]

We agree with our previous assessment and maintain our non-objection regarding the proposed injection formulation to be marketed under the same root name, Combogesic.

2.2.9 Safety Assessment of the Modifier, 'IV'

We previously assessed whether the inclusion of the modifier, 'IV', is appropriate for the proposed proprietary name, Combogesic IV.[a]

We agree with our previous assessment and maintain our non-objection regarding the proposed inclusion of the modifier 'IV'.

2.2.10 Medication Error Data Selection of Cases

On June 12, 2023 and July 10, 2023, we searched the FDA Adverse Event Reporting System (FAERS) database using the strategies listed in Table 2 and 3, respectively, (see Appendix A1 for a description of FAERS database) for name confusion errors associated with '***IV***' in proprietary names of currently marketed products that would be relevant for this review.

Table 2. FAERS Search Strategy 1	
FAERS Field	Search Terms
Initial FDA Receive Dates	10/01/2021 – 06/09/2023
Product Name	N/A
Verbatim Name(s)	N/A
Product Active Ingredient	N/A
Drug Role	Suspect

Event—LLT (Lower-Level Terms)	INTERCEPTED WRONG DRUG PRODUCT SELECTED; INTERCEPTED WRONG DRUG SELECTED; PRODUCT BARCODE ON WRONG PRODUCT; WRONG DEVICE DISPENSED; WRONG DRUG ADMINISTERED; WRONG DRUG DISPENSED; WRONG DRUG PRESCRIBED; WRONG DRUG PROCURED; WRONG DRUG PRODUCT DISPENSED; WRONG DRUG PRODUCT SELECTED; WRONG DRUG SELECTED; WRONG DRUG STOCKED; WRONG PRODUCT ADMINISTERED; WRONG PRODUCT PROCURED; WRONG PRODUCT SELECTED; WRONG PRODUCT STORED
Event—PT (Preferred Terms)	CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR; INTERCEPTED MEDICATION ERROR; MEDICATION ERROR; PRODUCT BARCODE ISSUE; PRODUCT IDENTIFICATION NUMBER ISSUE; PRODUCT NAME CONFUSION; WRONG DRUG;
Country (derived)	USA
Reporter Narrative	IV

Table 3. FAERS Search Strategy 2	
FAERS Field	Search Terms
Initial FDA Receive Dates	10/01/2021 – 06/09/2023
Product Name	PREVACID IV, NEXIUM I.V.
Verbatim Name(s)	PROTONIX I.V., PROTONIX I.V., PROTONIX IV
Product Active Ingredient	N/A
Drug Role	Suspect
Event—LLT	INTERCEPTED WRONG DRUG PRODUCT SELECTED; INTERCEPTED WRONG DRUG SELECTED; PRODUCT BARCODE ON WRONG PRODUCT; WRONG DEVICE DISPENSED; WRONG DRUG ADMINISTERED; WRONG DRUG DISPENSED; WRONG DRUG PRESCRIBED; WRONG DRUG PROCURED; WRONG DRUG PRODUCT DISPENSED; WRONG DRUG PRODUCT SELECTED; WRONG DRUG SELECTED; WRONG DRUG STOCKED; WRONG PRODUCT

	ADMINISTERED; WRONG PRODUCT PROCURED; WRONG PRODUCT SELECTED; WRONG PRODUCT STORED
Event—PT	CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR; INTERCEPTED MEDICATION ERROR; MEDICATION ERROR; PRODUCT BARCODE ISSUE; PRODUCT IDENTIFICATION NUMBER ISSUE; PRODUCT NAME CONFUSION; WRONG DRUG;
Country (derived)	USA
Reporter Narrative	N/A

A gap search was conducted to capture reports since the last Initial FDA Receive Dates reported in our previous review under OSE RCM# 2021-1044724158. We note that using the search strategy from the previous review, a total of 168,522 cases were retrieved for FAERS Search Strategy 1 and no reports were retrieved for FAERS Search Strategy 2. As a result, we restricted the search criteria in this review to the use of the LLT and PT terms related to the possible confusion with the names of the products to ensure we increase the likelihood that the results would be relevant to the evaluation of the "IV" modifier associated with the root name. As a result:

- our FAERS Search Strategy 1 under this review yielded 9,239 reports of which zero (0) described error related to the term 'IV' being used in proprietary names and resulting in a medication error.
- our FAERS Search Strategy 2 under this review yielded zero (0) reports.

2.2.11 Communication of DMEPA's Determination

On July 13, 2023, DMEPA 1 communicated our determination to the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP).

3 CONCLUSION

The proposed proprietary name, Combogesic IV, is conditionally acceptable.

If you have any questions or need clarifications, please contact Ruth Maduro, OSE project manager, at 240-402-4232.

3.1 COMMENTS TO AFT PHARMACEUTICALS, LTD.

We have completed our review of the proposed proprietary name, Combogesic IV, and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your submission, received on April 17, 2023, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [e]

[e] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@FDA, Cerner RxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.

- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[f]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

[f] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e., drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Combogesic IV Study (Conducted on May 5, 2023)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order: Combogesic IV 1,000mg/300mg intravenous	Combogesic IV Bring to clinic Dispense 1 vial
Outpatient Prescription: Patient _____ Date _____ Address _____ ℞ Combogesic IV Bring to clinic 1 Vial MEDWATCH 1-800-FDA-1088 Refill(s):_____ Dr. _____ DEA No._____ Address _____ Telephone _____	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Combogesic IV	

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Combogesic IV
As of Date 6/5/2023

256 People Received Study
78 People Responded

Study Name: Combogesic IV

INTERPRETATION	INPATIENT	CPOE	VOICE	OUTPATIENT	TOTAL
Total	17	19	23	19	

COMBIGESIC IV	0	0	1	0	1
COMBOGESIC	6	1	2	2	11
COMBOGESIC IV	7	18	19	16	60
COMBOQESIC	1	0	0	0	1
COMBOQESIC IV	1	0	0	0	1
COMBOSEGIC IV	0	0	1	0	1
COMBOSIC	1	0	0	0	1
COMBROGES IV	1	0	0	0	1
COMBROGESIC IV	0	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Combogesic IV **Established name:** acetaminophen and ibuprofen **Dosage form:** injection **Strength(s):** 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL **Usual Dose:** 1000 mg/300 mg intravenously over 15 minutes every 6 hours as necessary; (b) (4)	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Combogesic IV	100	This name is the subject of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
	NA	

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Combogesic IV **Established name:** acetaminophen and ibuprofen **Dosage form:** injection **Strength(s):** 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL **Usual Dose:** 1000 mg/300 mg intravenously over 15 minutes every 6 hours as necessary; (b) (4)	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	Combivent Respimat	56	This name pair has sufficient orthographic and phonetic differences.
2.	Ombitasvir	56	This name pair has sufficient orthographic and phonetic differences.
3.	Comfort Shield	55	This name pair has sufficient orthographic and phonetic differences.
4.	Microgestin	55	This name pair has sufficient orthographic and phonetic differences.
5.	Microgestin 1.5/30	55	This name pair has sufficient orthographic and phonetic differences.
6.	Microgestin 1/20	55	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
	NA	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	Camphoric Acid, (+)-	60	Product is not a drug. It is a white crystallizable substance obtained from the oxidation of camphor, naturally occurring in rosemary.
2.	Congestaid Ii	58	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.

No.	Name	POCA Score (%)	Failure preventions
3.	Dobesilic Acid	58	International product marketed in Turkey, Italy, China, Switzerland.
4.	Cinametic Acid	56	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
5.	Cucumber Seed Oil	56	Product is not a drug. It is a cold pressed oil from the cleaned and dried seeds of cucumbers that has a lot of nutrients in it, and it contains phytosterols, tocopherols, vitamins, minerals and essential fatty acids.
6.	Clodronic Acid	55	Veterinary product.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[g].

No.	Name	POCA Score (%)
1.	Bempedoic Acid	60
2.	Mobocertinib	56
3.	Ato Mepivacaine V	55
4.	Indomethacin	55

[g] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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/s/

SUSAN HAKEEM
07/13/2023 12:55:14 PM

VALERIE S VAUGHAN
07/13/2023 01:27:21 PM

IRENE Z CHAN
07/13/2023 01:29:16 PM

PROPRIETARY NAME 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:	November 29, 2021
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:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AFT Pharmaceuticals Ltd. (AFT Pharmaceuticals)
PNR ID #:	2021-1044724158
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Combogesic IV, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. AFT Pharmaceuticals did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

AFT Pharmaceuticals currently has an application under review, NDA 209471, for the proposed product, Combogesic***, a multi-ingredient tablet formulation consisting of acetaminophen and ibuprofen (see Section 1.2 for product information). AFT Pharmaceuticals previously submitted the proposed proprietary name, Combogesic***, which was found to be conditionally acceptable under IND 107435[a] and NDA 209471.[b,c,d] The application for Combogesic***, NDA 209471, is currently under review with a goal PDUFA date of January 27, 2022.

AFT Pharmaceuticals now proposes an injection formulation of acetaminophen and ibuprofen under NDA 215320, and thus submitted the proposed proprietary name, Combogesic IV, for the injection formulation, for review.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on August 31, 2021. Product information for the proposed Combogesic was excerpted from the proposed Prescribing Information available from: \\CDSESUB1\evsprod\nda209471\0036\m1\us\114-labeling\draft\labeling\spl\draft-labeling-text.docx

Table 1. Characteristics of the Proposed Combogesic IV (NDA 215320) and Combogesic (NDA 209471) Products

	Combogesic IV (NDA 215320)	Combogesic*** (NDA 209471)
Approval Date	Not Applicable	Not Applicable
Intended Pronunciation	kom-boh-ʻjē-zik ī-ˈvē	kom-boh-ʻjē-zik
Active Ingredient	Acetaminophen and ibuprofen	

[a] Wilson, V. Proprietary Name Review for Combogesic (IND 107435). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 28. PNR ID No. 2016-8594420.

[b] Shah, M. Proprietary Name Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 17. PNR ID No. 2017-13546269.

[c] Johnson, C. Proprietary Name Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 04. PNR ID No. 2020-39877623.

[d] Clark, C. Proprietary Name Review for Combogesic (NDA 209471). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 OCT 13. PND ID No. 2021- 1044724085.

Indications of Use	• the relief of mild to moderate pain (b) (4) (b) (4) • the management of moderate to severe pain as an adjunct to opioid analgesics.	• management of mild to moderate acute pain
Route of Administration	Intravenous	Oral
Dosage Form	Injection	Tablet
Strength	1,000 mg/300 mg per 100 mL (10 mg/3 mg per mL)	325 mg/97.5 mg
Dose and Frequency	• acetaminophen 1,000 mg/ibuprofen 300 mg (as sodium dihydrate) administered as 15-minute infusion every 6 hours, as necessary. (b) (4)	3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day
How Supplied		1 bottle containing 250 tablets
Storage	Controlled Room Temperature	

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Combogesic IV.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Combogesic IV would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1

(DMEPA 1) and the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) concurred with the findings of OPDP's assessment for Combogesic IV.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Combogesic IV.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name[e].

2.2.2 Components of the Proposed Proprietary Name

AFT Pharmaceuticals indicated in their submission that the proposed root proprietary name, Combogesic, is derived from "combination analgesic" and "combination pain reliever". This proprietary name is comprised of a root name, Combogesic, and the modifier, IV. An analysis of the appropriateness of the modifier, IV, is discussed in Section 2.2.8.

2.2.3 Comments from Other Review Disciplines at Initial Review

On October 6, 2021, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not forward any comments or concerns relating to Combogesic IV at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

One hundred eleven (111) practitioners participated in DMEPA's prescription studies for Combogesic IV. A participant in the computerized provider order entry (CPOE) prescription study, commented that "I don't think it is likely to get mixed up with Comboguard, but you never know". We evaluated this name pair and determined that the risk of confusion will be mitigated because Comboguard is a veterinary product indicated for the prevention of heartworm and fleas in dogs. See Appendix G for our assessment of this name pair. Appendix B contains the results from the prescription simulation studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[f] identified 132 names with the combined score of ≥55% or individual orthographic or phonetic score of ≥70%. We had identified and evaluated some of the names in our previous proprietary name review for the root name Combogesic. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We also evaluated previously identified names taking into account the difference in dosage form, route of administration, strength, dosage and frequency for the proposed injection formulation vs. the tablet formulation. We agree with the findings from our previous review for the names evaluated previously. Therefore, we identified one name not

[e] USAN stem search conducted on September 24, 2021.

[f] POCA search conducted on September 24, 2021 in version 4.4.

previously analyzed, which is the name subject under this review. This name is included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the name retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	1
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	0
Low similarity name pair: combined match percentage score ≤54%	0

2.2.7 Safety Assessment of the use of multiple dosage forms under the same root name

We considered the appropriateness of using the same root name, Combogesic, for the injection formulation proposed under NDA 215320, which would represent a product line extension if NDA 209471 for the proposed Combogesic tablet, is approved.

It is not uncommon to have a product line with multiple dosage forms and strengths share one proprietary root name, as proposed. We note that this proposed product shares the same active ingredients (acetaminophen and ibuprofen), and patient population (adults) as the currently proposed Combogesic tablets. The products differ in some characteristics including routes of administration (intravenous vs. oral), strengths (1000 mg/300 mg per 100 mL (10 mg/3 mg per mL) vs. 325 mg/97.5 mg), dosage forms (injection vs. tablet) and dosing (1000 mg/300 mg every 6 hours as needed for patients weighing greater than or equal to 50 kg and (b) (4) every 6 hours as needed for patients weighing less than 50 kg vs. 3 tablets orally every 6 hours as needed).

We consider the circumstances of each case individually to determine what risks may arise from confusion between differing dosage forms due to use of the same root name. In this particular case, we considered if Combogesic tablets and Combogesic IV are equivalent on a mg to mg basis, thus, we conferred with the Office of Clinical Pharmacology (OCP) reviewer. The OCP reviewer stated "From PK perspective, based on their PK profiles, we do not think that these two products will be [equivalent] on a mg-to-mg basis in terms of efficacy/safety. [T]he sponsor conducted a PK study comparing Combogesic IV (1000 mg acetaminophen/300 mg ibuprofen) to Combogesic tablets (3 tablets of 325 mg acetaminophen/97.5 mg ibuprofen in each tablet, a total dose of 975 mg acetaminophen and 292.5 ibuprofen). The PK results showed that these products exhibited different PK profiles mainly due to different routes of administration. Combogesic IV showed shorter Tmax, greater Cmax, although the AUCinf values are similar for both acetaminophen and ibuprofen between these products. Although Combogesic IV and

Combogesic tablet are comparable in terms of AUC values, these products are not comparable in terms of Cmax (Combogesic IV has 2-fold greater Cmax) and the Tmax values are very different (15 min for Combogesic IV and 2.6 h for Combogesic tablet). Thus, we do not think these two products will be [equivalent] on a mg-to-mg basis in terms of efficacy/safety."

Since these products are not equivalent on a mg-to-mg basis, we considered whether there were other factors that appropriately minimize the risk for confusion. In this case, the different dosing of the two formulations can help to minimize the likelihood for an error to reach the patient. Even in an instance where the strength, dosage form, or route of administration may be left off a prescription, the dosing difference (1000 mg/300 mg every 6 hours as needed for patients weighing greater than or equal to 50 kg and (b) (4) every 6 hours as needed for patients weighing less than 50 kg vs. 3 tablets orally every 6 hours as needed) on a prescription order would likely alert the healthcare professional to verify the correct dosage form to dispense. We determined that the differences can be appropriately managed via labeling. Therefore, we find it acceptable for the proposed injection formulation to be marketed under the same root name, Combogesic.

2.2.8 Safety Assessment of the Modifier, 'IV'

A tablet formulation of the multi-ingredient acetaminophen and ibuprofen drug product is currently proposed by the Applicant under NDA 209471 (Combogesic) and has a different route of administration, strength, and dosing regimen than the proposed injection product, Combogesic IV. The modifier 'IV' is intended to identify the new route of administration and to also differentiate the proposed product from the tablet formulation. However, we note that the modifier 'IV' is a standard medical abbreviation for intravenous that has been confused with other abbreviated routes of administration (e.g., IU, IM, IN).[g] Modifiers are associated with medication errors and the use of "IV" as an abbreviation is discouraged by the Institute of Safe Medication Practices (ISMP). [h,i]

We assessed whether the inclusion of the modifier, 'IV', is appropriate for the proposed product. The FDA generally discourages sponsors from incorporating medical abbreviations commonly used for prescription communication in the proprietary name; however, we are aware that there are products currently marketed with this modifier, and to our knowledge, no medication errors have occurred with its use within the context of a proprietary name. A FAERS search for medication errors associated with 'IV' in the proprietary name yielded no relevant reports of confusion (see section 2.2.10 below).

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[g] Institute for Safe Medication Practices, "List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

[h] PDUFA Pilot Project: proprietary name review (concept paper). 2008 Sep. p 38. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072229.pdf

[i] Drug name suffix confusion is a common source of errors. Pennsylvania Patient Safety Reporting System *Patient Safety Advisor*, Vol. 1, No. 4. December 2004.

Additionally, if the modifier were omitted or overlooked, the dose would be specified on a prescription order for Combogesic IV and there is no overlap in dose between Combogesic IV injection and Combogesic tablet (1 vial or 100 mL or 1000 mg/300 mg for patients weighing 50 kg or greater or (b) (4) for patients weighing less than 50 kg vs. 3 tablets). Thus, in this particular case, 'IV' is acceptable as a modifier since this specific formulation is only intended to be given intravenously and cannot be administered through different routes. While the abbreviation 'IV' has been documented by ISMP to be mistaken for other routes of administration (e.g., IU, IM, IN), we have determined that the risk of misinterpretation can be effectively handled through the product's labels and labeling and we do not object to its inclusion.

2.2.9 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the one name contained in Table 1 determined it will not pose a risk for confusion with Combogesic IV as described in Appendix C.

2.2.10 Medication Error Data Selection of Cases

On October 7, 2021, we searched the FDA Adverse Event Reporting System (FAERS) database using the strategies listed in Tables 2 and 3 (see Appendix A1 for a description of FAERS database) for name confusion errors associated with 'IV' in the proprietary name of currently marketed products that would be relevant for this review.

Table 2. FAERS Search Strategy 1	
Initial FDA Receive Dates	01/01/2015 – 10/01/2021
Product Name	N/A
Verbatim Name(s)	N/A
Product Active Ingredient	N/A
Drug Role	Suspect
Event – SMQ	MEDICATION ERRORS(Narrow)
Country (derived)	USA
Reporter Narrative	IV

Table 3. FAERS Search Strategy 2	
Initial FDA Receive Dates	– 10/01/2021
Product Name	PREVACID IV, NEXIUM I.V.
Verbatim Name(s)	PROTONIX I.V., PROTONIX I.V., PROTONIX IV
Product Active Ingredient	N/A
Drug Role	Suspect

Event – SMQ	MEDICATION ERRORS(Narrow)
Country (derived)	USA
Reporter Narrative	IV

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After review, all 5649 reports from our first FAERS search (Table 2) were not included in the final analysis for the following reasons: upon additional filtering of the narrative and preferred terms, no cases involved medication errors related to the IV modifier.

Furthermore, the 2 reports from our second FAERS search (Table 3) were not included in the final analysis for the following reasons: one case included as a medication error referred to the shipping process of the IV in-line filter; one case included as incorrect route of administration described a patient receiving intravenous Nexium IV who subsequently received a subcutaneous injection of the Nexium IV and experienced arm swelling. However, this case did not provide details indicating the administration of Nexium IV via the subcutaneous route of administration was due to misinterpretation of the modifier, IV.

2.2.11 Following exclusions, the searches yielded zero relevant cases. Communication of DMEPA's Analysis at Midpoint of Review

DMEPA 1 communicated our findings to the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP). At that time we also requested additional information or concerns that could inform our review. On November 26, 2021, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) stated no additional concerns with the proposed proprietary name, Combogesic IV.

3 CONCLUSION

The proposed proprietary name, Combogesic IV, is acceptable.

If you have any questions or need clarifications, please contact Tamika White, OSE project manager, at 301-796-0310.

3.1 COMMENTS TO AFT PHARMACEUTICALS LTD.

We have completed our review of the proposed proprietary name, Combogesic IV, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on August 31, 2021, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [j]

[j] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors Last accessed 10/05/2020.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.

- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[k]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign

[k] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

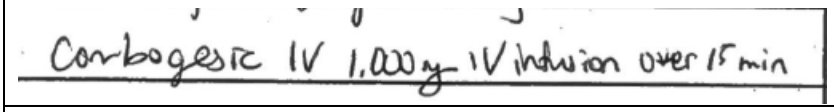
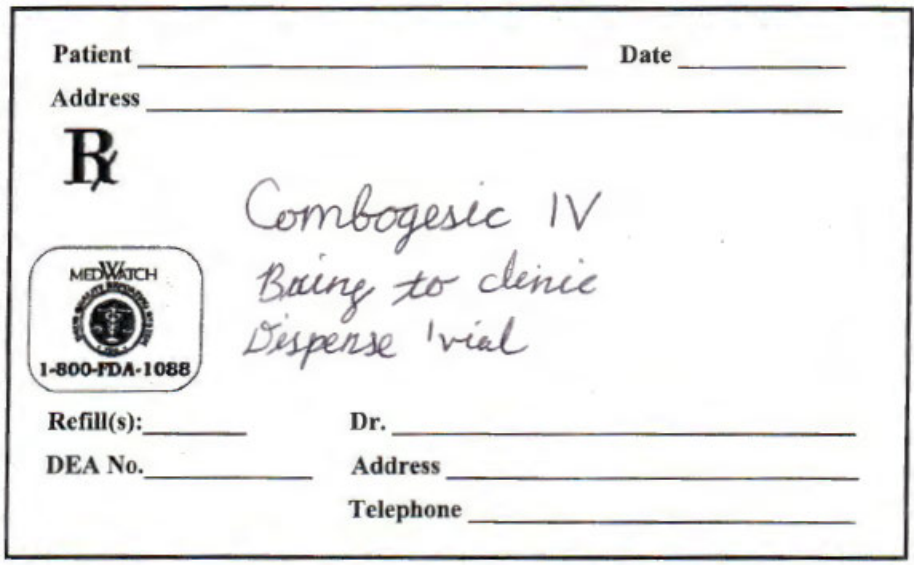
Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Combogesic IV Study (Conducted on September 10, 2021September 10, 2021)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order:  	Combogesic IV Bring to clinic Dispense 1 vial
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Combogesic IV	

FDA Prescription Simulation Responses (Aggregate Report)

261 People Received Study

111 People Responded

Study Name: Combogesic IV

Total	**29**	**34**	**24**	**24**	
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
CANBOGESIC	0	0	0	1	1
CARBOGER	0	0	0	1	1
CARBOGESIC	0	0	0	2	2
CARBOGESIC IV	0	0	0	1	1
COBOGESIC IV	1	0	0	0	1
COMBIGESIC	0	0	1	0	1
COMBIGESIC IV	0	0	1	0	1
COMBOGESIC	6	0	3	4	13
COMBOGESIC IV	22	34	18	8	82
CONBOGESIC	0	0	0	1	1
CONBOGESIC IV	0	0	0	1	1
CONVOGESIC IV	0	0	1	0	1
CORBOGESIC	0	0	0	3	3
CORBOGESIC IV	0	0	0	1	1
CORBOGESIE	0	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Combogesic IV **Established name:** acetaminophen and ibuprofen **Dosage form:** injection **Strength(s):** 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL) **Usual Dose:** 1000 mg/300 mg intravenously over 15 minutes every 6 hours as necessary; (b) (4)	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Combogesic IV	100	Name is subject of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
	N/A	

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Combogesic IV **Established name:** acetaminophen and ibuprofen **Dosage form:** injection **Strength(s):** 1000 mg/300 mg per 100 mL (10 mg/3 mg per mL) **Usual Dose:** 1000 mg/300 mg intravenously over 15 minutes every 6 hours as necessary; (b) (4)	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
	N/A		

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
	N/A	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
	N/A		

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[1].

No.	Name	POCA Score (%)
	N/A	

[1] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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CAMERON D CLARK
11/29/2021 02:38:53 PM

VALERIE S VAUGHAN
11/29/2021 02:40:57 PM

MISHALE P MISTRY
11/29/2021 02:42:09 PM