CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211843Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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:	December 10, 2018
Application Type and Number:	NDA 211843
Product Name and Strength:	Thiola EC (tiopronin) delayed-release tablet, 100 mg and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mission Pharmacal Company
Panorama #:	2018-26027918
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Acting Team Leader:	Sevan Kolejian, PharmD, MBA
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Thiola EC, 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. Mission Pharmacal Company did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Thiola (tiopronin) tablets were approved on August 11, 1988 under NDA 019569. Mission Pharmacal Company submitted a 505 (b) (2) NDA for the reformulated Thiola enteric-coated tablets, Thiola EC, (b) (4) Thiola EC tablets have the same active moiety (tiopronin) as Thiola and the same indication and associated dosing. The Applicant intends to introduce the new enteric-coated (Thiola EC Tablets) formulation into the marketplace upon approval by the FDA. (b) (4) Thus, the applicant submitted the proposed proprietary name, Thiola EC, for review on September 19, 2018.

1.2 PRODUCT INFORMATION

The following Thiola EC product information is provided in the proprietary name submission received on September 19, 2018 and in the proprietary name submission amendment received on October 17, 2018.

- Intended Pronunciation: Th-ī-ō-l-ə E-C
- Active Ingredient: tiopronin
- Indication of Use: reducing and cystine-binding thiol drug (CBTD) indicated for the prevention of cystine (kidney) stone formation in (b) (4) high fluid intake, alkali and diet modification. (b) (4)
- Route of Administration: oral
- Dosage Form: delayed-release tablet
- Strength: 100 mg and 300 mg
- Dose and Frequency:
  - THIOLA EC may be initiated at a dosage of 800 mg/day in adult patients with cystine stones. In a multiclinic trial, average dose of THIOLA was about 1000 mg/day. (b) (4)
  - In children, initial dosage may be based on 15 mg/kg/day. (b) (4), THIOLA EC should be taken in 3 divided doses with or without food at the same times each day.

— [redacted] (b) (4)

— In patients who had shown severe toxicity to d-penicillamine, THIOLA EC might be initiated at a lower dosage. Urinary cystine should be measured at 1 month after THIOLA EC treatment, and every 3 months thereafter. THIOLA EC dosage should be readjusted depending on the urinary cystine value. In vitro dissolution experiments indicate that alcohol may shorten the extended release of Thiola EC.

- How Supplied: THIOLA EC is an enteric-coated, delayed release tablet available for oral administration as 100-mg (NDC 0178-0902-01) and 300-mg (NDC 0178-0901-90) tablets. Thiola EC 100-mg tablets are in bottles of 300 tablets. Each 100-mg tablet is imprinted with "T1" on one side with red ink and blank on the other side. Thiola EC 300-mg tablets are in bottles of 90 tablets. Each 300-mg tablet is imprinted with "T3" on one side with red ink and blank on the other side.
- Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) *[see USP Controlled Room Temperature]*.
- Reference Listed Drug/Reference Product: Thiola (NDA 019569)

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Thiola EC would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) concurred with the findings of OPDP's assessment for Thiola EC. However, the Division of Cardiovascular and Renal Products (DCRP) provided additional comments for consideration (see section 2.2.5).

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Thiola EC.

2.2.1 United States Adopted Names (USAN) Search

The proposed proprietary name, Thiola EC, contains the United States Adopted Name (USAN) stem '-io-' in the infix position used by the USAN Council to indicate iodine-containing contrast media products.[a] Proprietary names should usually not incorporate USAN stems in the position

[a] USAN stem search conducted on October 11, 2018.

that USAN designates for the stem.[b] The use of a USAN stem within proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs, which may compromise patient safety. To reduce the potential for confusion, USAN stems should usually not be incorporated into proprietary names.

However, we determined that the two-letter stem 'io' is often not distinct enough to be recognized as a USAN stem. We also note that USAN has used the stem 'io' in established names (e.g., vortioxetine) as well as in other USAN stems (-tioxetine). This has resulted in conflicting stems, and therefore in those instances, the stem does not support the USAN Council naming system or accurately indicate the pharmacological or chemical trait of the drug. Additionally, based on our post marketing experience, we do not have the same safety concerns with the two-letter stems, including 'io', that we have identified with three or more letter USAN stems.[c,d]

Therefore, we do not object to the inclusion of the two-letter USAN stem 'io', incorporated into the proposed proprietary name Thiola EC.

2.2.2 Components of the Proposed Proprietary Name

Mission Pharmacal Company indicated in their submission that the proposed proprietary name, Thiola EC, is comprised of multiple words including the root name, Thiola (which is an immediate release oral tablet dosage form approved under NDA 019569) and a modifier, EC (established modifier nomenclature intended to convey the enteric-coated property of the proposed Thiola EC tablet).

The proposed Thiola EC will contain the same active ingredient (tiopronin) as the existing Thiola (tiopronin) immediate release oral tablet product. Additionally, we are not aware of any postmarketing cases of name confusion with the root name Thiola (See section 2.2.6). Thus, we find the use of the root name Thiola for the proposed product acceptable. The use of the modifier, EC, is evaluated in Section 2.2.5.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, October 5, 2018 e-mail, the Division of Cardiovascular and Renal Products (DCRP) did not forward any comments or concerns relating to Thiola EC at the initial phase of the review. However, DCRP provided additional comments for our consideration in response to our additional queries at a later time (see section 2.2.5).

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[b] Guidance for industry: Best practices in developing proprietary names for drugs. Draft Guidance May 2014. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM39899

[c] Institute for Safe Medication Practices. Safety briefs: Aripiprazole or rabeprazole? ISMP Med Saf Alert Acute Care. 2003;8(8):1-3.

[d] Institute for Safe Medication Practices. Safety Briefs. ISMP Med Saf Alert Acute Care. 2002;7(17):1-2.

2.2.4 FDA Name Simulation Studies

Seventy-six practitioners participated in DMEPA's prescription studies for Thiola EC. 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 verbal and written prescription studies.

2.2.5 Analysis of the Proposed Modifier "EC"

The Modifier "EC" is currently utilized in the marketplace. It is commonly used to convey the enteric coated property of the proposed product. The Applicant is using the modifier "EC" in the proposed name, Thiola EC, to denote the enteric coated property of the newly proposed and reformulated Thiola EC enteric-coated, delayed-release tablet. The use of the modifier "EC" to convey that the product is an enteric-coated, delayed-release tablet dosage form is contingent upon the product meeting the Agency's criteria for the designation.

We contacted the Division of Cardiovascular and Renal Products (DCRP) on October 16, 2018, via email communication to confirm that the proposed Thiola EC tablet is indeed a delayed-release, enteric coated oral dosage form as the modifier "EC" implies. DCRP communicated on October 16, 2018 via email communication that the proposed tablet has an enteric coating (b) (4) (b) (4) DCRP also communicated that per labeling guidance[e], only DR (for delayed release) or ER (for extended release) descriptors should be used, instead of the EC (for enteric coated) modifier for this product.

On November 19, 2018, via email communication, we acknowledged DCRP's concern regarding the appropriateness of using the modifier "EC" in the proposed proprietary name, and agreed that per the referenced labeling guidelines, the descriptor 'enteric coated' should not appear in the established name of this product. However, this guidance does not apply to proprietary naming. We informed DCRP that we do not object to the modifier "EC" in the proprietary name for this product since the reformulated tiopronin tablet is enteric coated, and thus, EC is not inaccurate, misleading, or unacceptable. There is also precedence for the use of the modifier "EC" in positions both before and after the root name in other currently marketed proprietary names which describe enteric coated, delayed release tablet dosage forms (e.g., Entocort EC, EC-Naprosyn, and Videx EC per ISMP's suffix list accessed at https://www.ismp.org/sites/default/files/attachments/2018-04/drugnamesuffixes.pdf). Of note, as an example, Videx EC prescribing information and container labels include the proprietary name "VIDEX EC" (containing the modifier "EC"), as well as the established name "(didanosine, USP) delayed-release capsules" (containing the dosage form descriptor "delayed-release"). Last, we have not identified any proprietary names containing the modifier "DR" for delayed release.

(b) (4) We informed DCRP on November 28, 2018, via email communication that we defer to DCRP for the determination of the established name for this product.

[e] https://www fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162038 htm

Additionally, on November 20, 2018, DCRP expressed concern about whether the proprietary name, Thiola EC, would suggest improved tolerability relative to the currently marketed tiopronin product (b) (4)

On November 27, 2018, we informed OPDP of DCRP's concerns via email communication and asked OPDP for their input on whether or not the proposed name, Thiola EC, would be misleading from a promotional or misbranding perspective, (b) (4) and whether there is precedent to support an objection to the name in this case.

OPDP responded on November 27, 2018 via email communication stating that "from a promotional perspective, OPDP does not have any objections to Thiola EC. The use of the modifier EC is not false or misleading", and "there is precedence for the use of the modifier in other currently marketed proprietary names which describe enteric coated drug products. Therefore, the suggestion that the accurate representation of the modifier for the proprietary name will misleadingly imply that the drug improves tolerability, without additional context, is tenuous." (b) (4) DCRP did not provide any further comments pertaining to the proposed proprietary name.

In our evaluation, we also considered the risk of name confusion if the modifier "EC" is dropped. We acknowledge that modifiers may be omitted or overlooked, thereby risking wrong drug formulation errors if the proposed Thiola EC is prescribed or transcribed without the modifier or with its established name tiopronin without the modifier EC. (b) (4) . The proposed Thiola EC (tiopronin) enteric-coated, delayed-release tablet and currently marketed Thiola immediate release tablet share a tablet strength (e.g., 100 mg) and the same dosing for their shared indication. We emailed DCRP on October 16, 2018 to inquire about the clinical outcome if there is a mix-up in clinical practice between the proposed Thiola EC (tiopronin) enteric-coated, delayed-release tablet and currently marketed Thiola immediate release tablet. DCRP confirmed on October 18, 2018 that there should be no difference in clinical outcome between the two formulations.

After assessing the benefit versus risk of the use of the modifier, we believe the modifier EC will help to identify the reformulated dosage formulation (e.g., enteric-coated, delayed-release tablet), accurately denotes the enteric coated property of the product, and may help to provide an incremental level of safety in preventing wrong drug formulation errors between Thiola and the proposed Thiola EC (b) (4) . Therefore, we find the use of the modifier "EC" for the proposed proprietary name, Thiola EC, acceptable.

2.2.6 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving Thiola that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	October 12, 2018
Drug Name	THIOLA [product name]
	All names associated with THIOLA [Product Verbatim]: THIOLA;THIOLA (TIOPRONIN);THIOLA (TIOPRONIN) (TIOPRONIN);THIOLA (TIOPRONIN) TABLETS;THIOLA 100 MG;THIOLA 100 MG, MISSION PHARMACAL COMPANY;TIOPRONAN (THIOLA)-MISSION
Event (MedDRA Terms)	**DMEPA Official PNR Name Confusion Search Terms Event List:** Preferred Terms: CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR DRUG ADMINISTRATION ERROR DRUG DISPENSING ERROR DRUG PRESCRIBING ERROR INTERCEPTED DRUG DISPENSING ERROR INTERCEPTED DRUG PRESCRIBING ERROR INTERCEPTED MEDICATION ERROR MEDICATION ERROR PRODUCT NAME CONFUSION TRANSCRIPTION MEDICATION ERROR Lower Level Terms: INTERCEPTED PRODUCT SELECTION ERROR INTERCEPTED WRONG DRUG PRODUCT SELECTED INTERCEPTED WRONG DRUG SELECTED PRODUCT SELECTION ERROR WRONG DEVICE DISPENSED WRONG DRUG ADMINISTERED WRONG DRUG DISPENSED WRONG DRUG PRESCRIBED WRONG DRUG PRODUCT SELECTED WRONG DRUG SELECTED WRONG PRODUCT SELECTED
Event Preferred Term	MEDICATION ERROR
Date Limits	N/A

The search retrieved one case, which after evaluation, was determined not to be relevant to this proprietary name review.

2.2.7 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Cardiovascular and Renal Products (DCRP) via e-mail on December 3, 2018. At that time, we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Cardiovascular and Renal Products (DCRP) on December 10, 2018, they stated no additional concerns with the proposed proprietary name, Thiola EC.

3 CONCLUSION

The proposed proprietary name, Thiola EC, is acceptable.

If you have any questions or need clarifications, please contact Wana Manitpisitkul, OSE project manager, at 240-402-4156.

3.1 COMMENTS TO MISSION PHARMACAL COMPANY

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

If any of the proposed product characteristics as stated in your proprietary name submission, received on September 19, 2018, and in your proprietary name submission amendment, received on October 17, 2018, 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. [f]

[f] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***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[g]. 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

[g] 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.

Three 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 or verbal pronunciation of the drug name. 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 orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

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%).

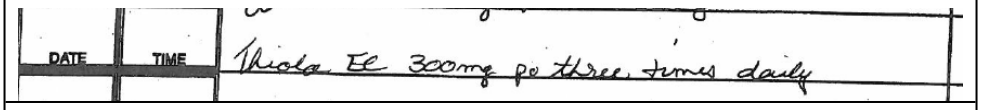
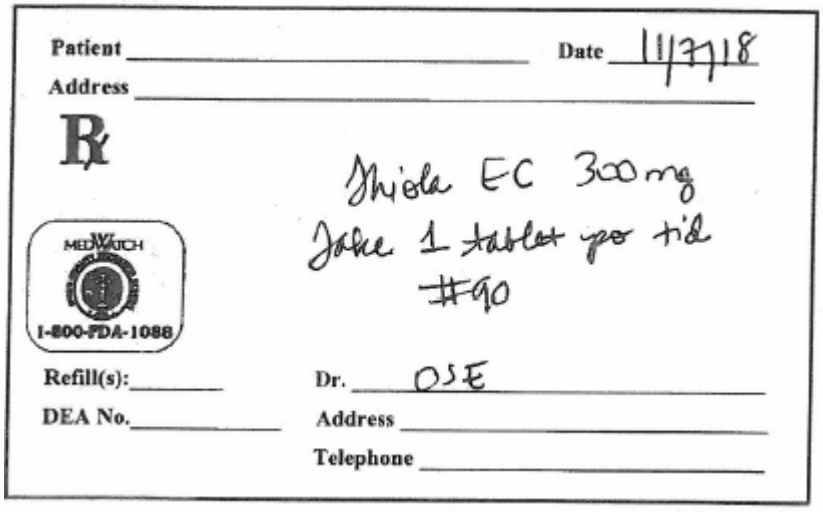
Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity 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. Thiola EC Study (Conducted on November 7, 2018)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  Outpatient Prescription:  	Thiola EC 300 mg Take 1 tablet by mouth three times a day Dispense #90

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Thiola EC

As of Date 11/27/2018

252 People Received Study

76 People Responded

Study Name: Thiola EC

Total	21	21	34	76
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
FIOLA EC	0	2	0	2
THILOA EC	0	0	1	1
THIOLA	2	0	0	2
THIOLA EC	17	7	10	34

THIOLA EC 300 MG	0	0	1	1
THIOLA ER	0	0	17	17
THIOLE EC	1	0	0	1
THISLA EC	1	0	0	1
THYOLA EC	0	3	0	3
TRIOLA EC	0	0	3	3
TRIOLA ER	0	0	2	2
VIOLA EC	0	7	0	7
XIOALA EC	0	1	0	1
ZYOLA EC	0	1	0	1

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

/s/

SARAH E THOMAS
12/10/2018

SEVAN H KOLEJIAN
12/10/2018

DANIELLE M HARRIS
12/10/2018