

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210365Orig1s000

PROPRIETARY NAME REVIEW(S)

Proprietary Name Review Memorandum

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:	April 19, 2018
Application Type and Number:	NDA 210365
Product Name and Strength:	Epidiolex (cannabidiol) oral solution 100 mg/mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Applicant Name:	GW Research Ltd
Panorama #:	2018-21548356
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS
DMEPA Director:	Todd Bridges, RPh

1. REASON FOR REVIEW

The memorandum is written because DMEPA management disagrees with some of Dr. Rider's position with respect to the acceptability of the proposed proprietary name, Epidiolex for cannabidiol oral solution (NDA 210365), and we describe the points of disagreement below. This memorandum is intended to summarize DMEPA's overall decision based on our evaluation of Dr. Rider's review (Panorama # 2018-21548356), and the supporting information submitted in the proposed proprietary name request for reconsideration received March 9, 2018, and the amendment to the request, received March 16, 2018 to NDA 210365.

2. REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Epidiolex*** on June 24, 2015 under IND 120055. However, we found the name, Epidiolex*** unacceptable due to 1) orthographic and phonetic similarities with the over-the-counter product name, Pedia-lax and 2) the presence of a USAN stem under IND 120055 on November 10, 2015.^a Thus, the Applicant submitted the name, (b) (4)***, for review on April 4, 2016. We found the name, (b) (4)*** conditionally acceptable under IND 120055 on September 26, 2016.^b The Applicant submitted a request for reconsideration of the proposed proprietary name, Epidiolex***, under NDA 210365 on March 9, 2018, and submitted an amendment to the request on March 16, 2018.

3. MATERIALS REVIEWED

We reviewed the following materials:

- Review authored by Ms. Justine Harris (Panorama #2015-792227)
- Review authored by Dr. Briana Rider (Panorama #2018-21548356; attached)
- Proposed proprietary name request for reconsideration for Epidiolex received March 9, 2018, and the amendment to the request, received March 16, 2018

4. DISCUSSION

In Panorama review # 2018-21548356, Dr. Rider documents her assessment of the materials submitted by GW Research Ltd in their request for reconsideration for Epidiolex. Given the amount of time that has passed since the original review (Panorama #2015-792227), Dr. Rider notes she conducted a full safety and misbranding review of the proposed proprietary name in addition to considering the information submitted by the applicant in the request for reconsideration. After careful consideration of the information submitted, Dr. Rider concludes that Epidiolex is prone to confusion with Pedialax and, thus, is unacceptable based on 21 CFR 201.10(c)(5), which states "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or

^a Harris, J. Proprietary Name Review for Epidiolex (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 10. Panorama No. 2015-792227.

^b Whaley, E. Proprietary Name Review for (b) (4) (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 26. Panorama No. 2016-7400543.

pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.”

As part of her assessment, Dr. Rider carefully considers each of the Applicant’s assertions and documents the following position for each:

- Dr. Rider agrees with the Applicant that the USAN stem ‘-io-’ in Epidiolex, is unlikely to be distinct enough to be recognized as a USAN stem.
- Dr. Rider disagrees with the Applicant that the differences in pronunciation are sufficient to prevent confusion between Epidiolex and Pedialax. She also asserts that the names are orthographically similar and cites the POCA scores and postmarketing cases of confusion with other name pairs to support her position.
- Dr. Rider disagrees with the Applicant that the proposed restricted distribution plan is sufficient to prevent confusion between Epidiolex and Pedialax.
- Dr. Rider disagrees with the Applicant that the differences in marketing status (OTC vs Rx) are sufficient to prevent confusion between Epidiolex and Pedialax.
- Dr. Rider disagrees with the Applicant that the differences in product characteristics (e.g., dosage forms, routes of administration, administration technique) are sufficient to prevent confusion between Epidiolex and Pedialax.
- Dr. Rider disagrees with the Applicant that the differences in carton labeling are sufficient to prevent confusion between Epidiolex and Pedialax. While she agrees the labels are labeling are well differentiated, she asserts that the labels and labeling cannot mitigate the risk of wrong drug medication errors that occur during the prescribing or transcribing phases of the medication use process.
- Dr. Rider disagrees with the Applicant that the absence of name confusion medication errors during clinical trial and expanded access program experience can be used to support the conclusion that consumer confusion would be rare. She notes that the conditions of the clinical trial and expanded access program may not be predictive of real use scenario.
- Dr. Rider agrees with the Applicant that missing one dose of Epidiolex is unlikely to result in harm. However, she cites a concern with prolonged wrong drug exposure and cites postmarketing cases of name confusion to support her position that wrong drug medication errors can persist for prolonged periods before the error is discovered.

We carefully considered Dr. Rider’s position and supporting documentation on each of the points above, and when considered independently, we agree with her assessment of each point. We agree none of the mitigations presented by the Applicant are sufficient to prevent name confusion between Epidiolex and Pedialax when considered independently. However, when all of the mitigations are considered in totality, we find the risk of name confusion is mitigated to an acceptable level. Additionally, the Pedialax product line consists of several products with differing active ingredients, dosage forms, and routes of administration, thus, it is likely that a prescription for Pedialax would indicate the intended product, which may further reduce the likelihood of confusion. We find that any residual risk of name confusion is further mitigated by the well-differentiated labels and labeling, which may further reduce the risk of a medication error reaching the patient.

We note that Dr. Rider did not address the Applicant’s assertion that there are serious and probable safety impacts that would result from changing the Epidiolex proprietary name, if the

name were to be found unacceptable, including the potential for counterfeiters to market unapproved imitations of Epidiolex and potential for confusion with patients who may already be familiar with the name Epidiolex. We acknowledge the Applicant's comments on this matter, however, we find the Applicant's assertions are not directly relevant to our safety assessment of the name Epidiolex, or to the risk of name confusion between Epidiolex and Pedialax.

In summary, we disagree with Dr. Rider's conclusion regarding the overall acceptability of the proprietary name, Epidiolex. We find that when considered in totality, the proposed mitigations minimize the likelihood of name confusion between Epidiolex and Pedialax resulting in errors in the clinical setting. Dr. Rider identified no other safety or regulatory basis for recommending against the acceptance of the Epidiolex name at this time. We reviewed the remainder of her evaluation and did not identify any outstanding concerns.

5. CONCLUSIONS AND RECOMMENDATIONS

We conclude that the proposed proprietary name, Epidiolex, for cannabidiol oral solution (NDA 210365) is conditionally acceptable and recommend that this be conveyed to the applicant.

If you have further questions or need clarifications, please contact Monique Killen, OSE project manager, at 240-402-1985.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the information submitted in support of your Request for Reconsideration of the proposed proprietary name, Epidiolex. We conclude that your proposed name, Epidiolex, is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 9, 2018, submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

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)

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Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Applicant Name:	GW Research Ltd
Panorama #:	2018-21548356
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

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1 INTRODUCTION

This review responds to a March 9, 2018, request from GW Research Ltd, to reconsider the proposed proprietary name, Epidiolex, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Epidiolex*** on June 24, 2015 under IND 120055. However, we found the name, Epidiolex*** unacceptable due to 1) orthographic and phonetic similarities with the over-the-counter product name, Pedia-lax and 2) the presence of a USAN stem under IND 120055 on November 10, 2015.^c Thus, the Applicant submitted the name, (b) (4)***, for review on April 4, 2016. We found the name, (b) (4)*** conditionally acceptable under IND 120055 on September 26, 2016.^d

The Applicant submitted a request for reconsideration of the proposed proprietary name, Epidiolex***, under NDA 210365 on March 9, 2018, and an amendment to the request on March 16, 2018.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on March 9, 2018.

- Intended Pronunciation: EH-pee-DIGH-oh-leks
- Active Ingredient: cannabidiol
- Indication of Use: Adjunctive treatment of seizures associated with Dravet Syndrome (DS) and seizures associated with Lennox-Gastaut Syndrome (LGS)
- Route of Administration: Oral
- Dosage Form: Solution
- Strength: 100 mg/mL
- Dose and Frequency: The recommended starting dose is 2.5 mg/kg twice daily (5 mg/kg per day) for 1 week. The daily dose should be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg per day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg per day). Based on individual clinical response and tolerability, the dose can be increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg per day) to 10 mg/kg twice daily (20 mg/kg per day). The maximum recommended effective dose is 20 mg/kg/day. (b) (4)
- How Supplied: (b) (4) mL amber glass multi-use bottle, a bottle adapter and two 5 mL oral syringes
- Storage: Store at room temperature between 68°F to 77°F (20°C to 25°C)

^c Harris, J. Proprietary Name Review for Epidiolex (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 10. Panorama No. 2015-792227.

^d Whaley, E. Proprietary Name Review for (b) (4) (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 26. Panorama No. 2016-7400543.

2 MATERIALS AND METHODS

We used Failure Mode and Effects Analysis (FMEA) in our review of GW Research Ltd.'s request for reconsideration. We also considered the safety concerns described in our previous review of the proposed proprietary name, Epidiolex, as well as information provided by GW Research Ltd in the request for reconsideration.

In the March 9, 2018 request for reconsideration and March 16, 2018 amendment, the Applicant stated that:

1. The inclusion of the USAN stem '-io-' presents a low risk of confusion, comparable to other FDA approved products (See section 2.2.1 for additional detail).
2. The proprietary name Epidiolex presents a low risk of confusion with Pedialax
 - a. The common and intended pronunciation of Epidiolex places the emphasis on the first and third syllables and the vowel pronunciation varies at every syllable except one, and the stress varies at that syllable.
 - b. Epidiolex will only be sold through a specialty pharmacy directly to patients' homes via mail (restricted distribution).
 - c. If a patient were to take a prescription for Epidiolex to a local pharmacy and the pharmacist were to mistake the product for Pedia-Lax, the pharmacist would not have any prescription Pedia-Lax product to dispense, because Pedia-Lax is only available OTC.
 - d. Within the patient's home setting, the risk of confusion is likely to be quite low because the products do not look alike.
 - e. The different dosing configurations between the two products will mitigate any potential confusion.
 - f. Data derived from clinical studies and expanded access programs has not produced any reports of consumers confusing Epidiolex with any other product, including Pedia-Lax and support the conclusion that any consumer confusion would likely be very rare.
3. A patient would experience few negative consequences from accidentally receiving a dose of Pedia-Lax rather than Epidiolex.
4. Altering the proprietary name, Epidiolex, will result in safety issues.

Given the length of time that has passed since our initial review of the proposed proprietary name, Epidiolex, we conducted a full safety and misbranding review of the name in addition to considering the information submitted by the applicant in the request for reconsideration. The following sections provide information obtained and considered in the overall reconsideration of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Neurology Products (DNP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

The proposed proprietary name, Epidiolex, 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.^e We previously determined the proposed proprietary name, Epidiolex, to be unacceptable because it contains the United States Adopted Name (USAN) stem, ‘-io-.’

We considered the safety concerns with respect to the incorporation of the USAN stem “io” in the infix position of the proposed proprietary name as described in our previous review as well as information provided by GW Research Ltd.

In their request for reconsideration, the Applicant provided the following information for our consideration:

1. The ‘io’ stem is regularly included in proprietary names that do not contain iodine.
2. The use of the ‘io’ in the infix of the name, Epidiolex, can be distinguished from the USAN stem designating iodine-containing contrast media.
3. Although USAN identifies both ‘io’ as a stem for nonproprietary names in both the prefix and infix position, the preference in naming iodine-containing contrast media is for the ‘io’ stem to appear in the prefix position and the National Library of Medicine now only identifies the iodine-containing contrast media by words with ‘io’ in the prefix position.
4. USAN uses ‘io’ in other stems, including ‘-tioxetine’ and ‘-tiostat’ and has endorsed the use of use of the letter string ‘diol’ in nonproprietary names, such as ‘bolandiol’.
5. The market has already come to expect that the ‘io’ vowel pair may be present in a proprietary or nonproprietary name for a drug that does not contain iodine.
6. Given the common use of ‘io’ in proprietary names, there is little risk of confusion of Epidiolex with an iodine-containing imaging agent.

In light of this information, we reconsidered the acceptability of the proprietary name, Epidiolex, and 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.^{f,g}

Therefore, we do not object to the inclusion of the two-letter USAN stem ‘io’, incorporated into the proposed proprietary name Epidiolex.

^e USAN stem search conducted on March 29, 2018.

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

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

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Epidiolex, contains the chemical compound name “diol”, which is a chemical compound containing two hydroxyl groups. We have determined that inclusion of the chemical compound name “diol” within the name would not be misleading or lead to confusion.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, March 30, 2018 e-mail, the Division of Neurology Products (DNP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Forty-nine practitioners participated in DMEPA’s prescription study #1, conducted March 16, 2018 and seventy practitioners participated in DMEPA’s prescription study #2, conducted March 23, 2018.^h The responses did not directly overlap with any currently marketed products or any products in the pipeline.

One respondent in the March 16th voice study interpreted the proposed proprietary name as “Pediolix”, which is a close hit to the marketed product, Pedialax. We evaluated the name pair, Epidiolex and Pedialax, further and find there is a risk for name confusion due to phonetic and orthographic similarity (See *Section 4.1*).

Appendix B.1 and Appendix B.2 contain the results from the verbal and written prescription studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA searchⁱ identified 196 names with the combined score of $\geq 55\%$ or individual orthographic or phonetic score of $\geq 70\%$. We had identified and evaluated some of the names in our previous proprietary name review. 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 55 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. Similarity Category	Number of Names
Highly similar name pair: combined match percentage score $\geq 70\%$	4

^h A second prescription study was conducted due to the fact that the first prescription study was closed prematurely to accommodate scheduled upgrades to the prescription simulation software.

ⁱ POCA search conducted on March 14, 2018 in version 4.2.

Moderately similar name pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$	36
Low similarity name pair: combined match percentage score $\leq 54\%$	15

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

We determined 54 of the 55 names will not pose a risk for confusion as described in Appendices C through H. However, the proposed name could be confused with Pedialax. The rationale for the risk of confusion is described in Section 4.1.

2.2.8 Communication of DMEPA’s Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Neurology Products (DNP) via e-mail on April 19, 2018. At that time, we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DNP on April 19, 2018, they stated no additional concerns with the proposed proprietary name, Epidiolex.

3 DISCUSSION

This section summarizes our evaluation of the information provided by the Applicant in support of a reconsideration of the proposed proprietary name, Epidiolex.

PHONETIC & ORTHOGRAPHIC DIFFERENCES

In their request for reconsideration, GW Research Ltd. clarifies that the ‘ordinary consumer pronunciation’ of Epidiolex is EH-pee-DIGH-oh-leks ^{(b) (4)} as previously indicated in their June 24, 2015 request for proprietary name review submitted under IND 120055. They also note that the vowel pronunciation between the two names, Epidiolex and Pedialax, varies at every syllable except one and the stress varies at that syllable (see below).

Pronunciation Guide: Epidiolex and Pedia-Lax

PR ¹⁵ :	EH	-	pee	-	DIGH	-	oh	-	leks
			PEE	-	dee	-	uh	-	laks
IPA ¹⁶ :	'ε	-	pi:	-	ˌdaɪ	-	oʊ	-	lɛks
			'pi:	-	di:	-	ʌ	-	læks

We acknowledge that, when comparing Epidiolex to Pedialax, the vowels within three of the syllables differ (i vs. e, o vs. a, e vs. a) and the vowel pronunciation may vary if pronounced as intended. However, the vowels may sound similar when pronounced depending on different accents, dialects, or pronunciations. Furthermore, FDA’s Phonetic and Orthographic Computer Analysis (POCA) software calculates an 83% phonetic score for this name pair, indicating high phonetic similarity.¹

The similarity in pronunciation of this name pair is further supported by the results of the FDA’s Name Simulation Studies where one respondent in the March 16, 2018 voice study (conducted using the intended pronunciation: EH-pee-DIGH-oh-leks) interpreted the proposed proprietary

name as “Pediolix”, which is a close hit to Pedialax. Given that the study was conducted with a relatively small number of participants and the likelihood of observing an error in such a small study is low, the findings further validate our safety concerns between this name pair.

Orthographically, we note that the names Epidiolex and Pedialax begin with different letters and postmarketing evidence does not suggest that the letters E and P look similar. However, evidence suggests that differences in the prefix of the name may not provide adequate differentiation if the rest of the name is highly similar. For example, reports of mix-ups between Alkeran and Leukeran have been reported and the same letter characters at the ending of these names has been identified as contributing to look-alike confusion.^j In another example, a handwritten prescription for Prenexa with instructions to take one tablet by mouth daily was misinterpreted and Ranexa 500 mg tablets were dispensed to the patient. The patient used Ranexa for a year before the error was discovered.^k Other examples from *ISMP’s List of Confused Drug Names* include, Apresoline and Priscoline, Natru-Vent and Atrovent, Enjuvia and Januvia, and Indinavir and Denavir.^l The orthographic similarity of the name pair, Epidiolex and Pedialax, is further supported by FDA’s Phonetic and Orthographic Computer Analysis (POCA) which calculates a 71% orthographic score, indicating high orthographic similarity.^l

Thus, the phonetic and orthographic differences of the names Epidiolex and Pedialax are not sufficient to minimize medication errors between these products.

USE OF SPECIALTY PHARMACY TO DISTRIBUTE EPIDIOLEX

The Applicant’s request for reconsideration states that ‘a local pharmacist would not fill an Epidiolex prescription because it will not be stocked in local pharmacies and the prescription will only be sent to the specialty pharmacy’. We have taken into consideration that Epidiolex is proposed to be dispensed by specialty pharmacies only (closed to public). However, restricted distribution of Epidiolex may not reduce risk associated with the confusion of similar names. We have reports of name confusion with other products marketed under restricted distribution systems.^{m,n} In one case, a physician wrote an order for Tricor 125 mg BID for a new admission with pulmonary arterial hypertension. The physician was not familiar with Tracleer and misheard the patient when he stated he had been taking Tracleer 125 mg BID at home.^m In another case, the progesterone receptor antagonist Mifeprex (mifepristone) was prescribed for a patient with meningioma. The prescriber did not realize that the drug would be supplied only to licensed physicians with a prescriber agreement. The prescription was filled at a community pharmacy where Cytotec (misoprostol) was mistakenly dispensed. The patient took the medication for approximately two weeks prior to the error being discovered.ⁿ Epidiolex’ restricted distribution

^j Institute for Safe Medication Practices. Safety briefs. *ISMP Med Saf Alert Acute Care*. 2000;5(1):1-2.

^k Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. *ISMP Med Saf Alert Community/Ambulatory Care*. 2012; 11(3): 1-4.

^l *ISMP’s List of Confused Drug Names* [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 APR 05]. Available from <https://www.ismp.org/recommendations/confused-drug-names-list>

^m Institute for Safe Medication Practices. Safety briefs: Don’t Confuse TRACLEER (bosentan) with TRICOR (fenofibrate). *ISMP Med Saf Alert Acute Care*. 2003;8(13):2.

ⁿ Institute for Safe Medication Practices. Safety briefs: Mifepristone (MIFEPREX) and Misoprostol (CYTOTEC) mix-up. *ISMP Med Saf Alert Community/Ambulatory Care*. 2003;2(1):1.

status and unavailability in the pharmacy may lead to unfamiliarity with the product which could contribute to wrong drug medication errors due to confirmation bias. Additionally, the restricted distribution the Applicant proposed is voluntary and can be stopped at any time. Therefore, our safety concern is not diminished with the proposed restricted distribution plan for this product.

DIFFERENCE IN PRESCRIPTION STATUS (RX VERSUS OVER-THE-COUNTER)

GW Research Ltd.'s request for reconsideration states that 'even if a patient were to take a prescription to a pharmacy and the pharmacist were to mistake the product for Pedia-Lax, the pharmacist would not have any prescription Pedia-Lax product to dispense, because Pedia-Lax is only available OTC'. We acknowledge Epidiolex will be available as a prescription drug product whereas, Pedialax is available over-the-counter (OTC). However, we have determined that this difference in marketing status may not prevent errors between these products because postmarketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and OTC drug products.^{o, p, q, r, s, t} Examples of reported errors involve confusion between:

- Sudafed (OTC) and Sotalol (rx)^o
- Benadryl (OTC) and Benazepril (rx)^p
- Cetirizine (OTC) and Sertraline (rx)^q
- Mucinex (OTC) and Mucomyst (rx)^r
- Motrin (OTC) and Neurontin (rx)^s
- Colace (OTC) and Cozaar (rx)^t

In the case of the Benadryl and Benazepril mix-up, a pharmacist misinterpreted a fax for Benazepril as Benadryl (diphenhydramine). A bottle of diphenhydramine capsules was dispensed to the patient and the patient took diphenhydramine daily for three weeks before the error was recognized.^p Furthermore, orders for both products, Epidiolex and Pedia-Lax, could be encountered in the inpatient setting. For example, if Epidiolex is misinterpreted as Pedia-Lax during medication reconciliation, a laxative could be ordered. This is evidenced by a mix-up involving Mirapex and Miralax where the physician misheard the patient while taking his

^o Institute for Safe Medication Practices. Safety briefs: Sudafed-Sotalol mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2006; 5(5): 1-5.

^p Institute for Safe Medication Practices. Safety briefs: Benazepril confused with Benadryl. ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.

^q Institute for Safe Medication Practices. Safety briefs: Sound-alike names. ISMP Medication Safety Alert! Community/Ambulatory Care Edition. 2009; 8(9): 1-7.

^r Institute for Safe Medication Practices. Safety briefs: Mucinex-Mucomyst: Too close for comfort. ISMP Med Saf Alert Community/Ambulatory Care. 2005; 4(1): 1-4.

^s Institute for Safe Medication Practices. Safety briefs: From the database (Regarding Motrin and Neurontin confusion). ISMP Medication Safety Alert! Community/Ambulatory Care Edition. 2009; 8(2): 1-5.

^t Institute for Safe Medication Practices. Safety briefs: More on confirmation bias. ISMP Med Saf Alert Acute Care. 1996;1(23):1-2.

medication history.^u Additionally, despite Pedialax' OTC status, approximately ^{(b) (4)} prescriptions for Pedialax were dispensed in 2017 through in the U.S. outpatient retail pharmacies.^v Therefore, the difference in marketing status is not sufficient to minimize medication errors between these products.

DIFFERENCE IN PRODUCT CHARACTERISTICS

In the Applicant's request for reconsideration, they state 'the different dosing configurations between the two products is also important to note and will mitigate any potential confusion'. We acknowledge the Pedialax product line consists of products with differing active ingredients, dosage forms, and routes of administration (see Table below) and that only one of the six available product configurations for Pedialax is an oral liquid, comparable to the Epidiolex oral solution.

Pedialax Products						
Active ingredient	Docusate sodium	Glycerin	Glycerin	Magnesium hydroxide	Sodium phosphate, dibasic and sodium phosphate, monobasic	<i>Lactobacillus reuteri</i>
Purpose	Stool Softener	Hyperosmotic Laxative	Hyperosmotic Laxative	Saline Laxative	Saline Laxative	Probiotic
Dosage Form	liquid	Liquid suppository	Suppository	Chewable tablet	Enema	Chewable tablet
Route	Oral	Rectal	Rectal	Oral	Rectal	Oral
Strength	50 mg in 15 mL	2.8 grams	1 gram	400 mg	3.5 grams and 9.5 grams in 66 mL	At least 100 million live cultures

^u Institute for Safe Medication Practices. Safety briefs: Mirapex and Miralax confusion. ISMP Med Saf Alert Acute Care. 2002;7(20):1-3.

^v IQVIA National Prescription Audit. Year 2017. Extracted April 6, 2018.

Dose & Frequency	Doses may be taken as a single daily dose or in divided doses. Children under 2: ask a doctor Children 2-12 years: 1-3 tablespoons. Maximum dose per day: 3 tablespoons	Children under 2: ask a doctor Children 2-6 years: 1 suppository per 24 hours, or as directed by a doctor	Children under 2: ask a doctor Children 2-6 years: 1 suppository per 24 hours, or as directed by a doctor	Doses may be taken as a single daily dose or in divided doses. Drink a full glass of liquid with each dose. Children under 2: ask a doctor Children 2-6 years: starting dose: 1-3 tablets. Maximum dose per day: 3 tablets Children 6-12 years: starting dose: 3-6 tablets. Maximum dose per day: 6 tablets	Children under 2: do not use Children 2-5 years: one-half bottle per day Children 5-11 years: 1 bottle per day or as directed by a doctor	Children 2-11 years: Chew 1 tablet daily.
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However, postmarketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and over-the-counter product line extensions. Similar to Pedialax, products in the Benadryl product-line also contain differing active ingredients (diphenhydramine, camphor, or diphenhydramine in combination with phenylephrine or zinc acetate), dosage forms (tablet, capsule, spray, cream, solution, gel, liquid), and routes of administration (oral, topical). Despite this, one reported error involved Benadryl capsules accidentally dispensed instead of the intended Benazepril tablets.^P Although the strength was not reported, Benazepril and oral Benadryl do not have overlapping strengths.

We acknowledge that only one of the six available product configurations for Pedialax is an oral liquid and the strength (50 mg in 15 mL) does not directly overlap with that of Epidiolex (100 mg/mL). However, both products are available as a single-strength. Thus, the strength may not be included on a prescription for Epidiolex to serve as a differentiating factor that can minimize the risk for confusion. Postmarketing reports of wrong drug errors involving single strength

products further support the potential for confusion with this name pair.^{w,x,y} Furthermore, there is potential for direct overlap in dose (e.g., 50 mg, 100 mg) and numerical similarity in dose (e.g., Epidiolex 1.5 mL *versus* Pedialax 15 mL, Epidiolex 3 mL *versus* Pedialax 30 mL, Epidiolex 1 mL *versus* Pedialax 1 tbsp.) between Epidiolex and Pedialax oral liquid. The potential for overlap in frequency of administration also exists as Epidiolex is dosed twice daily and doses of Pedialax oral liquid can be taken in divided doses. Thus, the differences in product characteristics between Epidiolex and Pedialax are not sufficient to minimize medication errors between these products.

DIFFERENCE IN CARTON LABELING

In GW Research Ltd.'s request for reconsideration, they state that 'the risk of confusion is likely to be quite low because the products do not look alike' and cite several differentiating features of the product labeling. We agree that the principal display panels of the Pedialax carton labeling and the proposed Epidiolex container label are adequately differentiated and we do not anticipate product selection errors to occur due to look-alike packaging. However, these differences would not mitigate the risk of a wrong drug medication error from occurring during the prescribing or transcription phases of the medication use process.

EXPERIENCE DURING CLINICAL TRIALS AND EXPANDED ACCESS PROGRAMS

In their request for reconsideration, the Applicant states that 'the extensive data derived from clinical studies and expanded access programs has not produced any reports of consumers confusing Epidiolex with any other product, including Pedia-Lax' and 'the data support the conclusion that any consumer confusion would likely be very rare'. While we agree that consumer confusion would be rare, we are concerned about confusion among healthcare professionals (e.g., pharmacy technician, pharmacists, prescribers). Epidiolex' restricted distribution status and unavailability in the pharmacy may lead to unfamiliarity with the product which could contribute to wrong drug medication errors due to confirmation bias. For example, if Epidiolex is misinterpreted as Pedia-Lax during medication reconciliation, a laxative could be ordered. Furthermore, clinical trial experience may not reflect what occurs in practice.

CONSEQUENCES OF WRONG DRUG ERRORS WOULD BE MINIMAL

GW Research Ltd.'s request for reconsideration states that 'a patient would experience few negative consequences from accidentally receiving a dose of Pedia-Lax rather than Epidiolex'. We agree with the Applicant that missing one dose of Epidiolex is unlikely to affect the therapeutic efficacy and the risk of harm associated with taking an unintended dose of Pedialax would be minor. However, we are concerned for a situation in which a patient may take multiple doses of Pedialax instead of Epidiolex. In this situation, the therapeutic efficacy of Epidiolex would likely be affected and adverse effects from taking Pedialax for a prolonged period would

^w Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. ISMP Med Saf Alert Community/Ambulatory Care. 2012; 11(3): 1-4.

^x Institute for Safe Medication Practices. Safety briefs: Vitamin D-angerous? ISMP Med Saf Alert Community/Ambulatory Care. 2012; 11(11): 1-4.

^y Institute for Safe Medication Practices. Voice mail: What's that you said? ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.

likely be experienced. Postmarketing experience shows that wrong drug errors can persist for prolonged periods before the error is discovered. For example, in the previously described mix-up between Prenexa and Ranexa, the patient used Ranexa for a year before the error was discovered.^w The potential for few negative consequences from accidentally receiving a dose of Pedialax rather than Epidiolex only represents one scenario and does not justify the risk for harm to occur with other worst case scenarios. Therefore, our safety concern is not diminished.

4 REVIEWER'S CONCLUSION

The proposed proprietary name is not acceptable from a safety perspective. The proposed name is vulnerable to name confusion with Pedialax.

4.1 REVIEWERS COMMENTS REGARDING THE PROPOSED PROPRIETARY NAME

We have completed our review of the information provided in your request for reconsideration of the proposed proprietary name, Epidiolex. We agree with your assessment that the inclusion of the United States Adopted Name (USAN) stem '-io-' presents a low risk of confusion. However, we maintain our position that the proposed proprietary name, Epidiolex, is unacceptable for the following reasons.

We have reviewed the information submitted in support of the name and we find the differences in product characteristics, prescription status (rx versus over-the-counter), distribution of Epidiolex via a specialty pharmacy, and the spelling, phonetic and orthographic differences of the names Epidiolex and Pedialax are not sufficient to minimize medication errors between these products.

PHONETIC (PRONUNCIATION) & ORTHOGRAPHIC (SPELLING) DIFFERENCES

We note in your request for reconsideration, you clarify that the 'ordinary consumer pronunciation' of Epidiolex is EH-pee-DIGH-oh-leks (b) (4) as previously indicated in your June 24, 2015 request for proprietary name review submitted under IND 120055. You also note that the vowel pronunciation between the two names, Epidiolex and Pedialax, varies at every syllable except one and the stress varies at that syllable.

We previously determined the proposed proprietary name, Epidiolex, to be unacceptable due to orthographic (spelling) and phonetic (pronunciation) similarities with Pedia-lax. We continue to note these similarities for this name pair, however we re-evaluated the (spelling) and phonetic (pronunciation) similarities. We acknowledge that, when comparing Epidiolex to Pedialax, the vowels within three of the syllables differ (i vs. e, o vs. a, e vs. a) and the vowel pronunciation may vary if pronounced as intended. However, the vowels may sound similar when pronounced depending on different accents, dialects, or pronunciations.

The similarity in phonetic pronunciation of this name pair is further supported by the results of the FDA's Name Simulation Studies where one respondent in the March 16, 2018 voice study (conducted using the intended pronunciation: EH-pee-DIGH-oh-leks) interpreted the proposed proprietary name as "Pediolix", which is a close hit to Pedialax. Furthermore, FDA's Phonetic and Orthographic Computer Analysis (POCA) software calculates an 83% phonetic score for this name pair, indicating high phonetic similarity.^z

^z POCA search conducted on March 14, 2018, POCA tool updated to incorporate a revised orthographic algorithm.

Orthographically, we note that the names Epidiolex and Pedialax begin with different letters and postmarketing evidence does not suggest that the letters E and P look similar. However, evidence suggests that differences in the prefix of the name may not provide adequate differentiation if the rest of the name is highly similar. For example, reports of mix-ups between Alkeran and Leukeran have been reported and the same letter characters at the ending of these names has been identified as contributing to look-alike confusion.^{aa} In another example, a handwritten prescription for Prenexa with instructions to take one tablet by mouth daily was misinterpreted and Ranexa 500 mg tablets were dispensed to the patient. The patient used Ranexa for a year before the error was discovered.^{bb} Other examples from *ISMP's List of Confused Drug Names* include, Apresoline and Priscoline, Natru-Vent and Atrovent, Enjuvia and Januvia, and Indinavir and Denavir.^{cc} The orthographic similarity of the name pair, Epidiolex and Pedialax, is further supported by FDA's Phonetic and Orthographic Computer Analysis (POCA) which calculates a 71% orthographic score, indicating high orthographic similarity.^z

Thus, the phonetic (pronunciation) and orthographic (spelling) differences of the names Epidiolex and Pedialax are not sufficient to minimize medication errors between these products.

USE OF SPECIALTY PHARMACY TO DISTRIBUTE EPIDIOLEX

Your request for reconsideration states that 'a local pharmacist would not fill an Epidiolex prescription because it will not be stocked in local pharmacies and the prescription will only be sent to the specialty pharmacy'.

When considering the distribution information for the proposed product, we have taken into consideration that Epidiolex is proposed to be dispensed by specialty pharmacies only (closed to public). However, restricted distribution of Epidiolex may not reduce risk associated with the confusion of similar names. We have reports of name confusion with other products marketed under restricted distribution systems.^{dd,ee} In one case, a physician wrote an order for Tricor 125 mg BID for a new admission with pulmonary arterial hypertension. The physician was not familiar with Tracleer and misheard the patient when he stated he had been taking Tracleer 125 mg BID at home.^{dd} In another case, the progesterone receptor antagonist Mifeprex (mifepristone) was prescribed for a patient with meningioma. The prescriber did not realize that the drug would be supplied only to licensed physicians with a prescriber agreement. The prescription was filled at a community pharmacy where Cytotec (misoprostol) was mistakenly dispensed. The patient took the medication for approximately two weeks prior to the error being discovered.^{ee} Epidiolex' restricted distribution status and unavailability in the pharmacy may lead to

^{aa} Institute for Safe Medication Practices. Safety briefs. *ISMP Med Saf Alert Acute Care*. 2000;5(1):1-2.

^{bb} Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. *ISMP Med Saf Alert Community/Ambulatory Care*. 2012; 11(3): 1-4.

^{cc} *ISMP's List of Confused Drug Names* [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 APR 05]. Available from <https://www.ismp.org/recommendations/confused-drug-names-list>

^{dd} Institute for Safe Medication Practices. Safety briefs: Don't Confuse TRACLEER (bosentan) with TRICOR (fenofibrate). *ISMP Med Saf Alert Acute Care*. 2003;8(13):2.

^{ee} Institute for Safe Medication Practices. Safety briefs: Mifepristone (MIFEPREX) and Misoprostol (CYTOTEC) mix-up. *ISMP Med Saf Alert Community/Ambulatory Care*. 2003;2(1):1.

unfamiliarity with the product which could contribute to wrong drug medication errors due to confirmation bias. Additionally, the restricted distribution you proposed is voluntary and can be stopped at any time. Therefore, our safety concern is not diminished with the proposed restricted distribution plan for this product.

DIFFERENCE IN PRESCRIPTION STATUS (RX VERSUS OVER-THE-COUNTER)

Your request for reconsideration states that ‘even if a patient were to take a prescription to a pharmacy and the pharmacist were to mistake the product for Pedia-Lax, the pharmacist would not have any prescription Pedia-Lax product to dispense, because Pedia-Lax is only available OTC’.

We acknowledge Epidiolex will be available as a prescription drug product whereas, PediaLax is available over-the-counter (OTC). However, we have determined that this difference in marketing status may not prevent errors between these products because postmarketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and OTC drug products.^{ff, gg, hh, ii, jj, kk} Examples of reported errors involve confusion between:

- Sudafed (OTC) and Sotalol (rx)^{ff}
- Benadryl (OTC) and Benazepril (rx)^{gg}
- Cetirizine (OTC) and Sertraline (rx)^{hh}
- Mucinex (OTC) and Mucomyst (rx)ⁱⁱ
- Motrin (OTC) and Neurontin (rx)^{jj}
- Colace (OTC) and Cozaar (rx)^{kk}

In the case of the Benadryl and Benazepril mix-up, a pharmacist misinterpreted a fax for Benazepril as Benadryl (diphenhydramine). A bottle of diphenhydramine capsules was dispensed to the patient and the patient took diphenhydramine daily for three weeks before the error was recognized.^{gg} Furthermore, orders for both products, Epidiolex and Pedia-Lax, could be encountered in the inpatient setting. For example, if Epidiolex is misinterpreted as Pedia-Lax during medication reconciliation, a laxative could be ordered. This is evidenced by a mix-up

^{ff} Institute for Safe Medication Practices. Safety briefs: Sudafed-Sotalol mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2006; 5(5): 1-5.

^{gg} Institute for Safe Medication Practices. Safety briefs: Benazepril confused with Benadryl. ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.

^{hh} Institute for Safe Medication Practices. Safety briefs: Sound-alike names. ISMP Medication Safety Alert! Community/Ambulatory Care Edition. 2009; 8(9): 1-7.

ⁱⁱ Institute for Safe Medication Practices. Safety briefs: Mucinex-Mucomyst: Too close for comfort. ISMP Med Saf Alert Community/Ambulatory Care. 2005; 4(1): 1-4.

^{jj} Institute for Safe Medication Practices. Safety briefs: From the database (Regarding Motrin and Neurontin confusion). ISMP Medication Safety Alert! Community/Ambulatory Care Edition. 2009; 8(2): 1-5.

^{kk} Institute for Safe Medication Practices. Safety briefs: More on confirmation bias. ISMP Med Saf Alert Acute Care. 1996;1(23):1-2.

involving Mirapex and Miralax where the physician misheard the patient while taking his medication history.^{ll} Therefore, the difference in marketing status is not sufficient to minimize medication errors between these products.

DIFFERENCE IN PRODUCT CHARACTERISTICS

In your request for reconsideration, you state ‘the different dosing configurations between the two products is also important to note and will mitigate any potential confusion’. We acknowledge the Pedialax product line consists of products with differing active ingredients, dosage forms, and routes of administration and that only one of the six available product configurations for Pedialax is an oral liquid, comparable to the Epidiolex oral solution.

However, postmarketing experience with other drug products suggests that name confusion can occur between similarly named prescription drug products and OTC product line extensions. Similar to Pedialax, products in the Benadryl product-line also contain differing active ingredients (diphenhydramine, camphor, or diphenhydramine in combination with phenylephrine or zinc acetate), dosage forms (tablet, capsule, spray, cream, solution, gel, liquid), and routes of administration (oral, topical). Despite this, one reported error involved Benadryl capsules accidentally dispensed instead of the intended Benazepril tablets.^{gg} Although the strength was not reported, Benazepril and oral Benadryl do not have overlapping strengths.

We acknowledge that only one of the six available product configurations for Pedialax is an oral liquid and the strength (50 mg in 15 mL) does not directly overlap with that of Epidiolex (100 mg/mL). However, both products are available as a single-strength. Thus, the strength may not be included on a prescription for Epidiolex to serve as a differentiating factor that can minimize the risk for confusion. Postmarketing reports of wrong drug errors involving single strength products further support the potential for confusion with this name pair.^{mmm,nn,oo} Furthermore, there is potential for direct overlap in dose (e.g., 50 mg, 100 mg) and numerical similarity in dose (e.g., Epidiolex 1.5 mL *versus* Pedialax 15 mL, Epidiolex 3 mL *versus* Pedialax 30 mL, Epidiolex 1 mL *versus* Pedialax 1 tbsp.) between Epidiolex and Pedialax oral liquid. The potential for overlap in frequency of administration also exists as Epidiolex is dosed twice daily and doses of Pedialax oral liquid can be taken in divided doses. Thus, the differences in product characteristics between Epidiolex and Pedialax are not sufficient to minimize medication errors between these products.

DIFFERENCE IN CARTON LABELING

^{ll} Institute for Safe Medication Practices. Safety briefs: Mirapex and Miralax confusion. ISMP Med Saf Alert Acute Care. 2002;7(20):1-3.

^{mmm} Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. ISMP Med Saf Alert Community/Ambulatory Care. 2012; 11(3): 1-4.

ⁿⁿ Institute for Safe Medication Practices. Safety briefs: Vitamin D-angerous? ISMP Med Saf Alert Community/Ambulatory Care. 2012; 11(11): 1-4.

^{oo} Institute for Safe Medication Practices. Voice mail: What's that you said? ISMP Med Saf Alert Community/Ambulatory Care. 2008; 7(12): 1-6.

In your request for reconsideration, you state that ‘the risk of confusion is likely to be quite low because the products do not look alike’ and cite several differentiating features of the product labeling.

Our review of the cartons find that the principal display panels of the Pedialax carton labeling and the proposed Epidiolex container label are differentiated. However, these differences would not mitigate the risk of a wrong drug medication error from occurring during the prescribing or transcription phases of the medication use process.

EXPERIENCE DURING CLINICAL TRIALS AND EXPANDED ACCESS PROGRAMS

In your request for reconsideration, you state that ‘the extensive data derived from clinical studies and expanded access programs has not produced any reports of consumers confusing Epidiolex with any other product, including Pedia-Lax’ and ‘the data support the conclusion that any consumer confusion would likely be very rare’.

We considered whether the conditions of a clinical trial and expanded access programs will predict real use scenario. However, as previously stated, we are concerned about confusion among healthcare professionals (e.g., pharmacy technician, pharmacists, prescribers). Epidiolex’ restricted distribution status and unavailability in the pharmacy may lead to unfamiliarity with the product which could contribute to wrong drug medication errors due to confirmation bias. For example, if Epidiolex is misinterpreted as Pedia-Lax during medication reconciliation, a laxative could be ordered. Furthermore, clinical trial experience may not reflect what occurs in practice.

CONSEQUENCES OF WRONG DRUG ERRORS WOULD BE MINIMAL

Your request for reconsideration states that ‘a patient would experience few negative consequences from accidentally receiving a dose of Pedia-Lax rather than Epidiolex’.

We considered your assertion that missing one dose of Epidiolex is unlikely to affect the therapeutic efficacy and the risk of harm associated with taking an unintended dose of Pedialax would be minor. However, we are concerned for a situation in which a patient may take multiple doses of Pedialax instead of Epidiolex. In this situation, the therapeutic efficacy of Epidiolex would likely be affected and adverse effects from taking Pedialax for a prolonged period would likely be experienced. Postmarketing experience shows that wrong drug errors can persist for prolonged periods before the error is discovered. For example, in the previously described mix-up between Prenexa and Ranexa, the patient used Ranexa for a year before the error was discovered.^{mmm} The potential for few negative consequences from accidentally receiving a dose of Pedialax rather than Epidiolex only represents one scenario and does not justify the risk for harm to occur with other worst case scenarios. Therefore, our safety concern is not diminished.

After considering the totality of the information submitted in your request for reconsideration, we maintain our position that the proposed proprietary name, Epidiolex, is unacceptable based on 21 CFR 201.10(c)(5), which states “The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling

or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.”

5 REFERENCES

1. **USAN Stems** (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

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.

3. Electronic Drug Registration and Listing System (eDRLS) database

The electronic Drug Registration and Listing System (eDRLS) was established to support the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

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. ^{PP}

^{PP} 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 $\geq 70\%$.
- Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.
- Low similarity: combined match percentage score $\leq 54\%$.

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 names⁹⁹. 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.

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

⁹⁹ Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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/Applicant 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.	
<u>Orthographic Checklist</u>	<u>Phonetic Checklist</u>

Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	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 as 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 $\geq 55\%$ to $\leq 69\%$).

Step 1	<p>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.</p> <p>For single strength products, also consider circumstances where the strength may not be expressed.</p> <p>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.</p> <p>To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion:</p> <ul style="list-style-type: none">• 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	<p>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.</p>

<p>Orthographic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> • 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 <i>z</i> and <i>f</i>), 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? 	<p>Phonetic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?
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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 B: Prescription Simulation Samples and Results

Figure 1. Epidiolex Study (Conducted on March 16, 2018 and March 23, 2018)

Handwritten Medication Order/Prescription	Verbal Prescription
<p>Medication Order:</p> <p>Epidiolex (b) (4) po bid</p>	<p>“Epidiolex Take 2.5 mL by mouth twice daily. Dispense one bottle.”</p>
<p>Outpatient Prescription:</p> <p>Epidiolex 2.5ml po twice daily # 1 bottle</p>	

B.1 Rx Study #1 (March 16, 2018) FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

303 People Received Study 49 People Responded				
Study Name: Epidiolex				
Total	12	15	22	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
APEDIOLEX	0	1	0	1
APEDIOLICS	0	1	0	1
APEDIOLIX	0	6	0	6
APIDEOLIX	0	1	0	1
APPEDIOLEX	0	1	0	1
EPEDIOLIX	0	1	0	1
EPIDIOLEX	12	0	20	32
EPIDIOLIX	0	1	0	1
EPIDOLEX	0	0	2	2

HEPEDIOLIX	0	1	0	1
HEPIDIOLICS	0	1	0	1
PEDIOLIX	0	1	0	1

B.2 Rx Study #2 (March 23, 2018) FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

					302 People Received Study 70 People Responded
Study Name: Epidiolex					
Total	17	18	13	22	
INTERPRETATION	OUTPATIENT	CPOE	VOICE	INPATIENT	TOTAL
APIDIOLEX	0	0	1	0	1
ATDIOULAX	0	0	1	0	1
EPICLIOLEX	0	0	0	2	2
EPIDEOLICS	0	0	1	0	1
EPIDIDEX	2	0	0	0	2
EPIDILEX	0	0	0	1	1
EPIDIOLEX	13	18	0	19	50
EPIDIOLIX	0	0	1	0	1
EPIDIOLUX	0	0	1	0	1
EPIDIOLYX	0	0	1	0	1
EPIDOLIX	0	0	1	0	1
EPIDROLEX	2	0	0	0	2
EPITDIDYOLIX	0	0	1	0	1
EPITIOLEX	0	0	1	0	1
HIPTOTILOIX	0	0	1	0	1
IPEDIOLEX	0	0	1	0	1
IPIDIOLOIX	0	0	1	0	1

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

No.	Proposed name: Epidiolex Established name: cannabidiol Dosage form: oral solution Strength(s): 100 mg/mL Usual Dose: Starting dose is 2.5 mg/kg twice daily for one week. Increase dose weekly by 2.5 mg/kg twice daily. Max dose is 10 mg/kg twice daily.	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.	Indoflex	70	International name formerly marketed in the UK and South Africa.
2.	Iodoflex	70	<p>This name pair has sufficient orthographic and phonetic differences.</p> <p>The prefixes (Epi- versus Io-) and infixes (-dio- versus -dof-) of this name pair have sufficient orthographic differences. Epidiolex contains the downstroke letter ‘p’ in the prefix whereas, Iodoflex does not contain any downstroke letters in the prefix. Additionally, Iodoflex contains the downstroke letter ‘f’ in the infix whereas, Epidiolex does not contain any downstroke letters in the infix.</p> <p>Phonetically, the first syllables (EH versus eye), second syllables (pee versus oh), third syllables (DIGH versus dough), and fourth syllables (oh versus flex) of the name pair sound different. Additionally, Epidiolex contains an extra syllable.</p> <p>There is no direct overlap in strength (100 mg/mL versus 0.9%). Additionally, there are no overlaps in dosage form (solution versus dressing) or route of administration (oral versus topical).</p>
3.	Pediox	70	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.
4.	Pedipirox-4	70	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.

Appendix D: Moderately Similar Names (e.g., combined POCA score is $\geq 55\%$ to $\leq 69\%$) 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 $\geq 55\%$ to $\leq 69\%$) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed name: Epidiolex Established name: cannabidiol Dosage form: oral solution Strength(s): 100 mg/mL Usual Dose: Starting dose is 2.5 mg/kg twice daily for one week. Increase dose weekly by 2.5 mg/kg twice daily. Max dose is 10 mg/kg twice daily.	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
5.	Neopolydex	58	This name pair has sufficient orthographic and phonetic differences.
6.	Locilex***	57	This name pair has sufficient orthographic and phonetic differences.
7.	Bioflexor	56	This name pair has sufficient orthographic and phonetic differences.
8.	Dorflex	56	This name pair has sufficient orthographic and phonetic differences.
9.	Epiduo Forte	56	This name pair has sufficient orthographic and phonetic differences.
10.	Folplex	56	This name pair has sufficient orthographic and phonetic differences.
11.	Hemoplex F	56	This name pair has sufficient orthographic and phonetic differences.
12.	Prepidil	56	This name pair has sufficient orthographic and phonetic differences.
13.	Darzalex	55	This name pair has sufficient orthographic and phonetic differences.
14.	Kleer Plex	55	This name pair has sufficient orthographic and phonetic differences.

No.	Proposed name: Epidiolex Established name: cannabidiol Dosage form: oral solution Strength(s): 100 mg/mL Usual Dose: Starting dose is 2.5 mg/kg twice daily for one week. Increase dose weekly by 2.5 mg/kg twice daily. Max dose is 10 mg/kg twice daily.	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
15.	Lipiodol	53	This name pair has sufficient orthographic and phonetic differences.
16.	Epiduo	52	<p>This name pair has sufficient orthographic and phonetic differences.</p> <p>The suffixes of this name pair ('-duo' vs '-lex') have sufficient orthographic differences. Additionally, the lengths of the names are dissimilar when scripted.</p> <p>Phonetically, the third syllables (DIGH versus doo) of the name pair sound different and Epidiolex contains an extra syllable.</p> <p>Additionally, there is no direct overlap in strength (100 mg/mL versus 0.1% and 2.5%), dosage form (solution versus gel), or route of administration (oral versus topical).</p>
17.	Lidex	52	This name pair has sufficient orthographic and phonetic differences.

No.	Proposed name: Epidiolex Established name: cannabidiol Dosage form: oral solution Strength(s): 100 mg/mL Usual Dose: Starting dose is 2.5 mg/kg twice daily for one week. Increase dose weekly by 2.5 mg/kg twice daily. Max dose is 10 mg/kg twice daily.	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
18.	Iopidine	50	<p>This name pair has sufficient orthographic and phonetic differences.</p> <p>The suffixes of this name pair have sufficient orthographic differences. Epidiolex contains the upstroke letter ‘l’ in the suffix whereas, Iopidine does not contain any upstroke letters in the suffix.</p> <p>Phonetically, the first syllables (EH versus eye), second syllables (pee versus oh), third syllables (DIGH versus puh), and fourth syllables (oh versus dine) of the name pair sound different. Additionally, Epidiolex contains an extra syllable.</p>
19.	Lidex-E	50	This name pair has sufficient orthographic and phonetic differences.
20.	Pepcid Complete	50	This name pair has sufficient orthographic and phonetic differences.
21.	Indole	48	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 (%)
	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
22.	Peg-32 Dioleate	60	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
23.	Serdolect	60	International product marketed in many countries.
24.	Depixol	56	International product marketed in the UK, Ireland, and New Zealand.
25.	Ricinoleth-40	56	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
26.	Bepridil	55	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
27.	Iprindole	55	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
28.	Pridinol	54	International product formerly marketed in Brazil.
29.	Benperidol	52	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
30.	Epidri	52	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
31.	Brexidol	48	International product marketed in Sweden, Norway, Italy, and formerly marketed in Austria, Denmark, Finland, the UK, Switzerland, Canada, and Germany.
32.	E-Pilo-1	46	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.
33.	E-Pilo-2	46	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.
34.	E-Pilo-4	46	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.
35.	E-Pilo-6	46	Name identified in RxNorm database. Product is deactivated (per Redbook) and no generic equivalents are available.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion^{rr}.

No.	Name	POCA Score (%)
36.	Otividex***	64
37.	Tedizolid	62
38.	Optil Xl	60
39.	I3odine Max***	58
40.	Nifedical Xl	58
41.	Polistirex	58
42.	(b) (4)***	56
43.	Difenor Xl	56
44.	Modisal Xl	56
45.	Pediacof	56
46.	Pedi-Cort V	56
47.	Pipenzolate	56
48.	Piperidolate	56
49.	Stiedex	56
50.	Trintellix	56
51.	Nail-Ex	55
52.	Pedia Relief	55
53.	Phiso hex	55
54.	Pindolol	55
55.	Stiedex Lp	55

Appendix I: Names identified in the eDRLS database not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name
	N/A

^{rr} 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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