CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218591Orig1s000, 207620Orig1s025

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	February 26, 2024
Application Type and Number:	NDA 218591
Product Name and Strength:	Entresto Sprinkle (sacubitril/valsartan) granules, 6 mg/6 mg and 15 mg/16 mg
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
PNR ID #:	2023-1044725485
DMEPA 2 Safety Evaluator:	Christina Topper, PharmD, BCPS
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1 INTRODUCTION

This review evaluates the proposed proprietary name, Entresto Sprinkle, 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. Novartis did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

Entresto (sacubitril and valsartan) tablets were approved on July 7, 2015 under NDA 207620 and currently available as 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg film-coated tablets.

On September 22, 2023, Novartis submitted the proposed proprietary name, (b) (4), for review for their new oral film-coated granule formulation supplied in capsules, which must be opened prior to administration. On November 15, 2023, DMEPA held a teleconference with the Applicant to discuss preliminary findings and concerns with the proposed name, (b) (4) and to provide regulatory options for the proposed product naming strategy.[a]

Thus, Novartis withdrew the name, (b) (4) and submitted the proposed proprietary name, Entresto Sprinkle, for review on November 28, 2023 under NDA 218591.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on November 28, 2023. Of note, the proposed granule product must be opened prior to administration, and the recommended mg/kg dose in pediatric patients (b) (4) are of the combined amount of both sacubitril and valsartan (i.e., proposed strength 6 mg/6 mg, when combined is 12 mg).

Table 1. Relevant Product Information for Entresto[b] and Entresto Sprinkle

	Entresto (NDA 207620)	Entresto Sprinkle (NDA 218591)
Approval Date	July 7, 2015	Pending
Intended Pronunciation	en-TRESS-toh	en-TRESS-toh SPRINK-el
Active ingredient	Sacubitril and valsartan	
Indication of Use	• To reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) normal.	

[a] Killen, M. Memorandum of Teleconference for NDA 218591, Entresto (sacubitril/valsartan). Silver Spring (MD): FDA, CDER, OSE (US); 2023 NOV 15.

[b] Entresto [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. February 2021 [cited 2024 FEB 02]. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207620s018lbl.pdf.

	• For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO® reduces NT-proBNP and is expected to improve cardiovascular outcomes.	
Route of Administration	Oral	
Dosage Form	Tablets	Granules
Strengths	24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg	6 mg/6 mg and 15 mg/16 mg
Dosage and Frequency[c]	**Adult Heart Failure**: • The recommended starting dose of ENTRESTO is 49/51 mg orally twice-daily. • Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. **Pediatric Heart Failure**: (b) (4) • <u>Dose Adjustment for Patients Not Taking ACE Inhibitor or ARB or Previously Taking Low Doses of These Agents</u> o In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].	

[c] Reference to the granules is for the proposed product only.

<table>
<tr><td></td><td>

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension or granules [see Dosage and Administration (2.3, 2.4, 2.5)].

• Dose Adjustment for Severe Renal Impairment:

In adults and pediatric patients with severe renal impairment estimated glomerular filtration rate (eGFR < 30 mL/min/1.73 m2), start at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter.
Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension or granules.
No starting dose adjustment is needed for mild or moderate renal impairment.

• Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter [see Dosage and Administration (2.2, 2.3)].
Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension or granules [see Dosage and Administration (2.3, 2.4, 2.5)].
No starting dose adjustment is needed for mild hepatic impairment.
Use in patients with severe hepatic impairment is not recommended.

</td></tr>
<tr><td>How Supplied</td><td>
ENTRESTO (sacubitril/valsartan) is available as unscored, ovaloid, biconvex, film-coated tablets, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan.

Sacubitril/Valsartan tablets
<table>
<tr><th rowspan="2">Strength</th><th rowspan="2">Color</th><th rowspan="2">Debossment</th><th colspan="2">NDC 0078-XXXX-XX</th></tr>
<tr><th>Bottle of 60</th><th>Bottle of 180</th></tr>
<tr><td>24 mg/26 mg</td><td>Violet white</td><td>"NVR" on one side and "LZ" on the other side</td><td>0659-20</td><td>0659-67</td></tr>
<tr><td>49 mg/51 mg</td><td>Pale yellow</td><td>"NVR" on one side and "L1" on the other side</td><td>0777-20</td><td>0777-67</td></tr>
<tr><td>97 mg/103 mg</td><td>Light pink</td><td>"NVR" on one side and "L11" on the other side</td><td>0696-20</td><td>0696-67</td></tr>
</table>
</td><td>
ENTRESTO® Sprinkle film-coated granules are round, biconvex in shape. Granules in capsules are available in two strengths, one containing a total of 6 mg of sacubitril and 6 mg of valsartan; and another containing a total of 15 mg of sacubitril and 16 mg of valsartan. Granules are provided in a hard capsule which must be opened prior to administration.
<table>
<tr><th rowspan="2">Strength</th><th rowspan="2">Color</th><th rowspan="2">Debossment</th><th colspan="2">NDC 0078-XXXX-XX</th></tr>
<tr><th>Bottle of 60</th><th></th></tr>
<tr><td>6 mg/6 mg</td><td>White cap and transparent body</td><td>"NVR" on the body, "04" on the cap and both parts with arrows</td><td>XXXX-XX</td><td></td></tr>
<tr><td>15 mg/16 mg</td><td>Yellow cap and transparent body</td><td>"NVR" on the body, "10" on the cap and both parts with arrows</td><td>XXXX-XX</td><td></td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td colspan="2">Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F). Protect from moisture.</td></tr>
</table>

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Entresto Sprinkle would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) concurred with the findings of OPDP's assessment for Entresto Sprinkle. The Division of Cardiology and Nephrology (DCN) concurred with the findings of OPDP's assessment for Entresto Sprinkle.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Entresto Sprinkle.

2.2.1 United States Adopted Names (USAN) Search

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

2.2.2 Components of the Proposed Proprietary Name

Novartis did not provide a derivation for the proposed proprietary name, Entresto Sprinkle. This proprietary name is comprised of the root name "Entresto" and the modifier "Sprinkle". Novartis indicated in their submission that the proposed modifier, Sprinkle, describes the product characteristics and conveys instructions for use which is to be sprinkled on food.

This proprietary name is comprised of multiple words, a root name "Entresto" that contains the letter strings '-tr' and '-es-' which are medical abbreviation for 'time release' and 'extra strength,' respectively. Additionally, the modifier "Sprinkle" contains the letter string "-in-" which is the medical abbreviation for 'intranasal'. Although we typically discourage the inclusion of medical abbreviations in proprietary names, we determined that due to the location of the abbreviations 'tr' and 'es' in the middle of the root name "Entresto" and 'in' in the middle of the modifier "Sprinkle", they are unlikely to be separated from the surrounding letters in a manner that could lead to confusion. Thus, we do not object to the inclusion of the abbreviations 'tr', 'es' and 'in' in this case.

We further evaluate the use of the root name, Entresto, and the proposed modifier, Sprinkle, in Section 2.2.5.

2.2.3 Comments from Other Review Disciplines at Initial Review

On December 20, 2023, the Division of Cardiology and Nephrology (DCN) did not forward any comments or concerns relating to Entresto Sprinkle at the initial phase of the review.

[e] USAN stem search conducted on November 29, 2023.

2.2.4 FDA Name Simulation Studies

Eighty-three (n=83) practitioners participated in DMEPA's prescription studies for Entresto Sprinkle. Two participants in the inpatient prescription study interpreted the proposed name as "Entresto" and "Entreto", omitting the modifier "Sprinkle" in both cases. We assess the risk of omitting the modifier in Section 2.2.5. Beyond these misinterpretations, the responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

2.2.5 Safety Analysis of the Proposed Modifier "Sprinkle"

The proposed proprietary name, Entresto Sprinkle, is comprised of the root name, "Entresto" and the modifier, "Sprinkle". Novartis proposes the modifier "Sprinkle" to differentiate the proposed granule from the currently marketed product, "Entresto" tablets. As such, we evaluated the following: (1) evaluation of the use of the same root name, (2) use of a modifier to differentiate the product, and (3) evaluation of the proposed modifier, "Sprinkle".

I. Evaluation of the use of the same root name 'Entresto'

Our routine postmarket surveillance has not identified name confusion medication errors associated with the root name, "Entresto". We note that currently marketed product name and Entresto Sprinkle share the same active ingredient (sacubitril and valsartan), with the only difference in the formulation or product presentation. See Table 1 for a comparison of product characteristics.

II. Evaluation of the use of a modifier to differentiate the products

The use of a modifier to differentiate product characteristics between products, such as a different formulation or product presentation, is a common naming practice as part of a product line extension. The addition of a modifier to "Entresto" may help differentiate the granules from the currently marketed tablets.

We note that omission and oversight of modifiers is cited in literature as a common cause of medication errors.[f] Postmarket experience shows that family branding may result in medication errors if the modifier is omitted, and the product characteristics are similar or overlap. We considered the risk of name confusion if the modifier is dropped. This was observed in the FDA Prescription Simulation Study, in which two participants in the inpatient study did not record the modifier as part of their response (See Section 2.2.4 above). However, given there is no overlap in strength between the currently marketed Entresto product and the proposed product, this risk may be minimized.

An alternative to using a modifier to distinguish this product from the currently marketed products is to use a different root name. However, marketing the new product under a unique proprietary name also carries a risk of medication errors, such as therapeutic duplication and overdoses.

[f] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587.

Although the proposed naming strategy is not devoid of risk because modifiers may be omitted, in this case, we agree that using a modifier may assist in differentiating the current and proposed products.

III. Evaluation of the proposed modifier 'Sprinkle'

The Applicant proposes the modifier "Sprinkle" as the proposed product is a film coated granule formulation stored in hard capsules that must be opened and the full content are sprinkled onto 1 to 2 teaspoons of soft food. We note the modifier "Sprinkle" has been used in drug nomenclature for approved products where capsules may be opened and sprinkled on food (e.g., Drizalma Sprinkle, Ezallor Sprinkle, etc.) or must be opened prior to administration (e.g., Alkindi Sprinkle). As the proposed product must be opened and sprinkled onto food prior to administration, the use of the modifier "Sprinkle" is consistent with its existing meaning and is appropriate for conveying the administration technique of this product formulation. The risks associated with users swallowing the capsule whole will be addressed within the product label and labeling review.

In summary, we find the use of the proposed naming strategy (the use of the same root name, Entresto, with a distinguishing modifier) acceptable. Additionally, we find the proposed modifier, "Sprinkle", sufficiently differentiates the proposed product from the currently marketed Entresto product(s). Therefore, based on the totality of information considered above, we do not object to the proposed name, Entresto Sprinkle, for the proposed product.

2.2.6 Communication of DMEPA's Determination

On February 26, 2024, DMEPA 2 communicated our determination to the Division of Cardiology and Nephrology (DCN).

3 CONCLUSION

The proposed proprietary name, Entresto Sprinkle, is conditionally acceptable.

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

3.1 COMMENTS TO NOVARTIS PHARMACEUTICALS CORPORATION

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

If any of the proposed product characteristics as stated in your submission, received on November 28, 2023 are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

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

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

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

Drugs@FDA

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

RxNorm

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

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

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

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

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

APPENDICES

Appendix A

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

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

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

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

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

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

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

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

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

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[h]. 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.

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

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

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

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

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

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

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

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

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

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

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names

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

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

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

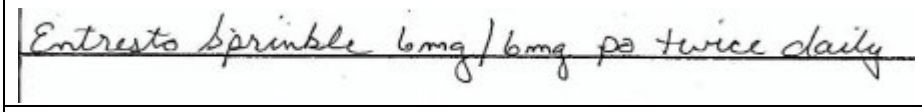
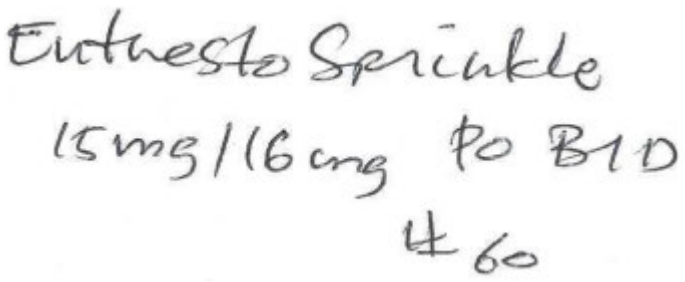
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length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

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

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

Appendix B: **Prescription Simulation Samples and Results**

Figure 1. Entresto Sprinkle Study (Conducted on December 8, 2023)

Handwritten Medication Order/Prescription	**Verbal Prescription**
Medication Order:  	Entresto Sprinkle 15 mg/16 mg by mouth twice daily Dispense 60
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Entresto Sprinkle	

FDA Prescription Simulation Responses (Aggregate Report)

Study Name: Entresto Sprinkle

People Received Study: 167

People Responded: 83

Total	19	20	17	27	83
INTERPRETATION	INPATIENT	OUTPATIENT	VOICE	CPOE	TOTAL
ANTRESTO SPRINKLE	0	0	1	0	1
ENTHESTO SPRINKLE	0	1	0	0	1
ENTRESTO	1	0	0	0	1
ENTRESTO SPRINKLE	17	16	16	27	76

ENTRETO	1	0	0	0	1
EUTHESTO SPRINKLE	0	2	0	0	2
EUTNESTO SPRINKLE	0	1	0	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/

CHRISTINA A TOPPER
02/26/2024 12:47:54 PM

NICOLE F IVERSON
02/26/2024 01:00:53 PM

CHI-MING TU
02/26/2024 03:41:22 PM