CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216354Orig1s000

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:	July 14, 2022
Application Type and Number:	NDA 216354
Product Name and Strength:	Austedo XR (deutetrabenazine) extended-release tablet 6 mg, 12 mg, and 24 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Teva Neuroscience, Inc. (Teva)
PNR ID #:	2022-1044724552
DMEPA 2 Safety Evaluator:	Beverly Weitzman
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD
DMEPA 2 Director:	Danielle Harris, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Austedo XR, 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. Teva submitted an external name study, conducted by (b) (4) for this proposed proprietary name. We reviewed the external study report conducted by (b) (4) and we did not identify any names of concern necessary to evaluate further in this review of the proposed proprietary name Austedo XR.

1.1 REGULATORY HISTORY

Austedo (deutetrabenazine) tablets, 6 mg, 9 mg, and 12 mg was approved under NDA 208082 on April 3, 2017, and is currently approved for the treatment of chorea associated with Huntington's disease and tardive dyskinesia.

The Applicant proposes to expand the Austedo product line to include a new dosage form of deutetrabenazine, 6 mg, 12 mg, and 24 mg extended-release tablets also for the treatment of chorea associated with Huntington's disease and tardive dyskinesia.

Thus, Teva submitted the name, Austedo XR, for review on April 21, 2022.

1.2 PRODUCT INFORMATION

The following product information for Austedo XR is provided in the proprietary name submission received on April 21, 2022 and from Drugs@FDA for the approved product, Austedo.

Table 1. Relevant Product Information for Austedo XR and Austedo

Product Name	Austedo XR	Austedo[a]
Intended Pronunciation	aw-STED-oh XR	aw-STED-oh
Application #	NDA 216354	NDA 208082
Initial Approval Date	N/A	April 3, 2017
Active Ingredient	deutetrabenazine	
Indication	Treatment of tardive dyskinesia and chorea associated with Huntington's disease	
Route of Administration	Oral	
Dosage Form	Extended-release tablet	Tablet (immediate-release)
Strength	6 mg, 12 mg, and 24 mg	6 mg, 9 mg, and 12 mg

[a] Austedo [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 May 04. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208082s011lbl.pdf

Reference ID: 5013936

<table>
<tr>
<td>Dose and Frequency</td>
<td>
The dose of AUSTEDO XR is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. When first prescribed to patients who are not being switched from tetrabenazine (a related VMAT2 inhibitor), the recommended starting dosage of AUSTEDO XR is 12 mg once daily for patients with Huntington’s disease or tardive dyskinesia.

The dose of AUSTEDO XR may be increased at weekly intervals in increments of 6 mg per day based on reduction of chorea or tardive dyskinesia and tolerability, up to a maximum recommended daily dosage of 48 mg.

<u>Switching Patients from Tetrabenazine to AUSTEDO XR</u>
Discontinue tetrabenazine and initiate AUSTEDO XR the following day. The recommended initial dosing regimen of AUSTEDO XR in patients switching from tetrabenazine to AUSTEDO XR shown in Table 2.
Table 2:
<table>
<tr><th>Current tetrabenazine daily dosage</th><th>Initial regimen of AUSTEDO XR extended-release tablet</th></tr>
<tr><td>12.5 mg</td><td>6 mg once daily</td></tr>
<tr><td>25 mg</td><td>12 mg once daily</td></tr>
<tr><td>37.5 mg</td><td>18 mg once daily</td></tr>
<tr><td>50 mg</td><td>24 mg once daily</td></tr>
<tr><td>62.5 mg</td><td>30 mg once daily</td></tr>
<tr><td>75 mg</td><td>36 mg once daily</td></tr>
<tr><td>87.5 mg</td><td>42 mg once daily</td></tr>
<tr><td>100 mg</td><td>48 mg once daily</td></tr>
</table>
<u>Switching Between AUSTEDO XR and AUSTEDO</u>
• Patients who are currently being treated with once-daily doses of AUSTEDO XR extended-release tablets, may be switched to AUSTEDO tablets at the same
</td>
<td>
The dose of AUSTEDO is determined individually for each patient based on Reduction of chorea or tardive dyskinesia and tolerability. When first prescribed to patients who are not being switched from tetrabenazine (a related VMAT2 inhibitor), the recommended starting dosage of AUSTEDO is 12 mg per day (6 mg twice daily) for patients with Huntington’s disease or tardive dyskinesia.

The dose of AUSTEDO may be increased at weekly intervals in increments of 6 mg per day based on reduction of chorea or tardive dyskinesia and tolerability, up to a maximum recommended daily dosage of 48 mg.

<u>Switching Patients from Tetrabenazine to AUSTEDO</u>
2.2 Switching Patients from Tetrabenazine (XENAZINE®) to AUSTEDO
Discontinue tetrabenazine (XENAZINE®) and initiate AUSTEDO the following day. The recommended initial dosing regimen of AUSTEDO in patients switching from tetrabenazine (XENAZINE®) to AUSTEDO is shown in Table 1.
Table 1: Recommended Initial Dosing Regimen when Switching from Tetrabenazine (XENAZINE®) to AUSTEDO
<table>
<tr><th>Current tetrabenazine daily dosage</th><th>Initial regimen of AUSTEDO</th></tr>
<tr><td>12.5 mg</td><td>6 mg once daily</td></tr>
<tr><td>25 mg</td><td>6 mg twice daily</td></tr>
<tr><td>37.5 mg</td><td>9 mg twice daily</td></tr>
<tr><td>50 mg</td><td>12 mg twice daily</td></tr>
<tr><td>62.5 mg</td><td>15 mg twice daily</td></tr>
<tr><td>75 mg</td><td>18 mg twice daily</td></tr>
<tr><td>87.5 mg</td><td>21 mg twice daily</td></tr>
<tr><td>100 mg</td><td>24 mg twice daily</td></tr>
</table>
After patients are switched to AUSTEDO, the dose may be adjusted at weekly intervals [see Dosage and Administration].
</td>
</tr>
</table>

	total daily dose, taken in two divided doses (twice daily). • Patients who are currently being treated with two divided doses of AUSTEDO tablets (twice daily), may be switched to AUSTEDO XR extended-release tablets at the same total daily dose, taken once daily.	
How Supplied	(b) (4)	AUSTEDO tablets are available in the following strengths and packages: 6 mg: round, purple-coated tablets, with "SD" over "6" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-170-60. 9 mg: round, blue-coated tablets, with "SD" over "9" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-171-60. 12 mg: round, beige-coated tablets, with "SD" over "12" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-172-60.
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.	

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Austedo XR 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 Austedo XR. The Division of Neurology 1 (DN 1) did not comment on the findings of OPDP's assessment for Austedo XR.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Austedo XR.

2.2.1 United States Adopted Names (USAN) Search

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

[b] USAN stem search conducted on June 13, 2022.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name, Austedo XR, is comprised of two components: (1) the root name, Austedo, and (2) the modifier "XR". The Applicant indicates that the root name "Austedo" is derived from the currently approved product Austedo, and that the modifier "XR" is intended to mean that the drug product is an extended-release formulation intended for once-daily administration.

The product with the root name Austedo was approved on April 3, 2017, and is currently marketed as an immediate-release tablet, which is usually administered twice-daily. The applicant proposes to add an extended-release formulation to the currently marketed Austedo product line. Therefore, we have evaluated the appropriateness of using the same root name and the appropriateness of the proposed modifier "XR" in Section 2.2.5 below.

2.2.3 Comments from Other Review Disciplines at Initial Review

The Division of Neurology 1 (DN 1) did not forward any comments or concerns relating to Austedo XR at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Eighty-seven practitioners participated in DMEPA's prescription studies for Austedo XR. 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.

One participant in the CPOE prescription study erroneously selected "Lyral" from a "dynamic contains" picklist. We note the participant entered the letter string "lyr", which is not a letter string in the proposed name; therefore, the correct name, Austedo XR, was not displayed in the picklist. Additionally, we note that Lyral is a synthetic fragrance, and not a drug product. Based on these factors, we determined the risk for a medication error between the name pair is unlikely.

Five participants (outpatient n=1, inpatient n=2, CPOE n=1, and verbal n=1) in the prescription study omitted the "XR" modifier in their responses (i.e., only listed "Austedo" or "different spelling variations of Austedo"). We discuss the risk associated with the omission of the modifier in Section 2.2.5.

One participant in the verbal study misinterpreted the modifier "XR" as "HR". We considered the risk of medication errors should one confuse Austedo XR with Austedo HR. We note that the "HR" is a standard medical abbreviation to describe a period of time (i.e., hour). However, the term "HR" would not be used alone (without the associated dosing interval (e.g., 24 HR)). We also note that "HR" is an abbreviation for other medical terms such as "heart rate", "Hamman-Rich syndrome, "hematologic response" and "hormone replacement, etc." We are unaware of any postmarket reports of medication errors documenting misinterpretation of the modifier XR for the standard medical abbreviation "HR" or for other medical terms as stated above. Additionally, the abbreviation "HR" is not listed on ISMP's List of Error-Prone

Abbreviations, Symbols, and Dose Designations[c], or on NCC MERP's list of Dangerous Abbreviations.[d] Therefore, we are not concerned the modifier, XR, will be misinterpreted as a medical abbreviation or medical term.

Appendix B contains the results from the prescription simulation studies.

2.2.5 Safety Assessment of the Root Name, Austedo, and Modifier, XR

The applicant currently markets the active ingredient, deutetrabenazine, under the name, Austedo, for the immediate release tablet formulation. The product is currently approved as 6 mg, 9 mg, and 12 mg immediate-release tablets for the treatment of tardive dyskinesia and chorea associated with Huntington's disease. For their proposed deutetrabenzine extended-release tablets, the applicant proposes to use the name, Austedo XR. The differences between the proposed formulation and the currently marketed formulation are listed in Table 1 under Section 1.2 of our review.

1. Evaluation of use of the same root name, "Austedo"

Austedo has been marketed as the proprietary name for deutetrabenazine since approval on April 3, 2017. We note that Austedo and Austedo XR share the same active ingredient and indication of use. Our routine postmarketing surveillance has not identified any signals attributed to name confusion involving Austedo. Thus, we do not object to the use of the root name, Austedo, for this product.

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

The proposed product represents a new dosage form (extended-release tablets vs. immediate-release tablets). Thus, the Applicant proposes to use the modifier "XR" to differentiate the proposed Austedo XR product from the currently marketed Austedo product. We evaluated the use of a modifier to determine if the naming strategy helps to differentiate the proposed Austedo XR product from the currently marketed Austedo product.

It is not uncommon to use modifiers to denote a specific product formulation as part of a product line extension. The addition of a modifier may signal to healthcare practitioners that this product differs from the currently marketed Austedo product.

We also considered the risk of name confusion if the modifier is omitted or overlooked, as seen in the FDA Prescription Simulation Study. We note that omission and oversight of a modifier is cited in literature as a common cause of medication errors.[e] Postmarketing experience shows that the introduction of product line extensions may result in medication errors if the modifier is omitted, and the product characteristics are similar or overlap. In this case, we note that both the immediate-release tablets and proposed extended-release tablets

[c] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2021 [cited 2021 FEB 5]. Available from: https://www.ismp.org/recommendations/error-prone-abbreviations-list

[d] NCC MERP. Dangerous Abbreviations. Available from: https://www.nccmerp.org/dangerous-abbreviations. Accessed June 28, 2022.

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

will be available in 6 mg and 12 mg strength tablets. Additionally, although the products typically have different frequencies of administration (i.e., once daily vs. twice daily), we note that the 6 mg strength for both products may be administered once daily for the initial dose when switching patients from Tetrabenazine to Austedo (i.e., Austedo XR (extended-release) 6 mg once daily vs. Austedo (immediate-release) 6 mg once daily). Therefore, these overlapping product characteristics may be a risk of medication errors if the modifier is omitted or overlooked.

As part of our evaluation of the appropriateness of the modifier "XR", we consulted with the Division of Neurology 1 (DN 1) Medical officer to determine the clinical significance of patient harm (if any) if the products were to be confused for one another, specifically for the 6 mg once-daily dosage overlap. For example:

- If a patient intended to receive Austedo XR (extended release) 6 mg once daily but instead receives Austedo (immediate release) 6 mg once daily.
- Alternatively, if a patient intended to receive Austedo (immediate release) 6 mg once daily but instead receives Austedo XR (extended release) 6 mg once daily).

According to the medical officer via email communication on June 27, 2022, a starting dose of 12 mg/day in either formulation is not expected to be therapeutic, thus, if an error was made and a patient was given one formulation in place of the other it is not going to cause an untoward reaction related to dose. Therefore, from a clinical perspective there is minimal concern if these products were to be confused for one another.

Although the proposed naming strategy is not devoid of risk because modifiers may be omitted, they can assist in differentiating products and may help to prevent potential selection errors when used. Thus, based on the totality of this information, we do not object to the use of a modifier for this product as it may provide an added measure of safety. Furthermore, label and labeling mitigations can help minimize the residual risk of product selection errors.

3. Evaluation of the proposed modifier, "XR"

The Applicant proposes the modifier "XR" to denote that the product is an extended-release formulation with a once daily frequency of administration. We note that the use of the modifier "XR" to convey that the proposed product is an extended-release dosage form is contingent upon the product meeting the Agency's criteria for this designation. Assuming these criteria are met, we note that products with the modifier "XR" have been approved in cases where a product is administered "every 12 hours", "twice daily", or "once daily" dosing schedule for an extended-release formulation. Based on the Institute for Safe Medication Practices (ISMP) List of Products with Drug Name Suffixes, the modifier "XR" is typically used to convey the meaning "extended-release" for products with modified-release formulations.[f] As the proposed product will be dosed once daily, the use of the modifier "XR" is consistent with its existing meaning and is appropriate for conveying the extended-release characteristic of this product formulation.

[f] ISMP's List of Products with Drug Name Suffixes [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2010. Available from: https://www.ismp.org/sites/default/files/attachments/2018-04/drugnamesuffixes.pdf

Therefore, we do not object to the use of modifier "XR" for the proposed product and find that "XR" is acceptable for conveying this characteristic of the product formulation.

In summary, we find the use of the root name, Austedo, acceptable for the proposed product. Additionally, we find that the addition of the modifier "XR" to the root name may provide an additional layer of safety in differentiating the proposed extended-release tablets from the currently marketed immediate-release tablets. Although the naming strategy presents some risk of product selection error if the modifier is dropped, we find the residual risk acceptable based on input from the clinical team. Therefore, based on the totality of information considered above, we do not object to the proposed name, Austedo XR, for the proposed product.

2.2.6 Communication of DMEPA's Determination

On July 14, 2022, DMEPA 2 communicated our determination to the Division of Neurology 1 (DN 1).

3 CONCLUSION

The proposed proprietary name, Austedo XR, is acceptable.

If you have any questions or need clarifications, please contact Lopa Thambi, OSE project manager, at 301-796-5354.

3.1 COMMENTS TO TEVA NEUROSCIENCE, INC.

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

If any of the proposed product characteristics as stated in your submission, received on April 21, 2022, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

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

USAN Stems List contains all the recognized USAN stems.

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

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

Reference ID: 5013936

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.

c. 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.

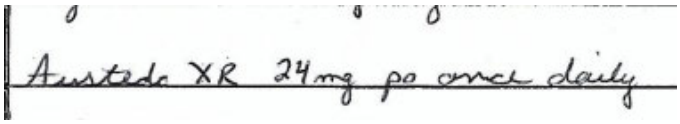
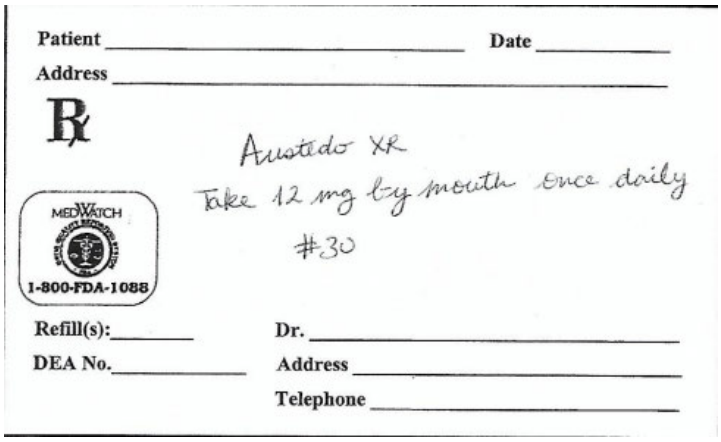
   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   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.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Study (Conducted on May 20, 2022)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Austedo XR Take 12 mg by mouth once daily #30
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Austedo XR	

FDA Prescription Simulation Responses (Aggregate Report)

262 People Received Study
87 People Responded

Study Name: Austedo XR

Total	20	19	25	23	87
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
URETOXR	0	0	0	1	1
AURTEDO XR	0	0	0	5	5
AUSTEDA XR	0	0	0	2	2
AUSTEDO	1	1	0	2	4

AUSTEDO XR	19	17	7	13	56
AUSTETO	0	0	1	0	1
AUSTETO XR	0	0	3	0	3
HOSTEDO XR	0	0	1	0	1
HOSTETO HR	0	0	1	0	1
LYRAL	0	1	0	0	1
OSTEDO XR	0	0	5	0	5
OSTETO XR	0	0	3	0	3
OSTETTO XR	0	0	3	0	3
POSTETO XR	0	0	1	0	1

Reference ID: 5013936

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/

BEVERLY WEITZMAN
07/14/2022 07:54:08 AM

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