

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216117Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME MEMORANDUM

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 23, 2022
Application Type and Number:	NDA 216117
Product Name and Strength:	Rel maxxii (methylphenidate hydrochloride extended-release tablets), 18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg, and 72 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Osmotica Kereskedelmi es Szolgáltato Kft (Osmotica)
PNR ID #:	2022-1044724573
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 INTRODUCTION

This memorandum is to reassess the proposed proprietary name, Relexxii, based on the addition of new product strengths. The proposed proprietary name, Relexxii, was found acceptable under NDA 216117 on November 16, 2021.^a

1.1 REGULATORY HISTORY

ANDA 205327 for methylphenidate hydrochloride extended-release tablets, 18 mg, 27 mg, 36 mg, 54 mg, and 72 mg (via approved suitability petition 05P-0257/CP1 dated November 14, 2005) was approved on July 28, 2017 under the non-proprietary name and is AB rated to Concerta. On December 15, 2017, Osmotica submitted the name Relexxii for review for the 72 mg strength. The name was found acceptable and the 72 mg strength is currently marketed under the name Relexxii.

On August 23, 2021, the name Relexxii was submitted for review under NDA 216117 for the proposed 45 mg and 63 mg strengths. The name was found conditionally acceptable on November 16, 2021.^a

On May 4, 2022, Osmotica resubmitted the name, Relexxii, for all of their methylphenidate hydrochloride strengths (18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg, and 72 mg) under NDA 216117.

2 METHODS AND DISCUSSION

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Relexxii would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Relexxii. The Division of Psychiatry (DP) concurred with the findings of OPDP's assessment for Relexxii.

2.2 SAFETY ASSESSMENT

For re-assessment of the proposed proprietary name, we evaluated the previously identified names taking into account the addition of new strengths. Our evaluation has not altered our previous conclusion regarding the acceptability of the proposed proprietary name, Relexxii.

Additionally, we searched the USAN stem list to determine if the proposed proprietary name contains any USAN stems as of the last USAN updates. The May 9, 2022 search of USAN stems did not find any USAN stems in the proposed proprietary name, Relexxii.

2.3 COMMUNICATION OF DMEPA'S DETERMINATION

On May 19, 2022, we communicated our determination to the Division of Psychiatry (DP).

^a Holmes, L. Proprietary Name Review for Relexxii (NDA 216117). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Nov 16. PNR ID No. 2021-1044724144.

3 CONCLUSION

Our re-assessment did not identify any names that represent a potential source of drug name confusion. Therefore, we maintain that the proposed proprietary name, Relexxii, is acceptable.

If you have any questions or need clarifications, please contact Phuong B. Nguyen, OSE Safety Regulatory Project Manager, at 240-402-5827.

3.1 COMMENTS TO OSMOTICA

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

If any of the proposed product characteristics as stated in your submission, received on May 4, 2022, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCE

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

USAN Stems List contains all the recognized USAN stems.

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/s/

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PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 16, 2021
Application Type and Number:	NDA 216117
Product Name and Strength:	Relexxii (methylphenidate hydrochloride extended-release tablets), 45 mg and 63 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Osmotica Kereskedelmi es Szolgaltato Kft (Osmotica)
PNR ID #:	2021-1044724144
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS
DMEPA 1 Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Relexxii, 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. Osmotica did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

ANDA 205327 for methylphenidate hydrochloride extended-release tablets, 18 mg, 27 mg, 36 mg, 54 mg, and 72 mg (via approved suitability petition 05P-0257/CP1 dated November 14, 2005) was approved on July 28, 2017. Relexxii is an approved name for the currently marketed 72 mg strength. According to Osmotica, they intended to add two intermediate strengths (45 mg and 63 mg) to ANDA 205327 but due to long timelines with suitability petition approvals, they opted for the 505(b)(2) regulatory pathway instead.

Osmotica is proposing 45 mg and 63 mg strengths of methylphenidate hydrochloride extended-release tablets under NDA 216117. Thus, Osmotica submitted the name, Relexxii, for review under NDA 216117 on August 23, 2021.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on August 23, 2021.

- Intended Pronunciation: Re lex ee
- Active Ingredient: methylphenidate hydrochloride
- Indication of Use: Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65
- Route of Administration: oral
- Dosage Form: Extended-release tablets
- Strengths: 45 mg and 63 mg
- Dose and Frequency: 45 mg or 63 mg once daily
- How Supplied: Bottles of 30 tablets and 100 tablets
- Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

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

(DMEPA 1) and the Division of Psychiatry (DP) concurred with the findings of OPDP’s assessment for Relexxii.

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary name.^a

2.2.2 Components of the Proposed Proprietary Name

Osmotica indicated in their submission that the proposed proprietary name, Relexxii, is derived from a blank canvas. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

On September 3, 2021, the Division of Psychiatry (DP) forwarded the following comments and concerns relating to Relexxii at the initial phase of the review:

“...concerned about the similarities between Relexxii (methylphenidate ER) and Rexulti (indicated for schizophrenia and adjunctive treatment of major depression). If an individual prescribed Rexulti for schizophrenia receives a stimulant (Relexxii) in error, this could lead to worsening of psychosis. In addition, ADHD is often co-morbid with major depression, so there theoretically could be individuals taking both medications and the name similarities could be confusing in that case...”

Considering DP’s comments, DMEPA conducted a FAERS search. Our FAERS search did not retrieve any postmarketing reports related to name confusion involving Relexxii (see Section 2.2.4).

2.2.4 Medication Error Data Selection of Cases

On September 29, 2021, we searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving Relexxii that would be relevant for this review.

Table 2. FAERS Search Strategy	
FAERS Field	Relexxii
Initial FDA Receive Dates	July 28, 2017 – September 29, 2021
Product Name	Relexxii

^a USAN stem search conducted on September 29, 2021.

Verbatim Name(s)	N/A
Product Active Ingredient	methylphenidate
Drug Role	N/A
Event	DMEPA Official PNR Name Confusion Search Terms
Country (derived)	USA

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

After individual review, no reports related to name confusion involving Relexxii were retrieved.

2.2.5 Safety Assessment of the Proposed Name, Relexxii

Osmotica proposes to extend the Relexxii product line to include two intermediate tablet strengths (45 mg and 63 mg). Per the Office of Pharmaceutical Quality (OPQ), the proposed strengths are equivalent on a mg-per-mg basis with the currently approved Relexxii strength of 72 mg and the other strengths approved under the ANDA. Thus, doses of 45 mg and 63 mg will be obtainable using a single tablet rather than a combination of lower strength tablets that are currently available under ANDA 205327 (e.g., 18 mg + 27 mg to obtain a 45 mg dose). Thus, we do not have any medication error safety concerns with the proposed 45 mg and 63 mg strengths. Additionally, our FAERS search did not retrieve any reports of name confusion involving Relexxii. Therefore, we have no safety concerns with the proposal to market the proposed tablets with the proprietary name, Relexxii.

2.2.6 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA 1 communicated our findings to the Division of Psychiatry (DP).

3 CONCLUSION

The proposed proprietary name, Relexxii, is acceptable.

If you have any questions or need clarifications, please contact Phuong B. Nguyen, OSE Project Manager, at 240-402-5827.

3.1 COMMENTS TO OSMOTICA KERESKEDELMI ES SZOLGALTATO KFT

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

If any of the proposed product characteristics as stated in your submission, received on August 23, 2021, 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.^b

***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)).

^b National Coordinating Council for Medication Error Reporting and Prevention. <https://www.nccmerp.org/about-medication-errors> Last accessed 10/05/2020.

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 names^c. 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.

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,

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

each consisting of a combination of marketed and unapproved drug products, including the proposed name.

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

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

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

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

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

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

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	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.
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	- 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 <u>with</u> 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 $\leq 54\%$).

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

Appendix A1: Description of FAERS

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

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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