CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211988Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	February 4, 2021
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam
Total Product Strength:	60 mg bupivacaine and 1.8 mg meloxicam in 2.3 mL; 200 mg bupivacaine and 6 mg meloxicam in 7 mL; 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL; 400 mg bupivacaine and 12 mg meloxicam in 14 mL
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics Inc. (Heron)
Panorama #:	2020-43934241
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Valerie Vaughan, PharmD

Contents

1 INTRODUCTION

This review reassesses the proposed proprietary name, Zynrelef, from a safety and misbranding perspective. We note that there is no change in product characteristics for this proposed product since our prior evaluation of the proposed proprietary name. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. Heron submitted a new external name study dated August 21, 2020, conducted by (b) (4) for this proposed proprietary name.

1.1 REGULATORY HISTORY

Heron previously submitted the proposed proprietary name, Zynrelef on December 21, 2017, which was found conditionally acceptable under IND 125927 on June 12, 2018. [a] Subsequently, the propose proprietary name was submitted for review under NDA 211988 on October 30, 2018, which was found conditionally acceptable on January 24, 2019.[b] However, a Complete Response (CR) letter was issued on April 30, 2019. Thus, Heron included a request for proprietary name review for the name, Zynrelef, on September 26, 2019 with the resubmission of the NDA. We found the proposed proprietary name, Zynrelef, conditionally acceptable under NDA 211988 on December 2, 2019.[c] However, a CR letter was issued on June 26, 2020.

Thus, Heron re-submitted the name, Zynrelef, for review with their class 2 resubmission of NDA 211988 on November 12, 2020.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on November 12, 2020.

- Intended Pronunciation: zin' reh lef
- Active Ingredient: bupivacaine and meloxicam
- Indication of Use: (b) (4) (b) (4)
- Route of Administration: (b) (4)
- Dosage Form: extended-release solution
- Strength: 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam
- Dose and Frequency:

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[a] Johnson, Cameron. Proprietary Name Review for Zynrelef (IND 125927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 12. Panorama No.: 2017-19886867.

[b] Johnson, Cameron. Proprietary Name Review Memo for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 24. Panorama No.: 2017-27001290.

[c] Johnson, Cameron. Proprietary Name Review Memo for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 2. Panorama No.: 2019-34747451.

- Intended for single-dose administration only. The recommended dose of Zynrelef is based on the following factors:
  - Size of the surgical site.
  - Volume required to cover the tissues within the surgical site that could result in pain generation.
  - Maximum total dose is 400 mg bupivacaine/12 mg meloxicam (14 mL).
- As general guidance in selecting the proper dosing, the following examples of dosing are provided:
  - Bunionectomy: up to 2.3 mL (60 mg/1.8 mg)
  - Open inguinal herniorrhaphy: up to 10.5 mL (300 mg/9 mg)
  - Total Knee Arthroplasty: up to 14 mL (400 mg/12 mg)

(b) (4)

- How Supplied:
  - Zynrelef will be supplied in kits containing one vented vial spike, one luer lock, one luer lock applicator, one syringe tip cap, and one vial of Zynrelef:
    - 60 mg and 1.8 mg in a 10 mL single-dose vial (to deliver (b) (4) mL of product)
    - 200 mg and 6 mg in a 10 mL single-dose vial (to deliver (b) (4) mL of product)
    - 300 mg and 6 mg in a 20 mL single-dose vial (to deliver (b) (4) mL of product)
    - 400 mg and 12 mg in a 20 mL single-dose vial (to deliver (b) (4) mL of product)
- Storage: Store ZYNRELEF kits at (b) (4) Protect from moisture and light. If ZYNRELEF vials are removed from the kit, store (b) (4) Protect from light during storage.

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Zynrelef would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) concurred with the findings of OPDP's assessment for Zynrelef.

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) Search

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

2.2.2 Components of the Proposed Proprietary Name

Heron did not provide a derivation or intended meaning for the proposed proprietary name, Zynrelef, in their submission. 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

In response to the OSE, December 2, 2020 e-mail, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not forward any comments or concerns relating to Zynrelef at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Eighty-nine (89) practitioners participated in DMEPA's prescription studies for Zynrelef. 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 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[e] identified sixty (60) names with the combined score of ≥55% or individual orthographic or phonetic score of ≥70%. We had identified and evaluated some of the names in our previous proprietary name review. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. Our evaluation has not altered our previous conclusion regarding the acceptability of the proposed proprietary name. 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, our December 11, 2020 search of POCA identified two (2) new proposed proprietary names (b) (4)*** and (b) (4)***. 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. Additionally, we identified three (3) names from the new external study, dated August 21, 2020, that were not previously reviewed. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Names Retrieved for Review Organized by Name Pair Similarity

[d] USAN stem search conducted on December 2, 2020.

[e] POCA search conducted on December 11, 2020 in version 4.2.

Similarity Category	Number of Names
Highly similar name pair: combined match percentage score ≥70%	0
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	2
Low similarity name pair: combined match percentage score ≤54%	3

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

Our analysis of the five (5) names contained in Table 1 determined none of the names will pose a risk for confusion with Zynrelef as described in Appendices C through H.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) via e-mail on February 2, 2021. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on February 4, 2021, they stated no additional concerns with the proposed proprietary name, Zynrelef.

3 CONCLUSION

The proposed proprietary name, Zynrelef, is acceptable.

If you have any questions or need clarifications, please contact Tamika White, OSE project manager, at 301-796-0310.

3.1 COMMENTS TO HERON THERAPEUTICS INC.

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

If any of the proposed product characteristics as stated in your submission, received on November 12, 2020, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

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

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

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

Drugs@FDA

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

RxNorm

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

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

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

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

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

APPENDICES

Appendix A

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

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

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

[f] National Coordinating Council for Medication Error Reporting and Prevention. 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, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

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

- Low similarity: combined match percentage score ≤54%.

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

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[g]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign

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

a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

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

   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. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

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

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

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

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

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

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

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

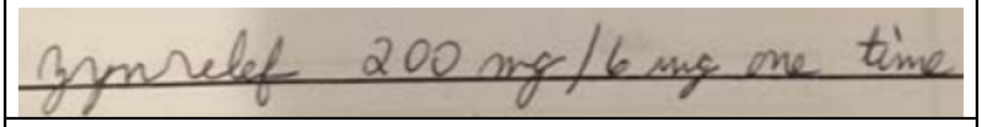
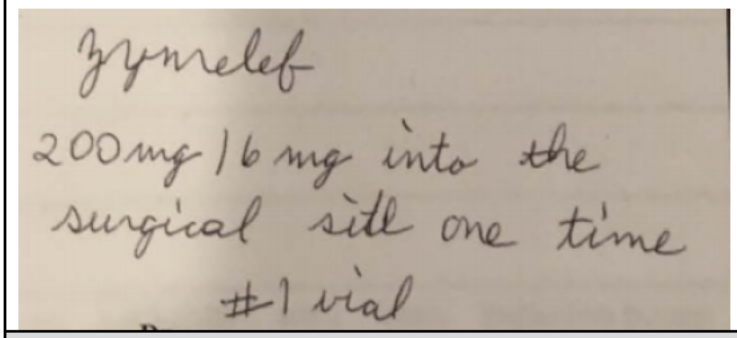
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length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

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

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

Appendix B: Prescription Simulation Samples and Results

Figure 1. Zynrelef Study (Conducted on December 18, 2020)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Zynrelef 200 mg into the surgical site one time
Outpatient Prescription:  	Dispense 1 vial
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Zynrelef	

FDA Prescription Simulation Responses (Aggregate Report)

209 People Received Study
89 People Responded

Study Name: Zynrelef

Total	34	15	14	26	
INTERPRETATION	**OUTPATIENT**	**CPOE**	**VOICE**	**INPATIENT**	**TOTAL**
CINRELYS	0	0	1	0	1
CYNRELOUS	0	0	1	0	1
CYRLYIS	0	0	1	0	1
SIMRELA	0	0	1	0	1
SIMRELLAS	0	0	1	0	1
SINRELIS	0	0	2	0	2
SINRELIX	0	0	1	0	1
SINRELLUS	0	0	1	0	1
SINRELUS	0	0	1	0	1

SIRELIS	0	0	1	0	1
SIRELLIS	0	0	1	0	1
SYMRELEX	0	0	1	0	1
ZENRELEF	2	0	0	0	2
ZENZEDI	0	1	0	0	1
ZERELLIS	0	0	1	0	1
ZYMELEF	5	0	0	0	5
ZYMELEF OR ZYNRELEF	1	0	0	0	1
ZYMRELEB	1	0	0	0	1
ZYMRELEF	0	0	0	1	1
ZYNELF	0	0	0	1	1
ZYNRELEB	1	0	0	0	1
ZYNRELEB 200MG/6 MG	1	0	0	0	1
ZYNRELEF	22	14	0	23	59
ZYNRELIEF	0	0	0	1	1
ZYURELEB	1	0	0	0	1

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

No.	**Proposed name:** Zynrelef **Established name:** bupivacaine and meloxicam **Dosage form:** extended-release solution **Strength(s):** 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam **Usual Dose:** single dose administration only; recommended dose range is 60 mg/1.8 mg to 400 mg/12 mg (approximately 2.3 to 14 mL)	**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.**
	N/A		

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

No.	**Proposed name:** Zynrelef **Established name:** bupivacaine and meloxicam **Dosage form:** extended-release solution **Strength(s):** 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam **Usual Dose:** single dose administration only; recommended dose range is 60 mg/1.8 mg to 400 mg/12 mg (approximately 2.3 to 14 mL)	**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**
	N/A		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 (%)
1.	Zentel	54
2.	Zirabev	48
3.	Zinc Sulfate	46

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
1.	(b) (4) ***	56	Proposed proprietary name for IND (b) (4) found to be unacceptable by DMEPA (2019-28736904 dated 7/11/2019). An alternative name has not been submitted to date.
2.	(b) (4) ***	57	Name identified in Names Entered by Safety Evaluator database. Unable to find product characteristics in internal databases.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[h].

No.	Name	POCA Score (%)
	N/A	

[h] 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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/s/

NASIM N ROOSTA
02/04/2021 08:49:12 AM

IRENE Z CHAN on behalf of VALERIE S VAUGHAN
02/04/2021 09:12:58 AM

PROPRIETARY NAME 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:	December 2, 2019
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam
Total Product Strength:	60 mg bupivacaine and 1.8 mg meloxicam in 2.3 mL; 200 mg bupivacaine and 6 mg meloxicam in 7 mL; 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL; 400 mg bupivacaine and 12 mg meloxicam 14 mL
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics, Inc.
Panorama #:	2019-34747451
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 INTRODUCTION

This memorandum is to reassess the proposed proprietary name, Zynrelef, which was found conditionally acceptable under IND 125927 and NDA 211988 on June 12, 2018 and January 24, 2019, respectively.[ab] However, a Complete Response (CR) letter was issued on April 30, 2019. Thus, Heron included a request for proprietary name review for the name, Zynrelef, on September 26, 2019 with the resubmission of the NDA.

We note that there is a change in the product strengths that will be available for NDA 211988. During our initial review of the name under IND 125927, Heron included the 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL product strength. However, Heron removed the 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL product strength when they previously submitted the NDA. For this resubmission of the NDA, Heron has added back the 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL product strength. All other product characteristics remain the same.

2 METHODS AND DISCUSSION

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Zynrelef would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) concurred with the findings of OPDP's assessment for Zynrelef. However the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) did not concur with the findings of OPDP's assessment for Zynrelef. DAAP provided the following concerns related to the name:

> "*when I read this at first I said to myself "Zen Relief" – seems promotional to me"*
>
> *" it seems promotional"*
>
> "*when I first read the name, I read it as Zen Relief."*

See section 2.2.1 for further details.

2.2 SAFETY ASSESSMENT

To re-assess the proposed proprietary name, we conducted a gap analysis and searched the Phonetic and Orthographic Computer Analysis (POCA) database to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name reviews. Additionally, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. Our evaluation has not altered our previous conclusion regarding the acceptability of the

[a] Johnson, Cameron. Proprietary Name Review for Zynrelef (IND 125927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 12. Panorama No.: 2017-19886867.

[b] Johnson, Cameron. Proprietary Name Review Memo for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 24. Panorama No.: 2017-27001290.

proposed proprietary name. Additionally, our October 19, 2019 search of POCA identified four new proposed proprietary names (b) (4)***, (b) (4)***, (b) (4)***, (b) (4)***. These names do not represent a potential source of drug name confusion (see Appendices).

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 October 19, 2019 search of USAN stems did not find any USAN stems in the proposed proprietary name, Zynrelef. As a result, we maintain that the name is acceptable.

2.2.1 COMMENTS FROM OTHER REVIEW DISCIPLINES AT INITIAL REVIEW

In response to the OSE, October 21, 2019 email DAAP expressed the following concerns related to the name:

> *"when I read this at first I said to myself "Zen Relief" – seems promotional to me"*
>
> *" it seems promotional"*
>
> *"when I first read the name, I read it as Zen Relief."*

OSE contacted OPDP on November 1, 2019 and requested a reassessment of the name taking into consideration the Division's comments. OPDP re-evaluated the proposed name and provided the following response:

"In light of the OND Review Division (DAAAP[c])'s concern noted in the email below, the OPDP PNR team re-evaluated the proposed tradename "Zynrelef." We continue to maintain our non-objection to the trade name Zynrelef. The team has concluded that the word does not imply "Zen" as it's literal name breakdown is "Zin", which does not have the same meaning as "Zen". In addition, although the word evokes "relief", it does not pose a promotional concern as "Zynrelef" is indicated (b) (4) This would in fact provide relief. Therefore, OPDP has determined that this name does not pose a promotional concern."

We concurred with OPDP's reassessment. On November 8, 2019 we informed DAAP of OPDP's final determination. DAAP did not forward any additional concerns related to the name.

2.3 COMMUNICATION OF DMEPA'S ANALYSIS AT MIDPOINT OF REVIEW

We communicated our findings to DAAP via e-mail on November 21, 2019. At that time we also requested additional information or concerns that could inform our review. DAAP did not provide any additional concerns with the proposed proprietary name, Zynrelef.

[c] Effective November 4, 2019, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), became the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP).

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, Zynrelef, is acceptable.

If you have any questions or need clarifications, please contact Corwin Howard, OSE project manager, at 240-402-8654.

3.1 COMMENTS TO HERON THERAPEUTICS, INC.

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

If any of the proposed product characteristics as stated in your submission, received on September 26, 2019, 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.

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.

5 APPENDICES

Appendix A: – N/A

Appendix B: – N/A

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

No.	**Proposed name:** Zynrelef **Established name:** bupivacaine and meloxicam **Dosage form:** extended-release solution **Strength(s):** 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam **Usual Dose:**	**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.**
	N/A		

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

No.	**Proposed name:** Zynrelef **Established name:** (b) (4) **Dosage form:** extended-release solution **Strength(s):** 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam **Usual Dose:**	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**
1.	(b) (4) ***	58	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
	N/A		

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[d].

[d] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially

No.	Name	POCA Score (%)
1.	(b) (4) ***	56
2.	(b) (4) ***	57
3.	(b) (4) ***	63

Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

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/s/

CAMERON D JOHNSON
12/02/2019 09:54:08 AM

OTTO L TOWNSEND
12/02/2019 10:37:10 AM

PROPRIETARY NAME 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:	January 24, 2019
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam
Total Product Strength:	60 mg bupivacaine and 1.8 mg meloxicam in 2.3 mL; 200 mg bupivacaine and 6 mg meloxicam in 7 mL; 400 mg bupivacaine and 12 mg meloxicam 14 mL
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics, Inc.
Panorama #:	2018-27001290
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 INTRODUCTION

This memorandum is to reassess the proposed proprietary name, Zynrelef, which was found conditionally acceptable under IND 125927 on June 12, 2018.[a]

We note that there is a change in the product strengths that will be available for NDA 211988. The Applicant has removed the 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL product strength that was previously proposed. All other product characteristics remain the same.

2 METHODS AND DISCUSSION

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Zynrelef would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) concurred with the findings of OPDP's assessment for Zynrelef.

2.2 SAFETY ASSESSMENT

For re-assessment of the proposed proprietary name, DMEPA evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. We also evaluated previously identified names taking into account the elimination of the product strength, 300 mg bupivacaine and 9 mg meloxicam in 10.5 mL from this submission. Our evaluation determined that our conclusions regarding previously identified names of concern has not changed.

During our re-assessment, the proposed proprietary name, (b) (4)***, was identified as a name of concern. The name was not evaluated in our previous review of Zynrelef because it was submitted to the agency after our review was completed. The risk for confusion between this name pair is discussed in the proprietary name review of (b) (4)***[b], (b) (4) Therefore, the proprietary name (b) (4)*** was issued a denial decision from DMEPA. Thus, based on this information, (b) (4)*** and Zynrelef will not coexist on the market.

Additionally, DMEPA searched the USAN stem list to determine if the proposed proprietary name contains any USAN stems as of the last USAN updates. The November 7, 2018 search of USAN stems did not find any USAN stems in the proposed proprietary name, Zynrelef.

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[a] Johnson, C. Proprietary Name Review for Zynrelef (IND 125927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 12. Panorama No.: 2017-19886867.

[b] Myers, D. Proprietary Name Review for (b) (4) (IND (b) (4) and IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 14. Panorama No.: 2018-24380138 and 2018-24406170.

2.3 COMMUNICATION OF DMEPA'S ANALYSIS AT MIDPOINT OF REVIEW

DMEPA communicated our findings to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) via e-mail on January 7, 2019. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on January 17, 2019, they stated no additional concerns with the proposed proprietary name, Zynrelef.

3 CONCLUSIONS

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, Zynrelef, is acceptable.

If you have any questions or need clarifications, please contact Davis Mathew, OSE project manager, at 240-402-4559.

3.1 COMMENTS TO HERON THERAPEUTICS, INC.

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

If any of the proposed product characteristics as stated in your submission, received on October 30, 2018, are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

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

   USAN Stems List contains all the recognized USAN stems.

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/s/

CAMERON D JOHNSON
01/24/2019 11:59:58 AM

OTTO L TOWNSEND
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