CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211988Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	May 11, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.5 mg/0.88 mg per mL
Applicant/Sponsor Name:	Heron Therapeutics
OSE RCM #:	2018-2410-1 and 2019-2030-1
DMEPA Team Leader:	Valerie S. Vaughan, PharmD.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, carton labeling, and Instructions for Use (IFU) received on May 10, 2021 for Zynrelef. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels, carton labeling, and IFU for Zynrelef (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additionally, the Applicant has proposed revisions to the storage statements on the container labels, carton labeling, and in the IFU to align with the Prescribing Information.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations with some minor edits to those implemented in the IFU, which we find acceptable. Additionally, we find the proposed revisions to the storage statements acceptable from a medication error perspective. Thus, we have no additional recommendations at this time.

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[a] Johnson, C. Label and Labeling Review for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 16. RCM No.: 2018-2410 and 2019-2030.

[b] Re: NDA 211988 Proposed Changes to Draft Zynrelef Instructions of Use and Carton and Container Labels for Storage Conditions. San Diego (CA): Heron Therapeutics. 2021 MAY 10. Available from: \\CDSESUB1\evsprod\nda211988\0079\m1\us\cover.pdf

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/s/

VALERIE S VAUGHAN
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 4/23/2021

To: Rita Joshi, PharmD, Regulatory Project Manager, (DAAP)

From: Phillip Williams, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZYNRELEF (bupivacaine and meloxicam) solution

NDA: 211988

In response to DAAP's consult request dated November 25, 2020, OPDP has reviewed the proposed product labeling (PI), for ZYNRELEF (bupivacaine and meloxicam) solution.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on April 21, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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PHILLIP A WILLIAMS
04/23/2021 01:43:29 PM

LABEL AND LABELING 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 16, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.5 mg/mL and 0.88 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics
FDA Received Date:	November 12, 2020 and November 24, 2020
OSE RCM #:	2018-2410 and 2019-2030
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Valerie Vaughan, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Zynrelef (bupivacaine and meloxicam) extended-release solution, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the Zynrelef human factors validation study results, prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 211988 is a 505(b)(2) NDA and the reference drug products are Marcaine (NDA 016964), Mobic (NDA 020938), Bupivacaine hydrochloride (NDA 018053), and Sensorcaine (NDA 018304).

Heron Therapeutics submitted their original NDA on September 21, 2018. During the review cycle we reviewed their human factors (HF) validation study results and Prescribing Information. The results of the HF validation study showed use errors and difficulties with the preparation and administration of the proposed product. However, we determined that the use errors and difficulties could be mitigated through additional risk mitigation measures and Heron would not need to submit the results of another human factors validation study for our review.

NDA 211988 received a complete response (CR) on April 30, 2019 due to product quality, nonclinical, and device deficiencies (i.e., syringe tip cap sterility concern). On September 26, 2019, Heron submitted their responses to the deficiencies included in the CR letter as a Class 2 Resubmission. We reviewed the PI, container labels, and carton labeling and identified areas of concern that could lead to medication errors. Our recommendations for the container labels and carton labeling were communicated to Heron. In response, Heron submitted revised container labels and carton labeling which incorporated our recommendations. Furthermore, during the previous review cycle, we discussed our revisions to the PI with the DAAP review team during the labeling meetings. Also, during labeling meetings there were discussions regarding specific revisions to the PI which would necessitate additional changes to the container labels and carton labeling. However, on June 26, 2020 the application received a second CR due to nonclinical deficiencies. Therefore, the revisions to the PI and additional corresponding recommendations for the container labels and carton labeling were not communicated to Heron.

On November 12, 2020, Heron submitted the responses to the nonclinical deficiencies included in the CR letter as a Class 2 Resubmission.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

In our label and labeling review[i] during the previous review cycle we recommended that Heron revise the established name format [redacted] (b) (4) so that the established name reads as "bupivacaine and meloxicam". In response to our recommendation, Heron revised the format of the established name from [redacted] (b) (4) to "bupivacaine and meloxicam."

Table 2 below includes the remaining identified medication error issues with the submitted PI, IFU, container labels and carton labeling our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Some of the recommendations below were previously identified but are included because they were not previously conveyed to the Applicant prior to the second CR action.

Table 2: Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information and Full Prescribing Information			
1.	In the Dosage Forms and Strengths section, (b) (4)	Postmarketing reports[a] have shown that (b) (4) may cause confusion to users. For example, healthcare professionals could believe (b) (4)	We recommend removing (b) (4) (b) (4) for each product strength presentation. For example, revise the Highlights to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution in single dose glass vials: 400 mg bupivacaine and 12 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam Revise the FPI to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution is a clear, pale yellow to yellow, viscous liquid in a single-dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam and is available in the following 4 presentations: 400 mg bupivacaine and 12 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam

[a] Institute for Safe Medication Practices. 2005 MAR 24. Your Reports at Work. ISMP Med Saf Alert Acute Care. 10 (6):1-3.

			200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam
2.	(b) (4) Highlights and Full Prescribing Information in the Dosage and Administration sections. For example, in the Highlights, (b) (4)	(b) (4) In our previous reviews and in consultation with the Office of Pharmaceutical Quality (OPQ), we determined that the strength/dose is best presented in terms of the withdrawal volume to deliver the amount of drug in milligrams, (b) (4) in order to reduce the risk of wrong dose medication errors and confusion between the withdrawal volume and the delivered volume.[b,c,d]	Revise the format of the dose in the Highlights and FPI to include the strength as the withdrawal volume needed to deliver the amount of drug in units of milligrams.. For example, change (b) (4) to "14 mL to deliver 400 mg/12 mg".

[b] Flint, J and Johnson, C. Human Factors Results and Labeling Review for bupivacaine and meloxicam extended release solution (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2018-2421 and 2018-2410.

[c] Johnson, C. Label and Labeling Review for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 19. RCM No.: 2019-2030.

[d] Johnson, C. Label and Labeling Review Memo for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 01. RCM No.: 2019-2030-1

Full Prescribing Information			
1.	In section 2.1, (b) (4) information about the excess volume contained in each vial is missing.	We are concerned that healthcare providers might inadvertently misinterpret the labeled volume, which includes overfill, as the dose volume.	We recommend adding the statement "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator and syringe(s) during drug withdrawal and administration." Consider adding the above statement as an additional bulleted point following the bulleted point, "The contents of the ZYNRELEF vial are sterile. The vial exterior is not sterile. Follow your facility's standard operating procedures regarding aseptic and sterile preparation."
2.	In the How Supplied/Storage and Handling section, the net quantity of drug in each vial presentation has been omitted (b) (4)	Postmarketing reports[e] have shown that including (b) (4) and not the net quantity may cause confusion to users. For example, healthcare professionals may confuse the labeled (b) (4)	We recommend deleting (b) (4) and adding a column in the table to include the volume to be withdrawn from each vial for desired labeled dose for each strength presentation. Furthermore, add a reference footnote to the net quantity volume and include the statement, "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration."
3.	In the How Supplied/Storage and	The color of the drug product is important	Include a description of the color of the solution (i.e. clear, pale

[e] Institute for Safe Medication Practices. 2005 MAR 24. Your Reports at Work. ISMP Med Saf Alert Acute Care. 10 (6):1-3.

	Handling section, the color of the solution has been omitted.	physical information used by health care providers to facilitate easy identification of the product. See 21 CFR 201.57.	yellow to yellow viscous liquid) in the How Supplied section in accordance with 21 CFR 201.57.
4.	The How Supplied/Storage and Handling section does not include information related to the vented vial spike, luer-lock applicator, and syringe replacement components.	This section should include the replacement component information to alert the healthcare provider that these components are available in instances where the components supplied with the kit have been dropped or damaged.	We recommend adding information to this section regarding the availability of the replacement components. For example: The following replacement components are individually supplied separate from the kit: •Carton containing 5 vented vial spikes •Carton containing 10 Luer lock applicators •Carton containing 10 sterile 3 mL Luer Lock syringes •Carton containing 8 sterile 12 mL Luer Lock syringes
Instructions for Use (IFU)			
1.	The warning statements included in the IFU, are not prominently displayed. For example, for the Preparation Instructions, Step 5 includes the warning statement "⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial" which looks similar to all other information in this step.	Other than the warning symbol, ⚠, these statements lack prominence and do not draw the user's attention to this important information. Based on the use difficulty observed during the HF validation study, the call-out warning statements can be revised to call the user's attention to the warning statements.	We recommend increasing the prominence of the warning statements. For example, you may consider using a different font color or size, highlighting, or some other means to draw user's attention to this important information (see example for the 400 mg/12 mg in 14 mL product strength below): "Fill the syringe with 7 mL of air before attaching to the vented vial spike. ⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and

			product has filled the neck of the vial."
2.	The Preparation and Administration sections of the IFU contain statements that may appear to the user as optional instructions. For example, (b) (4) (b) (4)	By including the term (b) (4) these statements create ambiguity and may cause the user to misinterpret the direction (b) (4) Therefore, the terminology can be strengthened to encourage users to perform the task as instructed. We note that the HF validation study results showed use difficulty with certain tasks that were presented as recommendations. For example, for Step 4 in the Preparation IFU, a sterile user experienced use difficulty when attempting to attach the vented vial spike to the vial while the non-sterile user held the vial above the surface (as opposed to on a firm, flat surface). The root cause analysis did not clearly identify a contributing factor or cause; however, reframing these so they are not interpreted as optional may help to optimize the use of this product.	These statements should be strengthened so that they do not appear as optional instructions. For example, in the Preparation section, Step 4, revise the statement "Hold the vial in place while sterile person attaches spike. *Note:* (b) (4) to "Place the vial on a firm, flat surface and hold in place while the sterile person attaches the spike." In the Administration section, Step 5, revise the statement (b) (4) to "When using monofilament sutures, use 3 or more knots as contact…".
3.	There is no statement in the IFU to provide	Due to the high viscosity of the drug, users may confuse the withdrawal	To inform users that the withdrawal volume is different from the total volume contained

	clarity about the overfill volume.	volume and the overfill volume that remains in the vial after withdrawal which may lead to wrong dose errors.	in the vial, we recommend adding a statement such as "Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration." We suggest adding this statement in a separate text box under the blue box for sterile user in step 1 to draw the user's attention to this important information. Furthermore, to draw attention to the correct withdrawal volume, under the "Preparing the Product" section at the top of the IFU, we recommend increasing prominence of the statement "Withdraw XX mL" (e.g., Withdraw 2.3 mL).
4.	The administration subsection of the IFU contains the statements: (b) (4)	The 14 mL volume is (b) (4) the amount of product that is withdrawn from the vial to deliver the dose of 400 mg bupivacaine and 12 mg meloxicam.	Revise these statements to read: "As a guide, the maximum withdrawal volume is 14 mL" and "ZYNRELEF spreads easily and covers a large area. For example, a withdrawal volume of 14 mL is sufficient to cover large surgical procedures such as total knee arthroplasty and will deliver a dose of 400 mg/12 mg."
Prescribing Information, IFU, Container Labels, Carton Labeling, Carton Labeling for the Kit			
1.	The dosage form description "extended-release" is included on all labels and labeling.	During the previous review cycle, DAAP noted that the "extended-release"	When a final determination is made on the appropriate dosage form that will be included in the PI, appropriate revisions should

		description in the dosage form was not appropriate for this product because it did not show extended-release properties in all the surgical models studied during the clinical trials.	be made by the applicant to the IFU, container labels, carton labeling for the drug vial, carton labeling for the kit, and replacement components for consistency.
2.	The route of administration (ROA), (b) (4) is included on all labels and labeling.	During the previous review cycle DAAP was considering revising the ROA to a statement such as "for soft tissue instillation and periarticular instillation use".	When a final determination is made on the appropriate ROA that will be included in the PI, appropriate revisions should be made by the applicant to the IFU, container labels, carton labeling for the drug vial, carton labeling for the kit, and replacement components for consistency.

5 CONCLUSION

Our evaluation of the proposed Zynrelef prescribing information (PI), container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Zynrelef that Heron Therapeutics submitted on November 12, 2020.

Table 3. Relevant Product Information for Zynrelef	
Initial Approval Date	N/A
Active Ingredient	Anesthetic with a nonsteroidal anti-inflammatory drug (NSAID)
Indication	Bupivacaine and meloxicam
Route of Administration	(b) (4)
Dosage Form	(b) (4)
Strength	29.5 mg/mL and 0.88 mg/mL in the following total product strengths: 60 mg/1.8 mg in 2.3 mL 200 mg/6 mg in 7 mL 300 mg/9 mg in 10.5 mL 400 mg/12 mg in 14 mL
Dose and Frequency	Apply to surgical site following final irrigation and suction and prior to suturing. If multiple tissue layers are involved, apply after irrigation and suction of each layer before closing.
How Supplied	Cardboard convenience kit containing: • One single-dose vial containing bupivacaine and meloxicam in a non-sterile carton • Sterile vented vial spike • One or Two sterile (b) (4) mL Norm-Ject Luer lock syringes OR One sterile 3 mL Norm-Ject Luer lock syringe • One or Two sterile luer lock applicators • One or Two sterile syringe tip caps IFU and PI
Storage	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 17, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, bupivacaine and meloxicam. Our search identified five previous reviews[f,g,h,i,j], and we confirmed that our previous recommendations were implemented.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

[f] Johnson, C. Human Factors Validation Study Protocol Review for bupivacaine and meloxicam extended release solution (IND 125927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 13. RCM No.: 2018-798.

[g] Johnson, C. Human Factors Validation Study Protocol Review Memorandum for bupivacaine and meloxicam extended release solution (IND 125927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 03. RCM No.: 2018-798-1.

[h] Flint, J and Johnson, C. Human Factors Results and Labeling Review for bupivacaine and meloxicam extended release solution (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2018-2421 and 2018-2410.

[i] Johnson, C. Label and Labeling Review for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 19. RCM No.: 2019-2030.

[j] Johnson, C. Label and Labeling Review Memo for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 01. RCM No.: 2019-2030-1.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Zynrelef labels and labeling submitted by Heron Therapeutics.

- Container label(s) received on November 12, 2020
- Carton labeling received on November 12, 2020
- Carton labeling for the Kit received on November 12, 2020
- Vented Vial Spike Replacement Carton received on November 12, 2020
- Luer Lock Applicator Replacement Carton received on November 12, 2020
- 3 mL Syringe Replacement Carton received on November 12, 2020
- 12 mL Syringe Replacement Carton received on November 12, 2020
- Instructions for Use (Images not shown) received on November 12, 2020 can be accessed in EDR via:
  - \\CDSESUB1\evsprod\nda211988\0066\m1\us\draft-ifu-60.pdf
  - \\CDSESUB1\evsprod\nda211988\0066\m1\us\draft-ifu-200.pdf
  - \\CDSESUB1\evsprod\nda211988\0066\m1\us\draft-ifu-300.pdf
  - \\CDSESUB1\evsprod\nda211988\0066\m1\us\draft-ifu-400.pdf
- Prescribing Information (Image not shown) received on November 24, 2020 can be accessed in EDR via:
  - \\CDSESUB1\evsprod\nda211988\0068\m1\us\draft-pi-word.docx

F.2 Label and Labeling Images

Container label(s)

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CAMERON D JOHNSON
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LUBNA A MERCHANT on behalf of VALERIE S VAUGHAN
02/18/2021 11:19:28 AM

LUBNA A MERCHANT on behalf of IRENE Z CHAN
02/18/2021 11:20:24 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	June 1, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.25 mg/mL and 0.88 mg/mL
Applicant/Sponsor Name:	Heron Therapeutics
OSE RCM #:	2019-2030-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised labels and labeling received on April 1, 2020 for Zynrelef. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised labels and labeling for Zynrelef (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

In our previous review[a] we recommended that the strength presentation be revised to include the volume delivered of the drug instead of the volume withdrawn. For example, we requested that the [redacted] (b) (4) be revised to "60 mg bupivacaine and 1.8 mg meloxicam per 2.05 mL volume". Heron did include the net contents statement (Vial Contents: 2.3 mL) on the bottom right corner of the principal display panel (PDP) as well as the statement "withdraw 2.3 mL to deliver 2.0 mL" on the side panel. We initially thought that having the equivalent volume below the total strength would be helpful; however, after further consideration, we agree with Heron's proposal because having multiple

[a] Johnson, C. Label and Labeling Review for Zynrelef (NDA 211988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 19. RCM No.: 2019-2030.

volumes (2.0 mL and 2.3 mL) on the PDP may lead to clutter as well as confusion if the user misinterprets the volume to be delivered with the withdraw/net contents volume. We discussed Heron's proposal with the Office of Pharmaceutical Quality (OPQ), and they agreed that Heron's revision avoids confusion and clutter. Therefore, we find Heron's revision acceptable from a medication error perspective.

During the Prescribing Information (PI) labeling meetings, DAAP noted that the "extended-release" description in the dosage form was not appropriate for this product because it did not show extended-release properties in all the surgical models studied during the clinical trials. Therefore, DAAP proposed to remove the "extended-release" description from the PI. We do not have a concern with the removal of "extended-release" from the dosage form, because the inclusion or exclusion does not affect the way a user would interact with or administer the product based on the instructions for use. DAAP also noted during the PI labeling meetings that the route of administration (ROA) that was originally proposed by DAAP, (b) (4) may not be appropriate as it is not recognized in the Data Standards Manual for ROA[b] and may be interpreted differently depending on the surgical site. Therefore, DAAP is considering revising the ROA, to a statement such as "for soft tissue instillation and periarticular instillation use". We note that Heron has proposed the ROA, (b) (4) on the container label, carton labeling for the drug vial and carton labeling for the kit which is also not included in the Data Standards Manual for ROA. From a medication error perspective we do not have a concern with the use of either ROA term (i.e., proposed by Heron or under consideration by DAAP) because either term could be used to appropriately convey the intended route of administration. Therefore, we defer to DAAP clinical to determine the most appropriate term based on clinical practice.

3 CONCLUSION

The revised container label, carton labeling for the drug vial, carton labeling for the kit, and replacement component labeling are acceptable from a medication error perspective. We have no further recommendations for Heron at this time. However, due to ongoing internal discussions regarding the "extended-release" description in the dosage form as well as the route of administration, we provide a recommendation below for DAAP to convey their final determination on these terms to Heron for all labels and labeling.

4 RECOMMENDATIONS FOR DAAP

We note that there are currently internal discussions regarding the inclusion of the "extended-release" description in the dosage form as well as the appropriate route of administration for this product. We note that, the description "extended-release" as well as the route of administration, (b) (4) is included on all Instructions for Use (IFU), container labels, carton labeling for the drug vial, carton labeling for the kit, and

[b] https://www.fda.gov/drugs/data-standards-manual-monographs/route-administration

replacement components. When a final determination is made on the appropriate terms that will be included in the PI, we defer to DAAP to inform the Applicant to also make the appropriate revisions to the IFU, container labels, carton labeling for the drug vial, carton labeling for the kit, and replacement components.

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/s/

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LABEL AND LABELING 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 19, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP)
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (bupivacaine and meloxicam) extended-release solution, 29.25 mg/mL and 0.88 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics
FDA Received Date:	January 31, 2019 and September 26, 2019
OSE RCM #:	2019-2030
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zynrelef (bupivacaine and meloxicam) extended-release solution, the Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) requested that we review the proposed Zynrelef labels and labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

Heron Therapeutics submitted their original NDA on September 21, 2018. During the review cycle we reviewed their human factors (HF) validation study results and Prescribing Information. The results of the HF validation study showed use errors and difficulties with the preparation and administration of the proposed product. However, we determined that the use errors and difficulties could be mitigated through labeling and Heron would not need to submit the results of another human factors validation study for our review. NDA 211988 received a complete response (CR) on April 30, 2019 due to product quality, nonclinical, and device deficiencies. On September 26, 2019, Heron submitted their responses to the deficiencies included in the CR letter as a Class 2 Resubmission.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information, Instructions for Use (IFU), container labels, carton labeling, carton labeling for the kit and replacement components, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. We note that some of our

recommendations included under the IFU section are based on the results of the HF validation study that we evaluated in our previous review.[a]

Table 2: Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information and Full Prescribing Information			
1.	In the Dosage Forms and Strengths section, (b) (4)	Including (b) (4) may cause confusion to users. This presentation has been documented in postmarket medication error reports to be error prone. For example, healthcare professionals could confuse (b) (4)	Remove (b) (4) for each product strength presentation. For example, revise the Highlights to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution in single dose glass vials: 400 mg bupivacaine and 12 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam Revise the FPI to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution is a clear, pale yellow to yellow, viscous liquid in a single-dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL

[a] Flint, J and Johnson, C. Human Factors Results and Labeling Review for bupivacaine and meloxicam extended release solution NDA 211988. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2018-2421 and 2018-2410.

			meloxicam and is available in the following 4 presentations: 400 mg bupivacaine and 12 mg meloxicam 300 mg bupivacaine and 9 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam
2.	In the Dosage and Administration sections, the format of the product strength and volume is different between the Highlights and Full Prescribing Information. In the Highlights, the product strength is presented as (b) (4) while in the FPI the product strength is presented as (b) (4)	To maintain consistency and to prevent confusion, the format of the product strength should be consistent throughout the Highlights and Full Prescribing Information.	Revise the format of the product strength in the Highlights and FPI for consistency for all strength presentations. For example, change (b) (4) to "14 mL to deliver 400 mg/12 mg".
Full Prescribing Information			
1.	In the Dosage and Administration section, section 2.1 is titled (b) (4) This section does not include information about the excess volume contained in each vial.	Section 2.1 includes important administration AND preparation instructions and should also include a statement related to the excess volume in the vial to inform users of the overfill.	Revise the title of section 2.1 to "Important Preparation and Administration Instructions". Also, after the bullet point (b) (4) add the statement "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, Luer lock applicator and syringe(s)

			during drug withdrawal and administration."
2.	In the How Supplied/Storage and Handling section, the net quantity of drug in each vial presentation has been omitted (b) (4)	Including (b) (4) and not the net quantity may cause confusion to users. This presentation has been documented in postmarket medication error reports to be error prone. For example, healthcare professionals could confuse (b) (4)	Add a column in the table to include the net quantity volume (i.e. volume to be withdrawn from each vial for desired labeled dose) for each strength presentation. Furthermore, add a reference footnote to the net quantity volume and include the statement, "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration."
3.	In the How Supplied/Storage and Handling section, the color of the solution has been omitted.	The color of the drug product is important information used by health care providers to facilitate easy identification of the product.	Include a description of the color of the solution (i.e. clear, pale yellow to yellow viscous liquid) in the How Supplied section.
Instructions for Use (IFU)			
1.	In the Administration section of the IFU, it is not clear what volume may be appropriate for different types of surgeries.	In Formative Study 2, a surgeon participant commented that, "I would like more information about how much product to apply to different types of incisions – it depends on depth and length of incision." Furthermore, during the Human Factors (HF) Validation study, a surgeon administered excess product to the surgical site which resulted in some product getting on	Revise the IFU to convey the specific volume (dose) needed to coat the tissue based on surgical type, as was done in the Prescribing Information.

		the skin. This error can result in skin irritation (i.e. incision site erythema and incision site edema). Based on the subjective data from Formative Study 2 and the root cause analysis for this use error that occurred during the HF Validation study, the Administration IFU can be improved to reduce the risk of surgeons administering excess product to the surgical site.	
2.	The call-out warning statements included in the Preparation and Administration Instructions for Use, are not prominently displayed. For example, for the Preparation Instructions, Step 5 includes the warning statement "⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial" which looks similar to all other information in this step.	Other than the warning symbol, ⚠, these statements lack prominence and do not draw the user's attention to this important information. Based on the use difficulty observed during the HF validation study, the call-out warning statements can be revised to call out the user's attention to minimize instances of the user overlooking the warning statements.	Increase the prominence of the call-out statements. For example, you may consider using a different font color or size, or highlighting these statements to draw user's attention to this important information (see example for the 400 mg/12 mg in 14 mL product strength below): "Fill the syringe with 7 mL of air before attaching to the vented vial spike. ⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial."
3.	The Preparation and Administration sections of the IFU contain (b) (4) statements.	The use of (b) (4) statements in the IFU may cause the user to misinterpret the direction (b) (4) The HF validation study	Revise the passive statements using active voice. For example, in the Preparation section, Step 4, revise the statement "Hold the vial in place while sterile person attaches spike. *Note:* (b) (4)

		results showed use difficulty with certain tasks that were presented using (b) (4) statements. For example, for Step 4 in the Preparation IFU, a sterile user experienced use difficulty when attempting to attach the vented vial spike to the vial while the non-sterile user held the vial above the surface (as opposed to on a firm, flat surface).	(b) (4) to "Place the vial on a firm, flat surface and hold in place while the sterile person attaches the spike." In the Administration section, Step 5, revise the statement (b) (4) to "When using monofilament sutures, use 3 or more knots as contact…".
4.	In the Preparation IFU and Administration IFU, for all strength presentations, the established name and product strength is presented as: (b) (4)	This format may cause confusion (b) (4)	To reduce confusion, revise the format of the product strength to list the strength of the active ingredients per volume delivered for each vial presentation listed in each version of the IFU. Furthermore, include the word "and" between the two active ingredients. For example, change the product strength presentation to: XX mg bupivacaine and YY mg meloxicam per ZZ mL volume Furthermore, directly below the strength presentation add the statement: "Each mL contains 20.25 mg bupivacaine and 0.88 mg meloxicam" in smaller font. We also suggest adding an asterisk (*) symbol next to the net quantity statement to refer the user to the overfill volume (see recommendation 9 below).

5.	In the Preparation IFU and Administration IFU, for all strength presentations, the established name is presented as: (b) (4) In the Prescribing Information the established name is presented as: (b) (4)	For consistency the established name should be presented in the same format throughout all labels and labeling.	Revise the established name format (b) (4) as below: bupivacaine and meloxicam
6.	There is no statement in the IFU to address the overfill volume.	Due to the high viscosity of the drug, users may confuse the withdrawal volume and the overfill volume that remains in the vial after withdrawal which may lead to wrong dose errors.	To inform users that the withdrawal volume is different from the total volume contained in the vial, add a statement such as "Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration." We suggest adding this statement in a separate text box under the blue box for sterile user in step 1 to draw the user's attention to this important information. Furthermore, to draw attention to the correct withdrawal volume, under the "Preparing the Product" section at the top of the IFU, bold the statement "Withdraw ZZ mL" (e.g., "Withdraw 2.3 mL).
7.	The Administration IFU contains the statements under Important Information: (b) (4)	The 14 mL volume is (b) (4) (b) (4) the amount of product that is withdrawn from the vial to obtain the dose of	Revise these statements to read: "As a guide, the maximum total volume is 14 mL" and "ZYNRELEF spreads easily and covers a large area. For example,

	(b) (4)	400 mg bupivacaine and 12 mg meloxicam.	the 14 mL volume is sufficient to cover large surgical procedures such as total knee arthroplasty.”
Container Labels, Carton Labeling, Carton Labeling for the Kit and Instructions for Use			
1.	The dosage form is included as “extended-release solution”.	We note that the Office of Pharmaceutical Quality (OPQ) consulted with their labeling workgroup who proposed that the Applicant revise the dosage form to “extended-release solution, for instillation use”.	We defer to OPQ to determine the appropriate dosage form and convey this to the Applicant.
Prescribing Information, Container Labels, Carton Labeling, Carton Labeling for the Kit and Instructions for Use			
1.	The package type term is included as “single-dose vial”.	We note OPQ consulted with their labeling workgroup who proposed the package type term as “Single patient use. Discard vial contents after use.”	We defer to OPQ to determine the appropriate package type term and convey this to the Applicant.

Table 3: : Identified Issues and Recommendations for Heron Therapeutics (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels, Carton Labeling and Carton Labeling for the Kit			
1.	The established name is not at least half the size of the proprietary name.	Per 21 CFR 201.10(g)(2), the established name should be at least half the size of the proprietary name.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
2.	For all strength presentations, the product code portion (middle 3-4 digits) of the National Drug Code (NDC) is the same for the container, carton, and the carton labeling for the kit.	The carton labeling for the kit that contains one carton as well as other components should have a different product code portion (middle 3-4 digits of the NDC) than the container and carton.	Revise the NDC numbers so that the kit has a different product code than the container and carton.
3.	For all strength presentations, the product strength is presented as: (b) (4) (b) (4)	This format may cause confusion (b) (4)	To reduce confusion, revise the format of the product strength to list the strength of the active ingredients per volume delivered. Furthermore, include the word “and” between the two active ingredients. For example, for the vial label revise the product strength to: 60 mg bupivacaine and 1.8mg meloxicam per 2.05 mL volume Furthermore, directly below the strength presentation add the statement:

			"Each mL contains 20.25 mg bupivacaine and 0.88 mg meloxicam" in smaller font. . We also suggest adding an asterisk (*) symbol next to the net quantity statement to refer the user to the overfill volume (see recommendation 5 below).
4.	The net quantity statement (withdrawal volume) is located directly below the strength. Also, there is no statement to address the overfill volume.	Due to the viscosity of the drug, users may confuse the withdrawal volume and the overfill volume that remains in the vial after withdrawal which may lead to overdose.	Relocate the net quantity statement (i.e. 2.3 mL, 7 mL, 10.5 mL, 14 mL) to the bottom right or bottom left corner of the PDP and display as "Vial Contents: XX mL". Also, add an asterisk (*) symbol next to the net quantity statement to refer the user to the overfill volume. To inform users that the withdrawal volume is different from the total volume contained in the vial, add a statement such as "*Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration" to the carton labeling and carton labeling for the kit. If space permits add a statement such as "*Vial contains overfill" to the vial container label as well.
5.	The side panel contains the statement, (b) (4)	The user should be alerted to the Preparation instructions in	Revise this statement to read: "See Prescribing Information for Dosage,

		addition to the Dosage and Administration instructions.	Preparation, and Administration."
Carton Labeling			
1.	The side panel does not contain a statement related to the withdrawal volume versus the delivered volume.	Due to the overfill contained in the vial it may be helpful to include a statement related to the withdrawal/delivered volume to reduce the risk of users withdrawing an incorrect volume.	Add a statement to the side panel to inform users of the withdrawal and delivered volumes. For example, for the 60 mg bupivacaine and 1.8 mg meloxicam vial add the statement: "Withdraw 2.3 mL to deliver 2.05 mL."
Carton Labeling and Carton Labeling for the Kit			
1.	The side panel of the labeling contains the statement (b) (4) . For example, for the 60 mg/1.8 mg strength presentation: (b) (4)	Due to the overfill this is not an accurate presentation of the vial contents. .	Revise the contents statement to: "Each vial delivers: 60 mg bupivacaine and 1.8 mg meloxicam".
Vented Vial Spike Replacement Carton, Luer Lock Applicator Replacement Carton, 3 mL Syringe Replacement Carton, 12 mL Syringe Replacement Carton			
1.	On all Replacement Component carton labeling the proprietary name is more prominently displayed than the replacement product name, even though the cartons do not contain drug product.	The prominence of the proprietary name may cause confusion among users because they may assume the cartons contain drug product.	Revise the cartons so that the proprietary name of the drug product is not as prominently displayed. For example, for the Vented Vial Spike carton, consider rearranging the information so that the words "Replacement Vented Vial Spikes" are located above the proprietary name and are the most prominent information on the labeling.

Container Labels, Carton Labeling, Carton Labeling for the Kit, Vented Vial Spike Replacement Carton, Luer Lock Applicator Replacement Carton, 3 mL Syringe Replacement Carton, 12 mL Syringe Replacement Carton			
1.	On all container labels and carton labeling, the established name is presented as: (b) (4) In the Prescribing Information the established name is presented as: (b) (4)	For consistency the established name should be presented in the same format throughout all labels and labeling.	Revise the established name format (b) (4) as below: bupivacaine and meloxicam

5 CONCLUSION

Our evaluation of the proposed Zynrelef labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Error! Reference source not found. for the Division and Error! Reference source not found. for the Applicant. We ask that the Division convey Error! Reference source not found. in its entirety to Heron Therapeutics so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Zynrelef that Heron Therapeutics submitted on September 26, 2019.

Table 4. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Anesthetic with a nonsteroidal anti-inflammatory drug (NSAID)
Active Ingredient (Drug or Biologic)	Bupivacaine and meloxicam
Indication	(b) (4)
Route of Administration	(b) (4)
Dosage Form	Extended release solution
Strength	60 mg/1.8 mg in 2.3 mL 200 mg/6 mg in 7 mL 300 mg/9 mg in 10.5 mL 400 mg/12 mg in 14 mL
Dose and Frequency	Apply to surgical site following final irrigation and suction and prior to suturing. If multiple tissue layers are involved, apply after irrigation and suction of each layer before closing.
How Supplied Container Closure/Device Constituent	Cardboard convenience kit containing: • One single-dose vial containing bupivacaine and meloxicam in a non-sterile carton • Sterile vented vial spike • One or Two sterile (b) (4) mL Norm-Ject Luer lock syringes OR One sterile 3 mL Norm-Ject Luer lock syringe • One or Two sterile luer lock applicators • One or Two sterile syringe tip caps IFU and PI
Storage	(b) (4)
Intended Users	Surgeons, Surgical Technicians and OR Nurses
Intended Use Environment	Surgical Suites

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 10, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, bupivacaine and meloxicam. Our search identified three previous reviews[b,c,d], and we confirmed that our previous recommendations were implemented.

APPENDIX C.
APPENDIX D.
APPENDIX E.

[b] Johnson, C. Human Factors Validation Study Protocol Review for bupivacaine and meloxicam extended release solution IND 125927. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 13. RCM No.: 2018-798.

[c] Johnson, C. Human Factors Validation Study Protocol Review Memorandum for bupivacaine and meloxicam extended release solution IND 125927. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 03. RCM No.: 2018-798-1.

[d] Flint, J and Johnson, C. Human Factors Results and Labeling Review for bupivacaine and meloxicam extended release solution NDA 211988. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 12. RCM No.: 2018-2421 and 2018-2410.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Zynrelef labels and labeling submitted by Heron Therapeutics.

- Container label(s) received on September 26, 2019
- Carton labeling received on September 26, 2019
- Carton labeling for the Kit received on September 26, 2019
- Vented Vial Spike Replacement Carton received on September 26, 2019
- Luer Lock Applicator Replacement Carton received on September 26, 2019
- 3 mL Syringe Replacement Carton received on September 26, 2019
- 12 mL Syringe Replacement Carton received on September 26, 2019
- Instructions for Use (Images not shown) but can be accessed in EDR via:
    - \\cdsesub1\evsprod\nda211988\0040\m1\us\draft-ifu-60.pdf received on September 26, 2019
    - \\cdsesub1\evsprod\nda211988\0040\m1\us\draft-ifu-200.pdf received on September 26, 2019
    - \\cdsesub1\evsprod\nda211988\0040\m1\us\draft-ifu-300.pdf received on September 26, 2019
    - \\cdsesub1\evsprod\nda211988\0023\m1\us\draft-ifu-400.pdf received on January 31, 2019
- Prescribing Information (Image not shown) but can be accessed in EDR via: received on September 26, 2019
    - \\cdsesub1\evsprod\nda211988\0040\m1\us\spl\21997562-20d4-4ef3-b61a-8f202cdb429c.xml

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING 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:	April 12, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 211988
Product Name and Strength:	Zynrelef (Bupivacaine and Meloxicam) extended release solution[a] (60 mg/1.8 mg in 2.3mL, 200 mg/6 mg in 7mL, and 400mg/12mg in 14mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Heron Therapeutics Inc. (Heron)
FDA Received Date:	October 30, 2018 and January 31, 2019
OSE RCM #:	2018-2421 and 2018-2410
DMEPA HF Reviewer:	Jason Flint, MBA, PMP
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD
DMEPA Associate Director for Human Factors	Quynh Nhu Nguyen, MS

[a] Dosage form "extended release solution" is pending final determination by Office of Pharmaceutical Quality (OPQ).

1 REASON FOR REVIEW

As part of the approval process for Zynrelef (bupivacaine and meloxicam) extended release solution, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors and the human factors (HF) validation study results submitted under NDA 211988.

1.1 PRODUCT DESCRIPTION

Zynrelef (bupivacaine and meloxicam) is a co-packaged combination product consisting of a drug vial with a vented vial spike, Norm-Ject® luer lock syringes, luer lock applicators and syringe tip cap device constituents. It is intended to (b) (4) (b) (4) Heron intends to market three different strengths of bupivacaine/meloxicam; 60mg/1.8mg, 200mg/6mg, and 400mg/12mg.

1.2 REGULATORY HISTORY

This application was granted fast-track status on October 24, 2017 and Breakthrough Therapy designation on June 14, 2018 under IND 125927. We provided HF comments to Heron at a Type B End of Phase 2 (EOP2) meeting on June 15, 2017 under IND 125927, requesting they submit a use-related risk analysis (URRA) and HF validation study protocol for review. DMEPA conducted an HF validation study protocol review in June 2018 and made recommendations for changes to the study design and product user interface.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D - N/A
FDA Adverse Event Reporting System (FAERS)*	E - N/A
Information Requests Issued During the Review	F
Labels and Labeling	G

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the HF study design, use errors/close calls/use difficulties observed, and our analysis to determine if the results support the safe and effective use of the proposed product. We also provide our assessment of the proposed labels and labeling to determine if they are vulnerable to medication error.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study was performed in a simulated operating room. Participants included surgical technicians and circulating nurses as "dyads" that performed the product preparation steps in tandem, and surgeons that performed drug administration steps. The study included 15 participants of each type, but the dyads were treated as one group in the analysis. Only the 400mg/12mg presentation was studied.

The dyads performed product preparation tasks in two replicates spaced 20 minutes apart to mimic the time required to prepare the operating room between surgeries. Dyads prepared a total of 60 syringes.

The surgeons administered the drug into two incision types; a large, multilayer incision to simulate a hernia repair, and a small, single layer incision to simulate a bunionectomy. The order of the two incision sizes were balanced in the study design; some surgeons operated on the large incision first, and some operated on the small incision first. As with the product preparation tasks, there was a 20-minute delay . between replicates.

The dyad teams did not receive training but had access to the instructions for use (IFU). Surgeons were asked how they would first learn about a new product. Based on their answer, 1 of 4 options were provided: (1) access to printed IFU; (2) go online to review an electronic copy of the IFU and watch an educational video; (3) ask a colleague; or (4) request information from a sales representative. Heron used this approach based on DMEPA recommendations to ensure that the study accurately represented clinical practice.

Following their simulated use, the dyads and surgeons responded to knowledge-based tasks. Moderators used observation and open-ended questions to conduct root cause analysis.

3.2 RESULTS AND ANALYSIS

The simulation task performance results were scored by the moderator as "Success" (S), "Use Difficulty" (UD), "Close Call" (CC), or "Use Error" (UE).

For product preparation, dyads experienced Use Difficulty in 3 of the 11 tasks and Use Error in 1 task.

Detailed information on incidences of use difficulty and use error in product preparation and administration are included in Tables 2 and 3.

During the product preparation testing, there were several warnings/cautions from the IFU that were not implemented by some test participants. The warnings/cautions in the IFU are not well differentiated

from other elements, which may make them less likely to be noticed. We provide recommendations in Section 4 of the review to address our concern.

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Table 2– Use difficulty during critical product preparation tasks:

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Push the vented vial spike through the septum of the vial until it snaps into place.	UD: 2 (n=30)	Difficulty attaching the vented vial spike.	The size of the spike is different from the gauge of standard needles used most frequently by users. The gauge of the spike results in the need for more application of force to penetrate the septum.	No mitigation provided	As noted in the URRA and HF Engineering Summary, these are known problems with vented vial spike (VVS) products. We reviewed the IFU and to address users having difficulty inserting the vial spike, Step 4 could be revised to use command language. This change is expected to further clarify the existing language that currently exists within the instructions and therefore, no additional HF validation data are necessary in this instance. Please see specific recommendation #3 in Section 4, Table 4.
		The vented vial spike was not fully attached to vial (did not snap on to vial lid).	The "snap" emitted from the vial adapter provides positive feedback to the user to confirm appropriate attachment.	No mitigation provided	
Attach air-filled syringe to Luer end of vented vial spike.	UD: 1 (n=60)	User attached the first syringe which had not been filled with air.	A potential root cause for this non-critical use issue is the novelty of this product, and first- time experience, as the	The risks associated with the non-critical use issues described are	We agree with the noted root cause; Zynrelef is a viscous product, and injecting air into the inverted vial helps the user withdraw the drug. We

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
			users filled all the subsequent syringes with air as instructed.	inherently low and acceptable. No changes in relation to the preparation issues are planned.	disagree that this is a critical task. The use difficulty is not likely to compromise safety or efficacy, because medications for use in the surgical field are typically drawn up prior to the start of the surgery.
Allow product to fill the neck and push air into vial.	UD: 11 (n=60)	Users pushed air into vial before inverting and waiting for the medication to fill the neck.	Users typically add air to vials when non-inverted in their current professional practice. The placement of the statement "Push air into vial and wait for the air bubble to rise" in Step 7 instead of Step 6 resulted in the user not seeing the information prior to making the decision that air should be pushed into the vial when not inverted.		We agree with the noted root cause. This appears to be negative transfer in some individuals, that is, their current practice of adding air before inverting the vial is interfering with their learning for this task. We disagree that this is a critical task. This use difficulty is not likely to affect the patient, since medications for use in the surgical field are typically drawn up prior to the start of the surgery.
Withdraw approximately	UE: 6 (n=60)	Users filled syringes to more than 7mL.	There was one primary root cause for the observation of these use errors. Participants	Given this root cause, additional changes to the	We agree that the root cause is probably negative transfer. We note that 4 dyads drew up a total volume

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
7 mL of product.			reported it was common clinical practice to withdraw a larger volume of a medication than needed because they would normally waste the extra drug product to achieve the recommended amount volume (i.e., 7 mL per syringe) just prior to handing off the syringe to a surgeon. In addition, users felt it was better to withdraw too much initially than to go back and have to reattach the syringe to the vial if more product was needed.	instructions are not likely to lower the risks any further. Moreover, the instructions were developed over the course of multiple studies that preceded the final Human Factors Validation test. During these studies, participant interpretation of this section of the instruction was evaluated several times and updates introduced as appropriate. Heron evaluated the observations,	from one vial that ranged between 15 and 17.5 mL of drug product that was labeled as containing 14 mL. After discussion with the clinical review team, we concluded that drawing up all of the medication and wasting excess is a standard practice in the operating room, and in the event excess product is administered, it is not likely to be clinically meaningful. In addition, we confirmed that the sponsor conducted formative human factors studies to inform the development of the IFU prior to finalizing the IFU for the final HF validation study. Our review of the IFU did not generate any recommendations.

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
				participant responses, and risk controls and found the residual risk associated with this observation to be acceptably low. The final instructions are effective as written.	
Would it be appropriate to use a component, other than what is supplied in the kit to prepare the product? If	UE: 6 (n=15)	Users stated that if the syringe from the kit was contaminated (no longer sterile), they would replace it with a syringe that was not supplied in the kit.	The Norm-Ject® Luer lock syringe appears to be similar in design to other syringes. One additional root cause may be a testing artifact where participants do not look for information that is not pertinent to the immediate task (i.e., no participant dropped a component on the floor)	As none of the Dyads had an experience that required a component to be replaced, the actual selection of the replacement was not tested in the simulation. Clearly labeled replacement	We agree that the similarity of the syringes, coupled with the user's previous experiences are contributing to the use errors. While we acknowledge that the IFU contains warning language in the IFU and on the carton, these use errors confirmed that the warning does not call out user's attention to overcome their confirmation bias.

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
so, what would be an example?				components will be available so that replacement components, if needed, can be used to prepare the product.	To help in our assessment of these use errors, we sent two Information Requests (IR) regarding compatibility of the different components. In their responses (See Appendix F), Heron stated that they have tested other components made from commonly used materials and noted that no incompatibilities had been identified. Additionally, they stated, "There are no specific concerns that the use of a different syringe other than the (b) (4) Norm-Ject syringes provided in the kit would impact the safety and effectiveness of HTX-011."We also note in the HF Engineering Summary, Heron states, "Clearly labeled replacement components will be available so that replacement components, if needed, can be used to prepare the product."

Critical Tasks	Number of Failures/Use Errors (UE), Close Calls (CC) and Use Difficulties (UD)	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
					Based on Heron's response to the information request, we find that this task is not critical, and have no further recommendations.

During the product application tasks, surgeons experienced Use Difficulty in one of five tasks and Use Error in one task. Incidences of use difficulty and use error in product application are included in Table 3.

Table 3 - Use Difficulty during product application:

Critical Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Heron's Root Cause Analysis	Heron's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Use a sufficient amount to coat. For small spaces, ensure there is not an excess that could be expressed from the site during closure.	UD: 3 (n=30)	Users administered excess product, causing product to get on to the skin.	The IFU states in Administration Step 3 to "Use a sufficient amount to coat the tissues. For small spaces, ensure there is not an excess that could be expressed from the site during closure." While P7 understood what the IFU intended, when applying HTX-011 to incision sites the first few times it is hard to determine what is "not an excess" without some experience of seeing how it flows and attaches to the skin. The pork shoulder used to simulate human tissue does not have the same structural properties or temperature	The risks associated with the non-critical administration issue described above are inherently low and therefore acceptable. No changes in relation to the issue described above are planned.	Heron identified two potential root causes for this use error: imprecise language (i.e., "Use a sufficient amount") and test artifact from the use of pork shoulder in lieu of living tissue. The Integrated Summary of Safety notes similar use errors during the clinical trials, so we find that the first root cause is more likely. The IFU states, "Use a sufficient amount to coat the tissues"; however, this statement does not convey to the user what would be considered as a sufficient amount and relies on the user to formulate their own judgment . We understand that the amount of product used is dependent on the size and type of incision, but from our expert and heuristic review of the instructions, we recommend to

			as living tissue. Moreover, living tissue would be more compliant than a refrigerated piece of pork, and HTX-011 would not be squeezed out as easily as compared to the 2 stiff sides of the pork incision being brought together.		convey the specific volume (dose) to coat the tissue for different surgeries in the IFU. Given that this change is to further clarifying the information, no additional HF data is needed. Please see specific recommendation #4 in Section 4, Table 4.
If multiple tissue layers are involved, apply TRADENAME after irrigation and suction and before closing each layer.	UE: 1 (n=30)	User irrigated and suctioned after applying the product and before suturing.	It appears that the root cause for this use error can be attributed to a test artifact because <the user> relies on his scrub nurse to make sure that he successfully completes closing of a surgical site.	The observed use error is attributable to a study artifact. The current risk control (i.e., the direction and warning in the IFU) is effective in mitigating the risk. All participants in the study…understood that to avoid under dosing the area, they should only apply HTX-011 after final irrigation and suction of each layer before closing. These control measures were evaluated, and the text refined over the course of several formative studies. Additional changes to the wording are not likely to further reduce the risks.	We disagree that this is a test artifact. While it is possible that the "scrub nurse" may have prevented this use error from occurring, it is also possible that the use error would still occur in the presence of the "scrub nurse". It's not clear from the material presented (Website, "Ask a Colleague" script, Sales Representative Script, or IFU) what the proper response from the surgical team is if the surgeon accidentally irrigates and suctions the incision after applying the product, but this is likely to be within the scope of clinical judgement, and we do not have any recommendations.

3.3 LABELS AND LABELING

Because the Application will be receiving a Complete Response, we will provide comments on the container labels, carton labeling, kit labeling, and replacement carton labeling under a separate cover during the review of the resubmission. Our evaluation of the proposed prescribing Information (PI) and IFU identified several areas of concern which are included in Table 4. Table 4 also includes our recommendations to minimize the risk for medication errors.

4 CONCLUSION

The results of the HF validation study showed use errors and difficulties with the preparing and administration of the proposed product. Our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Table 4 for the Division for the PI and IFU. We should note that some of our recommendation sections under the IFU section are based on the results of the HF validation study.

Table 4: Identified Issues and Recommendations for Division of Anesthetics, Analgesics and Addiction Products

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information and Full Prescribing Information			
1.	In the Dosage Forms and Strengths section, (b) (4) [redacted]	Including (b) (4) may cause confusion to users. This presentation has been documented in postmarket medication error reports to be error prone. For example, healthcare professionals could confuse (b) (4) [redacted]	Remove (b) (4) for each product strength presentation. For example, revise the Highlights to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution in single dose glass vials: 400 mg bupivacaine and 12 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam Revise the FPI to: ZYNRELEF (bupivacaine and meloxicam) extended-release solution is a clear, pale yellow to yellow, viscous liquid in a single-dose vial containing 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam and is available in the following 3 presentations: 400 mg bupivacaine and 12 mg meloxicam 200 mg bupivacaine and 6 mg meloxicam 60 mg bupivacaine and 1.8 mg meloxicam

2.	In the Dosage and Administration sections, the format of the product strength and volume is different between the Highlights and Full Prescribing Information. In the Highlights, the product strength is presented as (b) (4) while in the FPI the product strength is presented as (b) (4) (b) (4)	To maintain consistency and to prevent confusion, the format of the product strength should be consistent throughout the Highlights and Full Prescribing Information.	Revise the format of the product strength in the Highlights and FPI for consistency for all strength presentations. For example, change (b) (4) to "14 mL to deliver 400 mg/12 mg".
Full Prescribing Information			
1.	In the Dosage and Administration section, section 2.1 is titled (b) (4) This section does not include information about the excess volume contained in each vial.	Section 2.1 includes important administration AND preparation instructions and should also include a statement related to the excess volume in the vial to inform users of the overfill.	Revise the title of section 2.1 to "Important Preparation and Administration Instructions". Also, after the bullet point (b) (4) add the statement "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration."
2.	In the How Supplied/Storage and Handling section, the net quantity of drug in each vial presentation has been omitted (b) (4)	Including (b) (4) may cause confusion to users. This presentation has been documented in postmarket medication error reports to be error prone. For example, healthcare professionals could confuse	Add a column in the table to include the net quantity volume (i.e. volume to be withdrawn from each vial for desired labeled dose) for each strength presentation and remove the column (b) (4) Furthermore, add a reference footnote to the net quantity volume

		(b) (4)	and include the statement, "Each ZYNRELEF vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration."
3.	In the How Supplied/Storage and Handling section, the color of the solution has been omitted.	The color of the drug product is important information used by health care providers to facilitate easy identification of the product.	Include a description of the color of the solution (i.e. clear, pale yellow to yellow viscous liquid) in the How Supplied section.
Instructions for Use (IFU)			
4.	In the Administration section of the IFU, it is not clear what volume may be appropriate for different types of surgeries.	In Formative Study 2, a surgeon participant commented that, "I would like more information about how much product to apply to different types of incisions – it depends on depth and length of incision." Furthermore, during the Human Factors (HF) Validation study, a surgeon administered excess product to the surgical site which resulted in some product getting on the skin. This error can result in skin irritation (i.e. incision site erythema and incision site edema). Based on the subjective data from Formative Study 2 and the root cause analysis for this use error that occurred during the HF Validation	Revise the IFU to convey the specific volume (dose) to coat the tissue based on surgical type, as was done in the Prescribing Information.

		study, the Administration IFU can be improved to reduce the risk of surgeons administering excess product to the surgical site.	
5.	For the Preparation section of the 60 mg/1.8 mg and 200 mg/6 mg IFU's, Step 8 instructs the (b) (4) user to (b) (4) .	This step may cause confusion and wrong dose errors for users preparing the 60 mg/1.8 mg and 200 mg/6 mg products (b) (4)	To prevent confusion and errors, remove the (b) (4) instruction from Step 8.
6.	The call-out warning statements included in the Preparation and Administration Instructions for Use, are not prominently displayed. For example, for the Preparation Instructions, Step 5 includes the warning statement "⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial" which looks similar to all other information in this step.	Other than the warning symbol, ⚠, these statements lack prominence and do not draw the user's attention to this important information. Based on the use difficulty observed during the HF validation study, the call-out warning statements can be revised to call out the user's attention to minimize instances of the user overlooking the warning statements.	Increase the prominence of the call-out statements. For example, you may consider using a different font color or size, or highlighting these statements to draw user's attention to this important information (see example for the 400 mg/12 mg in 14 mL product strength below): "Fill the syringe with 7 mL of air before attaching to the vented vial spike. ⚠ Air from the syringe will be pushed into the vial at Step 7 after the vial has been inverted and product has filled the neck of the vial."
7.	The Preparation and Administration sections	The use of (b) (4) statements in the IFU may	Revise the passive statements using assertive language. For example, in

	of the IFU contain (b) (4) statements.	cause the user to misinterpret the direction (b) (4) (b) (4) The HF validation study results showed use difficulty with certain tasks that were presented using (b) (4) statements. For example, for Step 4 in the Preparation IFU, a sterile user experienced use difficulty when attempting to attach the vented vial spike to the vial while the non-sterile user held the vial above the surface (as opposed to on a firm, flat surface).	the Preparation section, Step 4, revise the statement "Hold the vial in place while sterile person attaches spike. *Note:* (b) (4) to "Place the vial on a firm, flat surface and hold in place while the sterile person attaches the spike." In the Administration section, Step 5, revise the statement (b) (4) to "When using monofilament sutures, use 3 or more knots as contact…".
8.	In the Preparation IFU and Administration IFU, for all strength presentations, the product strength is presented as: (b) (4) Furthermore, in the Preparation IFU, under the section "The ZYNRELEF Kit Contents" it states that one of the components is the "XX mL ZYNRELEF Vial (e.g. 2.3 mL ZYNRELEF Vial".	This format may cause confusion (b) (4)	To reduce confusion, remove the (b) (4) (b) (4) statement that is located below the product strength for each vial presentation listed in each version of the IFU. Furthermore, include the word "and" between the two active ingredients. For example, change the product strength presentation to: XX mg bupivacaine and YY mg meloxicam per vial Also, change the statement "ZZ mL ZYNRELEF Vial" to "ZYNRELEF Vial" (e.g. change "2.3 mL ZYNRELEF Vial" to "ZYNRELEF Vial".

9.	There is no statement in the IFU to address the overfill volume.	Due to the high viscosity of the drug, users may confuse the withdrawal volume and the overfill volume that remains in the vial after withdrawal which may lead to wrong dose errors.	To inform users that the withdrawal volume is different from the total volume contained in the vial, add a statement such as "Vial contains overfill to compensate for residual amounts that remain in the vial, vented vial spike, luer lock applicator and syringe(s) during drug withdrawal and administration." We suggest adding this statement in a separate text box under the blue box for sterile user in step 1 to draw the user's attention to this important information. Furthermore, to draw attention to the correct withdrawal volume, under the "Preparing the Product" section at the top of the IFU, bold the statement "Withdraw ZZ mL" (e.g., "Withdraw 2.3 mL).
10	The Administration IFU contains the statements under Important Information: "(b) (4)	The 14 mL volume is (b) (4) the amount of product that is withdrawn from the vial to obtain the dose of 400 mg bupivacaine and 12 mg meloxicam.	Revise these statements to read: "As a guide, the maximum total volume is 14 mL" and "ZYNRELEF spreads easily and covers a large area. For example, the 14 mL volume is sufficient to cover large surgical procedures such as total knee arthroplasty."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zynrelef that Heron submitted on October 30, 2018.

Table 2. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Anesthetic with a nonsteroidal anti-inflammatory drug (NSAID)
Active Ingredient (Drug or Biologic)	Bupivacaine and meloxicam
Indication	(b) (4)
Route of Administration	(b) (4)
Dosage Form	Extended release solution
Strength	60 mg/1.8 mg in 2.3 mL 200 mg/6 mg in 7 mL 400 mg/12 mg in 14 mL
Dose and Frequency	Apply to surgical site following final irrigation and suction and prior to suturing. If multiple tissue layers are involved, apply after irrigation and suction of each layer before closing.
How Supplied Container Closure/Device Constituent	Cardboard convenience kit containing: • One single-dose vial containing bupivacaine and meloxicam in a non-sterile carton • Sterile vented vial spike • Two sterile (b) (4) mL Norm-Ject Luer lock syringes • Two sterile luer lock applicators • Two sterile syringe tip caps IFU and PI
Storage	(b) (4)
Intended Users	Surgeons, Surgical Technicians and OR Nurses
Intended Use Environment	Surgical Suites

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

On November 19, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, bupivacaine and meloxicam. Our search identified 1 previous review[2], and 1 memo[3] agreeing to Heron's proposed implementation of our recommendations. We reviewed these documents and confirmed that our previous recommendations were implemented.

APPENDIX C. HUMAN FACTORS DOCUMENTS

C.1 Human Factors Validation Protocol

\\cdsesub1\evsprod\nda211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5354-other-stud-rep\hti-2018-htx-011-vt-101\hf-valid-prot-rev-b.pdf

C-2 Human Factors Validation Final Report

\\cdsesub1\evsprod\nda211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5354-other-stud-rep\hti-2018-htx-011-vt-101\hf-valid-report.pdf

C.3 Human Factors Engineering Summary Report

\\cdsesub1\evsprod\nda211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5354-other-stud-rep\hti-2018-htx-011-vt-101\hf-eng-sum-report.pdf

C.4 Use Related Risk Analysis

\\cdsesub1\evsprod\nda211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5354-other-stud-rep\hti-2018-htx-011-vt-101\hf-risk-analysis-worksheet.xlsx

APPENDIX D. – N/A

APPENDIX E. – N/A

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[2] Johnson, C. Human Factors Validation Study Protocol Review for bupivacaine and meloxicam extended release solution IND 125927. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-06-13. RCM No.: 2018-798.

[3] Johnson, C. Human Factors Validation Study Protocol Review Memorandum for bupivacaine and meloxicam extended release solution IND 125927. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018-06-13. RCM No.: 2018-798-1.

APPEARS THIS WAY ON ORIGINAL

APPENDIX F. INFORMATION REQUESTS ISSUED DURING THE REVIEW

IR 1: We reference your Document Number: HTI-2018-HTX-011-VT-503; "RESULTS FOR HTX-011 HUMAN FACTORS VALIDATION TEST" (Human Factors Report) and your HF Risk Analysis Worksheet, for NDA 211988 submitted on 2018-10-30. In section 5.2, table 20 on pages 79-83 of your Human Factors Report, we note that 6 of 15 dyads incorrectly responded that they would use a different syringe if they dropped one that was provided. You note that the "Potential Harm" associated with this is "Compromised therapy (compatibility of product with components)". This description does not explain the potential impact to the safety and effectiveness of your product if a user incorrectly substituted a syringe, then delivered the medication to the patient. Please provide detailed information on why the user cannot use a different syringe, and how the use of a different syringe would impact the safety and effectiveness of the drug product.

Summary of Heron's Response -

(b) (4) Norm-Ject (b) (4) syringes are supplied in the HTX-011 co-packaged combination kits. Several other commonly used, commercially available syringes have been studied with HTX-011, and no incompatibilities have been identified. There are no specific concerns that the use of a different syringe other than the (b) (4) Norm-Ject syringes provided in the kit would impact the safety and effectiveness of HTX-011. Heron Therapeutics (Heron) has conservatively proposed that users should only use the (b) (4) Norm-Ject (b) (4) syringes supplied in the kit because not every possible combination of syringe and stopper compositions could be evaluated. Heron has tested other syringes with barrels made of the most commonly used materials and their corresponding rubber stoppers. They include (b) (4) The vast majority of syringes used in a surgical setting are made (b) (4) with rubber stoppers.

The full IR response can be found at:

\\cdsesub1\evsprod\nda211988\0008\m1\us\clin-info-amend.pdf

IR 2: Please provide detailed information on which components cannot be substituted, and how the use of a substitute component would impact the safety and effectiveness of the drug product.

Summary of ***Heron***'s Response:

Heron does not consider substitution of similar devices for the same intended use a risk to effectiveness of HTX-011. The concern was a potential risk to safety if untested compounds might leach into the drug product. Based on the extensive compatibility testing that has been completed (Table 1), no risk to safety is envisioned;

The full IR response can be found at:

\\cdsesub1\evsprod\nda211988\0021\m1\us\clin-info-amend.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Zynrelef labels and labeling submitted by Heron Therapeutics Inc.

- Prescribing Information including tracked changes recommendations submitted on January 31, 2019
- Instructions for Use (submitted on January 31, 2019) available via the following links:
    - 60 mg bupivacaine and 1.8 mg meloxicam in 2.3 mL: \\cdsesub1\evsprod\nda211988\0023\m1\us\draft-ifu-60.pdf
    - 200 mg bupivacaine and 6 mg meloxicam in 7 mL: \\cdsesub1\evsprod\nda211988\0023\m1\us\draft-ifu-200.pdf
    - 400 mg bupivacaine and 12 mg meloxicam in 14 mL: \\cdsesub1\evsprod\nda211988\0023\m1\us\draft-ifu-400.pdf

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

JASON A FLINT
04/12/2019 09:12:38 AM

CAMERON D JOHNSON
04/12/2019 09:52:42 AM

OTTO L TOWNSEND
04/12/2019 12:03:44 PM

QUYNHNHU T NGUYEN
04/12/2019 12:05:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone: 301-796-2200
FAX: 301-796-9744

Maternal Health Labeling Review

Date: April 9, 2019 **Date consulted:** January 28, 2019

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health, Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Division Director, DPMH

To: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Drug: Zynrelef (bupivacaine & meloxicam) Extended-Release Solution

Class: Local anesthetics and NSAIDs

NDA: 211988

Applicant: Heron Therapeutics, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) format

Indication: Management of Postoperative Pain

Materials Reviewed:

- October 30, 2018, NDA 211988 initial submission for Zynrelef (bupivacaine & meloxicam)
- March 3, 2019, Applicant's "Response to Information Request-Clinical Information Ammendment" in response to the Division's Information Request (IR) of February 26,

2019

- Draft Labeling in PLLR format
- January 28, 2019, DAAAP's consult request to DPMH for Zynrelef (bupivacaine & meloxicam) Extended-Release Solution labeling review
- January 8, 2014, DPMH review by Erica Radden in DARRTS and Reference ID: 3432925 of Posimir (bupivacaine hydrochloride extended-release solution for instillation), NDA 204803[1]
- February 10, 2015, DPMH review by Miriam Dinatale in DARRTS and Reference ID: 3699226 of Exparel (bupivacaine liposome injectable suspension), NDA 22496
- April 11, 2018, DPMH review by Christos Mastroyannis in DARRTS and Reference ID: 4247083 of Anjeso (meloxicam) Injection for intravenous use, NDA210583
- August 29, 2018, DPMH review by Christos Mastroyannis in DARRTS and Reference ID: 4313589 of Meloxicam Orally Disintegrating Tablet (ODT), NDA 211210

Consult Question: Assist with Pregnancy and Lactation Labeling Rule (PLLR)

INTRODUCTION

On October 30, 2018, the applicant, Heron Therapeutics, Inc., submitted an original NDA for Zynrelef (bupivacaine & meloxicam), NDA 211988, for the management of postoperative pain. Zynrelef is a fixed-dose combination drug product and a co-packaged combination drug-device product. This is a 505(b)(2) application with listed drugs relied upon Marcaine (bupivacaine HCl Injection) NDA 016964, approved in 1972 and Mobic (meloxicam) NDA 020938, approved in 2000), for the management of postoperative pain (b) (4)

The proposed labeling of October 30, 2018, is in PLR and PLLR format. DAAAP consulted DPMH on January 28, 2019, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of Zynrelef (bupivacaine & meloxicam) Extended-Release Solution labeling for accuracy.

BACKGROUND

Regulatory History

The applicant submitted labeling in PLLR format. On February 26, 2019, DAAAP sent an IR to the applicant to support the labeling by providing:

- a review and summary of all available published literature regarding Zynrelef and its components use in pregnant and lactating women and the effects of Zynrelef and its components on male and female fertility (include search parameters and a copy of each reference publication),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present) including the Reference Listed Drugs (RLDs) , NDA 16964 and NDA 20938,
- a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval for the RLDs,
- an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy

[1] DPMH did not rely on data in the NDAs or the Agency's findings of safety and effectiveness for Posimir (bupivacaine hydrochloride extended-release solution for instillation), Exparel (bupivacaine liposome injectable suspension), Anjeso (meloxicam) Injection for intravenous, or Meloxicam Orally Disintegrating Tablet (ODT) to support labeling sections of this Zynrelef (bupivacaine & meloxicam) Extended-Release Solution NDA. Rather, the cross-reference to the past DPMH consults are included to avoid duplicating background information and literature relevant to the underlying medical conditions.

registry (if applicable),

- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

The applicant responded to the IR on March 3, 2019.

Zynrelef (bupivacaine & meloxicam) Drug Characteristics[2]

Zynrelef is a sterile, clear, pale yellow to yellow, viscous liquid. Each single-dose vial contains a solution of 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam formulated using a polymer. Therefore, the bupivacaine concentration in Zynrelef is 2.5% and meloxicam is 0.075%.

Table 1: Drug Characteristics

	Bupivacaine	**Meloxicam**
Molecular weight (Daltons/D)	288.4 D	351.4 D
Half-life (Hours/H)	14-15 H	22-25 H
Protein Binding (%)	95%	99.5%

After bupivacaine and meloxicam have been released from Zynrelef and are absorbed systemically, their excretion is expected to be the same as for other bupivacaine HCl solution formulations or meloxicam oral formulations.

Reviewer Comment

In discussions with the Clinical and Clinical Pharmocology teams, the meloxicam exposure after administration of Zynrelef is much lower than that observed after oral meloxicam administration. For Zynrelef 300 mg/9 mg, the Cmax represents approximately 20 to 30% of that observed after oral meloxicam administration (225 versus 1050 ng/mL). While the Mobic label does not include AUC data, calculated values (based on the clearance data presented in the label) suggest that meloxicam exposure after administration of the highest recommended dose of Zynrelef is approximately 13% of that observed after oral administration (AUC0-120). Because the exposure after Zynrelef administration is lower than that observed after oral administration, the PK bridge is adequate. For more detailed discussion, the reader is referred to the Clinical Pharmacology review.

Current Labelings for Listed Drugs Relied Upon

Marcaine Hydrochloride Injectable[3]

The current labeling for Marcaine Hydrochloride Injectable is neither in PLR nor in PLLR format. It states:

> **WARNINGS**
>
> **THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN**

[2]Zynrelef (bupivacaine & meloxicam) Extended-Release Solution proposed labeling as of March 3, 2019
[3] Marcaine Hydrochloride Injectable existing labeling as of November 2,2018

DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT.

INDICATIONS AND USAGE

MARCAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See WARNINGS.) Experience with nonobstetrical surgical procedures in pregnant women is not sufficient to recommend use of 0.75% concentration of MARCAINE in these patients. MARCAINE is not recommended for intravenous regional anesthesia (Bier Block). See WARNINGS.

CONTRAINDICATIONS

MARCAINE is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. This does not exclude the use of MARCAINE at term for obstetrical anesthesia or analgesia (See Labor and Delivery). Bupivacaine hydrochloride was administered subcutaneously to rats at doses of 4.4, 13.3, & 40 mg/kg and to rabbits at doses of 1.3, 5.8, & 22.2 mg/kg during the period of organogenesis (implantation to closure of the hard palate). The high doses are comparable to the daily maximum recommended human dose (MRHD) of 400 mg/day on a mg/m2 body surface area (BSA) basis. No embryo-fetal effects were observed in rats at the high dose which caused increased maternal lethality. An increase in embryo- fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity with the fetal No Observed Adverse Effect Level representing approximately 1/5th the RHD on a BSA basis.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at subcutaneous doses of 4.4, 13.3, & 40 mg/kg, decreased pup survival was observed at the high dose. The high dose is comparable to the daily MRHD of 400 mg/day on a BSA basis.

Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRICAL USE OF 0.75% MARCAINE.

MARCAINE is contraindicated for obstetrical paracervical block anesthesia. Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity (See CLINICAL PHARMACOLOGY, Pharmacokinetics). The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function. Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal

heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance. The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine. It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and gravid uterus displaced to the left.

Nursing Mothers:

Bupivacaine has been reported to be excreted in human milk suggesting that the nursing infant could be theoretically exposed to a dose of the drug. Because of the potential for serious adverse reactions in nursing infants from bupivacaine, a decision should be made whether to discontinue nursing or not administer bupivacaine, taking into account the importance of the drug to the mother.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of bupivacaine hydrochloride have not been conducted. The mutagenic potential and the effect on fertility of bupivacaine hydrochloride have not been determined.

Mobic Oral Tablets[4]

The current labeling for Mobic Oral Tablets is in PLLR format. It states:

- Meloxicam is an non-steroidal anti-inflammatory drug (NSAID) that should not be used after 30 weeks (third trimester) because it can cause closure of the fetal Ductus Arteriosus (DA).
- Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma. There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MOBIC and any potential adverse effects on the breastfed infant from the MOBIC or from the underlying maternal condition.
- NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.
- In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of MOBIC.
- Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD.
- In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times MRHD of meloxicam.

[4] Mobic Oral Tablets existing labeling of June 30, 2016

- No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD.

REVIEW

PREGNANCY

Animal Data

There are no animal reproduction studies that have been conducted on the combination product (bupivacaine & meloxicam).

Bupivacaine

The applicant did not perform any nonclinical studies, and is relying on FDA's findings on Marcaine, the RLD. Bupivacaine hydrochloride produced developmental toxicity when administered subcutaneously to pregnant rats and rabbits at clinically relevant doses. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose 2.1 times the bupivacaine maximum daily exposure. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.9 times the maximum daily exposure.

Meloxicam

The applicant did not perform any nonclinical studies, and depends on FDA's findings on Mobic. No additional information was identified by the applicant. Published literature states that placental transfer of meloxicam or its metabolites have been demonstrated in the rat.[5]

Review of Literature

Applicant's Review

A literature search was performed by the applicant of available published literature regarding Zynrelef and its components (bupivacaine and meloxicam) on its use in pregnant and lactating women, and the effects on male and female fertility. No publications were identified in regard to Zynrelef. From the literature search, the applicant concludes that "no new information regarding Zynrelef and its components was identified beyond the information contained in the prescribing information (PIs) for the listed drugs relied upon and the information proposed to the labeling for Zynrelef. The literature search is described below.

Bupivacaine

PubMed/MEDLINE searches were done with the following terms (MeSH terms): Bupivacaine AND Human AND Pregnancy NOT Labor NOT Delivery, Bupivacaine AND Human AND Abortion, AND Miscarriage AND Newborn, AND Neonatal NOT Labor NOT Delivery, AND Neonate, , AND Newborn, Fetal AND Toxicity, AND Fetal AND Adverse effects.

One hundred eleven (111) publications for Pregnancy, Lactation and Females and Males of Reproductive Potential were identified. After review, non-relevant publications were excluded. Reasons for exclusion of publications include non-English articles, data restricted to animals, use in animal pain models, or use in neonatal or pediatric populations. Seventeen (17) publications were

[5] Oiwa Y, Shibata T, Senda C, Kuritani M, Nagakura A, Matsumura R, Kobayashi S. [Metabolic fate of 14C-meloxicam 2. Placental transfer in rats]. Yakubutsu Dotai 1997;12:118-20

considered potentially relevant to pregnancy by the applicant (see Table 2). Five of the publications that the applicant considered relative, this reviewer considered them non-relevant.[6]

Meloxicam

PubMed/MEDLINE searches were done with the following terms (MeSH terms). There wereno limits on date of publication. Meloxicam AND Human AND Lactation, AND Breastfeeding, AND Pregnancy, AND Abortion, AND Miscarriage, AND Newborn, AND Neonatal, AND Neonate, AND Reproductive potential, AND Fertility, AND Toxicity, AND Adverse effects NOT Labor NOT Delivery.

Seventeen publications for Pregnancy, Lactation and Females and Males of Reproductive Potential were identified. After review, non-relevant publications were excluded. Reasons for exclusion of publications include non-English articles, data restricted to animals, use in animal pain models, or use in neonatal or pediatric populations. Two publications were relevant to pregnancy (see Table 3).

In addition, there is one case report in published literature by van de Vijver[7] of a male neonate born at 39 weeks gestation by emergency cesarean section for breech presentation. Before delivery, a spinal anesthetic for maternal analgesia was administered containing 2.5 mL of 0.5% bupivacaine with 0.3 mg diamorphine (total 12.5 mg intrathecal bupivacaine dose). The mother subsequently developed a high spinal blockade resulting in a respiratory arrest requiring conversion to general anesthetic. At delivery, the neonate required cardiopulmonary resuscitation with intubation at 3 minutes of age and blood gases showed a raised methemoglobin (MetHb) of 12.5% on venous and 11.5% on arterial gas. The neonate recovered and he was discharged home on Day 4 with a MetHb of 11.4%. Methemoglobinemia lasted for a long period and on Day 301 of life was 1.3%.

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[6] Study by Moore et al. was not relevant because it evaluated gabapentin vs placebo in women who had spinal anesthesia with 0.75% hyperbaric bupivacaine 12 mg, fentanyl 10 µg, and morphine 100 µg.
Moore A, Costello J, Wieczorek P, et al. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesth Analg 2011; 112(1): 167-173
Study by Nickells et al. was not relevant because it compared combined spinal epidural technique vs epidural using bupivacaine 2.5 mg and fentanyl 25 µg.
Nickells JS, Vaughan DJ, Lillywhite NK, et al. Speed of onset of regional analgesia in labour: a comparison of the epidural and spinal routes. Anaesthesia 2000; 55(1): 17-20
Study by Rickford et al. was not relevant because it compared patient positioning after epidural analgesia.
Rickford WJ, Reynolds F. Epidural analgesia in labour and maternal posture. Anaesthesia 1983; 38(12): 1169-1174.
Study by Sener et al. was not relevant because it compared parturient to assess the influence of anesthetic technique for cesarean section on neonatal outcome (general vs epidural).
Sener EB, Guldogus F, Karakaya D, et al. Comparison of neonatal effects of epidural and general anesthesia for cesarean section. Gynecol Obstet Invest 2003; 55(1): 41-45.
Study by Smith et al. was not relevant because it compared the efficacy between intravenous patient-controlled analgesia (IVPCA) and patient-controlled epidural analgesia (PCEA) in women undergoing medically induced second trimester termination of pregnancy. Smith RL, Siddiqui N, Henderson T, et al. Analgesia for Medically Induced Second Trimester Termination of Pregnancy: A Randomized Trial. J Obstet Gynaecol Can 2016; 38(2): 147-153.

[7] van de Vijver, M., E. Parish and N. Aladangady (2013). "Thinking outside of the blue box: a case presentation of neonatal methemoglobinemia." J Perinatol 33(11): 903-904.

Table 2: Published Literature for Bupivacaine use in Pregnancy as per applicant

Author/Year	Groups tested	Time of exposure	Outcomes
Alahuhta 1995[8]	A randomized, double-blind trial with healthy parturient women with singleton, uncomplicated pregnancies at term. They evaluated (1) blood flow velocity waveforms in uteroplacental and fetal arteries with color Doppler ultrasound and (2) fetal myocardial function	At delivery (cesarean section). Women received 115-140 mg 0.5% ropivacaine (n = 11) or 0.5% bupivacaine (n = 10) in incremental epidural doses.	Pulsatility indexes (PI) for the maternal placental and non-placental uterine arteries increased significantly 5 minutes after the main dose (p = 0.01 and p = 0.002) and when sensory analgesia had reached the T6-T4 level (p = 0.004 and p = 0.01) as compared with the baseline measurement. No effect on the Doppler indexes obtained from the umbilical artery was observed in either group. There were no significant differences relative to baseline values in any fetal myocardial measurement. Neither drug had any serious effect on Apgar scores or umbilical cord acid-base status. None of the neonates' conditions was markedly depressed according to neurobehavioral testing.
Belfrage 1983[9]	Randomly administered 47 pregnant women received 2% chloroprocaine (n=23) or 0.25% bupivacaine (n=24)	Paracervical block	Fetal bradycardia in 1 case of chloroprocaine and in 2 cases of bupivacaine
Bjornestad 1999[10]	A randomized, double-blind, multicenter trial	122 women received 20 mL of either ropivacaine 7.5 mg/mL or bupivacaine 5 mg/mL Anesthesia for elective cesarean section.	There were no significant differences in the onset time and the extent of the sensory spread or motor block. The perioperative quality of anesthesia and muscle relaxation was similar in both groups. No significant side effects were observed, except for a more profound drop in systolic blood pressure in the ropivacaine group. Neonates in both groups, evaluated by Apgar score and Neurologic and Adaptive Capacity Score (NACS), tolerated both well.

[8] Alahuhta S, Rasanen J, Jouppila P, et al. The effects of epidural ropivacaine and bupivacaine for cesarean section on uteroplacental and fetal circulation. Anesthesiology 1995; 83(1): 23-32.
[9] Belfrage P,Floberg J. Obstetrical paracervical block with chloroprocaine or bupivacaine. A comparison. Acta Obstet Gynecol Scand 1983; 62(3): 245-247.
[10] Bjornestad E, Smedvig JP, Bjerkreim T, et al. Epidural ropivacaine 7.5 mg/ml for elective Caesarean section: a double-blind comparison of efficacy and tolerability with bupivacaine 5 mg/ml. Acta Anaesthesiol Scand 1999; 43(6): 603-608.

Author/Year	Groups tested	Time of exposure	Outcomes
Cheng 2002[11]	A prospective, double-blind controlled trial in 45 American Society of Anesthesiologists (ASA) class I-II Taiwanese obstetric women undergoing elective cesarean section under extradural anesthesia	Elective cesarean section. Women were randomized to receive either 25 mL of 0.5% bupivacaine or 0.5% levobupivacaine.	No significant differences in maternal or neonatal AEs were found between the treatment groups. Efficacy (onset, fade-out, and quality of anesthesia) were the same.
Cohen 1979[12]	49 parturients were randomized to receive epidural anesthesia.	14 womenreceived chloroprocaine, 3%; 19 received bupivacaine, 0.5%; and 16 received a mixture containing chloroprocaine 1.5%, and bupivacaine 0.375%.	No sign of material or fetal toxicity with any of the three treatment regimens
Harms 1999[13]	67 full-term parturients requesting extradural analgesia	Bupivacaine 0.25% (Group A), 0.125% (Group B) or 0.0625% (Group C).	There were no differences in incidence of maternal hypotension, ephedrine requirements, fetal heart rate abnormalities, mode of delivery and neonatal outcome.
Jolly 2015[14]	A randomized, controlled, open-label trial. 68 women scheduled for elective cesarean section under spinal anesthesia. Womenreceived bupivacaine spinal anesthesia without intrathecal morphine. The intervention group also received subfascial levobupivacaine continuous infiltration through a multi-holed catheter, at 6.25 mg/h for 48 hours.	During delivery.	The intervention group had 6.7 mg less morphine consumption. Time to ambulation and first flatus were not significantly different between the 2 groups. No significant difference found for vomiting, nausea, sedation, or pruritus. No evidence of systemic levobupivacaine toxicity was observed.
Kanayama 1999[15]	20 severe pre-eclamptic women who admitted to the hospital from January 1994 to February 1998. Ten womenwere given long-term epidural anesthesia (epidural group), and 10 womenin the control group treated with bed rest, diet control, and antihypertensive drug. Continuous epidural bupivacaine, 0.25%,	During late pregnancy	Epidural was well tolerated. One patient developed vertigo a few hours afte epidural and was treated with saline transfusion and recovered the next day. Authors concluded that epidural prolongs pregnancy, improves pre-eclampsia, neonates had no complications. No block failure,

[11] Cheng CR, Su TH, Hung YC,Wang PT. A comparative study of the safety and efficacy of 0.5% levobupivacaine and 0.5% bupivacaine for epidural anesthesia in subjects undergoing elective caesarean section. Acta Anaesthesiol Sin 2002; 40(1): 13-20.
[12] Cohen SE,Thurlow A. Comparison of a chloroprocaine--bupivacaine mixture with chloroprocaine and bupivacaine used individually for obstetric epidural analgesia. Anesthesiology 1979; 51(4): 288-292.
[13] Harms C, Siegemund M, Marsch SC, et al. Initiating extradural analgesia during labour: comparison of three different bupivacaine concentrations used as the loading dose. Fetal Diagn Ther 1999; 14(6): 368-374.
[14] Jolly C, Jathieres F, Keita H, et al. Cesarean analgesia using levobupivacaine continuous wound infiltration: a randomized trial. Eur J Obstet Gynecol Reprod Biol 2015; 194: 125-130.
[15] Kanayama N, Belayet HM, Khatun S, et al. A new treatment of severe pre-eclampsia by longterm epidural anaesthesia. J Hum Hypertens 1999; 13(3): 167-171.

Author/Year	Groups tested	Time of exposure	Outcomes
	2 mL/h was given until delivery (15 to 26 days) to the epidural group.		infection or tachyphylaxis were observed to epidural women
Levin 1998[16]	48 women requesting labor analgesia. Three groups: 2.5 mg of intrathecal bupivacaine plus sufentanil 10 μg (B), 2 mg of intrathecal ropivacaine plus sufentanil 10 μg (R2), or 4 mg of intrathecal ropivacaine plus sufentanil 10 μg (R4).	During labor	No differences in motor block or side effects were detected among the groups. Hypotension occurred in 1 of 15 womenin Group R2, 0 of 15 womenin Group R4, and 1 of 15 womenin Group B (p-value not significant). Nausea was observed in one patient in Group R2 and 1 patient in Group B. Fetal heart rate decelerationsin: 2 women in group B and in 1 patient each in the other two groups
Puchalski 1990[17]	A double blind, randomized, controlled trial. 2.5 mL 0.5% isobaric bupivacaine administered either intrathecally (test group; n = 7) or epidurally (control group; n = 7).	Elective cesarean section	Maternal blood pressure, heart rate, and oxygen saturation as well as fetal heart rate were measured. Both maternal and fetal parameters were stable, requiring no intervention.
Simavli 2014[18]	121 women undergoing general anesthesia and elective cesarean section were randomized into a study group (n = 61) or a control group (n = 60) to investigate the efficacy of bupivacaine soaked Spongostan (Absorbable Hemostatic Gelatin Sponge) in cesarean section wound for postoperative anxiety level, satisfaction, and early postpartum depression rate.	Elective cesarean section	The anxiety level of the Spongostan group was lower than that of the control group and the difference was statistically significant at all time intervals (1, 6, 12, 18, 24, 30, 36 and 48 hours, $p < 0.001$, respectively). Postpartum depression rate again was significantly lower in the Spongostan group both on postoperative day 2 and day 9 ($p \leq 0.01$). No significant differences in wound erythema rate or wound infection rate were found and were very low in both groups on the postoperative second day and ninth day
Westholm 1970)[19]	A double-blind study evaluating para-cervical blocks with bupivacaine, physiological saline and bupivacaine with adrenalin 1:200 000	At delivery	One case of fetal death was possibly connected with para-cervical block using bupivacaine-adrenalin. The analgesic effect was good in nearly 80% of the cases with active substance and in about 20% of the cases with physiological saline. The duration of analgesia was shorter when physiological saline was used. No difference in duration of analgesia and how fast cervical dilatation occured between bupivacaine and

[16] Levin A, Datta S,Camann WR. Intrathecal ropivacaine for labor analgesia: a comparison with bupivacaine. Anesth Analg 1998; 87(3): 624-627.
[17] Puchalski SA,Morison DH. Onset of subarachnoid bupivacaine in caesarean section. Can J Anaesth 1990; 37(4 Pt 2): S35.
[18] Simavli S, Kaygusuz I,Kafali H. Effect of bupivacaine-soaked spongostan in cesarean section wound on postoperative maternal health. Arch Gynecol Obstet 2014; 290(2): 249-256
[19]Westholm H, Magno R,Berg AA. Experiences with paracervical block. A double-blind study with bupivacaine (Marcaine). Acta Obstet Gynecol Scand 1970; 49(4): 335-341.

Author/Year	Groups tested	Time of exposure	Outcomes
			bupivacaine-adrenalin. Bupivacaine-adrenalin seemed to be associated with more uterine inertia than bupivacaine and physiological saline. Fetal bradycardia was found in 4%. Two of the 8 cases of fetal bradycardia were after blocks with physiological saline.

Table 3: Published Literature for Meloxicam Use in Pregnancy as per Applicant

Author/Year	Groups tested	Time of exposure	Outcomes
Mirazi 2004[20]	Effects of dexamethasone on PGE2 output in term human placental cells with indomethacin (prostaglandin H synthase-1 [PGHS1] and prostaglandin H synthase-2 [PGHS2] inhibitor), meloxicam (PGHS2 inhibitor).		Meloxicam alone had no effect on basal output of PGE2. Meloxicam affects the glucocorticoid-stimulated output of PGE2 by placental cells. This may be attributable to both up-regulation of PGHS (prostaglandin H synthaseand) down-regulation of PGDH (15-hydroxyprostaglandin dehydrogenase).
Slattery 2001[21]	Compared the effects of 3 COX-2 inhibitors, nimesulide, meloxicam, and celecoxib, on contractile activity in pregnant (before and after labor) and nonpregnant human myometrial tissue in vitro.		Meloxicam, and celecoxib exerted significant relaxant effects on contractility in non-pregnant, pregnant non-labor, and pregnant labor myometrial strips.

[20] Mirazi N, Alfaidy N, Martin R,Challis JR. Effects of dexamethasone and sulfasalazine on prostaglandin E2 output by human placental cells in vitro. J Soc Gynecol Investig 2004; 11(1): 22-26.
[21] Slattery MM, Friel AM, Healy DG, Morrison JJ. Uterine relaxant effects of cyclooxygenase-2 inhibitors in vitro. Obstet Gynecol 2001; 98(4): 563-569.

DPMH Review

Bupivacaine

In addition to the search of published literature performed by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for bupivacaine and meloxicam use in pregnancy.

- Duartte *et al*.[22] evaluated 10 mothers and their newborns for maternal concentrations and placental transfer of bupivacaine (given at a dose of 75mg at a concentration of 0.5%) given during cesarean section with epidural anesthesia. No infants demonstrated any adverse reactions and all had an Apgar score 9 of 10 at the fifth minute of life. The maternal/fetal ratio was 0.33 ng/ml for the (+)-(R) enantiomer and 0.31 ng/ml for the (-)-(S) enantiomer of bupivacaine. There was no evidence of maternal hemodynamic instability with no signs of arterial hypotension. Adverse fetal or neonatal outcome related to paracervical block (PCB) like fetal bradycardia is rare, but the incidence remains unknown.
- The American College of Obstetricians and Gynecologists (ACOG)[23] includes PCB in its technical bulletin about obstetrical analgesia but warns that the technique should be avoided with evidence of uteroplacental insufficiency or non-reassuring fetal heart tracings, and advises not administering PCB if delivery is imminent. ACOG also recommends close monitoring before, during and after performance of a PCB.
- In a case report by Eisenburg[24], two infant deaths occurred after administration of PCB injection of 10 ml of 0.5% bupivacaine. In both cases, severe fetal bradycardia developed at 5 and 10 minutes respectively after PCB. Accidental injection of bupivacaine into the fetus could not be excluded in both cases.
- Dr. Miriam Dinatale provides a review of Exparel (bupivacaine liposome injectable suspension) in DARRTS and dated February 10, 2015 and Reference ID: 3699226.

Reprotox reports mean umbilical vein/maternal ratios of 1.12 for total drug and 1.20 for free drug.[25] GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation report that the mean umbilical vein:maternal vein (UV:MV) ratios for bupivacaine is 0.29 to 0.43. Intrathecal sufentanil (10 mcg), followed at least 1 hour later with bupivacaine epidural analgesia (N = 65), was compared with bupivacaine epidural analgesia alone (N = 64) in a 1996 report comparing the effects of the two analgesic regimens on fetal heart rate changes during labor. No statistical differences were observed between the groups in the incidence of clinically significant fetal heart rate tracing abnormalities

[22] Duarte, et al. Placental transfer of bupivacaine enantiomers in normal pregnant women receiving epidural anesthesia for cesarean section. European Journal of Clinical Pharmacology. 2007.

[23] Rosen, Mark. Paracervical block for labor analgesia: A brief historic review. American Journal of Obstetrics and Gynecology. 2002; 186, supplement 5: 127-130.

[24] Eisenberg. Perinatal deaths associated with paracervical anesthesia. Z Geburtshilfe Perinatol. 1975; 179 (5): 396-400

[25] Fernando R, Bonello E, Gill P, Urquhart J, Reynolds F, Morgan B: Neonatal welfare and placental transfer of fentanyl and bupivacaine during ambulatory combined spinal epidural analgesia for labour. Anaesthesia 1997;52:517-24

(recurrent late decelerations and/or bradycardia) or in maternal hypotension within the 1st hour of administration.[26]

Reviewer Comment

Bupivacaine and other regional anesthetic agents are different from inhaled anesthetics regarding neuronal apoptosis. As per the Medical Officer, "We do not have the same neurodevelopment/ neurocognitive concerns with the local anesthetics as we do with the inhalational and IV agents. (b) (4) (b) (4) *."*

Meloxicam

This reviewer has conducted a literature search for meloxicam in April 2018 in DARRTS and Reference ID: 4247083 and in August 2018 in DARRTS and Reference ID: 4313589. No additional new information has been identified since those reviews. The reader is referred to these reviews for DPMH's review of the reproductive toxicology databases and relevant published literature.

Pharmacovigilance Review

The pharmacovigilance database for Zynrelef includes 1 case report of a pregnancy in a subject who participated in a Phase 2b study who underwent elective augmentation mammoplasty. The drug was administered as a nerve block. The woman was found to be pregnant on Day 21 of the study. She had a negative urine pregnancy test during Screening and on Day 0 prior to surgery. On Day 25, she experienced a spontaneous abortion that was considered by the investigator and the applicant to be unlikely related to study drug. Her history of tobacco and alcohol use and a prior spontaneous abortion were assessed as contributory risk factors.

Utilization Review

The applicant states that ". . . a summary of drug utilization rates amongst females of reproductive potential calculated cumulatively since initial approval for the RLDs is not necessary because it would not add meaningful additional information to the prescriber beyond what is currently provided in the Zynrelef PI"

Reviewer Comment

Utilization review, in addition to labeling indication usage, provides information for any off label usage. Therefore, this reviewer does not agree with the applicant's statement. It would have been appropriate for the applicant to include utilization review.

There is no closed or ongoing pregnancy registry for Zynrelef or its components.

Summary

Bupivacaine 0.25% and 0.5% are commonly used as an epidural anesthetic/analgesic in women in labor and in women undergoing cesarean section. There are reports of fetal bradycardia and death when bupivacaine is given as a paracervical block. There are no consistent major adverse reactions observed during administration of bupivacaine either to the mother or the fetus. The current

[26] Nielsen PE, Erickson JR, Abouleish EI, Perriatt S, Sheppard C. Fetal heart rate changes after intrathecal sufentanil or epidural bupivicaine [sic] for labor analgesia: incidence and clinical significance. Anesth Analg 1996;83:742-60

preparation is only for one dose (it contains bupivacaine at 2.5% and meloxicam at 0.075%) and is applied to the incision site. Meloxicam and other NSAIDs and steroids exert inhibition of fetal membrane prostagland in output. Meloxicam is not mutagenic or genotoxic, and is not associated with major birth defects.

Review of the literature has failed to produce any human literature on meloxicam use in pregnancy, and therefore, no meloxicam-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes has been identified. Published literature reports that use of NSAIDs during the second and third trimesters of pregnancy increases the risk of oligohydramnios and premature closure of the fetal ductus arteriosus. Language consistent with the current NSAID class labeling includes a Warning and Precaution on premature closure of the fetal ductus arteriosus and will be included in the Zynrelef labeling. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first trimester of pregnancy are inconclusive.

LACTATION

Animal Data

Animal lactation studies that have been conducted with bupivacaine and meloxicam in lactating pigs, showed that both were detected in milk but only bupivacaine was detected in the plasma of piglets that were allowed to suckle milk from the treated animals. . As per approved Mobic labeling, meloxicam was present in rat milk.

Review of Literature

The applicant did not identify any publications in regards to Zynrelef or meloxicam use during lactation. There were 2 publications of bupivacaine use during delivery which looked at lactation outcomes (see Table 4).

Table 4: Published Literature for Bupivacaine Use during Delivery and Lactation Outcomes as per Applicant

Author/Year	Groups tested	Time of exposure	Outcomes
Hirose 1996)[27]	30 parturients undergoing elective cesarean section under spinal anesthesia	Randomly administered epidural bupivucaine (n=15) and no edidural (n=15) for postoperative pain management	For both groups the weights of breastmilk fed infants during the study were significantly more in the group receiving bupivacaine
Abouleish 1978[28]	241 Neonates after vaginal delivery whose mothers received either extradural (mepivacaine, lignocaine, or bupivacaine), spinal, or general anesthesia during delivery. The control group consisted of infants delivered without anesthesia.	Time of delivery	No significant difference in weight changes. No interaction between method of feeding (breast- and bottle-fed) and type of anesthesia.

[27] Hirose M, Hara Y, Hosokawa T,Tanaka Y. The effect of postoperative analgesia with continuous epidural bupivacaine after cesarean section on the amount of breast feeding and infant weight gain. Anesth Analg 1996; 82(6): 1166-1169.
[28] Abouleish E, Donck AV, Meeuwis H,Taylor F. Effect of anaesthesia for delivery on the weight of infants during the first 5 days of life. Br J Anaesth 1978; 50(6): 569-574

DPMH Review

Bupivacaine

DPMH conducted a literature search in PubMed, Embase and the LactMed databases for bupivacaine and use in lactation, as well as in GG Briggs and RK Freeman Drugs in Pregnancy and Lactation.

- The Drugs and Lactation Database (LactMed) notes that there are low levels of bupivacaine in breastmilk and no adverse events have been noted in breastfed infants. Bupivacaine is not orally absorbed. In a lactating patient who received bupivacaine for 5 days through an intrapleural catheter, milk concentrations were maximal immediately postoperatively and maternal blood concentrations peaked at 47 hours after commencement of bupivacaine infusion.[43] Bupivacaine was not detectable in the infant`s blood at any time, and no behavioral abnormalities were detected.[43]
- French investigators reported 22 women who received epidural lidocaine 2% and bupivacaine 0.5% for pain control during cesarean delivery.[29] Average milk bupivacaine concentrations were 90 mcg/L at 2 hours after delivery, 60 mcg/L at 4 hours after delivery, and 40 mcg/L at 12 hours after delivery. No adverse reactions were noted in the exposed infants.
- Among 20 women given epidural bupivacaine or levobupivacaine before cesarean delivery, concentrations of both agents showed constant and similar decreases in milk and plasma after delivery and were nearly undetectable at 24 hours.[30]
- Baker and Schroeder[31,32] calculated the daily relative infant dose for bupivacaine to be 0.1% of the maternal dose; a relative infant dose of less than 2% indicates low drug concentrations in breast milk and relatively safe drug use while breastfeeding.
- Previous DPMH review by Dr. Miriam Dinatale in DARRTS and dated February 10, 2015 and Reference ID: 3699226.

Meloxicam

DPMH conducted a literature search in PubMed, Embase and the LactMed databases for meloxicam and use in lactation as well as in GG Briggs and RK Freeman Drugs in Pregnancy and Lactation and Hale TW Medications and Mother's Milk. LactMed states that "no information is available on the use of meloxicam during breastfeeding. Therefore, other agents may be preferred, especially while nursing a newborn or preterm infant."

[29]Ortega D, Viviand X et al. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiol Scand. 1999;43:394-7.
[30] Bolat E, Bestas A, Bayar MK, Ozcan S, Erhan OL, Ustundag B. Evaluation of levobupivacaine passage to breast milk following epidural anesthesia for cesarean delivery. Int J Obstet Anesth. 2014 Aug;23(3):217-21.
[31] Baker P. A., Schroeder D., Interpleural Bupivacaine for Postoperative Pain during Lactation. Anesth Analog 1989; 69: 400-402.
[32] Sachs HC, and Committee on Drugs. The Transfer of Drugs and Therapeutics into Human Breast Milk: An Update on Selected Topics. Pediatrics 2013;132:e796–e809

No relevant information was identified about maternal and infant levels of meloxicam in association with breastfeeding (presence of meloxicam in breast milk) or the effects of meloxicam on the breastfed infant or on milk production. Hale TW in Medications and Mother's Milk[33] states "There are no data for transfer of the drug to human milk. Meloxicam was present in rodent milk…because of the long half-life and high bioavailability, another NSAID would be preferred during breastfeeding." Briggs GG & Freeman RK in Drugs in Pregnancy and Lactation also did not identify any publications/reports of the use of meloxicam during breastfeeding. They conclude that because of "the low molecular weight (351 Daltons), meloxicam should be present in breast milk". The American Academy of Pediatrics[34] classifies piroxicam, a similar drug, as compatible with breastfeeding.

Summary

Bupivacaine is present in breast milk. Bupivacaine is not absorbed orally. The daily relative infant dose for bupivacaine is about 0.1%. This indicates low drug concentration in breast milk. Therefore, bupivacaine is considered relatively safe drug while breastfeeding. There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. Meloxicam was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk. DPMH proposes to include the following "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYNRELEF and any potential adverse effects on the breastfed infant from ZYNRELEF or from the underlying maternal condition."

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

There have been no animal studies conducted to evaluate the effects of bupivacaine on fertility. For meloxicam, a significant decrease was observed in sperm count and motility in adult male rats that were treated orally with 1 mg/kg of meloxicam for 35 days, with damage in the seminiferous tubules which was identified on histopathological examination.[35]

Review of Literature

Bupivacaine

The applicant did not identify any reports of bupivacaine and its effects on Females and Males of reproductive potential. DPMH also did not identify any publications on bupivacaine and its effects on Females and Males of reproductive potential.

Meloxicam

The applicant identified 4 publications that were relevant to Females and Males of Reproductive Potential. (See Table 5.)

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[33] Hale WT. Medications & Mothers' Milk. 2017, Seventh Edition. Springer Publishing Co., NY, NY

[34] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk.Pediatrics 2001,;108:776-84

[35] Uzun B, Atli O, Perk BO, Burukoglu D, Ilgin S. Evaluation of the reproductive toxicity of naproxen sodium and meloxicam in male rats. Hum Exp Toxicol. 2015 Apr;34(4):415-29.

Table 5: Meloxicam use in Females and Males of Reproductive Potential

Author/Year	Study/Trial	Time of administration	Outcomes
Jesam 2010[36]	A single center, double blind, crossover study. Twenty-two women (18 to 40 years old, surgically sterilized with regular menstrual cycles) were administered meloxicam, 15 or 30 mg/day, orally for 5 consecutive days during the late follicular phase, starting when the leading follicle reached 18 mm diameter.	Late follicular phase	No differences between meloxicam doses in menstrual cycle length. All women had normal luteal phase progesterone levels. There were no SAEs, and no changes in luteinizing hormone (LH) and prostaglandin E2 (PGE2) levels. Dysfunctional ovulation was observed in 11/22 (50%) cycles treated with 15 mg/day and 20/22 (90.9%) cycles with 30 mg/day (p = 0.0068).
Jesam 2014[37]	Meloxicam was administered from menstrual cycle Days 5 to 22. Fifty-six healthy sterilized women were treated for 18 days, during 3 consecutive cycles. They were randomized to 15 or 30 mg/day.	Follow up to the previous study. Menstrual cycle Days 5 to 22	Ovulation was observed in 44.6% and in 21.7% of women respectively. Meloxicam administered on menstrual cycle Days 5 to 22 results in a dose-dependent inhibition of ovulation but more than 20% of subjects had normal ovulation with the highest dose.
Massai 2007[38]	They evaluated if the combination of meloxicam and levonorgestrel (LNG) would prevent follicular rupture even after the ovulatory process had been triggered by the gonadotrophin surge.	Forty-one women were studied in 2 groups, follicle size of 15 to 17 mm (n = 10) and ≥18 mm (n = 31).	Follicular rupture failed to occur within the 5-day period that followed treatment in 50 and 70% of cycles treated with LNG + Placebo and LNG + meloxicam, respectively, in the 15-17 mm group (p = 0.15) and in 16 and 39% of cycles treated with LNG + Placebo and LNG + meloxicam, respectively, in the >or=18 mm group (p <0.052).
Weiss 2016[39]	Literature review on the use of preferential COX-2 inhibitors as an alternative form of emergency contraception		Insufficient evidence exists to support the use of preferential COX-2 inhibitors as a form of emergency contraception. The trials in general resulted in a decrease in ovulatory cycles but outcomes varied depending on dose regimens and specific drugs. Larger human trials are necessary before the clinical utility of this method of emergency contraception can be fully appreciated.

[36] Jesam C, Salvatierra AM, Schwartz JL,Croxatto HB. Suppression of follicular rupture with meloxicam, a cyclooxygenase-2 inhibitor: potential for emergency contraception. Hum Reprod 2010; 25(2): 368-373.
[37] Jesam C, Salvatierra AM, Schwartz JL, Fuentes A,Croxatto HB. Effect of oral administration of a continuous 18 day regimen of meloxicam on ovulation: experience of a randomized controlled trial. Contraception 2014; 90(2): 168-173.
[38] Massai MR, Forcelledo ML, Brache V, et al. Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study. Hum Reprod 2007; 22(2): 434-439
[39] Weiss EA,Gandhi M. Preferential Cyclooxygenase 2 Inhibitors as a Nonhormonal Method of Emergency Contraception: A Look at the Evidence. J Pharm Pract 2016; 29(2): 160-164.

Summary
No impact on fertility or reproductive function was reported in the literature for bupivacaine. Different studies showed that oral meloxicam may impact ovulation but it is only partially effective in preventing ovulation. Meloxicam is not mutagenic or genotoxic, and is not associated with major birth defects. Therefore, there is no need the labeling to state any recommendations for pregnancy testing or contraception during treatment with Zynrelef or meloxicam. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including meloxicam in women who have difficulties conceiving or who are undergoing investigation of infertility.

CONCLUSIONS

DPMH has the following recommendations for the Zynrelef labeling:

- Pregnancy, Subsection 8.1.
  The "Pregnancy" subsection of Zynrelef labeling was formatted in the PLLR format to include: "Risk Summary", "Clinical Considerations" and "Data" headings.
- Lactation, Subsection 8.2.
  The "Lactation" subsection of Zynrelef labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" headings.
- Females and Males of Reproductive Potential, Subsection 8.3.
  The Females and Males of Reproductive Potential, Subsection of Zynrelef labeling was formatted in PLLR format to include "Infertility" heading.

RECOMMENDATIONS

The below includes DPMH recommendations for the Zynrelef labeling for compliance with the PLLR. DPMH presented these recommendations to the Division on March 25, 2019. DPMH refers to the final NDA action for final labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.11, 8.1).
- **Infertility:** NSAIDs are associated with reversible infertility. Consider withdrawal of ZYNRELEF in women who have difficulties conceiving (8.3)

FULL PRESCRIBING INFORMATION

5 WARNINGS AND PRECAUTIONS

5.11 Premature Closure of Fetal Ductus Arteriosus

Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, in pregnant women starting at 30 weeks of gestation (third trimester) *[See Use*

in Specific Populations (8.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data on use of ZYNRELEF in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, there are available data on the individual components of ZYNRELEF, bupivacaine and meloxicam.

Bupivacaine

Prolonged experience over several decades with bupivacaine use in pregnant women for neuraxial anesthesia (excluding paracervical block) have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, embryo-fetal deaths were observed with subcutaneous administration of bupivacaine to rabbits during organogenesis at a dose equivalent to 2.1 times the bupivacaine maximum daily exposure. Subcutaneous administration of bupivacaine to rats from implantation through weaning produced decreased pup survival at a dose equivalent to 1.9 times the maximum daily exposure *(see Data).* Based on animal data, pregnant women should be advised of the potential risks to a fetus.

Meloxicam

Use of NSAIDs, including meloxicam, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including meloxicam, in pregnant women starting at 30 weeks of gestation (third trimester) *[See Warnings and Precautions (5.11)]*.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5- times the maximum recommended human dose (MRHD) of meloxicam. Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival at 0.08-times the MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD. *(see Data).*

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicam, resulted in increased pre- and post-implantation loss.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of the Fetal Ductus Arteriosus: Avoid use of NSAID's in pregnant women after 30 weeks gestation because NSAIDs, including ZYNRELEF, can cause premature closure of the fetal ductus arteriosus (see Data).

Labor or Delivery

Bupivacaine

Bupivacaine is contraindicated in obstetrical paracervical block anesthesia. The use of bupivacaine for obstetrical paracervical block anesthesia has resulted in fetal bradycardia and death *[See Contraindications (4)]*.

Bupivacaine can rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity *[See Clinical Pharmacology (12.3)]*. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Meloxicam

There are no studies on the effects of meloxicam during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal Data

Bupivacaine

Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard palate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.14-, 0.43- and 1.3-times the maximum recommended human dose (MRHD) of 300 mg based on BSA comparisons and a 60 kg human weight) and rabbit doses were 1.3, 5.8, and 22.2 mg/kg/day (equivalent to 0.08-, 0.37- and 1.4-times the MRHD based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at up to 40 mg/kg, a dose that caused maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose (1.4 times the MHRD based on BSA) in the absence of maternal toxicity. Decreased pup survival was noted at 1.3-times the maximum daily exposure in a rat pre- and postnatal development study when pregnant animals were administered subcutaneous doses of 4.4, 13.3, and 40 mg/kg/day bupivacaine hydrochloride (equivalent to 0.21-, 0.62- and 1.9-times the maximum daily exposure, respectively, based on the BSA comparisons and a 60 kg human weight) from implantation through weaning (during pregnancy and lactation).

Meloxicam

Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (4.3-fold greater than the MRHD of 9 mg

of meloxicam based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (129-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (43-fold greater than the MRHD based on BSA conversion). In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (1.08 and 10.8-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.13-times MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

Limited published literature reports that bupivacaine and its primary metabolite, pipecoloxylidine (PPX), are present in human milk at low levels. There are no human data available on whether meloxicam is present in human milk. There is no available information on effects of bupivacaine or meloxicam in the breastfed infant or effects of the drugs on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYNRELEF and any potential adverse effects on the breastfed infant from ZYNRELEF or from the underlying maternal condition.

Data

Following administration of bupivacaine and meloxicam to lactating pigs, both were detected in milk, but only bupivacaine was detected in the plasma of piglets allowed to suckle milk from the treated animals. Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including meloxicam, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including ZYNRELEF, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Males

In a published study, oral administration of meloxicam to male rats for 35 days resulted in decreased sperm count and motility and histopathological evidence of testicular

degeneration *[See 13.1 Impairment of Fertility]*.

17 PATIENT COUNSELING INFORMATION

Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including meloxicam, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)]*.

Fetal Toxicity

Advise pregnant women to avoid use of meloxicam after 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. Advise females of reproductive potential to contact their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
04/09/2019 01:27:08 PM

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04/12/2019 02:31:29 PM

Clinical Inspection Summary

Date	April 2, 2019
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ogochukwu Ogoegbunam, Pharm.D., Regulatory Project Manager Renee Petit Scott, M.D., Medical Officer Martha Van Clief, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application	NDA 211988
Applicant	Heron Therapeutics, Inc.
Drug	Bupivacaine and meloxicam extended-release solution (Zynrelef®)
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	(b) (4)
Consultation Date	January 18, 2019
CIS Goal Date	March 30, 2019 (original); April 5, 2019 (extended)
Action Goal Date	April 30, 2019
PDUFA Due Date	April 30, 2019

I. OVERALL ASSESSMENT OF FINDINGS

The clinical sites of Drs. Muse and Pollack were inspected in support of this NDA review. Based on the inspections of these two clinical sites, the studies (HTX-011-301 and HTX-011-302) appear to have been conducted adequately, and the data generated at these sites appear acceptable in support of the respective proposed indication. The preliminary compliance classification of the inspection outcome for both clinical investigator site inspections is No Action Indicated (NAI).

II. BACKGROUND

This 505(b)(2) NDA supports the approval of Zynrelef®, an extended-release fixed-dose combination of bupivacaine and meloxicam to be used as a topical intraoperative analgesic (prior to suturing at end of surgery), (b) (4) (b) (4) The 505(b)(2) regulatory pathway relies on: the previous approval of Marcaine® (bupivacaine) and Mobic® (meloxicam) as reference products; their long history of clinical use; the published literature; and new (unpublished) studies sponsored by Heron, including two Phase 3 studies, HTX-011-301 and HTX-011-302, for which the review division requested inspections.

- Bupivacaine is an amide-type local anesthetic, and its intraoperative use is currently considered the standard of care for perioperative pain control. Bupivacaine is the active ingredient of the combination product Zynrelef®.
- Meloxicam is a nonsteroidal anti-inflammatory drug, which, when added to bupivacaine at low-dose, reduces local inflammation and enhances the uptake of bupivacaine into the nerves to potentiate the analgesic effect of bupivacaine.

The two Phase 3 studies were conducted in relatively simple surgeries typically completed with little to no blood loss, that is, bunionectomy and inguinal hernia repair. The sponsor acknowledges that the 505(b)(2) pathway excludes the regulatory consideration of Zynrelef® for use in vascular surgeries, including certain intrathoracic, spinal, and head/neck surgeries. This product development for Zynrelef® has been granted Fast Track, Breakthrough Therapy, and Priority Review regulatory designations.

Study HTX-011-301

A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy

This Phase 3 study was conducted between October 2017 and March 2018 in 412 subjects enrolled at 13 CI sites in the US. The primary study objective was to compare the analgesic efficacy of HTX-011 relative to saline placebo and bupivacaine active control (standard of care) over the first 72 hours after simple unilateral bunionectomy with osteotomy and internal fixation, following intra-operative instillation on the surgical wound (Time 0). Subjects were screened within 28 days prior to surgery, and eligible subjects were randomized (3/3/2 ratio, respectively) into the following three treatment groups:

- HTX-011 (bupivacaine/meloxicam), 60 mg/1.8 mg, instillation on surgical wound
- Bupivacaine (without epinephrine), 50 mg, injection into surgical wound
- Placebo (saline), instillation on surgical wound

Subject Selection

- Adults ≥ 18 years of age scheduled for primary unilateral bunionectomy
- American Society of Anesthesiologists Physical Status I, II, or III

Exclusion Criteria

- Contralateral bunionectomy in the past 3 months, or planned concurrent surgery
- Concurrent painful condition expected to require analgesic use
- Contraindication, hypersensitivity, or idiosyncratic reaction to anticipated study agents
- Opioid use for ≥ 7 consecutive days within previous 6 months
- NSAID use (including meloxicam) within 10 days prior to surgery
- Use of long-acting opioids within 3 days or any opioid within 24 hours before surgery
- Use of bupivacaine within 5 days or any local anesthetic within 72 hours before surgery

Study Procedures

- Bunionectomy was performed with ≤ 20 mL of 1% lidocaine without epinephrine. Intravenous (**IV**) fentanyl ≤ 4 µg/kg was permitted for intraoperative pain control.
- Intraoperative use of other opioids or analgesics, local anesthetics, or anti-inflammatory agents was prohibited. Epidural anesthesia was not permitted.
- Beginning at discharge (72 hours), subjects recorded on a diary the use of any opioid medication through Day 28. Subjects returned to clinic on Days 10, 28, and 42.

Efficacy Assessments

Pain intensity using the Numeric Rating Scale (**PI-NRS**) at rest (**NRS-R**) and with activity (**NRS-A**), use of opioid medication, discharge readiness assessed using the Modified Post-Anesthetic Discharge Scoring System (**MPADSS**), and Patient Global Assessment (**PGA**) of pain control, recorded as follows:

- PI-NRS scores: at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at Days 10 and 28
- Concomitant opioid use: Time 0 - 72 hours (CRF) and 72 hours - Day 28 (subject diary)
- MPADSS: at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours
- PGA of pain control: 2 4, 48, and 72 hours, and at Day 28

Efficacy Endpoints

- Primary: Mean area under the curve (**AUC**) of NRS-A scores for HTX-011 relative to placebo through 72 hours after intraoperative study medication instillation (**AUC $_{0\text{-}72}$**)
- Secondary: Mean AUC $_{0\text{-}72}$ of NRS-A scores for HTX-011 relative to bupivacaine

Safety Assessments

Adverse events (**AEs**) and serious AEs (**SAEs**), local anesthetic systemic toxicity (**LAST**), physical examinations, vital signs, electrocardiograms (**ECGs**), hematology and serum chemistry, surgical wound healing, and bone healing (X-ray)

Study HTX-011-302

A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy

This Phase 3 study was conducted between July 2017 and January 2018 in 418 subjects enrolled at 17 CI sites (16 US, one Belgium). The primary study objective was to compare the analgesic efficacy of HTX-011 relative to saline placebo over the first 72 hours after unilateral open inguinal herniorrhaphy, following (Time 0) intra-operative instillation on the surgical wound. Subjects were randomized (2/2/1 ratio, respectively) into the following three treatment groups:

- HTX-011 (bupivacaine/meloxicam), 300 mg/9 mg, instillation on surgical wound
- Bupivacaine (without epinephrine), 75 mg, injection into surgical wound
- Placebo (saline), instillation on surgical wound

Subject Selection

- Adults ≥ 18 years of age scheduled for unilateral open inguinal herniorrhaphy with mesh
- American Society of Anesthesiologists Physical Status of I, II, or III

Exclusion Criteria

- Any prior inguinal hernia repair except as a child (less than 6 years of age)
- Planned concurrent surgical procedure (e.g., bilateral herniorrhaphy)
- Concurrent painful condition expected to require analgesic treatment
- Contraindication, hypersensitivity, or idiosyncratic reaction to study agents
- Opioid use for ≥ 7 consecutive days within previous 6 months
- NSAID use (including meloxicam) within 10 days prior to surgery
- Use of long-acting opioids within 3 days prior to surgery
- Use of any opioid within 24 hours prior to surgery
- Bupivacaine administration within 5 days prior to surgery
- Significant use of any local anesthetic within 72 hours prior to surgery

Study Procedures

- Inguinal herniorrhaphy was performed under general anesthesia; spinal, epidural, or regional anesthesia was not permitted. IV fentanyl ≤ 4 µg/kg was permitted for intraoperative pain.
- Just prior to end of surgery, all subjects received an additional 50 µg IV fentanyl to minimize the variability of intraoperative pain control on immediate postoperative pain.
- Intra-operative administration of other opioids or other analgesics, local anesthetics, or anti-inflammatory agents was prohibited.
- Subjects were given a diary at discharge to record daily the use of any opioid medication, from 72 hours through Day 28. Subjects returned to clinic on Days 10, 28, and 42 for follow-up.

Efficacy Assessments

Pain intensity using NRS-R and NRS-A, use of opioid medication, discharge readiness using MPADSS, and pain control PGA, recorded as follows:

- PI-NRS scores: at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and at Days 10 and 28
- Concomitant opioid use: Time 0 to 72 hours (CRF), 72 hours to Day 28 (diary)
- MPADSS: at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours
- PGA of pain control: 2 4, 48, and 72 hours, and at Day 28

Efficacy Endpoints

- Primary: Mean AUC_{0-72} of NRS-A scores for HTX-011 relative to placebo
- Secondary: Mean AUC_{0-72} of NRS-A scores for HTX-011 relative to bupivacaine

Safety Assessments

AEs and SAEs, LAST, physical examinations, vital signs, ECGs, blood hematology/chemistry, and surgical wound healing (Southampton Wound Scoring)

III. INSPECTION OUTCOMES

Rationale for Site Selection

Participation in both Phase 3 studies; large subject enrollment; high incidence of (non-serious) AEs; large treatment effect size (test versus placebo groups)

	Clinical Investigator Site Address	Site, Study, Enrollment	Inspection Dates	Inspection Outcome*
1	Richard A. Pollak, D.P.M. Endeavor Clinical Trials 8042 Wurzbach Road San Antonio, TX	Site 5 Study 301 59 subjects Study 302 33 subjects	3/22 – 3/28, 2019	NAI*
2	Derek D. Muse, M.D. Jean Brown Research 1045 East 3900 South Salt Lake City, UT	Site 24 Study 301 58 subjects Study 302 69 subjects	2/27 – 3/6, 2019	NAI*

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

* For both inspections, the Establishment Inspection Report (**EIR**) has not been received from the field office and the results reported in this Clinical Inspection Summary (**CIS**) are based on preliminary communication with the field investigator. Upon receipt and review of the EIR at OSI, an addendum to this CIS will be forwarded to the review division if new significant findings are discovered; otherwise, OSI's written post-inspection correspondence letter to the inspected entity (to be copied to review division) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

1. Richard A. Pollak, D.P.M.

Study 301: 75 subjects screened, 59 enrolled, 58 and completed study
Study 302: 51 subjects screened, 33 enrolled, and 33 completed study

For each study, case records were reviewed in detail for 20 subjects completing the study. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, primary efficacy endpoint (mean AUC_{0-72} of NRS-A scores from Time 0 through 72 hours), and opioid and other concomitant medication use.

No significant deficiencies were observed. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Derek D. Muse, M.D.

Study 301: 98 subjects screened, 58 enrolled, 55 and completed study
Study 302: 111 subjects screened, 69 enrolled, and 67 completed study

For each study, case records were reviewed in detail for 20 subjects completing the study. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, primary efficacy endpoint (mean AUC 0-72 of NRS-A scores from Time 0 through 72 hours), and opioid and other concomitant medication use.

No significant deficiencies were observed. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

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/s/

JONG HOON LEE
04/01/2019 10:22:36 PM

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04/02/2019 08:50:37 AM

KASSA AYALEW
04/02/2019 10:59:01 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 211988
Submission Number	002
Submission Date	10/30/2018
Date Consult Received	11/7/2018
Clinical Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult requesting QT-IRT's review of the pertinent sections in the NDA dealing with the ECG intervals including QT. Heron submitted an application for Zynrelef (bupivacaine and meloxicam) ER Solution 60 mg/1.8 mg, 200 mg/6 mg, 400 mg/12 mg with a proposed indication for the management of postoperative pain.

The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND125927 dated 05/30/2017 in DARRTS (with cross-reference to a TQT study for bupivacaine under NDA 22496);
- Module 5, section 5.3.4.2. Integrated ECG Safety Report;
- Highlights of Clinical Pharmacology and Cardiac Safety;
- Proposed label; and
- Summary of Clinical Safety section 4.3 Electrocardiogram Findings.

1 SUMMARY

1.1 SUMMARY OF FINDINGS

No significant QTc prolongation effect of HTX-011 was detected in our QT assessment of Study HTX-011-09 which evaluated the highest proposed dose of HTX-001 (400 mg bupivacaine and 12 mg meloxicam) and included robust, high-quality ECG recordings and analysis to support a valid assay for ECG intervals in patients.

The data from Study HTX-011-09 were analyzed using central tendency analysis, which did not suggest that HTX-011 is associated with QTc prolongation (refer to sections 4.3) – see Table 1 for overall results. There was, however, a slight shortening of QTcF interval compared to placebo control. The findings of this analysis are further supported by the exposure-response relationship (section 4.5) and the lack of clinically meaningful QTc outliers (section 4.4). Although the study did not include a positive control for assay sensitivity, the QT/QTc measurements were found to be unbiased (section 4.2.2).

Table 1: The Largest Mean ΔΔQTcF and the 90% CIs by Time Post Dosing (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔ (ms)	90% CI (ms)
QTc	HTX-011 (400 mg bupivacaine and 12 mg meloxicam)	4 h	-0.7	-6.4, 5.0

The worst-case clinical scenario associated with highest exposure of bupivacaine and meloxicam following single dose are expected in patients with hepatic impairment (for bupivacaine) and elderly female population (for meloxicam). As compared to listed drugs, HTX-011 is intended for a single application and accumulation from multiple dosing is not relevant. Due to extended release (over 72 h) from viscous solution, the meloxicam peak concentrations with HTX-011 are much lower than those observed with 15 mg tablet formulation (Table 2). The sponsor's data indicate that the peak concentrations of bupivacaine would be expected to increase by 1.125-fold in patients with hepatic impairment (Child-Pugh Scores ranging from 5 to 15).

1.2 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.3 COMMENTS TO THE REVIEW DIVISION

Per the ICH guideline, a TQT study is generally not needed for a new formulation of an approved product if the new formulation does not result in significantly higher exposure *(i.e.*, Cmax or AUC) and if the drug has not been associated with QTc prolongation, torsades de pointes or sudden death during postmarketing surveillance. Bupivacaine liposomal injection at doses up to 750 mg (Cmax of 428 ng/mL) was evaluated in a TQT study and was shown not to prolong the QTc interval (*Clin Pharmacol*. 2013;9:1441-47). Meloxicam was approved in 2000 and has not been evaluated in a TQT study.

At the proposed highest recommended dose of Zynrelef (HTX-011-56; 400 mg/12 mg) in augmentation mammoplasty, the highest mean Cmax for bupivacaine was 710 ng/mL and for meloxicam it was 527 ng/mL. The exposure of meloxicam is lower than that observed with 15 mg MOBIC tablets. In general, the rate of systemic absorption of local anesthetics depends upon the total dose and concentration of drug administered, the route of administration, and the vascularity of the administration site. Higher mean peak concentrations have been reported for bupivacaine in literature (mean Cmax up to 2,160 ng/mL) across a range of doses in various surgical models (Reynolds 1971; Wildsmith 1977; Fletcher 1992).

Table 2: PK Parameters for Bupivacaine and Meloxicam Compared to Marketed Formulations (Mobic Tablets and Exparel Suspension)

Formulations	HTX-011-56 (400 mg/12 mg)		Exparel (266 mg) Liposomal Injectable suspension (20 mL)	Mobic tablet (15 mg)
	(400 mg HTX-011-56# instillation; n=21)	(12 mg HTX-011-56# instillation; n=21)	(single dose at surgical site via local infiltration in hemorrhoidectomy; n=25)	(15 mg; in elderly females; n=8)
Parameters	Bupivacaine	Meloxicam	Bupivacaine	Meloxicam

Cmax (ng/mL)	586 ±417	322 ±76.5	867 ± 353	3210 ±767
AUCinf (ng.h/mL)	26400 ±10600	22700 ±7740	16867 ± 7868[§]	51300 ±11286[*]
Tmax (h)	18.08 (3.13 - 60.05)	48.03 (12.05 - 96.55)	0.5 (0.25 - 36)	5 (Range N/A)
Half-life (h)	11.6 ±3.21	19.1 ±3.32	24 ± 39	24.2 ±8.13

*[#]Study # 202; *AUC,ss; [§]AUC0-t*

2 RECOMMENDATIONS

The clinical data support labeling in section 12.2 because the exposures to bupivacaine and meloxicam at the highest proposed dose of HTX-011 are lower than the exposures with the respective approved products, and the ECG measurements and analysis in Study HTX-011-009 are robust and show no QTc prolonging effect at the highest proposed dose level. Furthermore, a published TQT study for bupivacaine (submitted under NDA 22496) showed a slight shortening of the QTc interval which is consistent with the results our assessment of HTX-011.

Our changes are highlighted (*addition*, ~~*deletion*~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Effect on Cardiac Repolarization The effect of ZYNRELEF on cardiac repolarization as assessed by the QTc interval was evaluated *following single application* in patients undergoing surgical procedures. ZYNRELEF, at *single* doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Heron Therapeutics, Inc. is developing Zynrelef (HTX-011) (b) (4) (b) (4) HTX-011 is an extended-release viscous solution containing a fixed-ratio combination of a local anesthetic – bupivacaine (29.25 mg/mL), and a low-dose nonsteroidal anti-inflammatory drug – meloxicam (0.88 mg/mL). Similar to other aminoacyl local anesthetics, bupivacaine acts by blocking the generation and the conduction of nerve impulses and meloxicam acts by inhibition of cyclooxygenase (COX-1 and COX-2). Bupivacaine is available in the US since 1972 as

an injectable product as solution (MARCAINE) or as long-acting liposomal suspension (EXPAREL). Meloxicam is believed to enhance penetration of bupivacaine into the nerves by reducing local inflammation (from a surgical incision), thereby potentiating the its effect. Meloxicam is available in the US since 2000 as oral products (VIVLODEX, MOBIC, QMIIZ ODT). This sterile product (a single-dose vial 10 mL or 20 mL) is intended for single-dose application (instillation without a needle) into the surgical site following final irrigation and suction and prior to suturing. The recommended dose is based on the size of the surgical site up to a maximum dose of 400 mg bupivacaine and 12 mg meloxicam (14 mL).

The QT-IRT reviewed the QT assessment proposal previously (DARRTS 05/30/2017) and agreed that a TQT study was not needed prior to conducting phase 3 studies.

Although the sponsor evaluated ECG data from 4 clinical trials, our review focuses on the ECG data collected in Cohort 2 of Study HTX-011-209 which collected intensive 12-lead ECG in 222 subjects using Holter recordings over 72 h post-dosing and evaluated the highest dose (400 mg/ 12mg). See the appendix for a review of study design and ECG sampling schedule.

3.2 SPONSOR'S RESULTS FOR STUDY HTX-011-209, COHORT 2

3.2.1 Central Tendency Analysis

In Cohort 2, the bupivacaine HCl treatment group had a 0.3 ms increase in QTcF vs a 7-10 ms reduction in the HTX-011 treatment groups. These changes are judged to be of no clinical relevance.

Reviewer's comment: *The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.2 Categorical Analysis

New QTcF >500 ms was seen in 2% of each of the 4 treatment groups. For QTcF increase from baseline, no subject in any of the 4 treatment groups met the increase >60 ms criteria. The nonspecific outlier criterion of 30-60 ms change from baseline showed no increase in this finding in the HTX-011 or bupivacaine HCl treatment groups compared with saline placebo.

Reviewer's comment: *The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.*

3.2.3 Safety Analysis

There were no deaths.

In cohort 2, a total of 13 treatment-emergent SAEs were reported in 10 subjects during the study, including 4 SAEs in 3 subjects in the saline placebo group, 2 SAEs in 2 subjects in the bupivacaine HCl group, 2 SAEs in 1 subject in the HTX-011 400 mg/12 mg group, and 5 SAEs in 4 subjects in the HTX-011 400 mg/12 mg + low-dose

ropivacaine group. Two subjects [redacted] (b) (6) both in the HTX-011 400 mg/12 mg + low-dose ropivacaine group, withdrew from the study due to SAEs (severe urinary retention and pulmonary embolism, respectively.

The Holter monitoring data were examined for outliers of tachycardia or bradycardia, the majority of which were not reported as TEAEs. There was a small increase in tachycardic outliers in the HTX-011 groups in Cohort 1 (not seen in Cohort 2); however, the proportion of subjects with runs of non-sustained ventricular tachycardia was not different between saline placebo and HTX-011.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in HTX-011 treatment arm. There was 1 SAE report of syncope in the bupivacaine HCl group of cohort 1.*

3.2.4 Exposure-Response Analysis

The regression of ΔQTcF on bupivacaine concentration in the HTX-011 treatment groups in Cohorts 1 and 2 are based on the Garnett 2017 model. The slopes were slightly negative (-0.0169 and -0.0044 ms/ng) and the intercepts were negative (-44.242 and -37.415 ms). The model predicted ΔΔQTcF of –6.785 (90% CI -9.100, -4.300) ms at the mean C_{max} of 341.7 ng/mL in cohort 1, and -4.537(-6.600, -2.600) ms at the mean C_{max} of 687.8 ng/mL in cohort 2.

The regression of ΔQTcF on meloxicam concentration in the HTX-011 treatment groups in cohorts 1 and 2 are based on the Garnett 2017 model. The slopes were positive and negative (0.0211 and -0.0075 ms/ng) and the intercepts were negative (-41.550 and –36.798 ms). The models predicted ΔΔQTcF of –3.263 (90% CI -8.400, 1.700) ms at the group mean Cmax plasma concentration of 226.6 ng/mL in cohort 1, and -8.897 (-13.10, -4.900) ms at 531.3 ng/mL in cohort 2.

Reviewer's comment: *The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.5 for additional details. Of note, the slope of the bupivacaine concentration-QTc relationship in the TQT study was negative, -0.00945 ms per ng/ml bupivacaine.*

4 REVIEWERS' ASSESSMENT

To characterize the effect of HTX-011 on the QTc interval, the QT-IRT reviewer focused their analysis on the ECG data from Cohort 2 in Study HTX-011-209 that used 12-lead Holter ECG recordings and evaluated the highest HTX-011 dose of 400 mg/12mg.

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

QTcF was used for the primary analysis, which is acceptable as no significant (10 bpm) increases or decreases in heart rate were observed (see section 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation appears acceptable.

4.2.2 QT bias assessment

QT bias assessment was conducted on the ECG data from placebo, HTX-011 400 mg/12 mg instillation and combination, and bupivacaine treatments in Cohort 2. QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF (Table 3) and QT (

Table 4). This analysis does not suggest the presence of significant negative treatment bias.

Table 3: QTcF bias assessment by treatment

Treatment	# of ECGs	Mean (sd), ms	Slope [95% CI], ms per 100 ms
Overall	9339	-2.59 (15.4)	-1.82 [-2.64 to -1]
HTX-011	4691	-2.7 (15.81)	-1.91 [-3.08 to -0.74]
Placebo	2135	-3.02 (15.34)	-5.88 [-7.58 to -4.18]
Bupivacaine	2513	-2.04 (14.64)	1.59 [0.03 to 3.15]

Table 4: QT bias assessment by treatment

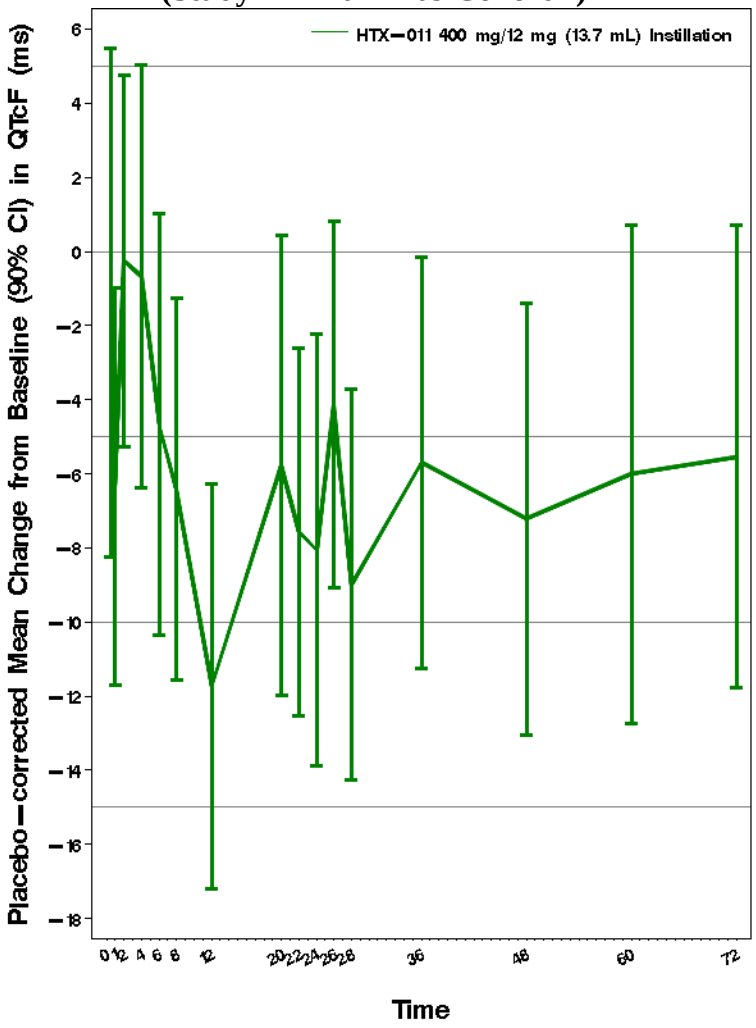
Treatment	# of ECGs	Mean (sd), ms	Slope [95% CI] , ms per 100 ms
Overall	9339	-2.24 (13.51)	-0.08 [-0.55 to 0.38]
HTX-011	4691	-2.34 (13.88)	-0.42 [-1.08 to 0.24]
Placebo	2135	-2.63 (13.23)	-1.45 [-2.39 to -0.5]
Bupivacaine	2513	-1.72 (13.01)	1.77 [0.87 to 2.67]

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTcF

Data from HTX-011 400 mg/12 mg instillation and saline placebo arms in Cohort 2 were used for central tendency analysis. The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, time point, and treatment by timepoint as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The following figure displays the time profile of ΔΔQTcF for treatment HTX-011 400 mg/12 mg instillation. The upper confidence intervals were below 10 ms for 72 hours post instillation.

Figure 1: Mean and 90% CI ΔΔQTcF Timecourse (unadjusted CIs) (Study HTX-011-209 Cohort 2)



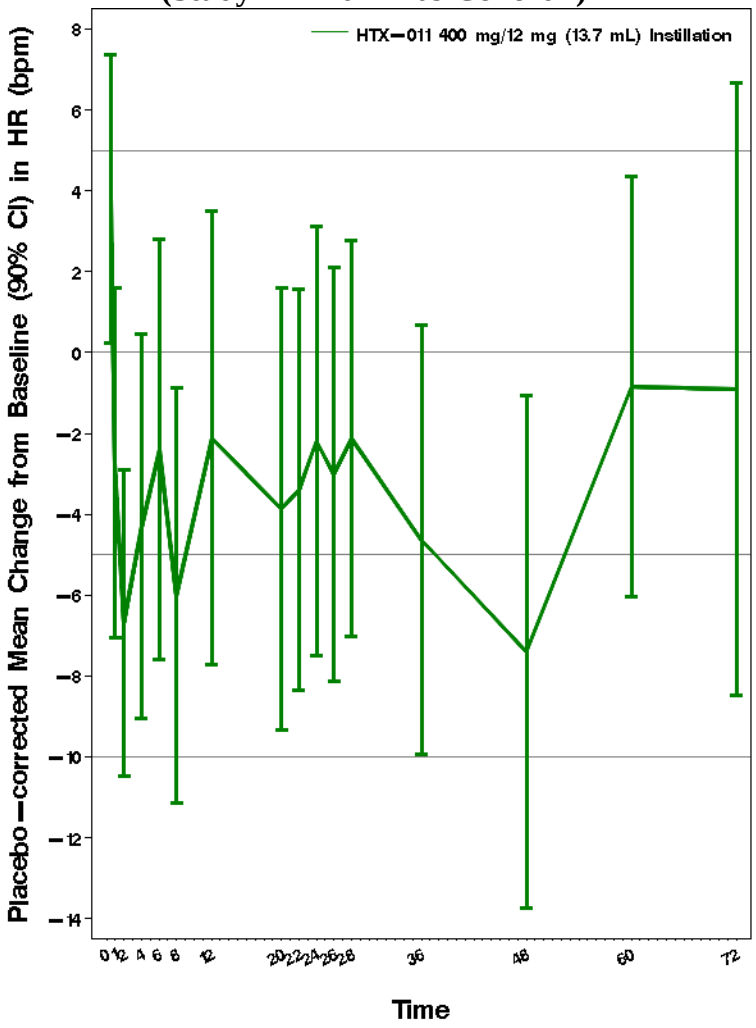
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 Heart Rate

The same statistical analysis was performed based on heart rate (HR, Figure 2). The results are similar to that of the sponsor.

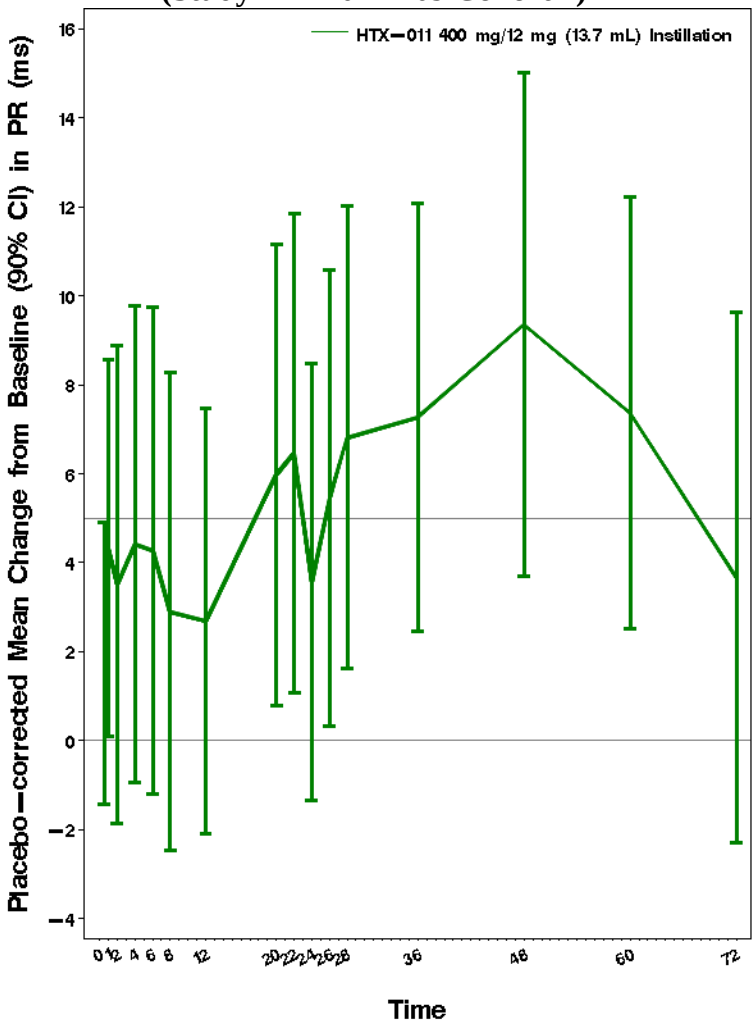
Figure 2: Mean and 90% CI ΔΔHR Timecourse (Study HTX-011-209 Cohort 2)



4.3.3 PR Interval

The same statistical analysis was performed based on the PR interval (Figure 3). The results are similar to that of the sponsor.

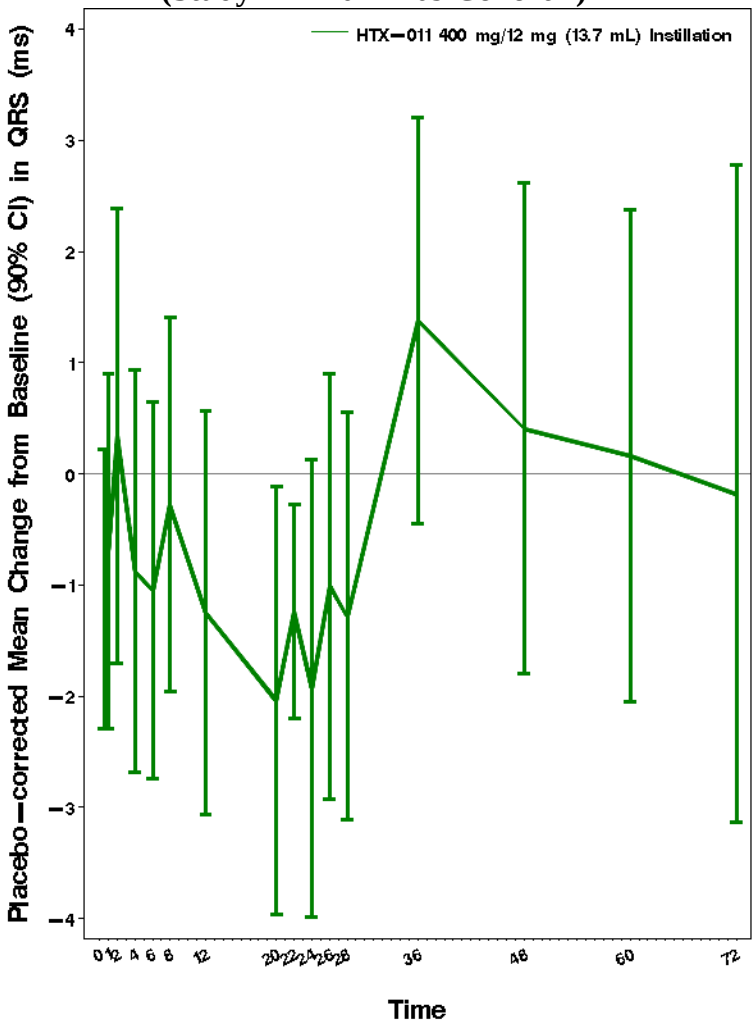
Figure 3: Mean and 90% CI ΔΔPR Timecourse (Study HTX-011-209 Cohort 2)



4.3.4 QRS Interval

The same statistical analysis was performed based on the QRS interval (Figure 4). The results are similar to that of the sponsor.

Figure 4: Mean and 90% CI ΔΔQRS Timecourse (Study HTX-011-209 Cohort 2)



4.4 CATEGORICAL ANALYSIS

4.4.1 QTcF Outliers

The statistical reviewer conducted categorical analysis for Cohort 2 of study; the treatment arm with ropivacaine injection was excluded. Table 5 lists the number of subjects as well as the number of observations whose QTcF values were between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. Compared to the sponsor's results, the reviewer's results show one more subject had QTcF >500 ms but one fewer subject had QTcF between 480 ms and 500 ms in the HTX-011 400 mg/12 mg instillation group.

Table 5: Categorical Analysis for QTcF
(Study HTX-011-209 Cohort 2)

	Total N		450<QTcF<=480 ms		480<QTcF<= 500 ms		QTcF>500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	144	144	35 (24.3%)	35 (24.3%)	3 (2.1%)	3 (2.1%)	3 (2.1%)	3 (2.1%)
HTX-011 400 mg/12 mg (13.7 mL) Instillation	56	738	12 (21.4%)	28 (3.8%)	4 (7.1%)	4 (0.5%)	2 (3.6%)	2 (0.3%)
Bupivacaine HCl 125 mg (30 mL)	55	790	12 (21.8%)	66 (8.4%)	6 (10.9%)	9 (1.1%)	2 (3.6%)	4 (0.5%)
Saline Placebo	53	672	18 (34.0%)	34 (5.1%)	4 (7.5%)	6 (0.9%)	1 (1.9%)	1 (0.1%)

Note: Total N for subject is the total number of subjects with non-missing values or changes for a specific ECG parameter. The sponsor's categorical analysis table for this cohort only includes subjects who had available ΔQTcF.

Table 6 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms. The results are the same as that of the sponsor.

Table 6: Categorical Analysis of ΔQTcF
(Study HTX-011-209 Cohort 2)

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
HTX-011 400 mg/12 mg (13.7 mL) Instillation	44	623	39 (88.6%)	617 (99.0%)	5 (11.4%)	6 (1.0%)
Bupivacaine HCl 125 mg (30 mL)	52	754	46 (88.5%)	747 (99.1%)	6 (11.5%)	7 (0.9%)
Saline Placebo	48	619	42 (87.5%)	611 (98.7%)	6 (12.5%)	8 (1.3%)

4.4.2 PR Outliers

The outlier analysis results for PR are presented in Table 7. Four subjects in the HTX-011 400 mg/12 mg instillation group had post-baseline PR values >220 ms; 2 of the 4 subjects had baseline PR values between 200 and 220 ms; the other 2 subjects had missing baseline PR values. Five other subjects in the HTX-011 400 mg/12 mg instillation group had post-baseline PR intervals between 200 ms and 220 ms; 3 of the 5 subjects had baseline PR values <200 ms; the remaining 2 subjects had missing baseline PR values.

The sponsor listed the number of subjects for PR >200 ms with an increase in ΔPR >25%; only 1 subject in the HTX-011 400 mg/12 mg instillation group had PR values that met this criteria.

Table 7: Categorical Analysis for PR (Study HTX-011-209 Cohort 2)

	Total N		PR<=200 ms		200<PR<=220 ms		PR>220 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	142	142	136 (95.8%)	136 (95.8%)	6 (4.2%)	6 (4.2%)	0 (0.0%)	0 (0.0%)
HTX-011 400 mg/12 mg (13.7 mL) Instillation	56	742	47 (83.9%)	691 (93.1%)	5 (8.9%)	35 (4.7%)	4 (7.1%)	16 (2.2%)
Bupivacaine HCl 125 mg (30 mL)	55	791	46 (83.6%)	753 (95.2%)	7 (12.7%)	31 (3.9%)	2 (3.6%)	7 (0.9%)
Saline Placebo	51	656	48 (94.1%)	645 (98.3%)	2 (3.9%)	9 (1.4%)	1 (2.0%)	2 (0.3%)

4.4.3 QRS Outliers

The outlier analysis results for QRS are presented in Table 8. Six subjects in the HTX-011 400 mg/12 mg instillation group had postbaseline QRS >110 ms; 3 of the 6 subjects' baseline QRS values were also >110 ms.

The sponsor listed the number of subjects for QRS >100 with an increase in ΔQRS >25%; no subject had QRS outlier in the HTX-011 400 mg/12 mg instillation group based on the sponsor's criteria.

Table 8: Categorical Analysis for QRS (Study HTX-011-209 Cohort 2)

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	144	144	130 (90.3%)	130 (90.3%)	14 (9.7%)	14 (9.7%)
HTX-011 400 mg/12 mg (13.7 mL) Instillation	56	744	50 (89.3%)	702 (94.4%)	6 (10.7%)	42 (5.6%)
Bupivacaine HCl 125 mg (30 mL)	55	791	48 (87.3%)	726 (91.8%)	7 (12.7%)	65 (8.2%)
Saline Placebo	53	672	45 (84.9%)	581 (86.5%)	8 (15.1%)	91 (13.5%)

4.4.4 HR Outliers

The outlier analysis results for HR are presented in Table 9. The sponsor listed the number of subjects for HR >100 bpm with an increase in ΔHR >25% and for HR <50 bpm with a decrease in ΔHR >25%. Based on the sponsor's criteria, no subject had HR bradycardic outliers but 27 subjects (27/44, 61%) had HR tachycardic outliers in the HTX-011 400 mg/12 mg instillation group.

Table 9: Categorical Analysis for HR (Study HTX-011-209 Cohort 2)

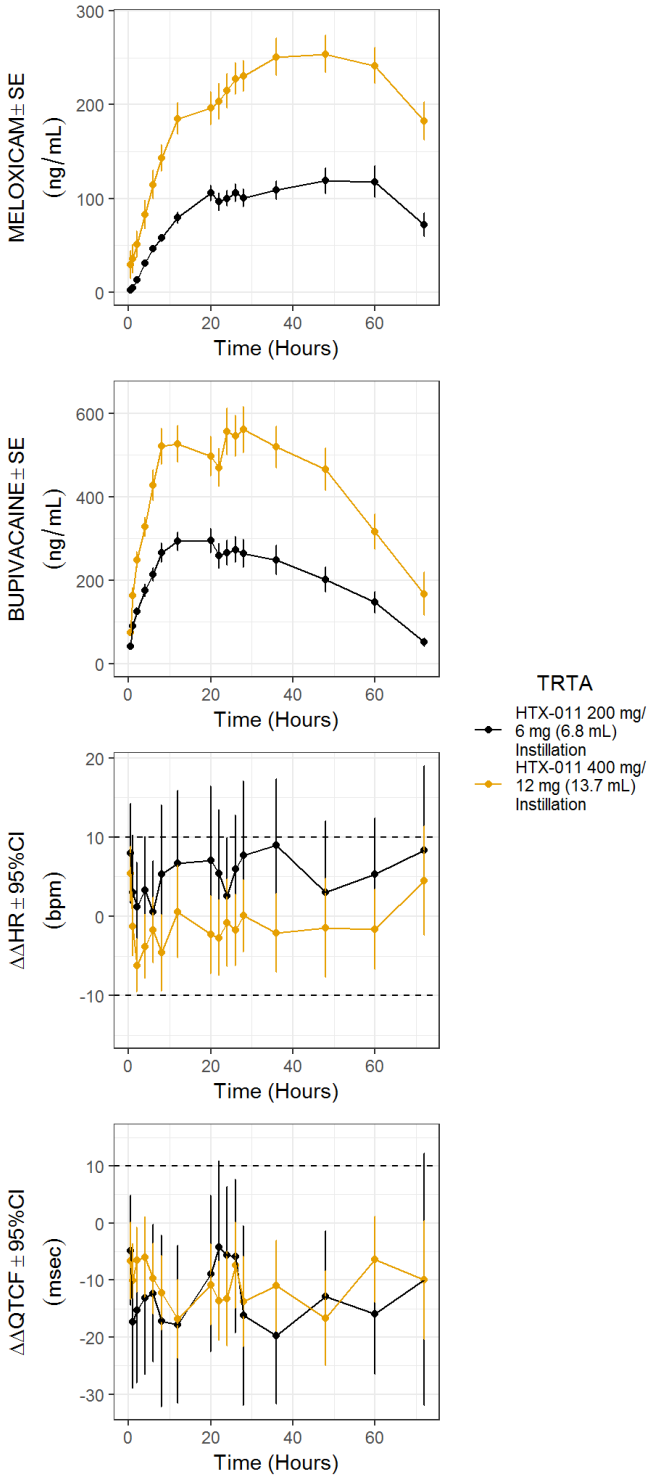
	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Baseline	144	141 (97.9%)	3 (2.1%)	144 (100%)	0 (0.0%)
HTX-011 400 mg/12 mg (13.7 mL) Instillation	56	21 (37.5%)	35 (62.5%)	56 (100%)	0 (0.0%)
Bupivacaine HCl 125 mg (30 mL)	55	18 (32.7%)	37 (67.3%)	54 (98.2%)	1 (1.8%)
Saline Placebo	53	12 (22.6%)	41 (77.4%)	51 (96.2%)	2 (3.8%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between bupivacaine concentrations and ΔQTcF. Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship.

An evaluation of the time-course of bupivacaine and meloxicam concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5, which shows an absence of significant changes in HR. Additional graphical analysis suggests a lack of significant hysteresis for bupivacaine and meloxicam concentrations. While there is a clear dose-dependent increase in bupivacaine and meloxicam concentrations, the maximum effect on ΔΔQTcF appears is not considerably different in the two treatment arms.

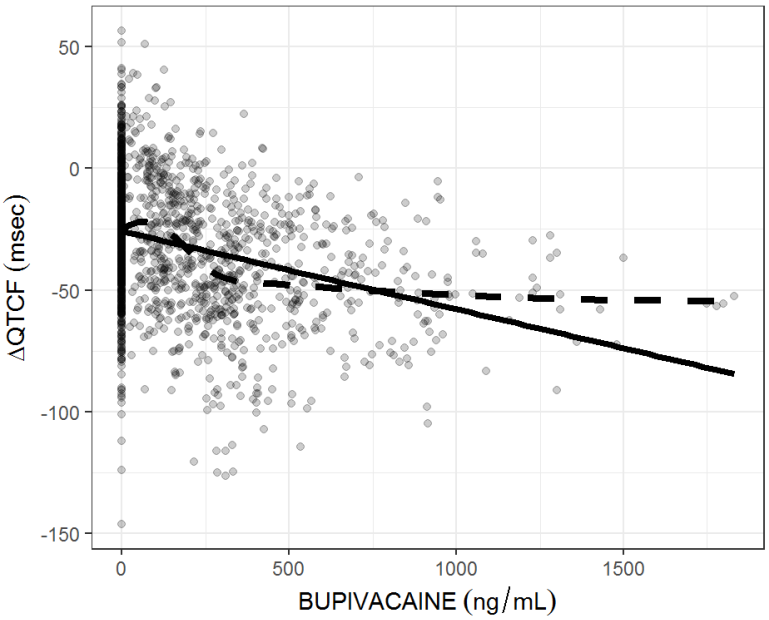
Figure 5: Time course of drug concentration for Meloxicam and Bupivacaine (top two), heart rate (third) and QTcF (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between bupivacaine concentration and ΔQTcF was evaluated to

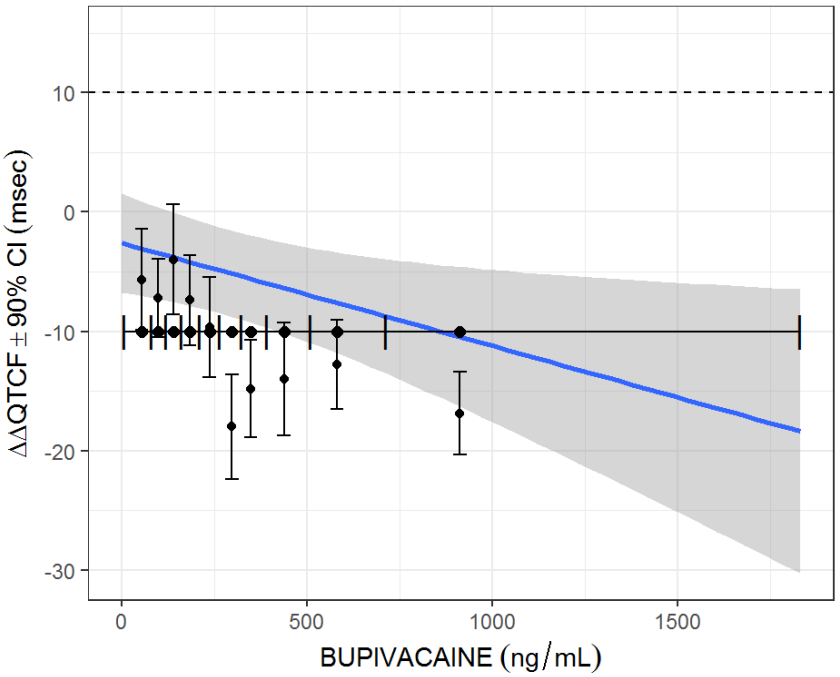
determine if a linear model would be appropriate. Figure 6 shows the relationship between bupivacaine concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of Bupivacaine concentration-QTc relationship (Study # HTX-011-209)



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7.

Figure 7: Goodness-of-fit plot for QTc



4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

4.7 OTHER ECG INTERVALS

No clinically significant changes in QRS were observed.

There were small mean increases (6-9 ms) in the PR interval. The largest mean increase was 9 ms (3.7, 15.0 ms) and occurred 48 h after instillation. Four subjects (7%) had PR interval >220 ms, and 1 subject had a PR internal >200 ms and an increase >25% of baseline. Based on the Cardiac Holter Arrhythmia analysis, there was not an imbalance in Mobitz 1 AV block in the HTX-011 treatment arm.

5 APPENDIX

5.1 EVALUATION OF QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Bupivacaine and Meloxicam	Brand Name	Zynrelef (HTX-011) ER Solution
Drug class	Local anesthetics + Nonsteroidal anti-inflammatory drug		
Combination product	Yes		
Indication	(b) (4)		
Therapeutic Dose	Based on the size of the surgical site; a maximum dose of 400 mg bupivacaine /12 mg meloxicam (14 mL)		
Maximum Tolerated Dose	Single doses up to 600 mg/18 mg		
Dosage Form	Extended-release Solution for Instillation	Route of Administration	Single-dose application (instillation without a needle) into the surgical site

3. Clinical cardiac safety
The sponsor reviewed all 1077 subjects who received HTX-011 for adverse events including QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or death. There has been a single episode of Ventricular Tachycardia occurring in a subject who received HTX-011 400 mg/12 mg and seven subjects who had syncope (4 in the 60 mg/1.8 mg group, and one each in the 200 mg/6 mg, 300 mg/9 mg, and 400 mg/12 mg groups). None of the other preferred terms have been reported (ISS). In addition, the standardized MedDRA query of torsades de pointes/QT prolongation was used to search the serious adverse event database, specifically including the following preferred terms: Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Long QT syndrome, Long QT syndrome congenital, Ventricular tachycardia, Torsades de pointes, Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Electrocardiogram repolarization abnormality, Electrocardiogram U-wave abnormality, Loss of consciousness, Sudden cardiac death, Sudden death, Syncope, Ventricular arrhythmia, Ventricular fibrillation,

Ventricular flutter and Ventricular tachyarrhythmia. There was one episode of syncope and one death, both in the bupivacaine HCl group.

4. Primary QT Study

Protocol number / HTX-011-009 Subjects undergoing total knee arthroplasty	ECG Quality		Arms		Sample size		ECG & PK assessments	
	Assessment	Ok?	Arms	High dose covers?	No subjects	Ok?	Timing	Ok?
Protocol number: HTX-011-209 Population: Patients	Central read? Yes Blinded? Yes Method? Manual Replicates? Yes	Yes	Highest dose: 400 mg/ 12mg Placebo: Yes Positive control: No	Therapeutic	56 subjects for 400 mg/12 mg	Yes	Baseline: Other Timing: 0.5, 1, 2, 4, 6, 8, 12, 20, 22 24, 26, 28, 36, 48, 60 and 72 hours	*Yes*

This was a Phase 2b, randomized, double-blind, saline placebo- and active-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered into the surgical site in subjects undergoing primary unilateral TKA. The study included 2 sequential cohorts. Cohort 1 was a dose- and administration technique-finding cohort, and Cohort 2 was an adequate and well-controlled cohort.

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