CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: September 6, 2019

To: Kenneth Bergman, Medical Officer
Division of Neurology Products (DNP)

Dave Podskalny, Clinical Team Leader, DNP

Taura Holmes, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for OZOBAX (baclofen) oral solution (Ozobax)

NDA: 208193

In response to DNP's consult request dated July 9, 2019, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for Ozobax.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Taura Holmes) on August 28, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 9, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.Bradshaw@fda.hhs.gov.

8 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CHRISTINE J BRADSHAW
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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 7, 2019

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Edward G. Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: OZOBAX™ (baclofen), NDA 208193
Trade Name, dosages, formulations, routes: OZOBAX™ (baclofen) oral solution, 5-20 mg TID
IND Number: 112300 (codaDOSE, Inc.)
Indication(s): spasticity resulting from multiple sclerosis
Sponsor: Metacel Pharmaceuticals, LLC
PDUFA Goal Date: September 18, 2019

Materials Reviewed:

- NDA 208193 Proposed label
- DARRTS; NDA 208193; Hawkins, Edward; 03/22/2018

I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Neurology Products (DNP) dated March 18, 2019 to review the labeling for NDA 208193 for Ozobax (baclofen) submitted by Metacel Pharmaceuticals. The Sponsor is seeking approval of Ozobax as a 1 mg/ml oral solution. Baclofen is currently indicated for the treatment of spasticity resulting from multiple sclerosis or spinal cord injury. The recommended dose for this product is 5 to 20 mg as an oral solution three times a day (TID). Baclofen was approved for medical use by FDA in 1992 and it functions as a γ-aminobutyric acid B ($GABA_B$) receptor agonist. It is not currently controlled in the Controlled Substances Act and does not have abuse potential. DNP would like CSS to comment on the adequacy of the labeling in regard to physical dependence and withdrawal.

A previous review by CSS mentioned that baclofen produces signs of physical dependence and withdrawal (DARRTS; NDA 208193; Hawkins, Edward; 03/22/2018). The Sponsor sufficiently addressed the abrupt discontinuation of baclofen (b) (4) in section 5.1 of their proposed labeling (Discussion section).

2. Conclusions

- The abrupt discontinuation of baclofen is adequately addressed (b) (4) in section 5.1 of the proposed drug label.

II. DISCUSSION

(b) (4)

Section 5.1
Abrupt discontinuation of baclofen, regardless of the cause, has resulted in (b) (4) high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure, and death. Therefore, (b) (4)
(b) (4)

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/s/

EDWARD G HAWKINS
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DOMINIC CHIAPPERINO
08/27/2019 03:14:18 PM

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:	July 12, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208193
Product Name and Strength:	Ozobax (baclofen) Oral Solution, 5 mg/5 mL
Applicant/Sponsor Name:	Metacel Pharmaceuticals, LLC (Metacel)
FDA Received Date:	July 9, 2019
OSE RCM #:	2018-87-2
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label received on July 9, 2019 for Ozobax. The Division of Neurology Products (DNP) requested that we review the revised container label for Ozobax (Appendix A) to determine if it is 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 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Little, C. Label and Labeling Review for Ozobax (NDA 208193). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 13. RCM No.: 2019-87-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 9, 2019

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/s/

COLLEEN L LITTLE
07/12/2019 04:08:56 PM

BRIANA B RIDER
07/12/2019 04:41:53 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:	June 13, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208193
Product Name and Strength:	Ozobax (baclofen) Oral Solution, 1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Metacel Pharmaceuticals, LLC (Metacel)
FDA Received Date:	March 18, 2019 and April 16, 2019
OSE RCM #:	2018-87-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ozobax, the Division of Neurology Products (DNP) requested that we review the proposed Ozobax prescribing information (PI) and container label to identify areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On January 9, 2016, Metacel submitted NDA 208193; however, on January 11, 2017 NDA 208193 received a Complete Response (CR) letter due to product quality issues. On January 28, 2018, Metacel submitted a Class 2 resubmission under NDA 208193 in response to the January 11, 2017 CR letter. However, on June 25, 2018, NDA 208193 received an additional CR letter[a], which included our Ozobax container label recommendations from a previous label and labeling review[b]. On March 18, 2019, Metacel submitted a Class 2 resubmission under NDA 208193 in response to the June 25, 2018 CR letter.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other – Information Request	F
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our evaluation of the proposed Ozobax PI and container label identified areas of vulnerability that may lead to medication errors.

[a] Holmes, T. FDA Communication: Complete Response for Ozobax. Silver Spring (MD): FDA, CDER, OND, OND DNP (US); 2018 JUN 25. NDA 208193.

[b] Morris, C. Label and Labeling Review for Ozobax (NDA 208193). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 17. RCM No.: 2018-87.

We note our previous Ozobax container label recommendations included in the June 25, 2018 CR letter were implemented. However, our review of the revised container label identified the following areas of needed improvement:

- The storage statement lacks prominence and may be overlooked which could pose risk of drug degradation medication error.
- It is unclear whether the product identifier required under the Drug Supply Chain Security Act is located on the container label.
- We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed container label and the expiration date format is not defined. The lot number and expiration date are required on the container label per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively.
- The strength is not expressed in accordance with United States Pharmacopeia (USP) General Chapter <Labeling> standard.
- The warning statement (b) (4) is inconsistent with Section 16 of the PI.

Upon evaluation of the proposed PI and container label, we noted the product storage statement, "Store at 2°C to 8°C (36°F to 46°F). (b) (4) so we contacted the Office of Pharmaceutical Quality (OPQ) via email communication on May 8, 2019 regarding the acceptability of the proposed storage statement. OPQ concurred with our recommendation to remove the (b) (4) statement from the PI and container label (b) (4) Therefore, we include this recommendation in Section 4.1 and Section 4.2 below.

Additionally, we note the proposed package size (i.e., 473 mL) for Ozobax (b) (4) We acknowledge that storing and dispensing multiple bottles of the proposed product may be inconvenient. However, requesting the Sponsor develop a larger bottle size or a more concentrated strength of the product may have unintended consequences. We considered whether the proposed package size could contribute to medication errors, but we could not identify a plausible risk based on the expected use of this product or based upon known causes of medication errors. Therefore, we find the proposed package size (i.e., 473 mL) acceptable from a medication error perspective. Our previous recommendations[b] for the Ozobax PI were not communicated to the Sponsor. We reviewed these previous recommendations and we include the relevant recommendations in Section 4.1 below.

4 CONCLUSION & RECOMMENDATIONS

The proposed Ozobax PI and container label can be revised to promote the safe use of this product as described in Section 4.1 and Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

    a. Revise [redacted] (b) (4) to include the unit of measurement appears after each numerical value to minimize misinterpretation.

    b. Ensure there is adequate space between each numerical value and the corresponding unit of measurement (e.g., 10 mg instead of 10mg) to decrease the chance for misinterpretation of the "m" for a zero or two zeros, risking a 10- to 100-fold overdose.

    c. Revise the statement [redacted] (b) (4) to include the recommended number of divided doses to minimize dosing errors and to improve clarity. For example, [redacted] (b) (4)

        i. Consider removing the statement, [redacted] (b) (4) to minimize redundancy and improve readability.

    d. Replace [redacted] (b) (4) to prevent misinterpretation and confusion.[c]

2. Dosage Forms and Strengths Section

    a. The product strength is not expressed in accordance with United States Pharmacopeia (USP) General Chapter <Labeling> standard (i.e., specified amount per 5 mL [5 mg/5 mL]) and will need to be updated to align with the container label once it is revised (see Section 4.2, recommendation A.5).

3. How Supplied/Storage and Handling Section

    a. See Section 4.1, recommendation 2.a above concerning expression of the product strength.

    b. Revise the product storage information to include the statement, "Must be refrigerated." and remove [redacted] (b) (4) For example, "Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F)".

[c] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 APR 22]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

c. Revise the statement, [redacted] to minimize product storage errors and to ensure consistency with the container label.

4. Patient Counseling Information Section

a. Add the statements, "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy." We recommend this due to evidence that suggests use of an oral syringe may decrease the risk of wrong dose error, particularly when measuring smaller doses.[d]

b. The statement [redacted] is inaccurate. [redacted] Therefore, the statement [redacted] should be removed from Section 17 of the PI.

4.2 RECOMMENDATIONS FOR METACEL PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The storage statement lacks prominence and may cause confusion, which can lead to product storage errors.

a. Remove the statement, [redacted]

b. Remove [redacted] and revise the Fahrenheit temperatures to "36°F" and "46°F" to minimize confusion and to maintain consistency with the Prescribing Information (PI).

c. Revise and bold the product storage statement to "Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F)" to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

[d] Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. Pediatrics. 2016; 138(4): e20160357.

[e] [redacted]

2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[f] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

3. The container label does not indicate where the lot number and expiration date will be located. The lot number and expiration date are required on the container label per 21 CFR 201.10(i)(1) and 21 CFR 211.137, respectively. Ensure that the lot number and expiration date are present on the container label in accordance with 21 CFR 201.10(i)(1) and 21 CFR 211.137.

    b. Ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number[g] and the lot number is clearly differentiated from the expiration date.[h]

4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

5. As proposed, the product strength statement is expressed (b) (4) Revise the product strength statement to express the strength as specified amount per 5 mL (i.e., 5 mg/5 mL) in accordance with United States Pharmacopeia (USP) General Chapter <Labeling> standard.

6. As presented, the warning statement (b) (4) is inconsistent with Section 16 of the PI. Revise the warning statement to "Keep out of reach of children" for consistency with the PI.

[f] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

[g] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

[h] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ozobax received on March 18, 2019 from Metacel Pharmaceuticals, LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Ozobax and the Listed Drug		
Product Name	Ozobax	Lioresal[i]
Initial Approval Date	N/A	November 22, 1977
Active Ingredient	baclofen	baclofen
Indication	(b) (4) spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. (b) (4) Ozobax may also be of some value in patients with spinal cord injuries and other spinal cord diseases.	Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity...
Route of Administration	Oral	Oral
Dosage Form	Oral Solution	Tablets
Strength	(b) (4)	10 mg and 20 mg
Dose and Frequency	(b) (4)	The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily). The following dosage titration schedule is suggested: • 5 mg t.i.d. for 3 days

[i] Lioresal [Prescribing Information]. DailyMed. DailyMed is the official provider of FDA label information (package inserts). APR 2006 [cited 2019 MAY 07]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c59b086d-8e2a-47fa-ae4f-135e65c37337.

	[redacted] (b) (4) • 5 mL (5 mg) three times a day for three days • 10 mL (10 mg) three times a day for three days • 15 mL (15 mg) three times a day for three days • 20 mL (20 mg) three times a day for three days [redacted] (b) (4)	• 10 mg t.i.d. for 3 days • 15 mg t.i.d. for 3 days • 20 mg t.i.d. for 3 days Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended.
How Supplied	Bottles of 473 mL	10 mg and 20 mg tablets in bottles of 100 and box of 100 unit dose blister packs
Storage	Store at 2°C to 8°C (36°F to 46°F). [redacted] (b) (4)	Do not store above 30°C (86°F). Dispense in tight container (USP).
Container Closure	16 oz. round amber container, white [redacted] (b) (4) child resistant cap with foil liner	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 17, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Ozobax and baclofen. Our search identified 2 previous reviews[j,k] and we considered our previous recommendations to see if they are applicable for this current review.

[j] Rider, B. Label and Labeling Review for Ozobax (NDA 208193). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 01. RCM No.: 2016-2017.

[k] Morris, C. Label and Labeling Review for Ozobax (NDA 208193). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 17. RCM No.: 2018-87.

APPENDIX F. METACEL'S RESPONSE TO THE AGENCY'S APRIL 12, 2019 INFORMATION REQUEST, RECEIVED APRIL 16, 2019

Accessible in EDR via: \\cdsesub1\evsprod\nda208193\0019\m1\us\1-2-cover-letters\1-2-cover-letters.pdf

Excerpted from submission:

1. *The image of your proposed container label resembles labeling consistent with a rectangular carton. Please clarify if you intend to package your proposed product in a carton (i.e., one 473 mL bottle in a carton). If you intend to package your proposed 473 mL bottle (container) in a carton, please ensure both the proposed container label and proposed carton labeling are submitted to the Agency for review.*

Response:

Metacel has revised the proposed container label image to more clearly represent that it is a container label and not a rectangular carton. We have also revised the file to include an area for serialization. The revised label is intended as a container label only and is available within Section 1.14.2. Metacel does not propose to package each bottle of product in an individual outer carton. Prescribing information will be attached to each bottle in the form of a folded leaflet.

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,[l] along with postmarket medication error data, we reviewed the following Ozobax labels and labeling submitted by Metacel Pharmaceuticals, LLC.

- Container label received on received on April 16, 2019
- Prescribing Information (Image not shown) received on March 18, 2018

G.2 Label and Labeling Images

Container Label

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

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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:	April 17, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 208193
Product Name and Strength:	Ozobax (baclofen) Oral Solution 1 mg/mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Metacel Pharmaceuticals, LLC
FDA Received Date:	July 20, 2016 and January 2, 2018
OSE RCM #:	2018-87
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested DMEPA review the proposed Prescribing Information (PI) labeling and container label for Ozobax (baclofen) 1 mg/mL oral solution (NDA 208193) for areas of vulnerability that could lead to medication errors.

2 REGULATORY HISTORY

Metacel submitted NDA 208193 for Ozobax on January 9, 2016; however, the application received a Complete Response Letter[a] (CRL) due to product quality issues. Therefore, Metacel submitted their response to the CRL as a Class 2 Resubmission on January 2, 2018. We note none of our previous PI labeling or container label recommendations were sent with the CRL.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our current review of the proposed container label identified an area of improvement to reduce the risk for medication errors.

A. The format for the expiration date is not defined.

In addition, we note our recommendations from a previous review of the container label and the Prescribing Information (PI) were not communicated to the sponsor. We reviewed these previous recommendations and the following recommendations are still applicable to reduce the risk of medication error.

[a] 1/11/17 CRL available from: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8041eeb5&_afrRedirect=1515177441412032

B. The current temperature statements within Section 16 How Supplied/Storage and Handling of the PI and on the container label lack clarity. Specifically, they do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value.
C. The container label contains the statement [redacted]
D. The Dosage and Administration section within the Highlights and Full Prescribing Information (PI) lacks clarity in dosing instructions (e.g. the instructions do not clearly indicate how to divide the daily dose, numeric doses are not consistently expressed with a corresponding unit of measure [redacted]), which may lead to confusion of dose.
E. The statement [redacted] in the Patient Counseling Information section of the PI is misleading [redacted]

We provide recommendations for DNP in section 5.1. and for Metacel in Section 5.2.

5 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed container label for Ozobax where additional information should be added or information should be clarified or revised to promote the safe use of the product. We provide recommendations in Section 5.1 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information- *Dosage and Administration* and Full Prescribing Information - Section 2 *Dosage and Administration*
    1. Numeric doses are not consistently expressed with a corresponding unit of measure throughout the PI. We are concerned that the numeric dose values could be misinterpreted and should therefore be revised for clarity. We recommend that throughout the PI, each recommended dose have a corresponding unit of measure 'mg' after the numeric value [redacted] In addition, we also recommend you place adequate space between the numerical dose and unit of measure (e.g. 10 mg instead of 10mg) to decrease the chance for misinterpretation of the "m" for zero or two zeros, risking a 10- to 100-fold overdose.
    2. We note that [redacted] the statement [redacted] lack clarity [redacted] To avoid confusion in dosing, we recommend revising the statements [redacted]

(b) (4)

3. (b) (4) We recommend avoiding the use of abbreviations to increase clarity. As such, we recommend you replace (b) (4) with its intended meaning (b) (4)

B. Full Prescribing Information - Section 16 *How Supplied/Storage and Handling*

1. The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. We recommend that the degree symbol and temperature scale follow each numeric value denoting temperature ranges, i.e., revise (b) (4) (b) (4) to increase clarity.

C. Full Prescribing Information – Section 17 *Patient Counseling Information*

1. The statement (b) (4) is inaccurate. (b) (4) Therefore, the statement (b) (4) should be removed from Section 17 of the PI.

5.2 RECOMMENDATIONS FOR METACEL

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either, DDMMMYYYY (e.g., 31JAN2013), MMMYYYY (e.g., JAN2013), YYYY-MMM-DD (e.g., 2013-JAN-31), or YYYY-MM-DD (e.g., 2013-01-31).
2. The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. We recommend you ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges to

[b] Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014;19(25):2-3.

(b) (4)

increase clarity. For example, revise [redacted] to read [redacted]

3. The following cautionary statement is present on the container label [redacted] which may mislead users [redacted] In response to an Information Request sent to the Sponsor on June 3, 2016, the Sponsor submitted an amendment to its NDA on June 10, 2016 [redacted] We recommend you remove the statement from the container label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ozobax received on January 2, 2018 from Metacel, and the listed drug (LD).

Table 2. Relevant Product Information for Ozobax and the Listed Drug

Product Name	**Ozobax**	**Lioresal**
Initial Approval Date	N/A	NDA 017851 approved November 22, 1977
Active Ingredient	baclofen	baclofen
Indication	(b) (4) spasticity resulting from multiple sclerosis; may also be of some value in patients with spinal cord injuries and other spinal cord diseases.	Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity...
Route of Administration	oral	oral
Dosage Form	oral solution	tablet
Strength	(b) (4)	10 mg and 20 mg
Dose and Frequency	(b) (4)	The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily). The following dosage titration schedule is suggested: 5 mg t.i.d. for 3 days 10 mg t.i.d. for 3 days 15 mg t.i.d. for 3 days 20 mg t.i.d. for 3 days Thereafter additional increases may be necessary but the total

	(b) (4)	daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended.
How Supplied	Bottles of 473 mL	10 mg and 20 mg tablets in bottles of 100 and box of 100 unit dose blister packs
Storage	(b) (4)	Do not store above 30°C (86°F). Dispense in tight container (USP).
Container Closure	16 ounce round amber container white (b) (4) child resistant cap with induction seal and foil liner	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 17, 2018, we searched DMEPA's previous reviews using the terms, Ozobax and lioresal. Our search identified 1 previous review[d], but our recommendations we not communicated to Metacel in the 1/11/17 CRL. The draft PI has been revised by Metacel and as such, some recommendations previously made are no longer valid. We include the relevant recommendations in the discussion (Section 4) and recommendation sections (Section 5.1 and 5.2) of this review.

[d] Rider, B. Label and Labeling Review for Ozobax (baclofen) NDA 208193. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 01. RCM No.: 2016-207.

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,[e] along with postmarket medication error data, we reviewed the following Ozobax labels and labeling submitted by Metacel.

- Container label received on July 20, 2016

G.2 Label and Labeling Images

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

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/s/

JOHN C MORRIS
04/17/2018

LOLITA G WHITE
04/18/2018

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 22, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Through: Dominic Chiapperino, Ph.D., Acting Director
Controlled Substance Staff (CDER/OCD/CSS)

From: Edward Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff (CDER/OCD/CSS)

Subject:

Trade name: Ozobax ((b)(4)baclofen)
NDA: 208193
Indication: Spasticity resulting from multiple sclerosis
Dosages: oral solution, 5-20 mg TID
Sponsor: Metacel Pharmaceuticals, LLC
PDUFA date: CR letter sent

Materials Reviewed:

- DARRTS; NDA 208193; Hawkins, Edward; 01/09/2017; consult review

I. Background

This memorandum is in response to a consult request dated January 2, 2018, from the Division of Neurology Products (DNP) to review NDA 208193 for a Class 2 resubmission of Ozobax (arbaclofen). CSS conducted a review of NDA 208193 for the first submission of the NDA and concluded that arbaclofen does not have abuse potential and does not require Section 9 of the drug label regarding abuse. However, CSS noted that dependence of baclofen was more evident and should be addressed in the label (DARRTS; NDA 208193; Hawkins, Edward; 01/09/2017; consult review). Arbaclofen is the active R-enantiomer of baclofen and would presumably have similar physical dependence to that seen of baclofen.

II. Conclusions

- The resubmission was accepted for a second cycle review. However, the CMC reviewer noted (b) (4)

  As a result, OPQ will recommend a CR of this NDA.

- Barring the submission and review of new studies, Ozobax (arbaclofen) will not need a section 9 of the label regarding abuse of the drug, but physical dependence should be addressed in product labeling. CSS is available for future assistance on this NDA if it becomes necessary.

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/s/

EDWARD G HAWKINS
03/22/2018

DOMINIC CHIAPPERINO
03/22/2018

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 5, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Edward G. Hawkins, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: OZOBAX™ (baclofen), NDA 208193
Trade Name, dosages, formulations, routes: OZOBAX™ (baclofen) oral solution, 5-20 mg TID
IND Number: 112300 (codaDOSE, Inc.)
Indication(s): spasticity resulting from multiple sclerosis
Sponsor: Metacel Pharmaceuticals, LLC
PDUFA Goal Date: January 11, 2017

Materials Reviewed:

1. DARRTS; NDA 208193; Yu, Bei; 09/07/2016; primary review
2. DAARTS; NDA 208193; Tobenkin, Anne; 09/12/2016; post-market safety review
3. NDA 208193; 5.3.1.2 Fasted Bioequivalence Study
4. NDA 208193; 1.6.3 Meeting correspondence

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) to evaluate abuse-related nonclinical and clinical data submitted by Metacel Pharmaceuticals regarding NDA 208193 for Ozobax (baclofen). The Sponsor is seeking approval of Ozobax as a 1 mg/ml oral solution. Baclofen is currently indicated for the treatment of spasticity resulting from multiple sclerosis or spinal cord injury. The recommended dose for this product is 5 to 20 mg as an oral solution three times a day (TID).

Baclofen was accepted for medical use by the Food and Drug Administration (FDA) in 1992 and functions as a γ-aminobutyric acid B ($GABA_B$) receptor agonist. Three previous baclofen containing products were approved by FDA (NDA 022462, NDA 020075, and NDA 021589). One was approved but withdrawn from the market (NDA 017851) (b) (4) The Sponsor is seeking approval under the 505(b)(2) pathway and will rely on the: 1) safety and effectiveness of the reference listed drug, Lioresal (NDA 017851), and 2) bioequivalence (BE) between baclofen oral solution (20 ml of 1 mg/mL) and baclofen tablets, 20 mg (Teva Pharmaceuticals, ANDA 073044). The review by the Office of Clinical Pharmacology deemed these studies to be sufficient to recommend acceptance of the NDA (DARRTS; Yu, Bei; 09/07/2016primary review).

The primary basis of our conclusions and recommendations derive from the lack of evidence indicating that baclofen has abuse potential. Baclofen is not currently listed in the schedules of the Controlled Substances Act (CSA). This submission, as well as previous NDA submissions for baclofen, did not contain an abuse potential assessment or a proposal for scheduling. There are also no reports or indications of abuse related adverse events in the bioequivalence study (CR-024-BE-2013) conducted as part of this NDA.

2. Conclusions

1. Baclofen is a $GABA_B$ receptor agonist that is not scheduled in the Controlled Substances Act (CSA). Overall, there is a lack of evidence that baclofen has abuse potential.

2. (b) (4) Section 5 of the label refer to the dangers of withdrawal, which is indicative of dependence (Section 9.3); however, these events are not associated with abuse or addiction of baclofen. These sections do not include information on neonatal withdrawal.

3. The Ozobax oral solution formulation, when administered as 20 mL dosage of 1 mg/mL solution, is bioequivalent to baclofen 20 mg tablets, as indicated by pharmacokinetic data from a single dose clinical trial (CR-024-BE-2013), reviewed by the Office of Clinical Pharmacology. No abuse related adverse events (e.g., euphoria and hallucinations) were reported in the human bioequivalence study. However, it is unlikely that the bioequivalence study, as designed, can provide any meaningful or useful data regarding abuse liability.

4. There are two reports of baclofen abuse at doses ranging from 60 mg to 600 mg (Perry et al., 1998; Richter et al., 2016). These doses are much higher than that tested in the Sponsor's bioequivalence study which used a dose of 20 mg. Both of these reports indicate that the patients were treated in the clinic for symptoms related to baclofen overdose and were released after several days of treatment.

3. Recommendations

Based on our findings listed in the Conclusions section, we recommend the following:

1. Cases of withdrawal from baclofen, after discontinuation from consistent use, are reported in the literature and demonstrate a clear sign of physical dependence. CSS defers to the Division as to whether Ozobax labeling warrants inclusion of dependence-related information in section 9.3 (Dependence) of the label. If this information is required, CSS can then advise on this section and other portions of section 9 of the label (i.e. 9 Drug Abuse and Dependence, 9.1 Controlled Substance and 9.2 Abuse).

2. With regard to the withdrawal effects of baclofen, data gathered by the Office of Pharmacovigilance and Epidemiology indicate that a neonatal withdrawal syndrome is a concern in pregnant females taking baclofen (DAARTS; NDA 208193; Tobenkin, Anne; 09/12/2016; Rev-Survepi-03(post-market safety review)). The occurrence of a withdrawal syndrome is indicative of drug dependence (usually addressed in Section 9.3). CSS agrees with the

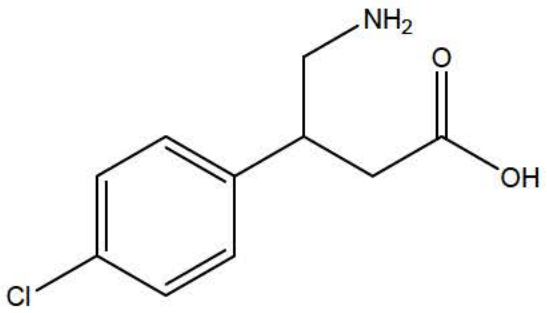
aforementioned review which states that warnings should be included in the label to address neonatal withdrawal.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Baclofen is a $GABA_B$ receptor agonist with IUPAC name (RS)-4-amino-3-(4-chlorophenyl)butanoic acid. It has a molecular formula of $C_{10}H_{12}ClNO_2$ and a molar mass of 213.67 g/mol. It is a white to off-white crystalline powder that is odorless, slightly soluble in water, very slightly soluble in methanol, and not soluble in chloroform. It is chemically related to gamma-hydroxybutyrate (GHB), which is a drug being abused for its euphoric, sedative and amnestic properties (Reeves et al., 2015).



baclofen

1.2 Potential Drug Isomers

Baclofen is composed of R and S stereoisomers that do not undergo inter-conversion. The R isomer is a more potent $GABA_B$ agonist than the S isomer and ranges in the literature are inconsistent, ranging from 3-5 fold to 100-1000 fold depending on the assay used (Smith, 1984; Falch et al., 1986). Considering previous NDA submissions and safety records from previously accepted NDA's, this does not appear to be an issue.

2. Nonclinical Pharmacology

The Sponsor did not conduct any non-clinical pharmacology studies as part of this NDA.

Baclofen is a $GABA_B$ agonist that functions as a central nervous system (CNS) depressant and is commonly used to treat the spasticity often seen in multiple sclerosis. The $GABA_B$ receptor is broadly

expressed in the CNS and links, via G-proteins, to activate K^+ channels hyperpolarizing the neuron thereby suppressing neuronal activity.

4. Clinical Studies

One clinical study was conducted by the Sponsor. In brief, study number CR-024-BE-2013 was an open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose bioavailability study. The primary objective was to measure the bioequivalence of the to-be-marketed formulation against baclofen tablets in healthy fasted subjects. The secondary objective was to monitor the safety and tolerability of a single dose of baclofen oral solution (1 mg/mL). The Sponsor is relying on the bioequivalence (BE) between baclofen oral solution 1 mg/mL and baclofen tablets 20 mg (Teva Pharmaceuticals) (ANDA 073044) for this NDA. A complete review was conducted by the office of clinical pharmacology which deemed this study to be sufficient to recommend acceptance of the NDA (DARRTS; Yu, Bei; 09/07/2016; primary review).

The adverse event profile of the study did not give an indication that the drug has abuse potential. The reported adverse events consisted of decreased hemoglobin/hematocrit, increased lymphocytes, increased alkaline phosphatase, and headache in the study population of 35 healthy adult males. All of these adverse events were reported in 5 different subjects.

There was no evidence of abuse or diversion of the drug in this clinical trial.

Adverse events from clinical trials in healthy and treatment populations are reported in the literature and listed in the baclofen label. The adverse events were typically related to high doses of baclofen (Beraha et al., 2016). Reports of very common neurological adverse events from baclofen use include somnolence (28%), drowsiness (18%), headache (16%), seizures (from discontinuation of therapy)(15%), sedation and dizziness (12%). Less common neurological adverse events (1 to 10%) include fatigue, ataxia, tremor, lightheadedness, lassitude, exhaustion, tingling, slurred speech, hypertonia, and paresthesia. Psychiatric adverse events have also been reported (1 to 10%) and include confusional state, hallucination, depression, insomnia, euphoric mood, and personality changes. There are several reports of overdose of baclofen. These reports and withdrawal caused from this type of use, which is indicative of physical dependence, is discussed below.

4.5 Tolerance and Physical Dependence in Humans

The Sponsor did not conduct any tolerance or physical dependence studies as part of this NDA. However, there are several reports in the literature of physical dependence associated with withdrawal syndromes which resulted from long term use of baclofen which will be reviewed here.

1. A review of the literature through 2004 resulted in 23 cases of proposed baclofen withdrawal resulting in psychiatric disturbances (Leo and Baer, 2005). These cases were a mixture of oral baclofen (18) and intrathecal baclofen (5) with 7 involving male patients and 16 in female patients with a mean age of 42.7 years. Gender differences did not play a statistical difference in the number or type of psychiatric disturbances resulting from baclofen withdrawal. Symptoms of baclofen withdrawal consisted of auditory and visual hallucinations, confusion, agitation,

disorientation, anxiety, and insomnia. Treatment ranged from the re-administration of baclofen to administration of baclofen with other drugs (benzodiazepines), or benzodiazepines alone. Patients took a range of 4-72 hours for complete resolution of the psychiatric symptoms.

2. In 2011, Nasti and Brakoulias published a report regarding a 61 year-old female who was obtaining baclofen from multiple doctors through a fictitious diagnosis of multiple sclerosis. The subject was consuming at least 75 mg of baclofen every day for 6 months although it is believed this dose was higher by the time hospitalization was required. The patient was hospitalized for psychiatric conditions (depression) and quickly deteriorated to a state where she was disorientated and was having visual hallucinations upon cessation of baclofen. Baclofen at 10 mg three times per day (tid) was administered and had little effect. The dose was raised to 25 mgs tds 6 days after admission to the hospital. By the ninth day of treatment, she was fully oriented and the hallucinations ceased. There is no indication of whether or not the patient was titrated off baclofen after this incidence.

3. This is a case of a 33 year-old French female who was prescribed 560 mg/day of baclofen by her psychiatrist for alcohol dependence. As a result of acute gastroenteritis the patient ceased treatment and was admitted to the ER for fatigue, vomiting, and neurological disorders. Baclofen was readministered with oxazepam and the patient fully recovered after several days (>2 days). The French medical regulatory authority states that a maximum dose of baclofen should be 300 mg/day while this individual was taking almost twice that dose (Richter et al., 2016).

These reports indicate that the sudden cessation of chronic baclofen at low or high doses, taken orally or intrathecally, will result in a withdrawal syndrome indicative of physical dependence. This is a well-known phenomenon that yields the following symptoms; fatigue, vomiting, auditory and visual hallucinations, confusion, agitation, disorientation, anxiety, and insomnia. Steps have been taken to address this in adults in the baclofen label and will be discussed in section 5 below.

Reports of withdrawal extend to instances of a neonatal withdrawal which was extensively reviewed by the Office of Pharmacovigilance and Epidemiology (DAARTS; NDA 208193; Tobenkin, Anne; 09/12/2016; post-market safety review). This review was conducted by evaluating the FDA Adverse Event Reporting System (FAERS) database and the published literature and a total of 5 cases were identified. Cases were present <1 to 3 days after delivery in dosages taken by the mother's ranging from 20 to 160 mg. Symptoms mimicked those of adult baclofen withdrawal and included seizures, hypertonicity, crying, diarrhea, and difficulty feeding. Successful treatment included a small dose of baclofen with a gradual weaning, all of which were conducted in the clinic. As a result, it was recommended including neonatal baclofen withdrawal in the boxed warning and in the Warnings and Precautions section of the oral solution baclofen labeling.

5. Regulatory Issues and Assessment

Baclofen is a marketed product that is not currently scheduled in any schedule of the Controlled Substances Act (CSA).

Sections of the label:

(b) (4)

Section 5: Warnings and Precautions and states

(b) (4)

Section 9: There is no section 9 of the label - This section typically relates to drug abuse and dependence. Reports of withdrawal indicate that baclofen causes physical dependence which is typically discussed in section 9.3 (Dependence) of the drug label. CSS defers to the Division of Neurology Products to determine if information on physical dependence should be added to section 9.3 of the label.

III. REFERENCES

Beraha EM, Salemink E, Goudriaan AE, Bakker A, de Jong D, Smits N, Zwart JW, Geest Dv, Bodewits P, Schiphof T, Defourny H, van Tricht M, van den Brink W and Wiers RW (2016) Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial. *European Neuropsychopharmacology* **26**:1950-1959.

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Leo RJ and Baer D (2005) Delirium associated with baclofen withdrawal: a review of common presentations and management strategies. *Psychosomatics* **46**:503-507.

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Perry HE, Wright RO, Shannon MW and Woolf AD (1998) Baclofen overdose: drug experimentation in a group of adolescents. *Pediatrics* **101**:1045-1048.

Reeves RR, Ladner ME, Perry CL, Burke RS and Laizer JT (2015) Abuse of medications that theoretically are without abuse potential. *South Med J* **108**:151-157.

Richter E, Baldovini A, Blasco V, Leone M and Albanese J (2016) About baclofen withdrawal syndrome. *Presse Med* **45**:547-548.

Smith DF (1984) Stereoselectivity of spinal neurotransmission: Effects of baclofen enantiomers on tail-flick reflex in rats. *Journal of Neural Transmission* **60**:63-67.

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/s/

EDWARD G HAWKINS
01/05/2017

MICHAEL KLEIN
01/09/2017

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:	December 1, 2016
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	NDA 208193
Product Name and Strength:	Ozobax (baclofen) Oral Solution 1 mg/mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Metacel Pharmaceuticals, LLC
Submission Date:	January 9, 2016
OSE RCM #:	2016-207
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested DMEPA review the proposed Prescribing Information (PI) labeling and container label for Ozobax (baclofen) 1 mg/mL oral solution (NDA 208193) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other – IR response letters dated June 10, 2016 and July 18, 2016 (no images)	F
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Ozobax PI labeling and container label identified the following areas of needed improvement that may contribute to medication errors:

1. The Dosage and Administration section within the Highlights and Full Prescribing Information (PI) lacks clarity in dosing instructions (e.g. the instructions do not clearly indicate how to divide the daily dose, numeric doses are not consistently expressed with a corresponding unit of measure, and (b) (4) may lead to confusion of dose.
2. The Dosage and Administration section of the Full Prescribing Information lacks instructions to appropriately measure and deliver the prescribed dose accurately which may lead to dosing errors.
3. Section 16 How Supplied/Storage and Handling of the PI lacks the strength of the product and appropriate information to facilitate identification (e.g., physical characteristics of the solution and container type) that is required per 21 CFR 201.57.

4. The current temperature statements within Section 16 How Supplied/Storage and Handling of the PI and on the container label lack clarity. The statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value and pose risk of misinterpretation.
5. The statement [redacted] in the Patient Counseling Information section of the PI is misleading [redacted]
6. The container label contains the statement [redacted]

We provide recommendations regarding these areas of needed improvement below in Section 4.1 and 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed PI labeling and container label for Ozobax where additional information should be added or information should be revised in order to promote the safe use of the product. We provide recommendations in Section 4.1 and Section 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information- *Dosage and Administration* and Full Prescribing Information - Section 2 *Dosage and Administration*
   1. Numeric doses are not consistently expressed with a corresponding unit of measure throughout the PI. We are concerned that the numeric dose values could be misinterpreted and should therefore be revised for clarity. We recommend that throughout the PI, each recommended dose have a corresponding unit of measure 'mg' after the numeric value [redacted] In addition, we also recommend you place adequate space between the numerical dose and unit of measure (e.g. 10 mg instead of 10mg) to decrease the chance for misinterpretation of the "m" for a zero or two zeros, risking a 10- to 100-fold overdose.
   2. We note that [redacted] and the statement [redacted] lack clarity [redacted] To avoid confusion in dosing, we

recommend revising the aforementioned statements [redacted]

3. [redacted] We recommend avoiding the use of abbreviations to increase clarity. As such, we recommend you replace [redacted] with its intended meaning [redacted]

C. Full Prescribing Information - Section 2 *Dosage and Administration*

1. The Dosage and Administration section of the Full Prescribing Information lacks information regarding how to appropriately measure and deliver the prescribed dose accurately. We are concerned that the lack of proper measuring information may lead to medication errors of overdose or under-dose. To avoid dosing errors, we recommend the following statement be added to Section 2 of the PI: "A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device."

D. Full Prescribing Information - Section 16 *How Supplied/Storage and Handling*

1. We note that the following information is provided in Section 16 of the PI: special handling and storage conditions; the National Drug Code number; and the units in which the product is ordinarily available for prescribing by practitioners (i.e., bottles of 473 mL). However, section 16 of the PI lacks the strength [redacted] of the product and important information to facilitate product identification (e.g., physical characteristics of the solution and container type) which is required per 21 CFR 201.57. Revise Section 16 of the PI to comply with the content requirements outlined in 21 CFR 201.57.

   For example:
   OZOBAX (baclofen) Oral Solution
   [redacted] is a clear, colorless, grape flavored liquid. It is supplied in amber bottles with a child-resistant closure.
   Bottle containing 473 mL……NDC 69528-301-16

[a] Institute for Safe Medication Practices. Safety briefs: Ambiguous course dosing leads to errors. ISMP Med Saf Alert Acute Care. 2014;19(25):2-3.

2. The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. We recommend that the degree symbol and temperature scale follow each numeric value denoting temperature ranges, i.e., revise (b) (4) to increase clarity.

E. Full Prescribing Information – Section 17 *Patient Counseling Information*

1. The statement (b) (4) is inaccurate. (b) (4) Therefore, the statement (b) (4) should be removed from Section 17 of the PI.

4.2 RECOMMENDATIONS FOR THE METACEL PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. The current temperature statements do not contain the temperature scale designation (i.e., "°C" or "°F") after each numerical value. We are concerned that this information could be misinterpreted and may pose a risk of drug degradation. Ensure that the degree symbol and temperature scale follows each numeric value denoting temperature ranges to increase clarity. For example, revise (b) (4) (b) (4)

2. The following cautionary statement is present on the container label (b) (4) which may mislead users (b) (4) In response to an Information Request sent to the Sponsor on June 3, 2016, the Sponsor submitted an amendment to its NDA on June 10, 2016 (b) (4) Therefore, we recommend you remove the statement from the container label.

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ozobax that Metacel Pharmaceuticals, LLC submitted on January 11, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Ozobax and the Listed Drug

Product Name	**Ozobax**	**Lioresal**
Initial Approval Date	N/A	NDA 017851 approved November 22, 1977
Active Ingredient	baclofen	baclofen
Indication	(b) (4) spasticity resulting from multiple sclerosis; may also be of some value in patients with spinal cord injuries and other spinal cord diseases.	Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity...
Route of Administration	oral	oral
Dosage Form	oral solution	tablet
Strength	(b) (4)	10 mg and 20 mg
Dose and Frequency	(b) (4)	The determination of optimal dosage requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily). The following dosage titration schedule is suggested: 5 mg t.i.d. for 3 days 10 mg t.i.d. for 3 days 15 mg t.i.d. for 3 days

	(b) (4)	20 mg t.i.d. for 3 days Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.). The lowest dose compatible with an optimal response is recommended.
How Supplied	Bottles of 473 mL	10 mg and 20 mg tablets in bottles of 100 and box of 100 unit dose blister packs
Storage	(b) (4)	Do not store above 30°C (86°F). Dispense in tight container (USP).
Container Closure	16 ounce round amber container white (b) (4) child resistant cap with induction seal and foil liner	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 29, 2016, we searched the L: drive and AIMS using the terms, Ozobax and baclofen to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews related to this review.

APPENDIX F. RESPONSES TO INFORMATION REQUESTS

Information Request (IR) response letters dated June 10, 2016 and July 18, 2016 (no images).[b,c]

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,[d] along with postmarket medication error data, we reviewed the following Ozobax labels and labeling submitted by Metacel Pharmaceuticals, LLC on July 20, 2016.

- Container label
- Full Prescribing Information (no image)

G.2 Label and Labeling Images

Container Label

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

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/s/

BRIANA B RIDER
12/01/2016

LOLITA G WHITE
12/01/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	September 12, 2016
Reviewer:	Anne C. Tobenkin, PharmD Division of Pharmacovigilance I
Team Leader:	Corrinne Kulick, PharmD Division of Pharmacovigilance
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Director:	Robert Levin, M.D. Division of Pharmacovigilance I
Product Name(s):	Ozobax (baclofen) oral solution, Lioresal (baclofen) tablet, Multiple Generic tablets
Subject:	Neonatal withdrawal syndrome
Application Type/Number:	NDA 208193, NDA 017851, ANDA 072234, ANDA 072235, ANDA 072284, ANDA 072825, ANDA 074584, ANDA 077068, ANDA 077088, ANDA 077089, ANDA 077121, ANDA 077156, ANDA 077181, ANDA 077241, ANDA 077862, ANDA 077971, ANDA 077984, ANDA 078146, ANDA 078220, ANDA 078401, ANDA 078504, ANDA 090334, ANDA 091193
Applicant/Sponsor:	Metacel Pharmaceuticals LLC
OSE RCM #:	2016-1825

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) database and the literature for an association between baclofen therapy and neonatal abstinence syndrome (NAS). This review was prompted by a literature report of NAS and baclofen we identified during routine pharmacovigilance.

Our review of FAERS identified four cases of NAS (also referred to as neonatal withdrawal syndrome) possibly associated with oral baclofen therapy. A review of the medical literature identified one additional oral baclofen case that described prophylactic use of baclofen to prevent withdrawal symptoms in a newborn. We did not identify any cases of NAS with intrathecal baclofen therapy. Our case series describes NAS in newborns that manifested <1-3 days after delivery. The baclofen dosages taken by the mother throughout pregnancy ranged from 20 mg to 160 mg per day in divided doses (n=5). The time to onset of withdrawal symptoms ranged from 12 hours to 3 days. Adult baclofen withdrawal is well recognized in the literature and is described in the Boxed Warning of intrathecal baclofen and the Warnings section of oral baclofen labeling. The symptoms described in the neonatal withdrawal cases mimicked adult withdrawal and included seizures and hypertonicity. Additional withdrawal symptoms described in the cases that were unique to newborns included: high pitched cries, excessive sucking, diarrhea, and feeding difficulties. Successful reported treatment, in which the dose was included (n=4), consisted of oral baclofen given through a feeding tube with doses ranging from 0.05 mg/kg/day to 0.5 mg/kg in divided doses followed by a gradual wean off of baclofen. All of the FAERS cases were considered serious; three were categorized as hospitalization either due to an extended stay throughout the withdrawal or weaning period or readmission due to the emergence of symptoms post-discharge.

NAS is a potentially serious adverse event that is both variable and complex. The clinical manifestations can vary in time to onset and severity. Consequently, the neonate discharge may be delayed to assure that baclofen withdrawal is complete without a re-emergence of symptoms. According to our case series, treatment for NAS with baclofen is oral baclofen administered via a feeding tube with a slow weaning based upon the symptoms exhibited by the neonate. Misdiagnosis of NAS can prolong the withdrawal and result in serious and possibly permanent consequences.

Based on the analysis of FAERS data, literature cases, biological plausibility, and known withdrawal symptoms in adults, DPV-I has concluded that there is adequate evidence to warrant including NAS in the Boxed Warning that describes abrupt discontinuation and in the corresponding Warnings and Precautions section of the oral solution baclofen labeling. We also recommend including this information in the Special Populations and Patient Counseling Information sections of the oral solution baclofen labeling. These updates should also be included in the generic oral tablet structured product label (SPL) format labeling where appropriate.

1 INTRODUCTION

This review describes postmarketing cases of neonatal abstinence syndrome (used interchangeably with neonatal withdrawal syndrome) in the FDA Adverse Event Reporting System (FAERS) database and literature with Lioresal (baclofen) oral use.

During routine pharmacovigilance, the Division of Pharmacovigilance I (DPV-I) identified a signal for neonatal withdrawal syndrome with baclofen, which is an unlabeled event. This review was prompted by an article by Freeman et al[1] describing neonatal withdrawal syndrome in a 39 1/7 weeks gestation baby delivered via cesarean section. The mother was taking baclofen 40 mg four times daily throughout her pregnancy. This literature case led the safety evaluator to characterize the clinical importance of this potentially serious adverse event in neonates because the symptoms described in this case are similar to the known baclofen withdrawal symptoms exhibited in adults.

1.1 BACKGROUND

Baclofen is a centrally acting gamma-Aminobutyric acid B ($GABA_B$) agonist. Baclofen is hydrophilic molecule and has a molecular weight of 213.66 Daltons (Da). The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. In animal studies, baclofen has been demonstrated to have general central nervous system (CNS) depressant properties as indicated by the production of sedation and tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated (in adults the half-life of baclofen in 2-6 hours). Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large intersubject variation in absorption and elimination.[3] Absorption may be dose-dependent, being reduced with increasing doses. Baclofen (Lioresal) is available in both injection and oral formulations. The determination of optimal dosage requires titration for both oral and injection formulations. For the oral formulation, the treatment is started with a low dose, preferably in divided doses and gradually increased to suit individual patient requirements. Total daily dose should not exceed a maximum of 80 mg daily.[2] The abrupt discontinuation of baclofen, regardless of the cause, has results in hallmark symptoms including; high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death. According to the Boxed Warning of the intrathecal labeling, special attention should be given to patients at apparent risk (e.g., spinal cord injuries at T6 or above, communication difficulties, or history of withdrawal symptoms with baclofen).[3]

A neonate born to a mother dependent on substances is at risk for drug withdrawal, commonly referred to as neonatal withdrawal syndrome (NAS). Drugs are transferred into the placenta and are absorbed and metabolized by the growing fetus. NAS is the end result of the sudden discontinuation of prolonged fetal exposure.[4] There are multiple factors that affect placental transfer of drugs including: low molecular weight, lipophilicity, and if the molecule is unbound by a large protein. Opioids (reference drug, OxyContin) are an example of a class of drugs that

are categorized as Pregnancy Category C and are known to result in NAS.[5] The OxyContin labeling includes a description of NAS in the Boxed Warning, Use in Special Populations, and Patient Counseling Information sections.

NAS is variable and complex, and typically involves a spectrum of signs of neonatal behavioral dysregulation. Altered levels of neurotransmitters such as norepinephrine, dopamine, and serotonin are thought to play a role; however, the factors that influence NAS are not completely understood. Clinical manifestations vary in time to onset and severity and can include the following symptoms: high-pitched cry, sleep and wake disorders, altered tone or movements, feeding difficulties, gastrointestinal disorders, autonomic dysfunction, failure to thrive, seizures, small birth weight, and respiratory complications.[6] Timing of withdrawal varies greatly and depends on the recent history of drug dose and the drug half-life. The length of hospitalization should be sufficient to monitor for any signs of NAS and consideration should be given to the possible delay of NAS symptoms. Symptoms are typically monitored using a scoring system, which provides a standardized measurement of the severity of the signs of withdrawal. The Finnegan Neonatal Abstinence scoring System is the most widely adapted system for this type of measurement.[7] The approach to treating NAS often involves a multidisciplinary team of providers and consists of supportive care, pharmacologic therapies, weaning of medications and measuring the signs of withdrawal, and discharge once the neonate is stabilized.[6]

1.2 REGULATORY HISTORY

Baclofen was first approved in tablet form in 1977. The original manufacturer, Novartis, discontinued production of the tablets and withdrew the NDA in 2009. Baclofen tablets are now manufactured exclusively by generic companies. Baclofen tablets are approved for the following indications: alleviation of signs and symptoms of spasticity resulting from multiple sclerosis (MS), spinal cord injuries or other spinal cord disease, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

There is a pending new application (NDA 208193) for Ozobax (baclofen oral solution) with the Division of Neurology Products (DNP) with a PDUFA date of December 21, 2016. The Applicant (Metacel Pharmaceuticals, LLC) submitted labeling in the structured product labeling (SPL) format with the original NDA application. Subsequently, a new submission, dated July 20, 2016, included revised baclofen labeling in the physician labeling rule (PLR) format.[8] The revised labeling includes:

(b) (4)

- Updated Section 8: Use in Specific Populations subheading; Pregnancy that includes a Risk Summary and Data for both Humans and Animals.

8.1 Pregnancy

Risk Summary

(b) (4)

Notably the one case referenced in Ozobax's proposed labeling with regard to late-onset neonatal seizures resembles FAERS Case # 7440719 (Ratnayaka et al.[9]).

1.3 Product Labeling

The current approved generic labeling for baclofen remains in SPL format and is not labeled for NAS. Pertinent SPL generic labeling for baclofen includes the following Warnings with regard to Abrupt Drug Withdrawal and Pregnancy:

Warnings: Abrupt Drug Withdrawal
Hallucinations and seizures have occurred on abrupt withdrawal of baclofen. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued.

Warnings: Pregnancy
Baclofen has been shown to increase the incidence of omphaloceles in fetuses of rats given approximately 13 times the maximum dose recommended for human use. There are no studies in pregnant women. Baclofen should be used during pregnancy only if the benefit clearly justified the potential risk to the fetus.

Notably, baclofen does not explicitly state a pregnancy category in the labeling, however as noted above, baclofen should be used only if the benefit clearly justifies the potential risk.

2 METHODS AND MATERIALS

2.1 Case Definition

Inclusion

- Reports with a patient age reported as < 1 year

- Maternal baclofen use reported throughout pregnancy
- Neonatal withdrawal symptoms described in case

Exclusion

- Reports with a baby born with physical deformities or malformations
- Withdrawal due to other drug

2.2 FAERS SEARCH STRATEGY

We searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	August 8, 2016
Time period of search	No limit – August 8, 2016
Search type	Quick query
Product Terms	Lioresal (Product name), baclofen (product active ingredient)
MedDRA Search Terms (Version 19.0)	SOC Pregnancy, puerperium, and perinatal conditions
* See Appendix A for a description of the FAERS database.	

2.3 LITERATURE SEARCH

We searched the medical literature with the strategy described in Table 2.

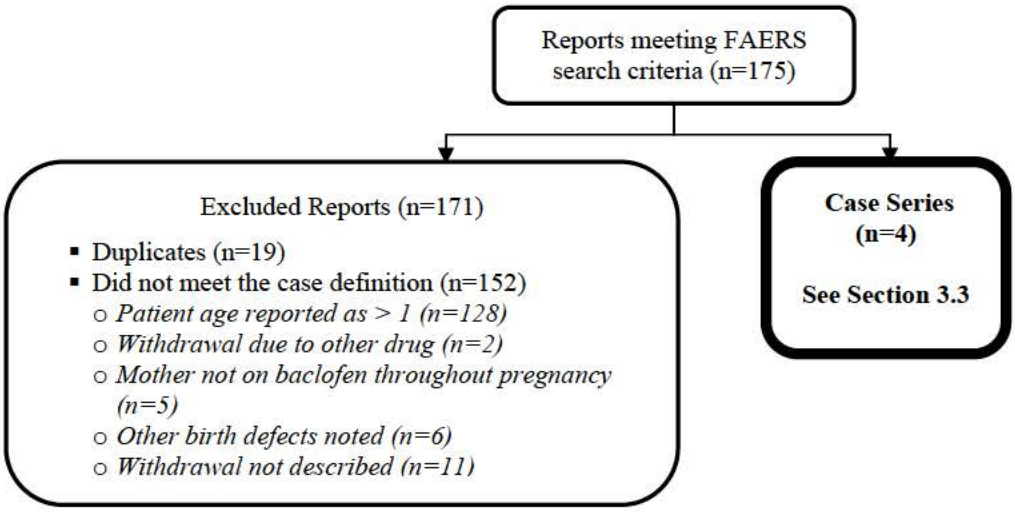
Table 2. Literature Search Strategy	
Date of search	August 8, 2016
Database	PubMed@FDA
Search Terms	("Substance-Related Disorders"[Mesh]) AND "Baclofen"[Mesh] AND "Infant, Newborn, Disease"[Mesh]
Years included in search	All

3 RESULTS

3.1 FAERS CASE SELECTION

Our FAERS search retrieved 175 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, four FAERS cases were included in the case series of NAS reported with baclofen use (see Figure 1).

Figure 1. FAERS Case Selection



3.2 LITERATURE SEARCH

The literature search identified four articles describing cases of baclofen and neonatal withdrawal. Three of these cases (Freeman et al[1], Ratnayaka et al[9], and Duncan et al[10]) were also identified in our FAERS search and included in our case series (FAERS Case #s: 10059546, 12305989, 7440719) and are described in Section 3.3. One additional article, Moran et al[11] not identified in FAERS, was included in our case series and is summarized in Section 3.3.

3.3 FAERS AND LITERATURE CASE NARRATIVE SUMMARIES

The five FAERS (n=4) and literature (n=1) cases of NAS reported with baclofen are summarized below.

3.3.1 FAERS Cases

FAERS Case # (b) (6), Manf # US-MDT-ADR-2016-00738, Expedited, USA 2016
This literature case submitted to FAERS describes a 35-year-old mother who gave birth to a female neonate at 39 1/7 weeks gestation. The mother's past medical history was significant for neurocysticerosis, status post removal of a spinal lesion resulting in paraplegia. Medication history included: low molecular weight heparin (LMWH), baclofen (40 mg four times daily), gabapentin, nitrofurantoin, trazodone, and tizanidine. Her pregnancy was complicated by advanced maternal age, anxiety, and depression. The birth history was notable for the presence of a nuchal cord and the Apgar scores were 8 and 9 at 1 and 5 minutes of life respectively. Initial examination revealed an alert, non-dysmorphic, and large for gestational age neonate girl. The remainder of the exam was unremarkable. The neonate fed well immediately after birth; however, at 12 hours after birth, she began gagging at nipple introduction with no interest in sucking. As the day progressed oral intake continued to decline despite multiple interventions. By 36-48 hours of life, she had developed loose green stools and mild tremors. The neonate was transferred to the NICU where she displayed symptoms of withdrawal including: hypertonicity,

tremors, hyperactive Moro reflect, sneezing, loose stools, and a disorganized sucking pattern. Meconium screening and images of head ultrasound were all negative. Given her intrauterine exposure to maternal medications, the team initiated oral baclofen at a dose of 0.05 mg/kg/dose four times daily. Within 24 hours of initiating baclofen, the patient improved, including significant increase in oral intake within 48 hours of baclofen initiation. She was ultimately discharged after 7 days of baclofen therapy and remained on baclofen with a gradual tapering.

Reviewer's comments: This case describes withdrawal symptoms in a newborn. There was temporal association with cessation of intrauterine baclofen therapy after birth. The newborn withdrawal symptoms described in this case are similar baclofen withdrawal symptoms demonstrated in adult patients (i.e., hypertonicity, tremors), and they are consistent with NAS in neonates (i.e., hyperactive Moro reflect, loose stools, and a disorganized sucking pattern). Also, the patient demonstrated a positive dechallenge; the withdrawal symptoms abated within 24 hours after initiating baclofen therapy which did not reoccur after slow weaning of baclofen therapy.

FAERS Case # (b) (6), Manf # GB-JNJFOC-20100606567, Expedited, GBR, 2010
This literature case submitted to FAERS describes convulsions in a seven day old girl who was exposed to baclofen during intrauterine life. A paraplegic women with a medication history of baclofen 80 mg/day, oxybutynin 9 mg/day, and trimethoprim 100 mg/daily which were continued throughout her uneventful pregnancy. The baby was born via ventouse extraction because of fetal tachycardia. The Apgar score was 10 at one and five minutes. Seven days later the baby was admitted with generalized convulsions; however, the mother noticed abnormal movements on the second day after birth. All investigations including: bacteriology and virology screens, complete blood count, and liver function tests, gave negative results. The convulsions did not respond to phenobarbitone, phenytoin, clonazepam, lignocaine, or pyridoxine, which were given in accordance with the hospital's guidelines for neonatal seizures. Electroencephalography on day 11 showed prolonged episodes of epileptic activity. Baclofen 1 mg/kg/day in divided doses was started. Thirty minutes after the first dose, the convulsions stopped. Baclofen was slowly withdrawn over the next two weeks. Magnetic resonance imaging of the brain on day 17 suggested a short hypoxic ischemic insult during the perinatal period.

Reviewer's comments: This case describes withdrawal symptoms in a newborn exposed to baclofen therapy throughout the pregnancy. The newborn exhibited the hallmark symptoms of baclofen withdrawal demonstrated in adult patients, including abnormal movements and generalized convulsions, and the mother was not taking any other drugs that are associated with withdrawal symptoms. The convulsions did not cease with multiple anticonvulsive therapies until finally the patient experienced a positive dechallenge within 30 minutes of receiving baclofen therapy.

FAERS Case # (b) (6), Manf # US-ACTAVIS-201406120, Expedited, 2014
This literature case submitted to FAERS describes withdrawal symptoms in a 3-day-old neonate who was exposed to baclofen during intrauterine life. The maternal history was significant for traumatic cervical spine fracture, resulting in paraplegia. Her medication history included baclofen 30 mg three times daily which was continued throughout pregnancy. No other drugs were mentioned in her medical history. She gave birth via cesarean section at 33 2/7

weeks gestation. The exam was consistent with the gestational age and required no resuscitation, but the neonate was admitted to the intermediate care nursery due to prematurity. Because of a maternal history of baclofen use, NAS scoring was begun on the first day of life. By the third day of life the neonate exhibited symptoms of withdrawal including; high-pitched cry, tremor, hypertonicity, excessive sucking, disordered sleep, hyperthermia, and mottling. Baclofen 0.5 mg/kg per day divided into four doses was initiated. The neonate exhibited improvement in withdrawal symptoms and a weaning schedule was devised. The final dose of baclofen was given on the 13th day of treatment and he was successfully discharged with a normal neurological examination.

Reviewer's comments: This case describes withdrawal symptoms in a newborn with baclofen exposure throughout pregnancy. The withdrawal symptoms ceased after initiating baclofen therapy, demonstrating a positive dechallenge. Additionally, the newborn withdrawal symptoms described in this case are similar to baclofen withdrawal symptoms demonstrated in adult patients (i.e., hypertonicity and hyperthermia) and NAS (i.e., high-pitched cry, tremor, excessive sucking, and disordered sleep).

FAERS Case # (b) (6) **Manf # NO-MYLANLABS-2012S1004617, Expedited, 2010,** GBR
This healthcare professional case submitted to FAERS describes a male neonate who was exposed to baclofen throughout the pregnancy period. The mother's medical history was significant for spinal cord injury. Her symptoms were treated with pregabalin 150 mg bid and baclofen 20 mg tid throughout the pregnancy. The newborn exhibited jitteriness, restlessness and irritability after birth. The symptoms were perceived as possible withdrawal symptoms and consequently a small dose of baclofen was given to the child "with good effect." The baclofen dose was slowly reduced and finally discontinued when symptoms abated.

Reviewer's comments: This case lacks detailed clinical descriptions of the birth and state of the newborn; however, it describes a temporal association of possible withdrawal symptoms in a newborn neonate who was exposed to baclofen therapy throughout the pregnancy. The case is somewhat confounded by the concomitant use of pregabalin which also may cause withdrawal symptoms. Although the withdrawal symptoms do not entirely describe the hallmark baclofen withdrawal symptoms, the neonate exhibited a positive dechallenge because the symptoms abated upon initiation of baclofen therapy.

3.3.2 Literature Case

The literature case described by Moran et al[11] describes prophylactic baclofen administration in the setting anticipated neonatal withdrawal issues. The mother was a 38-year-old with reflex sympathetic dystrophy. Her medication history was significant for baclofen 20 mg/day, clonazepam 2 mg/day, and controlled-release oxycodone 50 mg/day. She gave birth at 39 2/7 weeks via an uncomplicated cesarean section for breech presentation. The neonate girl had an Apgar score of 7 and 8 at 1 and 5 minutes, respectively, and at birth weighed 3.71 kg. No apparent anomalies were noted upon physical examination; however, shortly after delivery the patient had increased breathing difficulty. Radiographic findings were consistent with retained fetal lung fluid. Baclofen 0.05 mg/kg/day was initiated within the first hours of life. Neonatal

withdrawal scores over the first 24 hours of life ranged from 6 to 11, leading to the initiation of phenobarbital. Opiate withdrawal signs resolved promptly without the need for concomitant opioid therapy. The phenobarbital therapy was weaned every 3 days as tolerated and the baclofen therapy was discontinued after 9 days of weaning the dose. After a period of observation off of phenobarbital but still receiving low dose baclofen, no signs of clinical seizure activity were detected and the patient was discharged at day 16 of life. Her neurologic examination was normal at discharge.

Reviewer's comments: This case describes a newborn that had the potential for baclofen withdrawal that was possibly averted because of prophylactic baclofen dosing after birth. The case is confounded by the use of other medications known to result in NAS, including oxycodone and clonazepam, as well as the prophylactic doses of phenobarbital; however, the patient did not exhibit opioid withdrawal signs after 24 hours. The mother was also taking a small dose of baclofen, which may be less likely to result in withdrawal. However, it is possible that the newborn did not exhibit signs of baclofen withdrawal because of the prophylactic baclofen dose initiated within the first hours of life.

4 DISCUSSION

NAS is a potentially serious adverse event that is both variable and complex and can involve a constellation of symptoms. Clinical manifestations of NAS vary in time to onset and severity. Most drugs with a molecular weight less than 500 Daltons (Da) and non-protein bound tend to cross the placenta.[12] Baclofen is a relatively small (molecular weight: 213.7 Da), with low protein binding (30%) and hence has the potential for both significant transplacental passage and prolonged half-life in the neonate as a result of immature renal function and metabolic processes.[11] Adult baclofen withdrawal is a well-documented event that results from abrupt discontinuation of therapy.

Five [FAERS (n=4) and literature (n=1)] cases were included in our cases series of NAS with oral baclofen therapy. We did not identify any cases of NAS with intrathecal baclofen therapy. All of the mothers identified in our case series took baclofen throughout their pregnancy. Five cases included the baclofen dose, which ranged from 20 mg to 160 mg per day in divided doses. The time to onset of withdrawal symptoms, when included, ranged from 12 hours to 3 days. The withdrawal symptoms included in the reports were similar to those reported with adults and included seizures and hypertonicity, as well as those that were unique to the neonatal populations including: high pitched cries, excessive sucking, diarrhea, and feeding difficulties. Treatment, when reported, consisted of baclofen doses ranging from 0.05 mg/kg/day to 0.5 mg/kg/day in divided doses. All the FAERS cases were considered serious; three of the FAERS cases categorized as hospitalization due to the increased length of stay to treat the symptoms and gradually wean the neonate off of the baclofen.

One case by Ratnayaka et al[9] (FAERS Case # (b) (6)) describes a neonate with generalized tonic clonic seizures, which is also a hallmark symptom of baclofen withdrawal in adults. Prompt treatment of the seizures is required to avoid long term affects such as impaired brain activity. As described in the literature cases, other drugs do not quell the symptoms brought on by baclofen withdrawal, needlessly exposing a vulnerable neonate to drugs with known toxic qualities. Most discerning in the Ratnayaka et al case[9] was the lack of identification of baclofen

withdrawal symptoms resulting in administration of multiple anti-seizure medications for 10 days and consequent delay of baclofen.

Neonatal kidney function may explain the delay in the manifestation of withdrawal symptoms. The delay in withdrawal symptoms may be due to the longer half-lives in neonates because of the incomplete maturation of metabolic pathways. The timing of withdrawal symptoms is variable in newborns and may require longer stays to monitor for withdrawal symptoms. As noted in our case series, the emergence of symptoms can occur days after birth and in one case was not recognized until after discharge. Accordingly, some guidelines recommend increasing the length of stay for newborns with known drug withdrawal to ensure adequate time for the symptoms to emerge and treat the withdrawal as needed.[6] The dose the mother was taking during pregnancy may play a factor in terms of the severity of withdrawal. Due to the small number of cases in our case series, it is difficult to ascertain if the baclofen dose affects the likelihood or severity of the withdrawal, however, authors such as Duncan et al[10] suggest that higher doses could be more problematic.

Adult baclofen withdrawal is a well-documented consequence of abrupt discontinuation of baclofen therapy. Adult baclofen withdrawal is known to occur with both oral and intrathecal administration. Adult baclofen withdrawal is addressed in the Boxed Warning and Warnings section for the intrathecal formulation and the Warnings section for the oral formulation. The Warnings section in the baclofen oral formulation labeling recommends slow reduction when the drug is discontinued to avoid withdrawal symptoms. Our case series similarly describes treatment of withdrawal symptoms in neonates with a slow reduction of dose and careful attention to the reduction or recurrence of specific symptoms related to baclofen withdrawal. (b) (4) Notably, currently marketed drugs with updated PLR labeling and a known association with NAS (i.e., OxyContin) include a warning of NAS in the boxed warning.

Considering our findings describing the serious nature of NAS in newborns and the possible consequences of delayed treatment, communicating the possibility of NAS with maternal baclofen use is imperative for providers to safely prescribe, monitor, and treat both the mother and the newborn neonate.

5 CONCLUSION

Based on the analysis of FAERS data, literature cases, biological plausibility, and known withdrawal symptoms in adults, DPV-I has concluded that there is adequate evidence to warrant including NAS (b) (4) and the corresponding Warnings and Precautions section of the oral solution baclofen labeling. We also recommend including this information in the Special Populations and Patient Counseling Information sections of the oral baclofen labeling. These updates should also be included in the generic oral tablet SPL labeling where appropriate.

6 RECOMMENDATIONS

DPV offers the following labeling recommendations for the Ozobax oral solution labeling for DNP's consideration. The updates should also be included in the generic baclofen tablet labeling

as appropriate. (b) (4)

(b) (4)

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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09/12/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/24/2016

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208193

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Piramal Clinical Research	Mirra Kamshetty Mall, 3rd and 4th Floor, Ramanthapur, Hyderabad, Telangana, India
Analytical		(b) (4)

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/s/

SHILA S NKAH
07/01/2016