CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

<u>CLINICAL REVIEW(S)</u>

Cross-Discipline Team Leader Review

Date	6/25/2018
From	Gerald D. Podskalny, DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA	208193 Resubmission after Complete Response Action
Applicant	Metacel Pharmaceuticals, LLC
Date of Submission	01/01/2018
PDUFA Goal Date	07/02/2018
Proprietary Name / Established (USAN) names	Ozobax / Baclofen
Dosage forms / Strength	Oral Solution/1 mg/mL
Proposed Indication(s)	(b) (4) spasticity resulting from 1) multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, 2) (b) (4) spinal cord injuries and other spinal cord diseases.
Recommended:	*Complete Response*

1. Background

The applicant (Metacel) resubmitted this NDA on 1/2/2018 for baclofen oral solution following the FDA's Complete Response Action on 1/11/2017. The NDA is a 505(b)(2) application that relies on the FDA's finding of safety and effectiveness for the reference listed drug (RLD), Lioresal oral tablets (Novartis NDA 017851). Novartis requested withdrawal of NDA 17851 on 10/14/2008, five years after the company discontinued marketing of Lioresal tablets. Because Lioresal tablets are no longer available, the applicant conducted a relative bioavailability (BA) study using the reference standard baclofen oral tablet listed in the Orange Book (TEVA/IVAX, ANDA 072235) to bridge to FDA's findings for Lioresal tablets. The relative BA study was review by the Office of Clinical Pharmacology and the Clinical (safety) review team during the first cycle. There were no clinical or clinical pharmacology deficiencies identified during the review of the original NDA submission.

2. CMC/Device

Summary of Deficiencies in the Original Application
After the first review cycle, the FDA sent a Complete Response action letter to the applicant describing the deficiencies in the original application. However, a Complete Response action was recommended by the FDA's Office of Product Quality because of the following deficiencies:

- Deviations in the manufacturing process (b) (4)
- (b) (4)
- (b) (4)

- Deficiencies in the release and stability specifications

- Inadequate stability studies to support establishment of an expiration dating period
- Labeling deficiencies
- Missing certificates of analysis

The Complete Response (CR) action letter also included a request for updated certificates of analysis (CoA) reflecting specifications proposed in the NDA, and quantitative results for individual unspecified impurities.

Resubmission
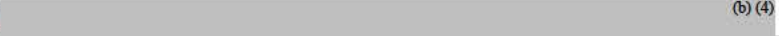The applicant provided responses to all items contained in the CR letter.

Quality Review Team, Review #2

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Thomas Wong	ONDP/DNDP1/Branch
Drug Product	Thomas Wong	ONDP/DNDP1/Branch
Process	Maotang Zhou	OPF/DPA III/Branch VII
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I
Facility	Derek Smith	OPF/DIA/Branch II
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Walters	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1

Drug Substance
The drug substance portion of the application remains adequate.

Drug Product
The applicant addressed   (b) (4)

                                                                (b) (4)

                    Dr. Wong recommended that "to establish the proper shelf-life for the drug product, the applicant should place an additional two batches of the drug product on stability". The CR letter (item #7) advised the applicant that "if the identity, assay, or related

substance method has to be modified to be fully validated, drug product samples may require retesting."

Dr. Wong's conclusions are as follows:

(b) (4)

It is clearly stated in the Complete Response Letter item #7 that if the identity, assay, or related substance method has to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated since the current data would not reliable. The applicant needs to place an additional 2 batches of the drug product on stability, according to ICH Q1A (R2).

Dr. Wong also identified information updates that would need to be included in a resubmission (Excerpt from the OPQ review):

- Perform a risk assessment screening   (b) (4)

- Provide batch analysis data on the drug product, batch C0412.

- Provide reference standard source information   (b) (4)

Manufacturing Process
The sponsor made minor changes in the manufacturing process   (b) (4)
                                            OPQ agrees this was a minor change that is acceptable.

Microbiology
All microbiology deficiencies were adequately addressed by the applicant during the first review cycle, and the microbiology portion of the application was deemed acceptable. However, if the product is reformulated, additional microbiology review will be required.

Facilities
All facilities involved in the manufacture and testing of baclofen USP and Ozobax (baclofen) oral solution are currently acceptable. Facility status will be reassessed when the applicant responds to the CR letter after this second review.

Labeling Issues
Labeling recommendations will be reassessed based to on the applicant's response to the deficiencies identified in this review.

Stability Testing
In item #7 of the CR letter, the applicant was informed that "if the identity, assay, or related substance method has to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated since the current data would not reliable."

OPQ commented that   (b) (4)

This approach is not acceptable to OPQ and the applicant will be required to place additional batches on stability."

CDTL Comment:
Although,   (b) (4) this
new information creates new deficiencies in the application that were not addressed in the
resubmission. OPQ recommends   (b) (4)

                                                    Additional stability data will
be needed because of the change to the analytical methods, and to determine an acceptable shelf-life.

In the Process portion of the final OPQ review entered in Panorama, the document inadvertently includes a "draft" watermark. Dr. Heimann confirmed that the Process review is the final version. The review cannot be replaced in Panorama with a version with the watermark removed.

4 Nonclinical Pharmacology/Toxicology

The resubmission did not include new nonclinical information. Dr. Freed provided comments regarding the approach   (b) (4) identified in the drug substance for the action letter:

- For a chronic indication, the general toxicity study should be of at least 3 months' duration.

5 Clinical Microbiology

Please refer to the CMC portion of this review for OPQ's comments on the microbiology information included in the applications.

6 Pediatrics

The applicant submitted a revised initial Pediatric Study Plan. The applicant requests a full waiver for patients < 12 years of age. The RLD is approved for use in children ages 12 years and older. The applicant argues that pediatric patients with spasticity caused by multiple sclerosis and spinal cord injury ages 12 years and younger are too few to study, making clinical trials impossible or highly impractical. The applicant's plan will be presented to Pediatric Review Committee (PeRC) when the deficiencies in the application have been resolved.

7 Other Relevant Regulatory Issues

Controlled Substance Staff (CSS) Recommendation
Dr. Edward Hawkins, Ph.D., was the CSS reviewer for this resubmission. CSS concluded that "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".

8 Labeling

Proprietary Name
The Division of Medication Error Prevention and Analysis completed their review of the proprietary name Ozobax, and concluded that it is conditionally acceptable. Todd Bridges, RPh, was the DMEPA reviewer for the resubmission of the proprietary name request.

DMEPA Labeling Recommendations for the Division
Chad Morris, PharmD, MPH was the primary reviewer for this resubmission and Lolita White, PharmD was the Team Leader who reviewed the resubmission.

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 ⁽ᵇ⁾⁽⁴⁾ 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 ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4) the statement ▇▇▇▇▇▇▇▇▇▇ (b) (4) lack clarity ▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4) To avoid confusion in dosing, we recommend revising the statements ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (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) (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) to increase clarity.

C. Full Prescribing Information – Section 17 *Patient Counseling Information*
   1. The statement ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4) is inaccurate. ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4) ▇▇▇▇▇▇▇ (b) (4) Therefore, the statement ▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4) should be removed from Section 17 of the PI.

Carton and Container labeling comments will be sent to the sponsor when the deficiencies have been addressed. Changes to labeling were not discussed with the applicant in light of the impending second Complete Response action.

a 1/11/17 Complete Response Letter

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.

c ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ (b) (4)

10 Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Complete Response.

Risk Benefit Assessment

The risks associated with treating patients with a baclofen product ⬛⬛⬛ (b) (4) ⬛⬛⬛ are not acceptable. Oral baclofen and intrathecal baclofen products are available, and patients will not be denied access to baclofen by a second complete response action.

Recommended Comments to Applicant

The following comments will be communicated to the sponsor in the Complete Response action letter.

The specific deficiencies are excerpted from the OPQ review.

The following Drug Product deficiencies should be communicated as reasons for a Complete Response.

(b) (4)

It is clearly stated in the January 11, 2017, Complete Response Letter, Item #7, that if the identity, assay, or related substance method have to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated, since the current data would not reliable. Therefore, place an additional 2 batches of the drug product on stability per ICH Q1A (R2). Submit sufficient long-term stability data to support the proposed shelf life.

Nonclinical Comment

(b) (4)

(b) (4)

The information requests below are not reasons for a CR, but should addressed in any resubmission.

1. Perform a risk assessment screening (b) (4)

2. Provide batch analysis data on the drug product, batch C0412.

3. Provide reference standard source information (b) (4)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208193
Applicant Name	Metacel Pharmaceuticals, LLC
Date of Submission	1/11/2016
PDUFA Goal Date	1/11/2017
Proprietary Name / **Established (USAN) Name**	Ozobax (Baclofen)
Dosage Forms / Strength	Oral Solution/ 1 mg/mL
Proposed Indication(s)	_____ (b) (4) spasticity resulting from1) multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, 2) spinal cord injuries and other spinal cord diseases.
Action	Complete Response

Material Reviewed/Consulted **OND Action Package, including:**	**Names of discipline reviewers**
CDTL Review	Gerald D. Podskalny
Project Manager	Taura Holmes
Clinical Pharmacology	Bei Yu
Clinical Review	Kenneth Bergmann
Labeling Review	Briana Rider
Pharmacovigilance Review	Anne C. Tobenkin
Drug Substance	Andrei Ponta
Drug Product	Andrei Ponta
Process	Sung Kim
Microbiology	Elizabeth Bearr
Facility	Quallyna Porte
Regulatory Business Process Manager	Dahlia A. Woody
Application Technical Lead	Martha Heimann

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

1. Introduction and Background

The 505(b)(2) application under review is for a new oral solution of baclofen. The application proposes to rely on the FDA's previous finding of safety and effectiveness for baclofen 20 mg oral tablets (reference listed drug). To provide a bridge to the reference listed drug, the applicant conducted a study to compare the pharmacokinetics of baclofen oral solution with those of baclofen tablets.

Baclofen tablets were originally approved in 1977 under the tradename Lioresal (NDA 17,851, owned by Ciba-Geigy, and later by Novartis). Novartis requested withdrawal of their NDA in 2008 because marketing of Lioresal oral tablets was discontinued. The current reference listed drug is under ANDA-A072235, manufactured by Ivax Pharmaceuticals Inc., a subsidiary of Teva Pharmaceuticals USA.

2. CMC

I concur with the conclusions reached by the Office of Product Quality (OPQ) review team that issues with product quality preclude approval of this application. Examples of the serious deficiencies identified by OPQ include a lack of a well-defined manufacturing process suitable for commercial production, product drug stability problems   (b) (4) failure to demonstrate   (b) (4)   and inadequate validation of analytical procedures used for product release and stability testing.

Given the nature of the outstanding deficiencies, there is no assurance to the OPQ review team that the applicant can manufacture a product that consistently delivers the intended dose. In addition,   (b) (4) that have not been identified or evaluated for safety.

3. Nonclinical Pharmacology/Toxicology

The applicant is relying on the nonclinical information from the reference listed drug. No new nonclinical information was submitted in this application.

4. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

Study 024-BE-2013, which compared the pharmacokinetics of baclofen oral solution with those of baclofen tablets, shows bioequivalence between the two products. This provides an adequate bridge between this new product and the reference listed drug.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

The applicant is relying on the clinical efficacy information from the reference listed drug. No new clinical efficacy information was submitted in this application.

7. Safety

The applicant is relying on the clinical safety information from the reference listed drug. No new clinical safety information was submitted in this application, beside the limited safety information from PK Study 024-BE-2013, which does not identify any significant new concern.

Dr. Podskalny also discusses postmarketing safety review findings of four cases of "neonatal withdrawal syndrome" that occurred 1-3 days after delivery from mothers treated with stable doses of oral baclofen. A review of the medical literature identified one additional case that describes prophylactic use of oral baclofen to prevent withdrawal symptoms in a newborn. The pharmacovigilance reviewer recommends describing "neonatal withdrawal syndrome" in a Boxed Warning in labeling. This issue potentially impacts all currently marketed formulations of baclofen, and will be the object of a separate review, which will inform the labeling for Ozobax.

8. Advisory Committee Meeting

No advisory committee meeting was required for this 505(b)(2) application.

9. Pediatrics

Current labeling for baclofen oral tablets states that "safety and effectiveness in pediatric patients below the age of 12 years have not been established." (b) (4)

As the proposed indication is beyond the scope of an orphan designation, the

applicant has been notified that this baclofen oral solution application is not exempt from PREA requirements, and will be required to submit a revised iPSP.

(b) (4)

10.   Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11.   Labeling

Labeling was not discussed with the sponsor during this review cycle because of the seriousness of the CMC deficiencies.

12.   Decision/Action/Risk Benefit Assessment

Because of the serious product quality deficiencies, I will issue a complete response letter for this application.

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/s/

ERIC P BASTINGS

01/11/2017

Cross-Discipline Team Leader Review

Date	1/3/2017
From	Gerald D. Podskalny, DO, MPHS
Subject	Cross-Discipline Team Leader Review
NDA	208193
Applicant	Metacel Pharmaceuticals, LLC
Date of Submission	1/11/2016
PDUFA Goal Date	1/11/2017
Proprietary Name / Established (USAN) names	Ozobax (Bacofen)
Dosage forms / Strength	Oral Solution/1 mg/mL
Proposed Indication(s)	(b) (4) spasticity resulting from1) multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, 2) (b) (4) spinal cord injuries and other spinal cord diseases.
Recommended:	*Complete Response*

1. Introduction

Metacel Pharmaceuticals, LLC submitted a 505(b)(2) NDA(208193) for Baclofen oral solution, 1 mg/mL (Ozobax). The initial development of baclofen oral solution was by the previous sponsor, CodaDOSE, Inc., under IND 112300. CodaDose transferred ownership of the product to Metacel Pharmaceuticals, LLC on December 31, 2014. (b) (4)

On 03/04/2016, FDA notified Metacel that the NDA was not fileable because the proposed indication expanded the population and it no longer met the conditions of FDA's orphan designation, The sponsor was also required to submit a user fee. However, FDA granted the sponsor's request for a Small Business waiver from the PDUFA application fee for baclofen. The sponsor was also informed that their NDA was not exempt from Pediatric Research Equity Act (PREA) requirements.

This 505 (b)(2) application for a new dosage form relies on the FDA's previous finding of safety and effectiveness for the reference listed drug (per the Orange Book), Baclofen 20 mg oral tablets, manufactured by Ivax Pharmaceuticals Inc., a subsidiary of Teva Pharmaceuticals USA (ANDA- A072235). This NDA for baclofen oral solution included the results of a single Bioavailability/Bioequivalence (BA/BE) study (024-BE-2013), conducted in male healthy subjects under fasting conditions comparing baclofen oral solution (1mg/mL) to baclofen tablets USP 20 mg (b) (4)

(b) (4)   There were no other clinical investigations
conducted by the applicant in support of this NDA.

The applicant's BA/BE study is intended to establish a bridge linking baclofen oral solution
and the reference product through bioequivalence. Review of the safety information from the
healthy subjects who participated in study 024-BE-2013, do not alter the conclusion regarding
the FDA's previous findings of safety for oral baclofen.

2. Background

The Ciba-Geigy NDA 017851 for Lioresal (baclofen) tablets was approved on 11/22/1977.
Novartis was created through the merger of Ciba-Geigy and Sandoz, in 1996. Novartis
requested withdrawal of their NDA on 10/14/2008 because marketing of Lioresal oral tablets
was "discontinued from marketing over five years ago".   (b) (4)

Current labeling for baclofen
oral tablets (Ivax/Teva) states, "Safety and effectiveness in pediatric patients below the age of
12 years have not been established."

The current full indication for baclofen tablets is as follows (Ivax/Teva Product Labeling):

> **INDICATIONS AND USAGE**
> Baclofen tablets USP are useful for the 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.
>
> Patients should have reversible spasticity so that baclofen treatment will aid in
> restoring residual function. Baclofen tablets USP may also be of some value in patients
> with spinal cord injuries and other spinal cord diseases.
>
> Baclofen tablets USP are not indicated in the treatment of skeletal muscle spasm
> resulting from rheumatic disorders.
>
> The efficacy of baclofen in stroke, cerebral palsy, and Parkinson's disease has not been
> established and, therefore, it is not recommended for these conditions.

The precise mechanism of action of baclofen is not fully known. Baclofen is capable of
inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by
hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur
and contribute to its clinical effect. Although baclofen is an analog of the putative inhibitory
neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that
actions on GABA systems are involved in the production of its clinical effects.

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.

Labeling was not discussed with the sponsor during this review cycle because deficiencies in Chemistry, Manufacturing and Controls (CMC) were found during the review of the application that precludes approval of this NDA. The sponsor is aware of the CMC deficiencies because they were the subject of multiple information requests from FDA's CMC/Office Product Quality (OPQ) Review team. The sponsor has submitted 8 separate CMC amendments in response to FDA CMC information requests since 5/20/2016.

Table 1: Reviews Referenced in this Review

DISCIPLINE	REVIEWER	FDA Office/Division
Clinical Pharmacology	Bei Yu, Ph.D	CDER/Office of Clinical Pharmacology
Clinical Review	Kenneth Bergmann, MD	CDER/OND I/DNP
CMC	See Table 2	See Table 2
Label And Labeling Review	Briana Rider, PharmD	CDER/OSE/OMEPRM/DMEPA
Pharmacovigilance Review	Anne C. Tobenkin, PharmD	CDER/OSE/Division of Pharmacovigilance I

Source: CDTL

3. CMC/Device

Table 2: Office of Product Quality Review (OPQ) Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION	Recommended Action
Drug Substance	Andrei Ponta	ONDP/DNDP1/Branch I	Approvable with minor corrections
Drug Product	Andrei Ponta	ONDP/DNDP1/Branch I	Complete Response
Process	Sung Kim	OPF/DPAIII/Branch VII	Complete Response
Microbiology	Elizabeth Bearr	OPF/DMA/Branch I	
Facility	Quallyna Porte	OPF/DIA/Branch II	
Biopharmaceutics	N/A		
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I	
Application Technical Lead	Martha Heimann	ONDP/DNDP1/Branch 1	Complete Response
Laboratory (OTR)	N/A		
ORA Lead	N/A		
Environmental Analysis (EA)	N/A		

Source: FDA Quality Review

The proposed product is an aqueous oral solution containing baclofen 1 mg/mL with glycerin, citric acid, sucralose, sodium citrate, methylparaben, propylparaben, and grape flavor as inactive ingredients.

Drug Substance

The primary drug substance reviewer was Andrei Ponta, Ph.D., and Wendy Wilson- Lee, Ph.D., provided the secondary drug substance review.

(b) (4)

Table 4: The Release Testing (CoA) Results from Three Drug Substance Batches

Test	Specifications	50057	50058	50059
Appearance	See above	Conforms	Conforms	Conforms
Identification (b) (4)	See above	Conforms	Conforms	Conforms

(b) (4)

Source: FDA Drug Substance Quality Review

Dr. Ponta and OPQ considered this to be a minor deficiency related to the drug substance specification and reporting of impurities that is easily correctable and it is not a reason for recommending a CR action. The deficiency will be included in comment in the CR letter to obtain the necessary information in the applicant's resubmission.

The Drug Substance Container Closure
The drug substance container closure system for DMF # (b) (4) was recently reviewed in September 2016 and it was found to be adequate.

Drug Substance Stability
The Applicant has set a (b) (4) retest date for the drug substance. This is consistent with the DMF holder's retest date, and it is acceptable.

Drug Product

The OPQ recommendation for a Complete Response action originated, in part, from the drug product quality review. The primary drug product reviewer was Andrei Ponta, Ph.D., and Wendy Wilson- Lee, Ph.D., provided the secondary drug product review.

Pharmaceutical Development

(b) (4)

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Reference ID: 4039293

(b) (4)

(b) (4)

Labeling Comments
- The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains ⬚ (b) (4) information which is not appropriate for the dosage form and strength section. Remove this information.
- The drug substance structure in the description section is blurry. Update the label with a clear structure.
- The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g. color). It also does not have information for in-use storage. Update the how supplied section with this information.

CDTL Comment:
I agree with OPQ's recommendation for a Complete Response action based on the numerous product quality deficiencies described in the OPQ review. The sponsor was made aware of several of the deficiencies in the 74 day letter. This gave the sponsor the earliest notification and the maximum amount of time to address the deficiencies during this review cycle. The complete lists of product quality deficiencies are located in the Comments to The Sponsor section of this review. The deficiencies require modification and of the commercial scale manufacturing process, controls, analytical procedures, or container closure system in order to address these deficiencies will require new stability studies. The needed modifications and testing could not be completed, submitted and reviewed within an extended review cycle.

3. Nonclinical Pharmacology/Toxicology

The applicant is relying on the nonclinical information in the oral baclofen tablet label and the FDA's finding of safety and effectiveness for oral baclofen. The sponsor did not submit new nonclinical study reports in support of this 505(b)(2) NDA.

4. Clinical Pharmacology/Biopharmaceutics

Study 024-BE-2013

The study design used was an open label, balanced, randomized, two-period, two-sequence, single dose cross-over study (Figure 3)comparing the bioavailability study under fasting conditions. The study was conducted in 36 healthy male subjects. Subjects received a single dose of baclofen oral solution 1 mg / mL (Metacel Pharmaceuticals, LLC) or Baclofen USP 20 mg tablets (TEVA pharmaceuticals, Lot number 7478023).

The protocol specified that the pharmacist measured the 1 mg/ ml of baclofen oral solution by using 5 ml syringes as per the randomization schedule (total dose is 20 ml of 1 mg/ ml baclofen oral solution) or dispense the 20 mg baclofen oral tablet.

Figure 3: Design of Study 024-BE-2013
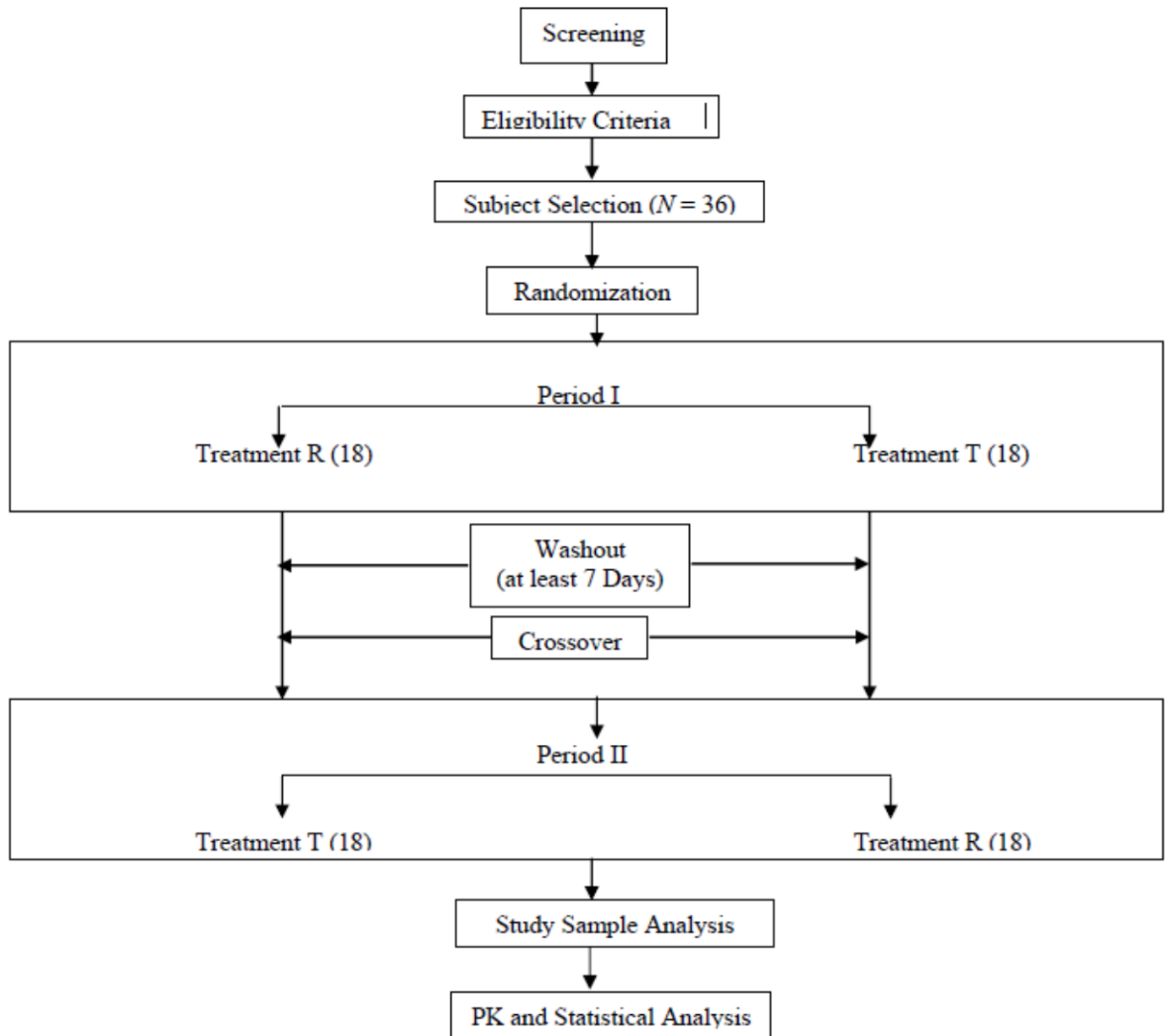
Source: CSR Study 024-BE-2013

Inclusion Criteria

- The study population included 36 healthy, adult, male subjects within the age range of 18 to 45 years (inclusive).

- Body-mass index of at least 18.5 kg/m2 and no more than 24.9 kg/m2, with body weight not less than 50 kg

- Normal 12 lead ECG, Chest X-Ray, and the absence of a clinically significant abnormal medical history, physical exam or clinical laboratory testing.

Exclusion Criteria

- Personal / family history of allergy or hypersensitivity to baclofen or related drugs

- Smokers, who smoke 10 or more than 10 cigarettes / day or inability to abstain from smoking during the study
- Past history of anaphylaxis or angioedema
- History of major illness in the past three months or any clinically significant ongoing chronic medical illness e.g., congestive heart failure, hepatitis, pancreatitis etc.
- Presence of any clinically significant abnormal values during screening e.g. significant abnormality of Liver Function Test (LFT), Renal (kidney) Function Test (RFT), etc.
- History of cardiac, renal or liver impairment, any other organ or system impairment
- History of seizure or psychiatric disorders or stroke
- Presence of disease markers of HIV 1 and 2, and hepatitis B and C virus.
- Consumption of alcohol for more than two years, or consumption of more than three alcoholic drinks per day or consumption of alcohol within 48 hours prior to dosing and during the study [one drink is equal to one unit of alcohol [one glass wine, half pint beer, and one measure (one ounce) of spirit]
- Consumption of xanthine containing derivatives (coffee, tea, cola drinks, chocolate) within 48 hours before check-in of each period
- History of any usage of recreational drug or a history of drug addiction
- History of participation in any clinical trial within the past 3 months
- Inaccessibility of veins in left and right arm
- History of donation of blood (one unit or 330 mL) within 3 months prior to study check-in
- History of use of any prescription drug therapy within two weeks or over-the-counter (OTC) drugs within two weeks prior to study check-in
- History of unusual diet, for whatever reason e.g. low sodium diet, for two weeks prior to study check-in
- History of consumption of grapefruit- containing food or beverages within 48 hours prior to the study check-in
- Recent history of dehydration from diarrhea, vomiting or any other reason within a period of 7 days prior to study check-in.

All medicines, including over the counter medicines, were prohibited for two weeks prior to the study and during the study.

Pharmacokinetic Parameters Assessed
Blood samples up to 24.00 hours post dose were collected to assess Baclofen concentrations in plasma.

Based on the time *vs* concentration plot, pharmacokinetic variables C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$,

$t_{1/2}$, K_{el} and AUC_%Extrap_Obs were derived

The pharmacokinetic parameters were calculated as follows:

PrimaryParameters:

C_{max}: Maximum measured plasma concentration following each 'treatment'.
AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.

$AUC_{0-\infty}$:   The area under the plasma concentration versus time curve, from zero to infinity. $AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant.

SecondaryParameters:

T_{max}: Time of maximum measured plasma concentration. If the maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period.
K_{el}:   Apparent first order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameters will be calculated by linear least square regression analysis using the last three (or more) non-zero plasma concentrations.
$t_{1/2}$:   Time required for the plasma drug concentration to decrease by one half.

AUC_%Extrap_Obs: The residual area in percentage was determined by the following
                formula $(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} * 100$.

Primary Pharmacokinetic Variable(s)
Maximum plasma drug concentration (Cmax), area under the plasma concentration curve versus time curve from time zero to the last measurable concentration (AUC0-t) and area under the plasma concentration versus time curve from time zero to infinity (AUC0-∞).

Sampling Schedule and Procedure:
Single venous blood sample was withdrawn at pre-dose (0.00), and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post-dose.

Pharmacokinetic Results
Bei Yu, Ph.D., was the primary clinical pharmacology reviewer and Sreedharan Sabarinath, Ph.D provided the secondary review for this application.

Mean plasma concentration versus time profiles of baclofen following administration of OZOBAX baclofen oral solution (1 mg/mL) and baclofen IR tablet at 20 mg under fasted conditions is shown below in Tables 12 and 13 and Figure 4.

Table 12: PK Comparison between treatments of Test and Reference baclofen at 20 mg under fasted conditions:

Pharmacokinetic Results of Baclofen :

PK Parameters	Baclofen Mean (± S.D.)	
	T	R
T_{max} (hr)*	0.75 (±0.7194)	1.00 (±0.5987)
C_{max} (ng/mL)	417.7061 (±103.32671)	389.2647 (±78.27936)
AUC_{0-t} (ng.hr/mL)	2138.0587 (±539.54505)	2227.4420 (±506.12497)
$AUC_{0-\infty}$ (ng.hr /mL)	2415.3036 (±585.53731)	2481.3817 (±539.20292)
$T_{1/2}$ (hr)	5.743 (±1.0622)	5.619 (±1.3026)
K_{el} (1/hr)	0.12462 (±0.022461)	0.12986 (±0.030276)
AUC_%Extrap_Obs	11.6335 (±2.59406)	10.4675 (±3.12781)

*: Median (± S.D.)

Source: OCP review

Table 13: PK Comparison of the PK Profiles of Baclofen Tablets and Oral Solution

Geometric Least Square Mean, Ratio of Geometric Least Square Mean and 90% Confidence Intervals for log-transformed data for Baclofen.

Parameters	Geometric Least Square Mean		T/R Ratio	90% C.I.
	Test (T)	Reference (R)		
C_{max} (ng/mL)	404.1131	381.4139	105.95	99.47 - 112.86
AUC_{0-t} (ng.hr/mL)	2075.8636	2173.2523	95.52	91.40 - 99.83
$AUC_{0-\infty}$ (ng.hr/mL)	2350.2470	2429.2929	96.75	92.87 - 100.78

Source: OCP review

Figure 4

Comparative Linear Plots of Baclofen mean plasma Concentrations versus Time in Healthy, Adult Male Subjects (*N=35*)
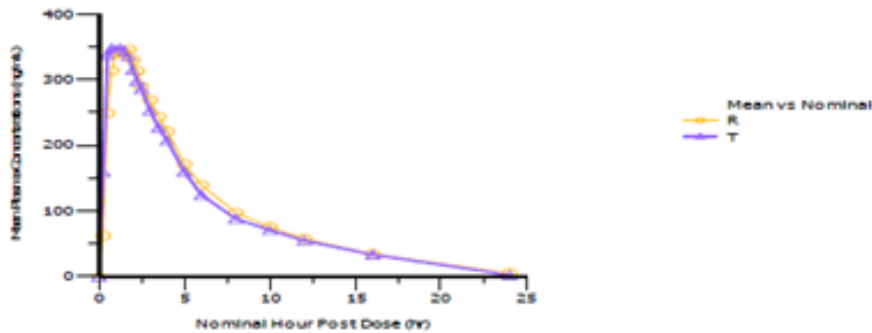
Source: OCP review

The study result indicated that PK profiles of baclofen are comparable between baclofen oral solution (1 mg/mL) and baclofen IR tablet at 20 mg with acceptance range of 90% CI for ratios of two treatments of geometric least squares means (Table 13) for Cmax and AUC falling into BE criteria, 80-125%. The absorption rates are comparable between two products: median Tmax of 0.75 hr. for baclofen oral solution vs., that of 1 hr. for baclofen IR tablet.

Baclofen IR tablets can be taken with or without food, and the label does not make any statements about the effect of food on absorption or administration. Food should not have an effect on baclofen PK for the baclofen oral solution.

Clinical Pharmacology Conclusion:
Reviewer's comments: PK profiles of baclofen are bioequivalent between treatments of the Test and Reference Baclofen product at a dose of 20 mg under fasted conditions.

Bioequivalence Testing Site Facilities Review/Inspection

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) submitted a memorandum (dated 6/24/2016) on 07/01/2016 containing their recommendations to accept the BE study data (from the centers listed in Table 11 without an on-site inspection. Their rationale for this decision was based on the fact that OSIS had recently inspected the sites listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Table 14: Clinical Pharmacology Study 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)

CDTL Conclusion:

I agree with the Office of Clinical Pharmacology Review team that the sponsor has demonstrated bioequivalence (BE) between oral baclofen solution 1 mg/mL and the referenced listed oral baclofen 20 mg tablet (Ivax/Teva). The finding of BE establishes an adequate bridge between the two products to support the sponsor's reliance on the FDA's finding of safety and effectiveness for oral baclofen tablets.

5. Clinical Microbiology

See the Chemistry, Manufacturing and Controls (CMC) section of this review.

6. Clinical/Statistical- Efficacy

The Sponsor is relying on the FDA's finding of effectiveness and a scientific bridge to the information for approved oral baclofen tablets. There were no clinical studies submitted in support of this 505(b)(2) application.

7. Safety

Dr. Kenneth Bergmann, MD completed the primary Clinical Review for this application. This reviewer provided the secondary review.

Thirty-six male subjects enrolled in the study and 35 subjects complete both periods of the crossover study. A single subject discontinued after the first treatment period.

Adverse Events

There were no deaths and no serious adverse events reported during the study. . One subject reported a single adverse event of headache that resolved spontaneously.

Clinical Laboratory

Dr. Bergmann found there were no significant clinical laboratory abnormalities at baseline and at the conclusion of the second dosing period. Dr. Ponta, was the primary drug substance and drug product quality reviewer. He expressed concern that a decline in hemoglobin (Hgb) or drop in hematocrit (Hct) may be due to a laxative effect caused by glycerin (Table 15). Although a few subjects experience a small, transient drop in hematocrit; diarrhea was not

reported as an adverse event buy any subject in the study. It does not appear that the transient decline in Hgb/Hct is related to a laxative effect caused by glycerin.

Table 15: End of study abnormal clinical laboratory results (source: compiled from the Clinical Study Report)

Subject No.	Adverse Event	End of Study Value	Normal Range	Treatment Sequence	Repeat	Baseline Screening
13	↓ Hgb	10.6 g/dL	13 - 18 g/dL	tab/sol	12.0 gm/dL	14.2 g/dL
13	↓ Hct	33.70%	40-54%	tab/sol	39.60%	45.40%
23	↓Hgb	10.3 g/dL	13 - 18 g/dL	sol/tab	11.8 gm/dl	12.1 g/dL
23	↓ Hct	33.20%	40-54%	sol/tab	38.10%	36.20%
33	↑ Lymphocytes	44.40%	20-40%	sol/tab	33.60%	37.50%
35	↑Alk Phos	135 U/L	30-120 U/L	tab/sol	104 U/L	106 U/L
35	↑ Total Bilirubin	1.3 mg/dL	0.3 - 1.2 mg/dL	tab/sol	1.3 mg/dL	0.9 mg/dL

Source: Dr. Bergmann's Review

There were no changes in ECG or clinically significant changes in vital signs recorded for any subject at baseline or at the conclusion of the study.

Postmarketing Pharmacovigilance Review
Anne C. Tobenkin, PharmD completed the primary Postmarketing Pharmacovigilance review and Corrinne Kulick, PharmD, completed the secondary review.

A review of FAERS identified four cases of neonatal withdrawal syndrome (NAS) that occurred 1-3 days after delivery from mothers treated with stable doses of oral baclofen. 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. No cases of NAS were reported in newborns of mothers treated with intrathecal baclofen therapy

DPV-I concluded that there is adequate evidence to warrant including NAS in a Boxed Warning that describes abrupt discontinuation and in the corresponding Warnings and Precautions section of the oral solution baclofen labeling.

No cases of NAS were reported in newborns of mothers treated with intrathecal baclofen therapy

CDTL Safety Conclusion:
There was no additional safety information was obtained from subjects enrolled in the bioequivalence study. However, the postmarketing information supports a relationship of baclofen withdrawal and neonatal seizures. I agree that information describing neonatal withdrawal seizures should be included in labeling. Whether this new safety information supports elevation of the existing information about withdrawal from Warnings to a Boxed Warning will be considered for Ozobax when the sponsor resubmits the application. The division will consider whether this information should be elevated to a boxed waning for all oral baclofen products in a separate discussion with members of the safety team and DPV.

8. Advisory Committee Meeting

Not applicable.

9. Pediatrics

The submission of the NDA for new form oral solution dose triggers the requirements for pediatric studies under the Pediatric Research Equity Act (PREA).

The sponsor reminded the FDA   (b) (4)
                                              the orphan drug designation for baclofen granted by the Office of Orphan Products Development on 12-16-1991 for the indication of "Treatment of intractable spasticity due to multiple sclerosis or spinal cord injury". Officially designated orphan drug products are exempt from the requirements of the Pediatric Research Equity Act 2007, therefore the requirement to assess pediatric effectiveness and safety does not apply."

In addition, pediatric plan in the NDA included a pediatric study plan requesting a full waiver for children younger than age 12 because "The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients." The formulation of baclofen oral solution is likely to be used in children with generalized spasticity.

The sponsor (Metacel) was informed that their NDA was not exempt from (PREA) requirements in the same letter notifying the sponsor that the expanded indication differs from the orphan designated indication.   (b) (4)

(b) (4)

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10. Other Relevant Regulatory Issues

Previous Orphan Designation

Metacel Pharmaceuticals, LLC submitted NDA 208193 for Baclofen oral solution, 1 mg/mL (Ozobax). The application is a 505(b)(2) NDA .Initial development of the baclofen oral solution was by the previous sponsor, CodaDOSE, Inc., under IND 112300. CodaDose transferred ownership pf the product to Metacel Pharmaceuticals, LLC on December 31, 2014. On December 16, 1991, the FDA granted orphan designation ⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛ for Baclofen ⬛⬛ (b) (4) solution for the treatment of intractable spasticity due to multiple sclerosis or spinal cord injury. (b) (4)

On 03/04/2016, FDA notified Metacel that the NDA was not files because their proposed indication expanded the population that no longer met the conditions of FDA's orphan designation as a result; the sponsor was required to submit a user fee. However, FDA granted the sponsor's request for a Small Business waiver from the PDUFA application fee for baclofen. The sponsor was also informed that their NDA was not exempt from Pediatric Research Equity Act (PREA) requirements.

Compliance with Good Clinical Practices

The sponsor and investigators performing the study attested the study was performed in compliance with Good Clinical Practices ICH E6, in conformance with Indian guidelines, and the Declaration of Helsinki.

Appropriate approval from the local Independent Ethics Committee was obtained for the original protocol and the two amendments. All participants gave written informed consent prior to participate in the study.

The sponsor audited the study and raw data for compliance to Standard Operating Procedures, Study Protocol, Good Clinical Practice (GCP) and principles on Good Laboratory Practice (GLP). They found "no significant deviations" that would affect the integrity of the study.

Debarment Certification

The individuals involved in conducting the trial were not on the FDA's Debarment List.

Financial Disclosures

The sponsor for the principal investigator submitted FDA Form 3454 for the certification of financial interests. There were no study personnel who had a disclosable financial relationship with the sponsor.

11. Labeling

On 12/19/2016, the Division notified the sponsor by letter that deficiencies in their NDA precluded labeling discussions.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

COMPLETE RESPONSE
Based on the deficiencies in CMC/product quality described in the OPQ review.

Recommended Comments to Applicant

PRODUCT QUALITY

The proposed manufacturing and control strategy for Ozobax (baclofen oral solution) is inadequate to assure the identity, purity, strength, and quality of the commercial drug product. The strategy lacks sufficient controls over all of the identified critical quality attributes, at release and over the product shelf life. Address the gaps in the control strategy outlined below. Note that any changes made to the product, manufacturing process used for registration batches, analytical procedures, or container closure system in order to address these deficiencies will require new stability studies.

(b) (4)

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(b) (4)

Labeling

12. The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, it also contains [(b) (4)] information which is not appropriate for the dosage form and strength section. Remove this information.

13. The drug substance structure in the description section is blurry. Update the label with a clear structure.

14. The how supplied section does not contain the dosage form, strength of the dosage form, or the identification of dosage form (e.g. color). It also does not have information for in-use storage. Update the how supplied section with this information.

CLINICAL REVIEW

Application Type	NDA, 505 (b)(2)
Application Number	208193
Priority or Standard	Standard
Submit Date	2016 January 9
Received Date	2016 January 11
PDUFA Goal Date	2017 January 11
Division / Office	CDER / OND / ODE1 / DNP
Reviewer Name	Kenneth Bergmann, MD
Review Completion Date	2016 Nov 22 (rev. 2017 Jan 3)
Established Name	Baclofen
(Proposed) Trade Name	Ozobax
Therapeutic Class	GABA B agonist (muscle relaxant and anti-spastic)
Applicant	Metacel Pharmaceuticals, LLC
Formulation	Oral solution, 1 mg/mL
Dosing Regimen	Titration to maximum oral dose of 20 mg QID
Indication(s)	Spasticity in Multiple Sclerosis
Intended Population	Adults and children 12 years of age or older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is a 505(b)(2) application for oral baclofen solution (Ozobax, 1mg/mL) for the treatment of spasticity based upon bioequivalence to the reference listed drug, baclofen, 20 mg oral tablet (ANDA 072235, IVAX, Teva).

A single bioequivalence study in 36 healthy volunteers is the basis for approval. It has been judged by Clinical Pharmacology review to be adequate. Clinical review of the study reveals no new, novel or unexpected treatment events.

However, the quality assessment performed by the Division of New Drug Products, Office of Pharmaceutical Quality, has determined ⁽ᵇ⁾ ⁽⁴⁾ among other deficiencies. These have not been resolved by the PDUFA goal date, and therefore this application is **unapprovable**.

1.2 Risk Benefit Assessment

Baclofen was initially approved in 1977 and the risk and benefits for use are well established. This oral solution formulation would allow its use where tablets may not be easily administered, i.e.: young children and adults with dysphagia or altered mental state that require a feeding tube. Occurrences of a neonatal withdrawal syndrome have been identified by recent pharmacovigilance review by the Office of Surveillance and Epidemiology. Oral solution of baclofen could potentially be used (after appropriate study) to treat this serious reaction in the newborns of mothers on oral baclofen therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

The IND for this product received orphan designation for the treatment of intractable spasticity. That indication was not studied and so the orphan designation is lost. This makes the application subject to the requirements of the Pediatric Research Equity Act of 2007. ⁽ᵇ⁾ ⁽⁴⁾

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2 Introduction and Regulatory Background

2.1 Product Information

Baclofen, a racemic mixture of 4-amino-3-(4-chlorophenyl)-butanoic acid, is a GABA-B receptor agonist. Initially approved as Lioresal (Novartis) in 1977, it is indicated for the oral treatment of spasticity due to multiple sclerosis and spinal cord injury. The original proprietary product was taken off the market for commercial reasons unrelated to safety or efficacy. The current reference listed drug (RLD) is the IVAX Baclofen 20 mg tablet (ANDA 0722335, Teva Pharmaceuticals).

Only Lioresal Intrathecal (baclofen for intrathecal injection, NDA 20075) is labeled for use in children with data down to age 8. Oral baclofen carries no such labeling.

2.2 Currently Available Treatments for Proposed Indications

Five drugs are approved in the US for the treatment of spasticity: baclofen, dantrolene, tizanidine, botulinum toxin products (Botox and Xeomin) and diazepam. These act in pharmacologically different mechanisms though alteration of GABA neurotransmitter physiology is common to all but botulinum toxins. The toxins act at the peripheral neuromuscular junction.

Several other products related to those above or with a pharmacological action related to the pathophysiology of spasticity are used in off-label fashion. These include other benzodiazepines such as clonazepam, and anticonvulsants that also act via GABAergic mechanisms (e.g.: gabapentin).

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance is manufactured by   (b) (4)   (DMF #
         (b) (4)

2.4 Important Safety Issues With Consideration to Related Drugs

Baclofen has been authorized for commercial use since 1977 (Lioresal, NDA 17851, Novartis) and is a well-studied moiety. While Lioresal tablets are no longer marketed for commercial reasons, baclofen is still commercially available in generic form.

Labeled concerns include withdrawal with hallucinations or seizures and therefore must be tapered following chronic use. Because baclofen is primarily excreted unchanged by the kidneys, dosage must be adjusted in patients with impairment of renal function. Deterioration of seizure control has been seen in patients who have seizures and are treated with baclofen.

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(b) (4)

Neonatal Withdrawal Syndrome

During this review cycle, the Division of Pharmacovigilance, Office of Surveillance and Epidemiology, documented the occurrence of a neonatal withdrawal syndrome analogous to that seen in adults following abrupt discontinuation of baclofen. (Lioresal Intrathecal carries a boxed warning for a withdrawal syndrome following abrupt cessation of treatment. The oral products do not have this warning boxed in the label.) Their review assessed the findings from 23 NDA and ANDA products containing baclofen:

> *Our review of FAERS identified four cases of NAS* [neonatal abstinence syndrome] *(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…*

> *… 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.*

Product label recommendations suggested in the DPV OSE review are included in **Appendix 9.2** of this review. These suggestions will impact the labeling for the safe use of all oral baclofen products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 112300
<u>PreIND Meeting (September 2, 2011)</u>

codaDOSE, Inc. was granted a pre-IND meeting in order to obtain advice about developing oral baclofen solution   (b) (4)
for submission as a 505(b)(2) application based upon the demonstration of safety and effectiveness in NDA 17851 Lioresal (baclofen) Tablets   (b) (4)

As recorded in the meeting minutes, the Division advised the sponsor   (b) (4)

                                              In addition, the sponsor was advised:
                                                                                              (b) (4)
"Your proposed indication
                                        must be supported by data from your clinical trials
                                                                                              (b) (4)
program.

"You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified."

"If you choose to rely on FDA's finding of safety and/or effectiveness for a discontinued listed drug(s), you may use a bioequivalent ANDA product as the comparator in a comparative clinical trial to establish a bridge between your proposed drug product and the specified listed drug(s).

In meeting discussion *"the Division clarified that, if the sponsor proposes to rely on the Division's finding of safety and efficacy for the baclofen tablet (Lioresal) NDA, their product could be labeled down to age 12…*   (b) (4)
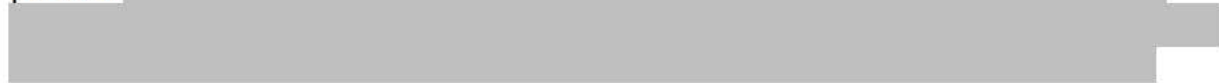
(b) (4)

IND Application (January 11, 2013)

The sponsor submitted an initial IND application on January 11, 2013. The purpose of this submission was to provide CMC data for both the drug substance and the drug product (b) (4)

A letter from the sponsor on January 30, 2013, indicated that the sponsor now intended to pursue an indication in the same population as the Reference Listed Drug, i.e.: patients 12 years and older. The sponsor still misunderstood that they were required to perform in-vivo bioavailability studies for the oral solution.

In correspondence to the Division dated November 12, 2013, the sponsor submitted Protocol No.: 024-BE-2012, an open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study of baclofen oral Solution 1mg/mL with baclofen tablets 20mg (TEVA ANDA 072235) in healthy, adult, human subjects, under fasting conditions to be performed in India.

The sponsor indicated that Metacel Pharmaceuticals would be their development partner in this endeavor and responsible for commercialization.

(b) (4)

The IND was allowed to proceed with the comment to the sponsor that the protocol did not adequately define the study population. The sponsor was reminded that in vivo bioequivalence studies should be conducted in individuals who represent the range of patients who are likely to use their product, taking into account factors such as age, sex, and race.

NDA 208193
No pre-NDA meeting was requested for this submission.

2.6 Other Relevant Background Information

On December 31st, 2014, codaDOSE, Inc., the original sponsor, filed a Transfer in Ownership to Metacel Pharmaceuticals, LLC for IND 112300.

The sponsor obtained ⬛⬛⬛⬛ (b) (4) the rights to the orphan drug designation for baclofen granted by the Office of Orphan Products Development on Dec 16th, 1991 for the indication of "treatment of intractable spasticity due to multiple sclerosis or spinal cord injury." Officially designated orphan drug products are exempt from the requirements of the Pediatric Research Equity Act of 2007. However, following advice from the Office of Orphan Products Development, the designation does not apply as the indication for this product has changed with dropping of the word "intractable". As such, PREA requirements do apply and the sponsor was notified of this. (b) (4)

The proprietary name for baclofen oral solution in this submission, Ozobax has passed preliminary review by the Division of Medication Error Prevention and Analysis (DMEPA, OSE) and is conditionally acceptable.

Metacel Pharmaceuticals was granted a waiver for the application user fee (Waiver Request 2014.068) under the small business waiver provision, section 736(d)(I)(D)2 of the Federal Food, Drug, and Cosmetic Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This reviewer defers to the Clinical Pharmacology reviewer as to whether bioequivalence findings adequately support this submission. With regard to the integrity

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of the study, the clinical site for this BE study, Piramal Clinical Research in Hyderabad, India, has been recently inspected by the Office of Study Integrity and Surveillance for another application. No action was recommended as a result of that inspection and the Division of New Drug Bioequivalence Evaluation, OSIS declined to re-inspect with the recommendation to accept the data.

The sponsor audited the study and raw data for compliance to Standard Operating Procedures, Study Protocol, Good Clinical Practice (GCP) and principles on Good Laboratory Practice (GLP). They found "no significant deviations" that would affect the integrity of the study.

Reviewer's Comment:
This crossover study with 35 participants required two days of multiple plasma samples taken 7 days apart via indwelling catheter. The study was completed in 10 days suggesting remarkable efficiency. For this reason, the blood drawing logs and the electrocardiograms in the case report forms for each participant were assessed by this reviewer.

The first and second phase of the study lasted 3 days each and the 36 participants were distributed accordingly. Each participant had a day log of printed scheduled times for blood draws following dose administration. Starting times for each participant were staggered and this left enough time for appropriately sequenced samples of plasma. The initials of the phlebotomist on the CRF marking each sample drawn reveal that there were sufficient different personnel to accomplish the draws. Finally, the electrocardiograms for each participant had the heart rate and the P, QRS, and T axes calculated automatically and printed on the electrocardiogram machine output. There were no duplicates of these measures. Taken together these suggest that the data represent individual participants in this study with plasma sampled as described in the study protocol.

3.2 Compliance with Good Clinical Practices

The sponsor and investigators performing the study assert the study was performed in compliance with Good Clinical Practices ICH E6, in conformance with Indian guidelines, and the Declaration of Helsinki.

Appropriate approval from the local Independent Ethics Committee was obtained for the original protocol and the two amendments. All participants gave written informed consent prior to participate in the study.

The study was performed by appropriately trained and certified individuals that were not on the Debarment List.

3.3 Financial Disclosures

FDA Form 3454 for the certification of financial interests was submitted by the sponsor for the principal investigator. No financial arrangements were disclosed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Baclofen is an almost odorless white crystalline powder. The drug substance is manufactured for Metacel by ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) (DMF # (b) (4)), ⬛⬛⬛⬛⬛ (b) (4)

The manufacturing, processing, packaging, and labeling of the drug product (Baclofen Oral Solution, 1 mg/mL) will be performed ⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛ (b) (4)

Table 1 Drug product composition (source: Overall Quality Summary, page 1)

Ingredient	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)
Baclofen	USP	API	(b) (4)	1.0
Glycerin	USP			
Citric Acid, Anhydrous	USP			
Sodium Citrate, Dihydrate	USP			
Sucralose	NF			
Methylparaben	NF			
Propylparaben	NF			
Grape Flavor	MFR			
Purified Water	USP			

(b) (4)

When calculated for the maximum labeled daily dose of the RLD (baclofen 80 mg/d), the excipients do not exceed maximum allowable levels for inactive ingredients in the FDA database.

According to the quality assessment performed by the Office of Product Quality, (b) (4)

The applicant was asked to perform a root cause analysis of this (b) (4)

It was also noted by OPQ that there was inadequate validation of the sponsor's analytical procedures used for product release and stability testing. In addition, a robust, well-defined, manufacturing process suitable for commercial production was lacking in this application.

*Reviewer's comment: These issues were the source of interaction between OPQ and the sponsor throughout the review period as well as the focus of a Discipline Review Letter prior to the action date.   It is apparent that these issues are unable to be resolved during this review cycle and therefore **the application is unapprovable and subject to a complete response**.*

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable in this 505(b)(2) application.

4.4 Clinical Pharmacology

4.4.1   Mechanism of Action

Baclofen is a well-established GABA-B agonist, capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect.

In studies with animals, baclofen has been shown to have general depressant properties in the central nervous system as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

4.4.2   Pharmacodynamics

Pharmacodynamics data were not submitted in this application.

4.4.3   Pharmacokinetics

This section of my review relies upon the expertise of the primary review discipline for this application, Clinical Pharmacology, and reiterates their opinion. The bioequivalence of the proposed product to the RLD is the primary basis for approval of this application and the preliminary perspective from the primary Clinical Pharmacology reviewer is that the BE study is acceptable.

Oral baclofen is rapidly and extensively absorbed and eliminated, mostly excreted unchanged in the urine (70 to 80%) and feces. About 15% of a dose is metabolized, primarily by deamination. The peak plasma concentration is reached about 1½ hours after oral administration. The elimination half-life of an oral dose of baclofen is approximately 5½ hours. Excretion is complete within 72 hours after administration.

Peak plasma concentrations of baclofen occurred in about 0.75 hour following baclofen oral solution (Ozobax, 1 mg/mL) administration at 20 mg in fasted subjects compared to 1 hour for the RLD tablets.

Table 2 Summary of pharmacokinetic findings (source: Clinical Study Report, page 63)

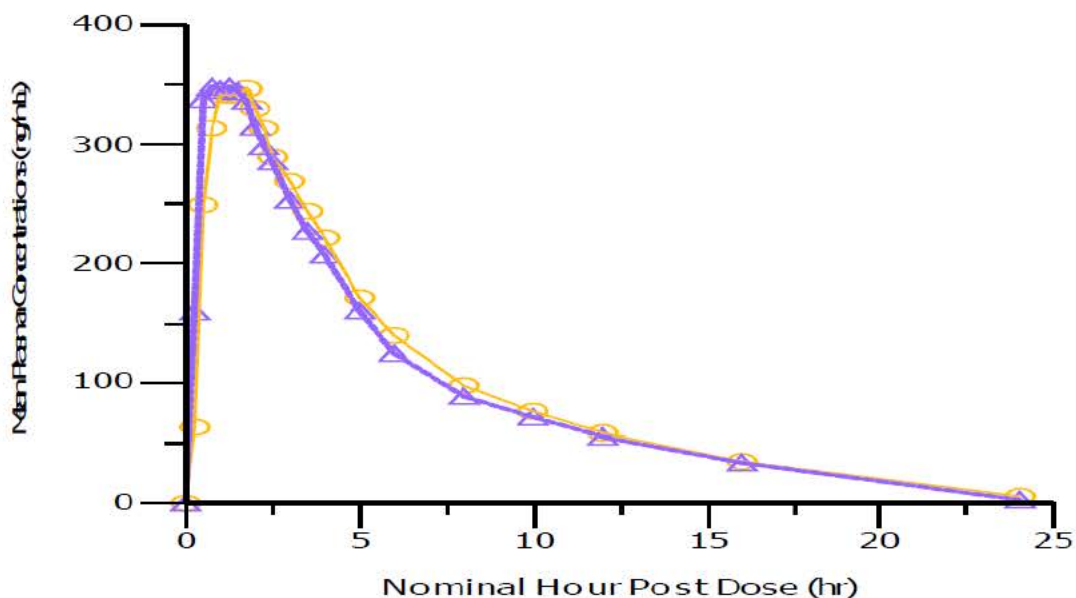| Parameter	Mean Parameters ($\pm$ SD)	
	Baclofen	
	Test	Reference
C_{max} (ng/mL)	417.7061 ($\pm$103.32671)	389.2647 ($\pm$78.27936)
T_{max} (hr)*	0.75 ($\pm$0.7194)	1.00 ($\pm$0.5987)
AUC_{0-t} (ng.hr/mL)	2138.0587 ($\pm$539.54505)	2227.4420 ($\pm$506.12497)
$AUC_{0-\infty}$ (ng.hr/mL)	2415.3036 ($\pm$585.53731)	2481.3817 ($\pm$539.20292)
$t_{½}$ (hr)	5.743 ($\pm$1.0622)	5.619 ($\pm$1.3026)
k_{el} (hr^{-1})	0.12462 ($\pm$0.022461)	0.12986 ($\pm$0.030276)
AUC_%Extrap_obs	11.6335 ($\pm$2.59406)	10.4675 ($\pm$3.12781)

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Figure 1 Plot of concentration vs. time: 20 mg Ozobax oral solution (purple) vs. baclofen 20 mg tablet (yellow) (source: Clinical Study Report, page 82)

The approved label for baclofen tablets does not include statements concerning the effect of food on the absorption of baclofen and baclofen may be administered without regard for food intake.

Product label recommendations suggested in the Clinical Pharmacology review are included in Appendix 9.2 of this review.

5 Sources of Clinical Data

No efficacy or safety trials were performed in support of this application which constitutes a change in dosage form from baclofen tablet to baclofen oral solution. In this regard only one bioequivalence study, a single dose cross-over design performed in 36 healthy adult volunteers, is submitted:

Protocol 024-BE-2013, Version 01, May 16, 2013:
"An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study of Baclofen Oral solution 1 mg/mL of Metacel Pharmaceuticals, LLC 282 Skyland Drive, Roswell, GA 30075 comparing with Baclofen tablets USP 20 mg Manufactured (b) (4)

in healthy, adult, human subjects, under fasting conditions"

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The adequacy of this study to support bioequivalence is evaluated by the Clinical Pharmacology review discipline.   This clinical review focuses upon the safety of the solution as represented in this small study.

Section 6 Review of Efficacy is deleted from this review. No pharmacodynamic results were submitted in this application.

7 Review of Safety

Safety Summary

No new, novel, or previously unknown adverse drug effects of baclofen were identified in this single dose cross-over study of oral baclofen 20 mg solution or tablet.

7.1 Methods

7.1.1   Study No. 024-BE-2013

Objective
- To assess bioequivalence by comparing the single oral dose bioavailability of baclofen oral solution 1 mg/mL with the reference product baclofen 20 mg tablets (IVAX Teva) in 36 healthy adult volunteers under fasting conditions.
- To monitor the safety and tolerability of single dose of baclofen oral solution 1 mg/mL

Design
The clinical phase of the study was carried out at the clinical facility of Piramal Clinical Research. Subjects were admitted and housed in the clinical facility for at least 11 hours prior to administration of the investigational drug product until 24 hours post dose in each study period. In each period, subjects were discharged after 24 hours post dose provided they were not suffering from any adverse events. In case of any adverse events, the subjects were to be followed up until resolution of the adverse events.

Figure 2 Study design (source: study protocol, page 30)
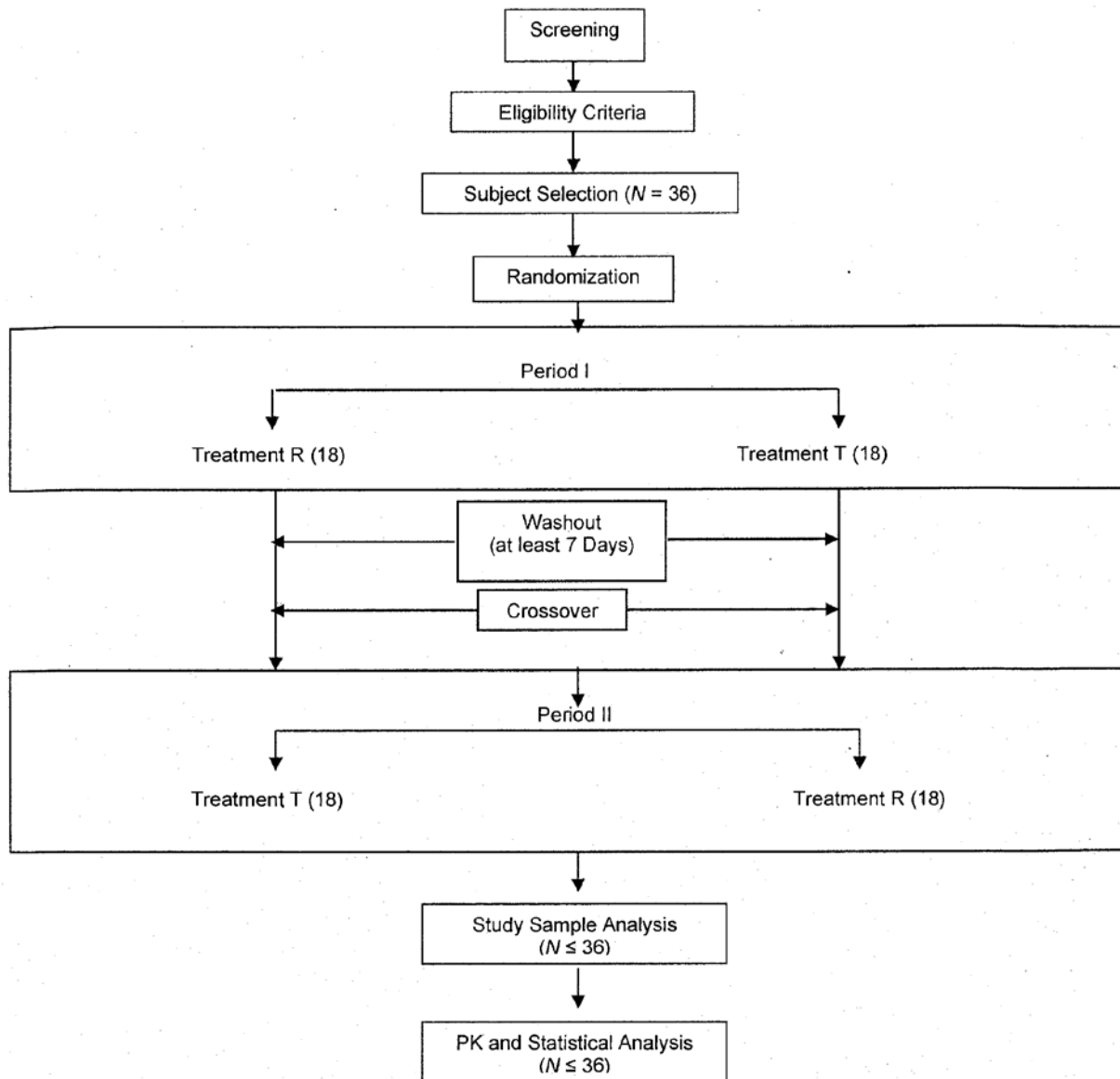
N - Number of subjects R - Reference Product T - Test Product PK - Pharmacokinetic

After written informed consent was obtained, screening was performed as indicated in the schedule of events below. The schedule also indicates the timing of clinical laboratory assessments.

Table 3 Study schedule of events (source: study protocol)

S. No.	Requirement	Screening	Period I Check-in	Period I Investigational products administration day	Period I Check-out	Period II Check-in	Period II Investigational products administration day	Period II Check-out
1.	Written informed consent	*	*					
2.	Demographics	*						
3.	Medical and treatment history	*						
4.	Medical Examination (General and systemic)	*	*			*		**
5.	Vital signs (BP, Pulse, Body Temperature, Respiratory)	*	*	*	*	*	*	**
6.	Clinical laboratory tests — Haemogram: Hemoglobin, RBC count, PCV, total WBC count, differential leucocyte count and platelet count	*						**
	Biochemistry: Blood glucose (random), serum phosphorous, serum calcium and total cholesterol), Hepatic profile (Liver Enzymes (GGT, ALT, AST, Alkaline Phosphatase) and Bilirubin (total and direct), Renal profile (serum creatinine, sodium, potassium, chloride, and blood urea nitrogen)	*						**
	12 lead ECG	*						**
	Chest X-ray PA view (if not taken within 6 months)	*						
	Urine (physical examination (Colour, Appearance, Specific gravity, Deposits and PH) chemical (Protein, Glucose, Nitrites, Blood, Ketones, Urobilinogen and Bilirubin) examination, and microscopic examination (if any abnormality in URINE BIOCHEMICAL EXAMINATION)	*						
	Urine Drugs of abuse (Opiates, Benzodiazepines, Tetra Hydro Cannabinoids (THC), Barbiturates, Cocaine and Amphetamines)		*			*		
	Infectious diseases (HIV 1 and 2, HBsAg, HCV)	*						
	Urine pregnancy test (β-hCG) (for female volunteers)	*	*			*		
	Breath Alcohol Test		*			*		
7.	Investigational Product administration			*			*	
8.	Blood sampling			*			*	

Inclusion Criteria
− Healthy subjects within the age range of 18 to 45 years inclusive.
− Willingness to provide written informed consent to participate in the study

- Body-mass index between 18.5 and 24.9 kg/m^2, with body weight ≥ 50 kg
- Absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluations, medical history or physical examination during the screening
- Normal 12-lead ECG or one with abnormality considered to be clinically insignificant
- Normal chest X-ray PA view
- Comprehension of and compliance with the requirements of the protocol
- Women use acceptable birth control, are post-menopausal or surgically sterile

Exclusion Criteria
- Tobacco use
- Major illness or ongoing chronic illness including hepatitis or HIV
- Abnormality of screening laboratory test
- Seizure or psychiatric disorder
- Excessive alcohol use
- Use of coffee, tea, cola drinks, or chocolate within 48 hours of check-in of each period
- Blood donation within 3 months of participation
- Any prescription or over the counter drug use within two weeks of check-in
- Grapefruit within 48 hours of check-in
- Failed screening for drugs of abuse

Test Dose Administration
Volunteers were given a standard dinner the night before and fasted for at least 10 h overnight. After dosing, the participant was fed at 4, 8 and 13 hours post dose. Drinking water was restricted for one hour before and one hour after test dose administration except 240 ml of water given at the time of administration of the test dose. Subjects were dosed while in sitting position and were instructed to remain seated in the upright position for first two hours following the Investigational Product administration. Following this, the volunteers were allowed to engage in normal activities.

Dose
Volunteers were randomized to a sequence of a single open label oral dose of baclofen 20 mg tablet or 20 ml of baclofen 1 mg/mL oral solution, both administered with 240 ml of water. After a minimum of 7 days, the participant was given the other dose.

Blood Sample Schedule
Besides screening laboratory tests, a total of 21 venous blood samples of 5 ml each were collected by indwelling catheter at the following times: pre-dose (0 h), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose. For each subject, the total volume of blood withdrawn was not to exceed 256 ml including screening laboratory.

<u>Study Timeline and Amendments</u>
     Screening: May 7, 2014 to May 20, 2014
     Period I: May 21, 2014 to May 23, 2014
     Period II: May 28, 2014 to May 30, 2014
     First subject enrolled May 21, 2014
     Last subject completed   May 30, 2014

Two amendments to the protocol were made on December 6, 2013 and May 16, 2014 prior to the beginning of the study. They were administrative in nature and not related to design.

<u>Protocol Deviations</u>
There were 15 deviations (out of 1491 samples) from the timeline for blood drawing following administration of the test dose. These are listed in the study report. I defer to the judgment of the Clinical Pharmacology reviewer as to whether these significantly affect the outcome of the study.

7.1.2   Categorization of Adverse Events

During the course of the study, participants were monitored for any adverse event, which was recorded in the appropriate case report forms and evaluated for appropriate treatment. AEs were actively inquired about. All noxious and unintended responses to the test products were considered Adverse Drug Reactions (ADR). The sponsor had in place a Standard Operating Procedure document (CR-CV-13) for the monitoring and reporting of adverse events during the course of the study. The SOP covered categorization of the adverse events and the procedure for notification of higher authorities including the sponsor's medical monitor, the IEC and appropriate regulatory authorities.

A Medical Officer was to be available round the clock during the time of housing at the clinical facility of Piramal Clinical Research. All adverse events were evaluated for duration, severity, action taken, date and time of resolution and association with the study treatment.

7.2 Adequacy of Safety Assessments

7.2.1   Overall Exposure and Demographics of Target Populations

Of the 36 participants enrolled in the study, all 36 had the first randomized treatment dose but one subject (no.17) did not return for the second treatment dose. As a result there were 71 doses of baclofen 20 mg administered; the dropout received only the test product (baclofen oral solution) and not the reference tablet.

The participants in this study were 36 healthy adult volunteers. All were Asian males, non-vegetarians, age range 19 to 41 years, 141 to 200 pounds, without significant medical history.
 Tables: CSR, p 77 Summary of demographic data.

Table 4 Demographic summary (source: Clinical Study Report, page 77)

Criteria	Minimum	Maximum	Mean ± S.D.
Age (years)	19	41	28.22 ± 5.91
Height (meter)	1.52	1.76	1.67 ± 0.06
Weight (kg)	52.60	74.80	62.76 ± 6.14
BMI (kg/m^2)	18.68	24.84	22.49 ±2.04

(*N*=36)

At screening, no one had any clinically significant abnormality detected during the general medical examination, electrocardiogram, or chest x-ray.

At the conclusion of the study after the second dose, the patient was examined for adverse events and vital signs were taken. An electrocardiogram and clinical laboratories were performed. Laboratory tests included hematological and biochemistry parameters (discussed below in Section 7.4.2).

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported.

7.3.3 Dropouts and/or Discontinuations

One patient (no. 17) dropped out by not returning to the second dosing session.

7.3.4 Significant Adverse Events

No significant adverse events were reported.

7.3.5 Submission Specific Primary Safety Concerns

There are no submission specific safety concerns.

7.4 Supportive Safety Results

7.4.1   Common Adverse Events

One AE was reported for a single participant (no. 36) during the study. He developed a headache during the first dosing period approximately 4.75 h after receiving the test dose (baclofen oral solution). It resolved, unmedicated, after an hour. It was deemed "mild" and possibly related by the investigator.

7.4.2   Laboratory Findings

Clinical laboratory samples performed at screening and again at the conclusion of the study consisted of hematology and biochemistry.

Hematology: hemoglobin, red blood cell count, hematocrit, total white blood cell count, differential leucocyte count and platelet count.

Biochemistry: Blood glucose (random), serum phosphorous, serum calcium and total cholesterol, hepatic function tests (ALT, AST, GGT, alkaline phosphatase, total and direct bilirubin) and renal function tests: (serum creatinine, sodium, potassium, chloride, and blood urea nitrogen)

A baseline screening some clinical laboratory parameters fell "outside the normal range." It appears that this was mostly were due to insufficient sample for measurement and none were considered to be of concern. All hepatic function tests were in the normal range for all subjects at screening.

Table 5 Baseline clinical laboratory (source: Clinical Study Report, Table 14.1.4 page 79)

	Laboratory Parameters	Within Normal Range	Outside Normal Range	
			(Clinically Not Significant)	(Clinically Significant)
Complete Blood Count	RBC Count	33	03	00
	Haemoglobin	26	10	00
	PCV / HCT	28	08	00
	WBC Count	36	00	00
	Neutrophils	36	00	00
	Eosinophils	30	06	00
	Lymphocytes	32	04	00
	Monocytes	32	04	00
	Basophils	36	00	00
	Platelets	36	00	00

	Laboratory Parameters	Within Normal Range	Outside Normal Range	
			(Clinically Not Significant)	(Clinically Significant)
Biochemistry	Random Glucose	35	01	00
	Serum Sodium	35	01	00
	Serum Potassium	36	00	00
	Serum Chlorides	35	01	00
	Serum Calcium	36	00	00
	Serum Creatinine	32	04	00
	Serum Phosphorus	35	01	00
	BUN	31	05	00
	Total Bilirubin	36	00	00
	Direct Bilirubin	36	00	00

At the conclusion of the study the following tests fell "outside the normal range" as well. Again, most of these were due to insufficient quantity of sample for measurement.

Table 6 Final clinical laboratory results (source: Clinical Study Report, page 80)

	Laboratory Parameters	Within Normal Range	Outside Normal Range		Repeat Safety Assessment
			Clinically Not Significant	Clinically Significant	
Complete Blood Count	RBC Count	33	03	00	00
	Haemoglobin	20	16	00	00
	PCV / HCT	26	10	00	00
	WBC Count	36	00	00	00
	Neutrophils	36	00	00	00
	Eosinophils	31	05	00	00
	Lymphocytes	32	04	00	00
	Monocytes	35	01	00	00
	Basophils	36	00	00	00
	Platelets	36	00	00	00
	Laboratory Parameters	Within Normal Range	(Clinically Not Significant)	(Clinically Significant)	Repeat Safety Assessment
Biochemistry	Random Glucose	36	00	00	00
	Serum Sodium	35	01	00	00
	Serum Potassium	35	01	00	00
	Serum Chlorides	35	01	00	00
	Serum Calcium	34	02	00	00
	Serum Creatinine	30	06	00	00
	BUN	22	14	00	00
	Serum Phosphorus	35	01	00	00
	Total Bilirubin	35	01	00	00
	Direct Bilirubin	36	00	00	00
	Laboratory Parameters	Within Normal Range	(Clinically Not Significant)	(Clinically Significant)	Repeat Safety Assessment
Hepatic Profile	Alkaline Phosphatase	36	00	00	00
	GGT	35	01	00	00
	AST	36	00	00	00
	ALT	36	00	00	00

At repeat assessment all were in the normal range or had returned to the normal range but in 5 cases, the end-of-study laboratory value was considered to be valid and abnormal:

Table 7 End of study abnormal clinical laboratory results (source: compiled from the Clinical Study Report)

Subject No.	Adverse Event	End of Study Value	Normal Range	Treatment Sequence	Repeat	Baseline Screening
13	↓ Hgb	10.6 g/dL	13 - 18 g/dL	tab/sol	12.0 gm/dL	14.2 g/dL

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13	↓ Hct	33.70%	40-54%	tab/sol	39.60%	45.40%
23	↓Hgb	10.3 g/dL	13 - 18 g/dL	sol/tab	11.8 gm/dl	12.1 g/dL
23	↓ Hct	33.20%	40-54%	sol/tab	38.10%	36.20%
33	↑ Lymphocytes	44.40%	20-40%	sol/tab	33.60%	37.50%
35	↑Alk Phos	135 U/L	30-120 U/L	tab/sol	104 U/L	106 U/L
35	↑ Total Bilirubin	1.3 mg/dL	0.3 - 1.2 mg/dL	tab/sol	1.3 mg/dL	0.9 mg/dL

On repeat sampling (which was drawn several months) after the end of the study, the lab values had returned to normal or were moving in that direction. It is difficult to establish causality or even clinical significance of the findings.

The package insert for the RLD product that is referenced by this application reports the following: "The following laboratory tests have been found to be abnormal in a few patients receiving baclofen: increased SGOT, elevated alkaline phosphatase, and elevation of blood sugar."

7.4.3   Vital Signs

No clinically significant changes in vital signs (blood pressure, pulse) were noted during the infusions or at the end of the study compared to baseline.

7.4.4   Electrocardiograms (ECGs)

No changes in electrocardiograms were noted at the end of the study compared to baseline.

7.5 Other Safety Explorations

No other safety explorations were performed in this study.

8 Postmarket Experience

Ozobax oral baclofen solution is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

Because this application is unapprovable, final label recommendations were not agreed upon with the Sponsor.

The Clinical Pharmacology reviewer has recommended the following addition to the label for this product:

> In a crossover study in healthy male subjects, baclofen oral solution was shown to be bioequivalent to baclofen immediate release tablets at 20 mg dose level under fasted conditions. The peak plasma concentration of baclofen was reached in about 0.75 hour following the administration of 20 mg baclofen oral solution (OZOBAX®, 1 mg/mL) in this study.

In light of the pharmacovigilance review from the Office of Surveillance and Epidemiology documenting the occurrence of a neonatal withdrawal syndrome analogous to that seen in adults, future label recommendations will consider inclusion of this phenomenon. Current oral baclofen labels carry a warning against abrupt discontinuation of baclofen in adults. The warning is given a black box in the Lioresal Intrathecal label.

The Division of Pharmacovigilance, OSE, has made the following recommendations for this products label (and all baclofen product labels):

> **Boxed Warning**
> Baclofen use during pregnancy can result in neonatal withdrawal syndrome, which may have severe outcomes if not recognized and treated, and requires management according to protocols developed by neonatology experts. If baclofen use is required during pregnancy, advise the patient of the risk of neonatal withdrawal syndrome and ensure the appropriate treatment will be available.
>
> **8   Use in Specific Populations**
>
> **8.1   Pregnancy**
>
> Risk Summary

(b) (4)

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of baclofen during pregnancy can result in neonatal withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal withdrawal syndrome, such as poor feeding, diarrhea, irritability, hypertonicity, and seizures, and manage accordingly.

Human Data

Remove the proposed statements [redacted] (b) (4)

Patient Counseling Information

Neonatal Withdrawal Syndrome

Inform female patients of reproductive potential that use of baclofen during pregnancy can result in neonatal withdrawal syndrome, which can be serious if not recognized and treated.

9.3 Advisory Committee Meeting

This application is for an approved non-NME drug substance in a new dosage formulation for the same indication as the RLD. Advisory Committee opinion was not sought for this application.

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Reference ID: 4036320