CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA#	208193
Date of submission:	1/9/16 & 3/11/16
Brand Name:	OZOBAX®
Generic Name:	Baclofen
Administration Route:	Oral
Strength and Formulation:	Solution, 1 mg/mL
Sponsor:	Metacel Pharmaceuticals, LLC.
Indication:	Treatment of intractable spasticity due to multiple sclerosis or spinal cord injury
Submission Type:	505(b)(2) Standard Review
Primary Reviewer :	Bei Yu, Ph.D.
Team Leader:	Sreedharan Sabarinath, Ph.D.

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1. EXECUTIVE SUMMARY

The sponsor is seeking approval for OZOBAX® baclofen oral solution (1 mg/mL) under 505(b)(2) pathway. The NDA relies on 1) the FDA's previous finding of safety and effectiveness for the reference listed drug Lioresal® (Baclofen) tablets via cross reference to NDA 17851 sponsored by Novartis Pharmaceuticals Corporation and 2) a bioequivalence (BE) study between Baclofen Oral Solution 1mg/mL and BACLOFEN Tablets USP 20 mg of TEVA PHARMACEUTICALS USA in healthy male subjects under fasted conditions. This review focuses on the pivotal BE study and additional clinical pharmacology information on baclofen is available in previous OCP reviews and in approved label of baclofen.

1.1 RECOMMENDATION

The NDA submission is acceptable from a Clinical Pharmacology perspective and the OCP recommends approval of NDA 208193.

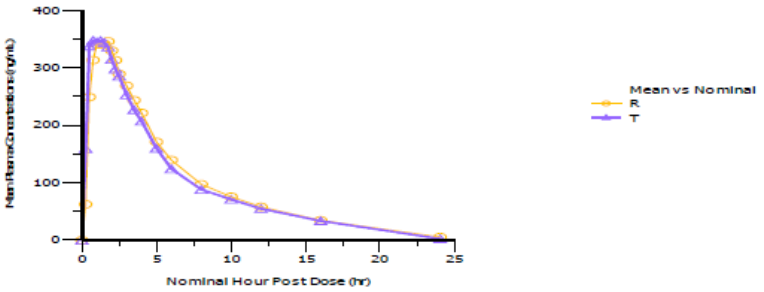
1.2 PHASE IV COMMITMENT/REQUIREMNT

None.

1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY

Following the administration of OZOBAX® (baclofen oral solution 1 mg/mL) at 20 mg dose in fasted subjects, absorption of baclofen was rapid, with peak plasma concentrations occurring in about 0.75 hour. OZOBAX® was shown to be bioequivalent to baclofen immediate release (IR) tablets under fasted conditions.

Mean plasma concentration versus time profiles of baclofen and PK parameters following administration of OZOBAX® and baclofen IR tablet under fasted conditions are shown below:



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

2 QUESTION BASED REVIEW (QBR)

2.1 Specific Questions

2.1.1 Are the PK profiles of baclofen comparable between OZOBAX® baclofen oral solution (1 mg/mL) and Baclofen IR tablet (RLD)?

Yes. A 2-way crossover, single dose BE study (CR-024-BE-2013) was conducted to compare the PK profiles of baclofen from OZOBAX baclofen oral solution and baclofen IR tablet at 20 mg dose level under fasted conditions. The study results demonstrated that the PK profiles of baclofen are similar between OZOBAX® and Baclofen IR tablets. The 90% CI for the ratios of geometric least square means of C_{max} and AUC were within acceptable BE limits of 80-125%. The absorption rates were also comparable between the two products (median t_{max} of 0.75 hr for baclofen oral solution and 1 hr for baclofen IR tablet).

2.1.2 Will administration of OZOBAX baclofen oral solution (1 mg/mL) with food have an effect on baclofen PK?

Not likely. The approved label of Baclofen IR tablet (RLD) does not include any statements about the effect of food on the absorption of baclofen. Baclofen IR tablets can be taken with or without food. Therefore, it can be assumed that food should not have an effect on baclofen PK from the oral solution formulation as well.

3. DETAILED LABELING RECOMMENDATIONS

The ~~strike through~~ represents the text to be deleted and red fonts shows proposed addition to the label.

7. DESCRIPTION

OZOBAX® ~~(baclofen) oral solution~~, (b) (4)

Its chemical name is 4-amino-3-(4-chlorophenyl)- butanoic acid, and its structural formula is…

8.2 Pharmacokinetics

(b) (4)

(b) (4)

(b) (4)

The peak plasma concentration

(b) (4) in about 0.75 hour

(b) (4)

(b) (4)

(b) (4)

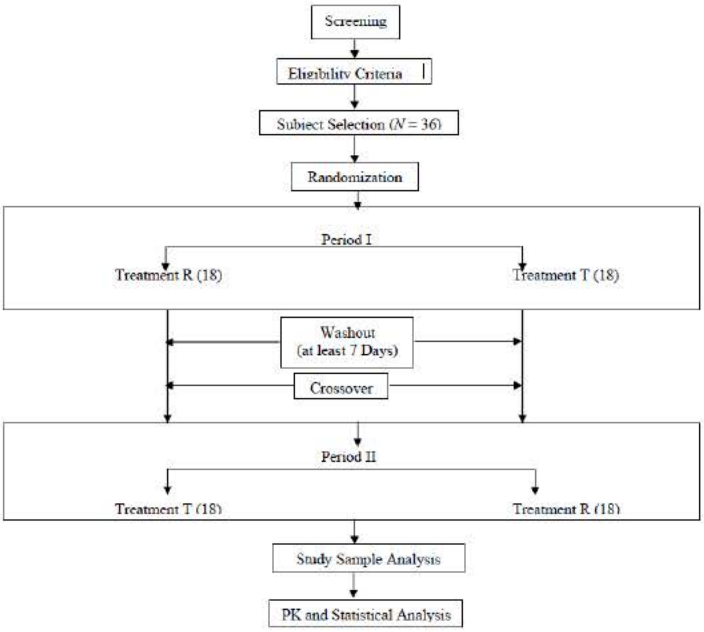

(b) (4)

APPENDIX: INDIVIDUAL STUDY REVIEW

Bioequivalence (BE) study

Study **CR-024-BE-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 comparing with Baclofen tablets USP 20 mg in healthy, adult, human subjects, under fasting conditions.
Principle Investigator	Dr. Anitha Singareddy. M.B.B.S.
Study Site	Piramal Clinical Research, Mirra Kamshetty Mall (3rd and 4th floor), Ramanthapur, R.R.District, Hyderabad - 500 013, India.
Study Period	5/7/14 – 5/30/14
Study Objectives	1) To assess bioequivalence by comparing the single oral dose bioavailability of test product of Baclofen Oral solution 1 mg / mL (T) with reference product (R) Baclofen tablets USP 20 mg in healthy, adult, human subjects under fasting conditions. 2) To monitor the safety and tolerability of single dose of Baclofen oral solution 1 mg/mL.
Study Design and Dose Administration	The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose comparative bioavailability study under fasted conditions.
Study Population	Thirty-six subjects completed period-I of the study. Thirty-five subjects

Figure 9.1: Overall study design and plan

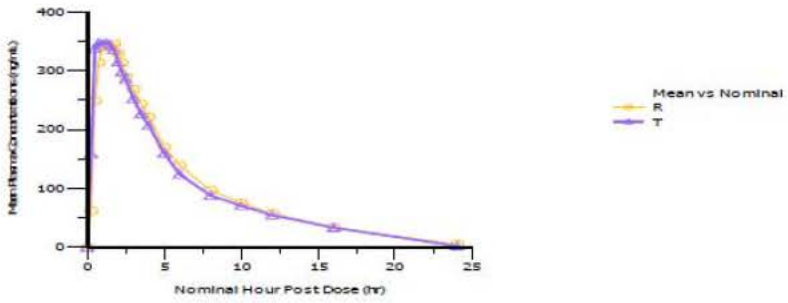


Reference (R): Baclofen tablets USP 20 mg Manufactured In Croatia By PLIVA HRVATSKA d.o.o. Zagreb, Croatia, Manufactured For TEVA PHARMACEUTICALS USA. Sellersville, PA 18960.

Test (T): Baclofen Oral solution 1 mg / mL of Metacel Pharmaceuticals, LLC 282 Skyland Drive, Roswell, GA 30075.

N: Number of subjects PK: Pharmacokinetic;

	entered period-II of the study [Participant ID: 17 did not report to the facility for Period-II check in, hence considered as a dropout of the study]. Thirty-five subjects completed both the periods of the study. Age: 19-41 (mean: 28) years Gender: Males Race: Asian (n=35).
Investigational Product	Test (T): Baclofen Oral solution Dosage form: Oral Solution Lot No.: K1026 Manufacturing Date: 10/15/2012 Expiry Date: 07/2014 Manufactured by: (b) (4) Distributed by: Strength: 1 mg / mL Mode of administration: Oral Storage conditions: Controlled room temperature Reference (R): Baclofen tablets USP 20 mg Dosage form: Tablet Lot No.: 7478023 Manufacturing Date: N/AV Expiry Date: 02/2015 Manufactured by: (b) (4) Manufactured for: TEVA PHARMACEUTICALS USA, Sellersville, PA 18960 Strength: 20 mg Mode of administration: Oral Storage conditions: At 20° C to 25° C (68° F to 77° F)
Sampling: Blood	Blood samples up to 24 hours post dose were collected to assess baclofen concentrations in plasma. Twenty-one (21) blood samples (1 x 5 mL) were collected in pre-labelled K2 EDTA vacutainers, during each period. Single venous blood sample was withdrawn at pre-dose (0), 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, 5, 6, 8, 10, 12, 16 and 24 hours post-dose. The total volume of blood loss for each subject did not exceed 247 mL.
Urine	none
Feces	none
Analysis	A validated LC-MS/MS method was employed for the estimation of Baclofen in human plasma, and the sample analysis was performed at: (b) (4) The sample analysis was performed between (b) (4) including re-assays and incurred samples.

	<table><tr><td>Parameter</td><td>Baclofen</td></tr><tr><td>Matrix</td><td>Plasma</td></tr><tr><td>Method</td><td>LC/MS/MS</td></tr><tr><td>Linearity Range (ng/ml)</td><td>20.2- 1004.0</td></tr><tr><td>LLOQ (ng/mL)</td><td>20.2</td></tr><tr><td>QCs</td><td>60.5, 111.0, 509.4, 754.6 ng/mL</td></tr><tr><td>Inter-run precision</td><td>3.5 - 4.6%</td></tr><tr><td>Inter-run accuracy</td><td>100.0 – 103.5 %</td></tr></table> *The analytical method developed for the analysis of baclofen was adequately validated and acceptable. Sample analysis is also acceptable.*
PK Assessment	The PK parameters included C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el}, $t_{1/2}$ and $AUC\_\%_{Extrap\_Obs}$. The bioequivalence of test with reference product of log-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were determined for baclofen.
Safety Assessment	Vital signs, ECG, Clinical laboratory, and AEs.
PD Assessment	None
Pharmacokinetic Results	The mean plasma concentration versus time profiles on linear scales for baclofen is presented below:  PK Comparison between treatments of Test and Reference baclofen at 20 mg under fasted conditions: **Pharmacokinetic Results of Baclofen :** <table><tr><td rowspan="2">**PK Parameters**</td><td colspan="2">**Baclofen** **Mean (± S.D.)**</td></tr><tr><td>**T**</td><td>**R**</td></tr><tr><td>**T_{max} (hr)***</td><td>0.75 (±0.7194)</td><td>1.00 (±0.5987)</td></tr><tr><td>**C_{max} (ng/mL)**</td><td>417.7061 (±103.32671)</td><td>389.2647 (±78.27936)</td></tr><tr><td>**AUC_{0-t} (ng.hr/mL)**</td><td>2138.0587 (±539.54505)</td><td>2227.4420 (±506.12497)</td></tr><tr><td>**$AUC_{0-\infty}$ (ng.hr /mL)**</td><td>2415.3036 (±585.53731)</td><td>2481.3817 (±539.20292)</td></tr><tr><td>**$T_{½}$ (hr)**</td><td>5.743 (±1.0622)</td><td>5.619 (±1.3026)</td></tr><tr><td>**K_{el} (1/hr)**</td><td>0.12462 (±0.022461)</td><td>0.12986 (±0.030276)</td></tr><tr><td>**AUC_%Extrap_Obs**</td><td>11.6335 (±2.59406)</td><td>10.4675 (±3.12781)</td></tr></table> *: Median (± S.D.)

<table>
<tr><td></td><td>
Geometric Least Square Mean, Ratio of Geometric Least Square Mean and 90% Confidence Intervals for log-transformed data for Baclofen.
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</table>
Reviewer's comments: Based on reviewer's assessment, PK parameters of baclofen are BE between Test and Reference treatments of Baclofen at 20 mg under fasted conditions.
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<tr><td>Safety</td><td>There was no SAE or death in the study.</td></tr>
<tr><td>Conclusion</td><td>The test product, baclofen oral solution 1 mg / mL (20 mL) of Metacel Pharmaceuticals is bioequivalent to the Reference product, Baclofen tablets USP 20 mg by TEVA PHARMACEUTICALS USA in healthy, adult, male subjects, under fasted conditions.
There were no reports of death, serious or unexpected adverse events.

Reviewer's comments: Biopharmaceutical inspection for clinical site and analytical site of the study was requested. The Division of New Drug Bioequivalence Evaluation (DNDBE) / Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection because OSIS recently inspected the sites and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).</td></tr>
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/s/

BEI YU
09/02/2016

SREEDHARAN N SABARINATH
09/07/2016