CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210833Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

NDA- 210833 (SYMPAZAN)

CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	210833
Link to EDR	\\CDSESUB1\evsprod\NDA210833\0000
Submission Date(s)	31-Oct-2017
Submission Type	505(b)(2) (Standard Review)
Brand Name	Sympazan
Generic Name	Clobazam
Formulation and Strength	Oral Soluble Film 5 mg, 10 mg and 20 mg
Route of Administration	Oral Administration
Proposed Indication	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Applicant	MonoSol Rx LLC
Associated IND	IND-129383
Reviewers	Dawei Li, Ph.D.
Team Leader	Angela Men, MD., Ph.D.
OCP Division	Division of Clinical Pharmacology 1
Division Director	Mehul Mehta, Ph.D.

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1 Executive Summary

In the current submission, MonoSol Rx LLC is seeking approval for Sympazan (Clobazam Oral Soluble Film 5 mg, 10 mg and 20 mg) as an adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older using ONFI® tablets (NDA-202067) as the reference listed drug (RLD).

The Applicant proposed indications of Sympazan are same as the RLD. Two Clobazam Oral Soluble Film (COSF) bioavailability/ bioequivalence studies (Study 1895 and Study 162018), with comparison to ONFI tablets, in healthy, non-smoking male and female volunteers under fasting conditions, are submitted as the bridging studies for the submission of this 505(b)(2) NDA. The primary focus of this review is the evaluation of bridging information between COSF and ONFI tablets.

1.1 Recommendation

The Division of Clinical Pharmacology 1 has reviewed the submitted application and has found it acceptable from a clinical pharmacology standpoint provided that a mutual agreement can be reached on the labeling languages.

1.2 Post-marketing Requirements

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics

All three key PK parameters, AUC0-t, AUC0-inf, and Cmax, are within the 80.00% to 125.00% acceptance range in a pivotal crossover bioavailability study in healthy volunteers comparing COSF 20 mg and 10 mg with Onfi (clobazam) 20 mg and 10 mg tablets under fasting conditions (study162018).

In addition, this Study showed that the rate and extent of absorption of COSF were dose-proportional from 10 mg to 20 mg under fasting conditions.

No food effect study of COSF was conducted. The sponsor requested a biowaiver for Clobazam

Oral Soluble Film 5 mg and conducted in vitro dissolution study in comparison to ONFI® tablets 5 mg. According to the CMC reviewer, a biowaiver is granted for the lower strength of COSF 5 mg (Please, see CMC review for more details).

2 Question-Based Review

This is an abbreviated version of the Question-Based Review. For review of the clinical pharmacology studies supporting the approval of RLD, ONFI®, please refer to the reviews associated with tablet formulation (NDA-202067) and oral suspension formulation (NDA-203993).

2.1 General Attributes of The Drug Product

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The Clobazam Oral Soluble Film (COSF) product is designed to rapidly disintegrate in saliva. Absorption is expected to occur primarily through the gastrointestinal tract after the dissolved film is swallowed. COSF contains the active ingredient clobazam (b) (4) (b) (4). The COSF product is a white rectangular film. The physical dimensions, film weight, and the clobazam content of COSF 5 mg, 10 mg, and 20 mg strengths are provided in Table 1. (b) (4) (b) (4)

The proportionality of these doses is intended to provide consistent, proportional absorption of the active ingredient through the gastrointestinal tract following application to the lingual surface, subsequent dissolution in the oral cavity, and deglutition.

Table 1. Description of COSF Doses

COSF Strength (mg)	Film Dimension (mm)	Nominal Film Weight (mg)
5	(b) (4)	
10		
20		

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor. Clobazam is approved as adjunctive treatment

of seizures associated with LGS in patients 2 years of age or older. The sponsor is seeking approval of the COSF for the same indications as the approved ONFI® tablets (NDA-202067).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

COSF 5 mg, 10 mg and 20 mg is to be administered orally. The oral dissolving film is designed to be applied on top of the tongue where it adheres and rapidly dissolves. The proposed doses are the same as those for the RLD (Table 2).

Table 2. Recommended Total Daily Dosing by Weight Group

	≤30 kg Body Weight	>30 kg Body Weight
Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

2.2 General Biopharmaceutics

2.2.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the reference product?

Clobazam Oral Soluble Film 10 mg and 20 mg were shown to be bioequivalent to the RLD, Onfi (clobazam) tablets, in the pivotal study 162018, as the 90% confidence intervals of the ratios of geometric means for AUC and Cmax were within the range of 80.00% to 125.00% for bioequivalence. (Please see Table 3)

Table 3. Ratio and 90% confidence intervals of test versus reference for clobazam in study 162018

Parameters	T/R (20mg)	Inter-Subject CV	90% CI	T/R (10mg)	Inter-Subject CV	90% CI
Cmax (ng/mL)	102.59%	14.37%	95.43%-110.28%	95.45%	17.12%	90.19%-101.03%
AUC0-t (ng*hr/mL)	103.74%	24.63%	101.32%-106.21%	99.38%	25.76%	96.81%-102.02%
AUC0--inf (ng·hr/mL)	103.55%	24.74%	101.16%-106.00%	99.05%	25.44%	96.72%-101.43%

In addition, the 90% confidence intervals of the ratios of geometric means of AUC and Cmax for the active metabolite, N-desmethyl clobazam, were within the range of 80.00% to 125.00% for bioequivalence. (Please see Table V)

Details of this individual study review is in Section 4.1**.**

2.2.2 What is the food effect associated with the product?

According to PIND Minutes-Written Response (IND 129383, dated March/19/2016), the agency agreed that a food effect study for COSF is unnecessary. The justification includes the extent of clobazam gastrointestinal absorption, the insignificant food effect for ONFI tablet and no food

effect study conducted for the approval of ONFI oral suspension. Therefore, the food effect on COSF has not been studied.

The Onfi [clobazam] Prescribing Information prescribing information states that "the administration of Onfi (clobazam) tablets (the RLD) with food or when crushed in applesauce does not affect absorption. Although not studied, the oral bioavailability of the oral suspension is unlikely to be affected under fed conditions.

Considering the bioequivalence has been established between single-dose Onfi tablet and COSF under fasted conditions and a relatively wide therapeutic window for clobazam, we believe that clinically significant food effect on the clobazam exposure is not likely to occur for COSF.

2.3 Analytical Section

2.3.1 Are the bioanalytical methods properly validated to measure clobazam in plasma samples in the pivotal bioequivalence studies?

Plasma clobazam levels were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) method with Clobazam-d8 as internal standard.

The lower limit of quantitation was 1.00 ng/mL and the upper limit of quantitation was 1000.00 ng/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in the bioequivalence studies is provided in Table 4.

Table 4. Summary of Bioanalytical Methods used in Bioequivalence Study

	Project No. Analyte	Calibration Range (ng/mL)	QCs (ng/mL)	Inter-Run Precision (%CV)	Inter-Run Accuracy (%RE)
Method Validation	165254APYS Clobazam	1.00 to 1000.00	1.00, 3.00, 500.00, 750.00	3.13 to 7.37	-0.50 to 4.39
Assay Performance	162018APQD Clobazam	1.00 to 1000.00	3.00, 50.00, 500.00, 750.00	1.67 to 3.15	-4.64 to 6.19

The analytical methods for the active metabolite, N-desmethyl clobazam are also acceptable. However, since the metabolite was used as supportive information for the relative bioavailability evaluation between COSF and the RLD, the details of method validation and performance for the metabolite are only described in the individual study reviews.

2.3.2 Analytical site inspection

An OSIS consult request for biopharmaceutic inspections of the analytical site for Study 162018 was issued on 12/22/2017. On 01/11/2018 OSIS recommended to accept data without on-site inspection because a recent inspection of the analytical site was completed and site was classified as 'No Action Required' (CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review)).

3 Detailed Labeling Recommendations

In section 12, Clinical Pharmacology information is borrowed from the approved label of the reference product. The sponsor added Bioequivalence subsection under 12.3 Pharmacokinetics to describe findings of bioequivalence studies. In this section, review of new information in the label is done. The format review will be deferred until labeling negotiation. The sponsor proposed label language in section 12 is acceptable from clinical pharmacology standpoint.

4 Appendices

4.1 Pivotal Bioequivalence Study (162018)

Study # 162018	**Study Period** First Subject First Dose: 09-DEC-2016 Last Subject Last Visit: 26-MAY-2017	**EDR Link** \\CDSESUB1\evsprod\NDA210833\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study162018\162018-csr-fr.pdf
Title	A Pivotal, Open-Label, Randomized, Single-Dose, Four-period, Four-arm, Crossover, Comparative Bioavailability Study of Clobazam 20 mg And 10 mg Oral Soluble Films And ONFI® 20 mg And 10 mg Tablets in Healthy Male and Female Volunteers under Fasting Conditions.	
Objectives: The primary objective of this pivotal study is to evaluate the comparative bioavailability of clobazam and N-desmethylclobazam from Clobazam Oral Soluble films 20 and 10 mg (MonoSol Rx, LLC) and ONFI® Tablets 20 and 10 mg (Lundbeck, US) in healthy, non-smoking male and female volunteers under fasting conditions. The secondary objective of this pivotal study is to assess the safety and tolerability of Clobazam Oral Soluble films (MonoSol Rx, LLC)		
Study Design: This was a pivotal, randomized, single-dose, open-label, four-period, four-arm, crossover, comparative bioavailability study, performed under fasting conditions. Subjects were confined to the inVentiv Clinical Facility from at least 14 hours prior to drug administration on and were discharged from the clinic after at least 36 hours post dose. Subjects came back to the clinical facility for subsequent blood draws. This study consisted of 4 study periods with a washout period of 28 days between dosing.		
Subjects: For clobazam: N=45 for comparisons A vs B and C vs. A, N=47 for comparisons C vs D and D vs B; For N-desmethylclobazam: N=44 for comparisons A vs B and C vs. A, N=46 for comparisons C vs D and D vs B		
Main Criteria for Inclusion: Subjects had to be healthy, non-smoking (for at least 6 months prior to first screening) male and female volunteers, 18 to 64 years of age, inclusive, with a body mass index (BMI) within 18.5-29.9 kg/m2, inclusive. All subjects had to be in compliance with the inclusion and exclusion		

criteria described in the protocol and were judged eligible for enrolment in this study based on medical and medication histories, demographic data (including sex, age, race, ethnicity, body weight [kg], height [cm], and BMI [kg/m2]), vital signs measurements, 12-lead electrocardiogram (ECG), physical examination, urine drug screen, alcohol breath test, urine cotinine test, serum pregnancy test, and clinical laboratory tests (biochemistry, hematology, urinalysis, human immunodeficiency virus [HIV], hepatitis C virus [HCV] antibodies, and hepatitis B surface antigen [HBSAg]).

Treatment:
TRT A: Clobazam Oral Soluble Film 20 mg; Lot No: E16LB106-158; (MonoSol Rx, LLC.,USA)
TRT B: ONFI® 20mg Tablets; Lot No: 1583320A; (Lundbeck, U.S.)
TRT C: Clobazam Oral Soluble Film 10 mg; Lot No: E16KZ102-154; (MonoSol Rx, LLC.,USA)
TRT D: ONFI® 10mg Tablets; Lot No: 1542876A; (Lundbeck, U.S.)

Duration of Treatment:
In each period, subjects were administered a single oral dose of either 1 x 20 mg Clobazam Oral Soluble film, centered on the top surface (dorsal aspect) of the tongue (Treatment A), 1 x 20 mg ONFI® Tablets (Lundbeck, US)-administered with 240 mL of water (Treatment B), 1 x 10 mg Clobazam Oral Soluble film, centered on the top surface (dorsal aspect) of the tongue (Treatment C), or 1 x 10 mg ONFI® Tablets (Lundbeck, US)-administered with 240 mL of water (Treatment D). The treatment phases were separated by a washout period of 28 days.

Blood Sampling Points:
Blood samples were collected prior to drug administration and at 0.333, 0.667, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, 28.0, 36.0, 48.0, 72.0, 96.0, 144, 240, 360, and 504 hours post-dose in each period.

Criteria for Evaluation:
Pharmacokinetic:
AUC0-t, AUC0-inf, Cmax, Residual area, Tmax, Kel, T½ el, Cl/F, and Vd/F. The clearance and volume of distribution were also normalized for the body weight.
Safety:
Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, oral visual inspection, and standard laboratory evaluations.

Analytical Method:
Clobazam: See Section 2.3
N-Desmethyl Clobazam: Plasma N-Desmethyl clobazam levels were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS-MS) method with N-desmethyl clobazam-$^{13}C_6$ as internal standard.
The lower limit of quantitation was 0.25 ug/mL and the upper limit of quantitation was 250.00 ug/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Summary of bioanalytical methods used in the bioequivalence studies is provided in the Table below:

	Project No. Analyte	Calibration Range (ug/mL)	QCs (ug/mL)	Inter-Run Precision (%CV)	Inter-Run Accuracy (%RE)
Method Validation	165254APYS N-Desmethyl Clobazam	0.25 to 250	0.25, 0.75, 125.00, 187.50	3.05 to 7.64	-5.39 to 3.78
Assay Performance	162018APQD N-Desmethyl Clobazam	0.25 to 250	0.25, 0.75, 125.00, 187.50	1.88 to 4.17	-4.00 to 9.78

Reviewer's comments:
All method validations for the LC-MS/MS bioanalytical assay for Clobazam and N-Desmethyl Clobazam appear acceptable with reasonable precision and accuracy.

Statistical Methods:
Pharmacokinetic analyses:
Individual and mean plasma concentration versus time curves are presented using linear and semi-log scales for clobazam and N-desmethylclobazam. Geometric mean concentration profiles are also presented for both analytes. Listings and descriptive statistics (number of observations, arithmetic mean, SD, coefficient of variation [CV%], median, Min, Max, and geometric mean) of the concentrations for both analytes are provided.
Plasma PK parameters were listed and summarized by treatment group using descriptive statistics. N, arithmetic mean, SD, Min, Max, median, CV% and geometric means. Additionally, geometric means least-square means were calculated for AUC0-t, AUC0-inf, and Cmax.
Average Bioequivalence
For clobazam, comparisons between treatment groups (A vs. B and C vs. D) were evaluated using an analysis of variance (ANOVA) with Group, Sequence, Sequence*Group, Period(Group), Treatment, and Treatment*Group as fixed factors and Subject (Sequence*Group) as a random factor on the ln-transformed values of AUC0-t, AUC0-inf, Cmax, Cl/F, Cl/F/kg, Vd/F, Vd/F/kg, and on the untransformed values for Tmax, Kel, and T½ el.
Probability (p) values were derived from Type III sums of squares and statistical tests were performed at the alpha level of 0.05. Using the General Linear Model (GLM) procedure, ANOVA for each parameter included calculations of least-squares (LS-) means for each treatment, the LS-mean for treatment differences using the ESTIMATE statement, and the standard error associated with this difference. Tmax was analyzed using an additional nonparametric test (Wilcoxon signed-rank test).
The ratios of geometric means (A/B and C/D) and corresponding 90% confidence interval (CI), based on least-squares means from the ANOVA of the ln-transformed data, were calculated for

AUC0-t, AUC0-inf, and Cmax.

For N-desmethylclobazam, ANOVA, ratio of geometric least-square means and 90% geometric CI calculations were repeated but limited to AUC0-t, AUC0-inf, and Cmax.

Criteria for Average Bioequivalence for Clobazam 20 mg

For clobazam, the 90% CIs for the ratio of geometric means (A/B) based on least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf, and Cmax must be within 80.00% to 125.00%.

Criteria for Average Bioequivalence for Clobazam 10 mg

For clobazam, the 90% CIs for the ratio of geometric means (C/D) based on least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf, and Cmax must be within 80.00% to 125.00%.

Dose Proportionality

For clobazam and N-desmethylclobazam, PK parameters AUC0-t, AUC0-inf and Cmax dose normalized to 20 mg were provided with descriptive statistics for each treatment. For each comparison (C vs. A and D vs. B), an additional table presenting the individual ratios for AUC0-t, AUC0-inf, and Cmax dose normalized to 20 mg was provided. Mean (± SD) AUC0-t, AUC0-inf and Cmax versus Dose was presented graphically.

Results:

Pharmacokinetic:

Clobazam:

Table I: Summary of Pharmacokinetic Parameters for Clobazam – PK Population

Parameters	Clobazam 20 mg Oral Soluble Film (A)	ONFI® 20 mg Tablet (B)	Clobazam 10 mg Oral Soluble Film (C)	ONFI® 10 mg Tablet (D)
N	45	47	47	47
AUC0-t (ng*h/mL) Mean (CV%)	10871.43 (26.08)	10304.23 (27.86)	4737.49 (28.14)	4735.07 (26.40)
AUC0-inf (ng*h/mL) Mean (CV%)	11054.21 (26.32)	10493.78 (27.63)	4895.17 (27.37)	4918.00 (26.26)
Cmax (ng/mL) Mean (CV%)	389.30 (26.25)	387.04 (26.40)	185.36 (26.90)	191.88 (19.49)
T½ el (h) Mean (CV%)	45.51 (28.03)	45.50 (28.78)	42.82 (28.08)	43.93 (29.82)

Cl/F (L/h) Mean (CV%)	1.93 (25.22)	2.05 (27.25)	2.19 (26.68)	2.16 (24.23)
Vd/F (L) Mean (CV%)	120.19 (20.12)	126.71 (20.23)	128.15 (21.40)	130.57 (24.87)
Tmax (h) Not calculated Median (Range)	1.516 (0.333 - 4.000)	2.000 (0.658 - 6.000)	1.500 (0.663 - 3.517)	1.500 (0.664 - 4.000)

Table II: Ratios (A/B and C/D), 90% Geometric Confidence Intervals, Intra- and Inter-Subjects CV (%) for Clobazam: AUC0-t, AUC0-inf, and Cmax - PK Population

Treatment Comparison	Parameter	Geometric LSM A	Geometric LSM B	Ratio[1]	90% Geometric C.I.[2] Lower	90% Geometric C.I.[2] Upper	Intra-Subject CV	Inter-Subject CV
COSF 20 mg (A) - ONFI® 20 mg (B)	AUC_{0-t}	10531.45	10152.24	103.74%	101.32%	106.21%	6.48%	24.63%
	AUC_{0-inf}	10712.10	10344.68	103.55%	101.16%	106.00%	6.41%	24.74%
	C_{max}	386.59	376.84	102.59%	95.43%	110.28%	20.05%	14.37%
		Geometric LSM C	Geometric LSM D					
COSF 10 mg (C) - ONFI® 10 mg (D)	AUC_{0-t}	4554.83	4583.30	99.38%	96.81%	102.02%	7.49%	25.76%
	AUC_{0-inf}	4714.55	4759.87	99.05%	96.72%	101.43%	6.79%	25.44%
	C_{max}	179.96	188.53	95.45%	90.19%	101.03%	16.29%	17.12%

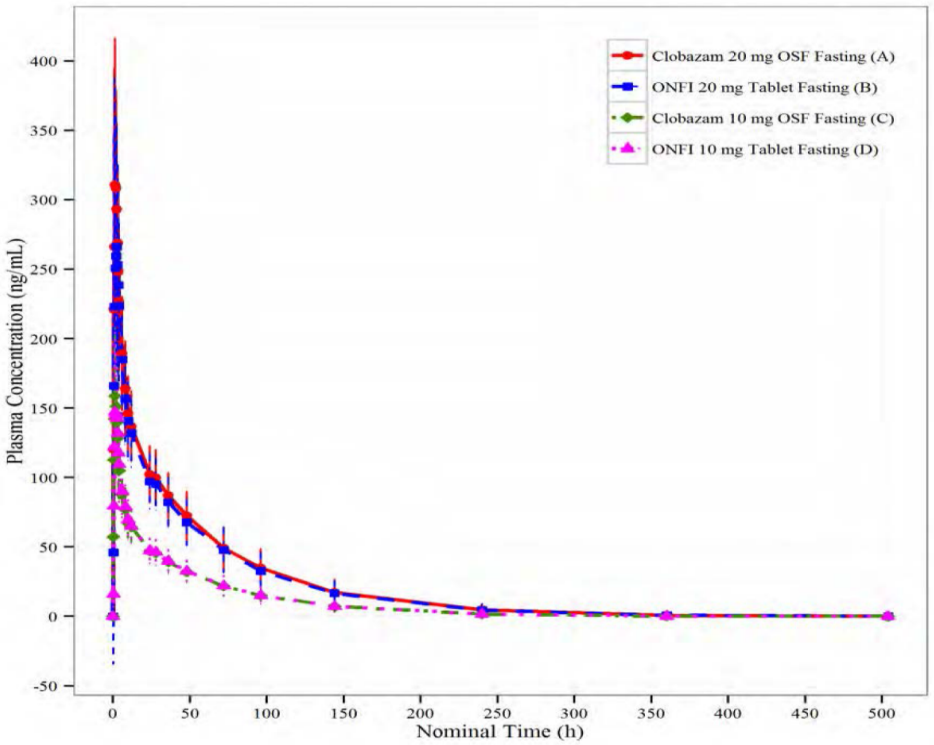
COSF=Clobazam Oral Soluble Film
[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
LSM: Least-Squares Mean

Table III: P-values for Clobazam: AUC0-t, AUC0-inf, and Cmax, Dose Normalized to 20 mg - PK Population

Comparison	Parameter	p-values Sequence	p-values Period	p-values Treatment
COSF 10 mg (C) - COSF 20 mg (A)	AUC_{0-t}	0.5795	0.4962	<0.0001
	AUC_{0-inf}	0.5671	0.5513	<0.0001
	C_{max}	0.7137	0.9263	0.2205
ONFI® 10 mg (D) - ONFI® 20 mg (B)	AUC_{0-t}	0.5912	0.0200	<0.0001
	AUC_{0-inf}	0.5554	0.0396	0.0002
	C_{max}	0.3861	0.7163	0.8871

COSF=Clobazam Oral Soluble Film

Figure I: Mean (±SD) Concentration-Time Profile for Clobazam for Each Treatment - Linear Scale



N-desmethyl clobazam:

Table IV: Summary of Pharmacokinetic Parameters for N-desmethyl clobazam: – PK Population

Parameters	Clobazam 20 mg Oral Soluble Film (A)	ONFI® 20 mg Tablet (B)	Clobazam 10 mg Oral Soluble Film (C)	ONFI® 10 mg Tablet (D)
N	45	45	45	45
AUC0-t (ng*h/mL) Mean (CV%)	15828.56 (35.98)	14432.49 (33.51)	6238.77 (33.99)	6183.98 (33.11)
AUC0-inf (ng*h/mL) Mean (CV%)	16371.97 (39.03)	14813.20 (35.85)	6397.13 (35.09)	6321.88 (33.96)
Cmax (ng/mL) Mean (CV%)	74.60 (17.14)	71.41 (22.08)	32.77 (21.84)	33.01 (21.74)
T½ el (h) Mean (CV%)	76.57 (27.07)	72.07 (25.26)	69.44 (27.32)	68.74 (26.50)

Cl/F (L/h) Mean (CV%)	1.40 (37.88)	1.53 (37.59)	1.76 (36.58)	1.77 (35.93)
Vd/F (L) Mean (CV%)	140.41 (24.17)	144.94 (23.51)	164.04 (23.64)	164.62 (24.57)
Tmax (h) Mean (CV%)	68.835 (29.353)	64.744 (40.370)	59.953 (43.306)	59.515 (32.153)

Table V Ratios (A/B and C/D), 90% Geometric Confidence Intervals, Intra- and Inter-Subjects CV (%) for N-desmethyl clobazam: AUC0-t, AUC0-inf, and Cmax - PK Population

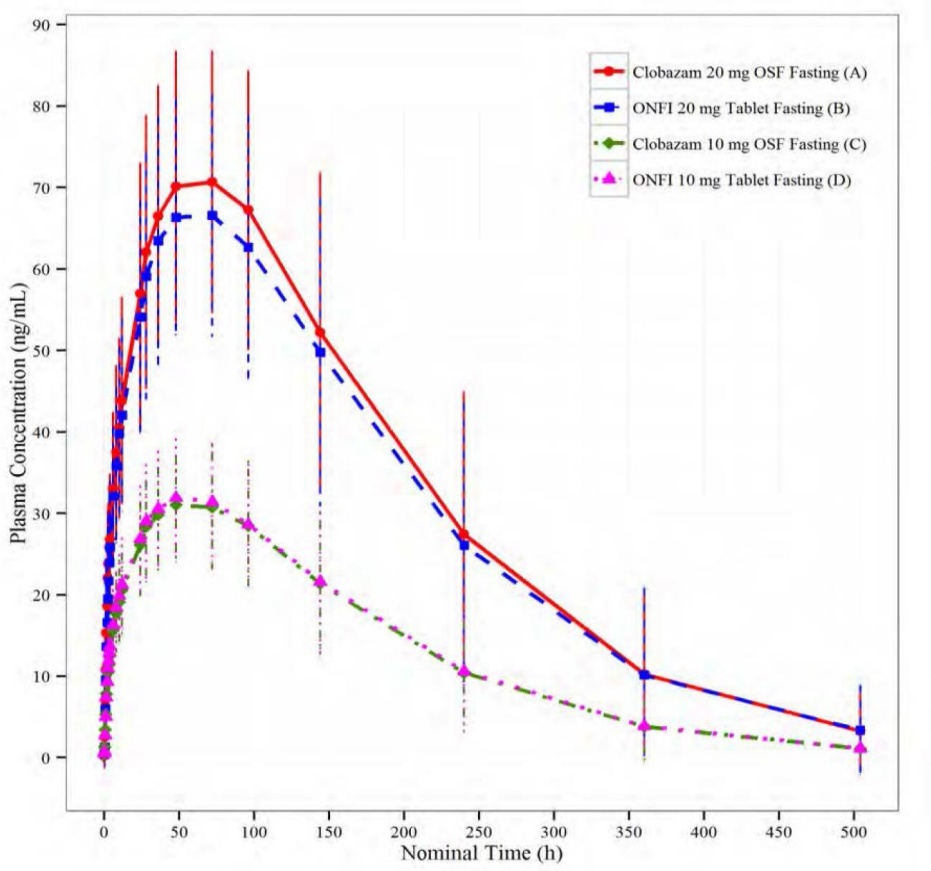
Parameter	COSF 20 mg (A)- ONFI® 20 mg Tablet (B)		COSF 10 mg (C)- ONFI® 10 mg Tablet (D)	
	T/R Ratio of Geometric Means (90% Confidence Intervals)	Inter-Subject CV (%)	T/R Ratio of Geometric Means (90% Confidence Intervals)	Intra-Subject CV (%)
AUC0-t	102.96% (100.40%-105.58%)	33.36%	98.61% (97.13%-100.11%)	32.87%
AUC0-inf	103.00% (100.25%-105.82%)	35.04%	98.54% (96.94%-100.16%)	33.31%
Cmax	102.69% (100.33%-105.11%)	22.54%	98.70% (96.65%-100.79%)	21.96%

Table VI: P-values for N-desmethylclobazam: AUC0-t , AUC0-inf , and Cmax , Dose Normalized to 20 mg - PK Population

		p-values		
Comparison	Parameter	Sequence	Period	Treatment
COSF 10 mg (C) - COSF 20 mg (A)	AUC_{0-t}	0.2092	0.0485	<0.0001
	AUC_{0-inf}	0.2092	0.1411	<0.0001
	C_{max}	0.8365	0.0037	<0.0001
ONFI® 10 mg (D) - ONFI® 20 mg (B)	AUC_{0-t}	0.4154	0.4932	<0.0001
	AUC_{0-inf}	0.4068	0.2882	<0.0001
	C_{max}	0.7815	<0.0001	<0.0001

COSF=Clobazam Oral Soluble Film

Figure II: Mean (±SD) Concentration-Time Profile for N-desmethyl Clobazam for Each Treatment - Linear Scale



Safety:

A total of 106 TEAEs were reported by 34 (66.7%) of the 51 subjects who received at least one dose of the study medication (safety population). A dose-related increase in the number of AEs and the number of subjects experiencing AEs across the treatment groups was observed in this study, especially for the AEs in the SOC Nervous system disorders (PT Somnolence). A slightly higher number of TEAEs was observed following dosing with the oral soluble film when compared to the tablet formulation for both concentrations, but the difference was deemed not significant since there were no relevant differences between each treatment group when comparing the number of subjects for each PT. None of these TEAEs was severe or serious and only one subject was discontinued due to an AE.

The most frequently reported TEAEs were Somnolence (43.1%) Headache (27.5%), and Dizziness (11.8%). Somnolence was reported in a dose-related manner across treatment groups. With the exception of Vomitting, Diarrhoea, and Influenza like illness, all other TEAEs were each reported by at most one subject by treatment group.

No safety issues were observed with respect to clinical laboratory tests and vital signs. Overall, no relevant differences in mean values and changes or shifts from screening to study exit were observed for clinical laboratory results and vital signs measurements.

No deaths or serious AEs were reported during this study. Only one subject was discontinued due to AEs (Blood pressure increased and Heart rate increased) but his safety was not at risk

during the study. Upon conclusion of the clinical portion of the study, the results from the subjects who completed study exit procedures, including laboratory tests and vital signs measurements, confirmed the absence of significant changes in the subjects' state of health. Although some AEs remained ongoing at the end of the study, no safety concerns were expected as they were all mild in severity.

Conclusion:

Pharmacokinetics:

Average Bioequivalence: Based on these results, it can be concluded that the test Clobazam Oral Soluble films 20 mg (MonoSol Rx, LLC) is bioequivalent to the reference ONFI® Tablets 20 mg (Lundbeck, US) following a 1 x 20 mg dose under fasting conditions; and the test Clobazam Oral Soluble films 10 mg (MonoSol Rx, LLC) is bioequivalent to the reference ONFI® Tablets 10 mg (Lundbeck, US) following a 1 x 10 mg dose under fasting conditions. Overall, it can also be concluded that the rate and extent of absorption (AUC and Cmax) generally increase in a dose-proportional manner from a dose of 10 to 20 mg under fasting conditions.

Dose Proportionality: Overall, for COSF and ONFI Tablets, the rate and extent of absorption generally increase in a dose-proportional manner from a dose of 10 to 20 mg under fasting conditions.

Safety:

The administration of clobazam was safe and well tolerated in healthy subjects following a single oral dose of 10 mg, or 20 mg as an oral soluble film or a tablet under fasting conditions. No major side effects and no relevant differences in safety profiles observed between the treatments, with the exception of Somnolence that was reported in a dose-related manner across treatment groups, particularly with respect to the number of AEs.

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/s/

DAWEI LI
07/20/2018

YUXIN MEN
07/20/2018

MEHUL U MEHTA
07/20/2018