CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202067Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

Individual Study Reviews

(Question-Based Review for ONFI is in DARRTS dated 10/09/2011)

NDA:	**202067**
Brand Name:	Onfi®
Generic Name:	Clobazam
Dosage Form & Strength:	Immediate Release Tablet (5, 10 and 20 mg)
Indication:	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients ≥2 years of age
Applicant:	Lundbeck Inc.
Submission:	505(b)(1), Standard
Submission Dates:	12/23/2010, 02/07/2011, 02/10/2011, 04/01/2011, 05/10/2011, 06/10/2011, 09/02/2011
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Division of Clinical Pharmacology 1 (DCP-1)
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Pharmacometrics Reviewer:	Joo-Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Hobart Rogers, Pharm.D., Ph.D.
Pharmacogenomics Team Leader:	Michael Pacanowski, Pharm.D., M.P.H.

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4. Appendices

4.4 Individual Study Reviews

4.4.1 General Clinical Pharmacology

Report # LC-010	**Study Period**: N/A	
Title	PHARMACOKINETICS AND METABOLISM OF CLOBAZAM (HR 376) AFTER THREE DIFFERENT SINGLE ORAL DOSES TO NORMAL MEN	
Study Design open-label, single-center, single-ascending-dose study		
☐ Bioequivalence	☑ Bioavailability	
Single-Dose Randomized Open-Label Single-Center 1-Peiod Healthy Vonuteers		
Screening: ≤7 days	**Washout:** 14 days, outpatient	
Period 1/2	10 days, Inpatient stay ☑Y ☐ N:	

Objectives: This study was conducted to define more precisely the half-life of clobazam in plasma, to calculate the areas under the plasma concentration time curves for three different doses, and to determine whether the pharmacokinetic parameters change proportionally with increases in dose.

Treatments: (Active Ingredient: clobazam)
All subjects fasted for 12 hours before and 4 hours after drug administration. Blood samples were obtained before dosing and at serial collection times for up to 144 hours. Urine samples were collected for 72 hours after dosing.

Subjects	Study Day 1	Washout Interval	Study Day 2	Washout Interval	Study Day 3
1 - 4	10 mg	14 days	20 mg	14 days	40 mg
5 - 8	20 mg	14 days	40 mg	14 days	10 mg
9 - 12	40 mg	14 days	10 mg	14 days	20 mg

Formulation (J):

Materials	mg/tablet
Clobazam Powder (HR 376)	10.0
Lactose, USP	(b) (4)
Food Starch,	(b) (4)
(b) (4)	
Magnesium Stearate, USP	
Talc, USP	
Theoretical Weight	(b) (4)

Sampling Times (plasma for PK)

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Pharmacokinetic blood collection times: 0 (predose), 0.33, 0.66, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 144.0 hours postdose.
The total volume of urine was collected in disposable containers at 0-2, 2-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours after dosing. In each sample, the total volume of urine and the amount of creatinine excreted were recorded.

Analytical Method: gas-liquid chromatograph with an electron capture detector.
The performance of the analytical method is acceptable. Yes ☐ No ☐

Statistical Method: The AUC0-144, log AUC0-144 and peak plasma levels (Cmax) were normalized to 10 mg before the statistical analyses were performed. The ratio of the paired doses with respect to the normalized AUCs and Cmax and the 95% confidence intervals for this ratio were calculated. A linear regression analysis was performed to evaluate the linearity of Cmax and AUC.
The plasma levels for each subject for each dose group were fitted to a 2-compartment open model which is characterized by a 3-term exponential equation.

Study Population : 12 healthy male volunteers (ages of 18 and 27 years, were 68 to 77 inches tall, and weighed 152 to 174 pounds). All subjects refrained from taking any drugs 10 days before the first day of study drug administration.

Results

The plasma concentrations of clobazam for the 7 subjects (Subjects No.1, 6, 7, 8, 10, 11, and 12) with complete data were used for estimating pharmacokinetic parameters. Subjects No.2 and 3 were excluded because of incomplete sets of plasma samples. Plasma samples for Subjects No. 4, 5, and 9 were lost and therefore not available for reanalysis. Urine samples were not reanalyzed because none of the hydroxylated derivatives of clobazam and desmethylclobazam were available for quantitative measurements.

Dose-normalized peak plasma levels for clobazam and 95% confidence limits

Variable	Mean †			Mean Difference		
	10 mg	20 mg	40 mg	10 mg vs 20 mg	20 mg vs 40 mg	10 mg vs 40 mg
Peak Plasma Level (ng/ml)	187.0 (187.0)	187.3 (374.7)	170.8 (683.3)	-0.3 (-30.3,30.2)††	16.5 (-14.0,47.0)	16.2 (-14.3,46.7)
Time-to-Peak (Hours)	1.86	1.88	2.57	-0.02 (-1.08,1.04)	-0.69 (-1.75,0.37)	-0.71 (-1.77,0.35)

Dose-normalized AUC for clobazam and 95% confidence limits

Variable	Mean †			Mean Difference		
	10 mg	20 mg	40 mg	10 mg vs 20 mg	20 mg vs 40 mg	10 mg vs 40 mg
$AUC_{0-144\ hrs}$ (ng/ml.hrs)	3518.3 (3518.3)	3595.1 (7190.1)	3494.9 (13979.6)	-76.8 (-476.7,323.1)††	100.2 (-299.7,500.1)	23.4 (-376.5,423.3)
Anti-log ($AUC_{0-144\ hrs}$) (ng/ml.hrs)	3404.1	3467.4	3396.3	0.9817 ††† (0.8730,1.1041)	1.0209 (0.9878,1.1482)	1.0023 (0.8913,1.1272)

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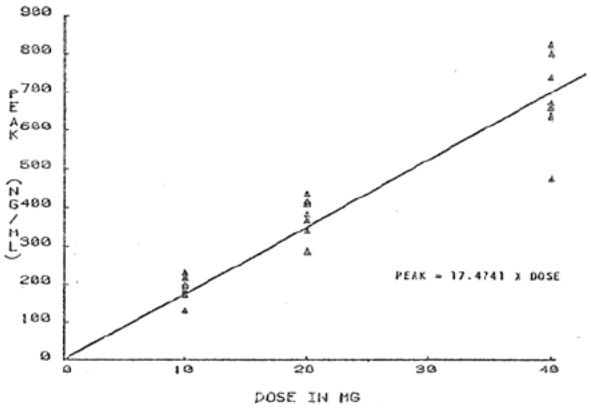
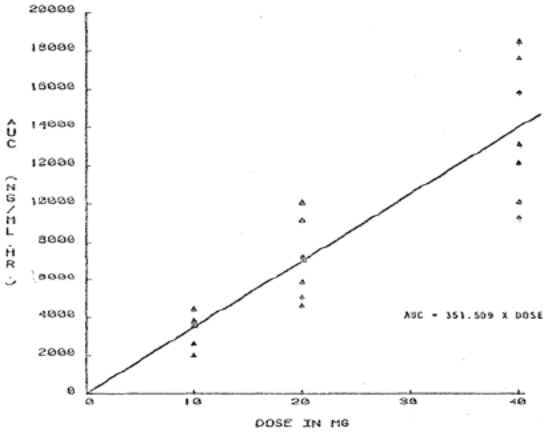
Cmax



AUC



The average fast disposition half-lives were 2.6 hours for the 10 mg and 20 mg group, and 1.6 hours for the 40 mg group. The average slow disposition half-lives for the 3 dose groups ranged from 17.4 to 25.5 hours.

Site Inspected

Requested: Yes☐ No ☑	**Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☑ No ☐ NA

Conclusion

- The plasma levels of clobazam increased with increasing doses from 10 mg to 40 mg. Linear relationships between the 3 doses versus AUC and peak plasma level were observed. No significant differences were found between any pair of the dose groups for normalized peak plasma levels or AUCs.
- After reaching peak concentrations, clobazam levels decreased in a bi-exponential fashion.
- Five subjects reported side effects. Mild lightheadedness, heavy feeling in legs or feet, and drowsiness were possibly drug-related. No treatment was required.

Comments

This study does not have a supporting QA validation report. The study was conducted in 1970's, at which time a stand-alone validation report containing currently required QA data was not conventional. However, given that the Cmax and AUC of 20 mg in this study (375 ng/ml and 7190 ng/ml.hrs, respectively) are comparable to the values from recent studies with validated assays (OV-1017), the results in this study appear reliable.

Report # OV1038	**Study Period**: 09/30/08 to (first subject dosed)	

Reference ID: 3032655

	to 12/01/08 (last subject completed):	
Title	The Safety, Tolerability, and Pharmacokinetic Evaluation of Clobazam Following Administration of Multiple Ascending Twice Daily Doses of Clobazam Tablets in Healthy Volunteers	
Study Design open-label, single-center, titrated, multiple-ascending-dose study		
☐ Bioequivalence	☑ Bioavailability	
Multiple-Dose Randomized Open-Label Single-Center 1-Peiod Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** N/A	

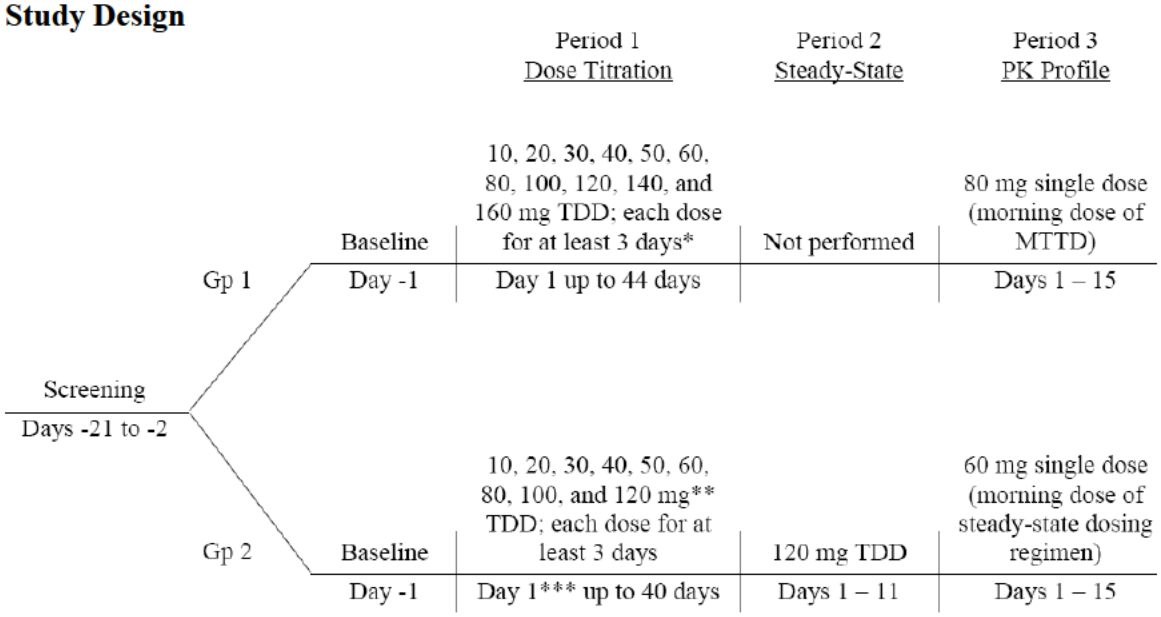
Primary Objectives

1. To evaluate the safety and tolerability of titrated multiple ascending oral doses of clobazam tablets given every 12 hours (BID) and to determine a maximum tolerated titrated dose (MTTD) in healthy subjects.
2. To evaluate the safety and tolerability of multiple oral doses of clobazam tablets

Secondary Objective

To characterize the multiple dose and steady-state pharmacokinetic profile of clobazam following BID administration of clobazam tablets.

Study Design



*** There was to be a minimum of 7 days between Day 1 of Group 1 and Day 1 of Group 2.
The purpose of Group 1 was to establish the MTTD, while that of Group 2 was to characterize the safety and steady-state pharmacokinetic profiles of clobazam at higher doses.

Treatments: (clobazam tablets manufactured by Catalent Pharma Solutions)
All study medication was administered BID under fasting conditions. In Group 1, clobazam was titrated from 10 mg total daily dose (TDD) (5 mg BID) to 160 mg TDD (80 mg BID) in Period 1 with each dose administered for at least 3 days prior to dose escalation; the TDD was incrementally increased by 10 mg through 60 mg TDD, and then by 20 mg until either 160 mg TDD was reached or the dose level was deemed intolerable by the Investigator. Tolerability was determined at the Investigator's discretion and included, but was not limited

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to, assessment scales and adverse event monitoring. The MTTD was defined as the highest dose in excess of 60 mg TDD that was tolerated for 3 consecutive days by at least 70% of the individuals who had previously tolerated 60 mg TDD. Period 2 was not conducted for Group 1, and Group 1 subjects proceeded directly from Period 1 to Period 3 following determination of the MTTD. In Period 3, subjects received a single morning dose of the MTTD (80 mg), and then remained in the clinic for approximately 2 weeks for pharmacokinetic and safety assessments.

In Group 2, dose titration was performed in a manner similar to Group 1, with the highest scheduled dose of 140 mg TDD. However, based on preliminary safety and pharmacokinetic assumptions, the highest dose actually administered in Group 2 was 120 mg TDD. Once subjects had been titrated to 120 mg TDD and demonstrated tolerability for 3 days in Period 1, they then received 120 mg TDD (60 mg BID) for an additional 11 days in Period 2, and a single morning dose of 60 mg on Day 1 of Period 3. Group 2 subjects also remained in the clinic for approximately 2 weeks following the final dose of study medication for pharmacokinetic and safety assessments.
All dosing took place under fasting conditions.

Sampling Times (plasma and urine)
In both groups, blood samples for pharmacokinetic analyses were collected predose on Day 1 of Period 1, predose and at 2 hours postdose on Day 3 of Period 1 for each dose level, and serial blood samples were collected from predose through 360 hours postdose in Period 3. In addition, in Group 2, predose blood samples were also collected on Days 9, 10, and 11 in Period 2. Urine samples were collected predose on Day 1 of Period 1, and over the 168-hour postdose interval in Period 3 in Groups 1 and 2.

Group	Day	Collection Time
1 and 2	Period 1, Day 1	Plasma: 0 (predose) Urine: -10 to 0 hr
1 and 2	Period 1, Day 3 of each dose	Plasma: 0 (predose) and 2 hr postdose
2	Period 2, Days 9, 10, 11	Plasma: 0 (predose)
1 and 2	Period 3, Day 1	Plasma: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 120, 168, 216, 264, 312 and 360 hr postdose Urine: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hr postdose.

A blood sample for possible CYP2C19 genotyping was collected at 0 hour (pre-dose) on Day 1 of Period 1.

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐

Statistical Method: Log-transformed AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F values of clobazam were evaluated by an analysis of variance (ANOVA) model using treatment, sequence, and period as fixed effects and subject within sequence as a random effect. A point estimate and a 90% confidence interval (CI) were obtained for the difference in means for the log-transformed values of AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/20/3
Age [Mean (range)]	37.1 (27.0 – 45.8)
Male/Female	12/12

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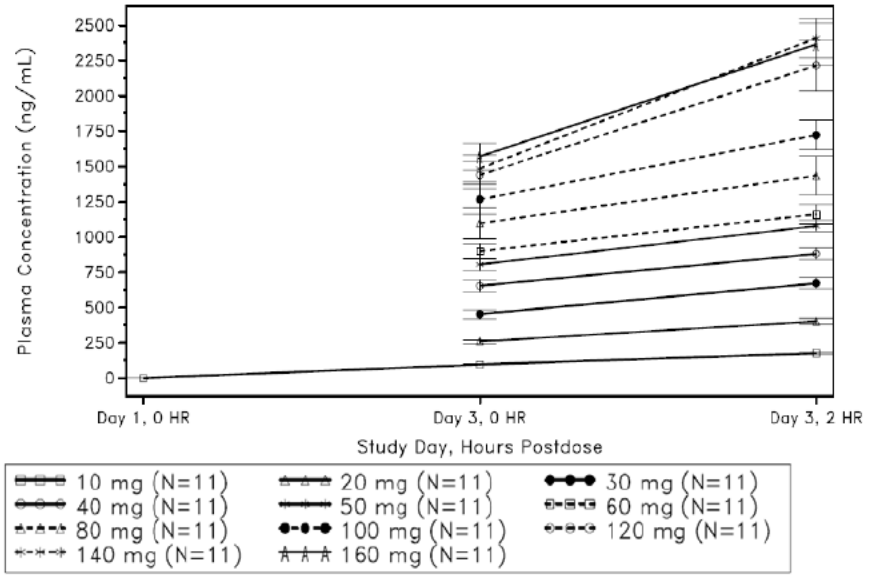
Race (Caucasian/Black/Asian/other)			21/2/0/1
	Group 1	**Group 2**	**Total**
	N = 12	**N = 12**	**N = 24**
Enrolled	12 (100.0%)	12 (100.0%)	24 (100.0%)
Completed (a)	10 (83.3%)	10 (83.3%)	20 (83.3%)
Discontinued	2 (16.7%)	2 (16.7%)	4 (16.7%)
Adverse Event	1 (8.3%)	2 (16.7%)	3 (12.5%)
Withdrew Consent	1 (8.3%)	0	1 (8.3%)

Results

Subject 2003 in Group 2 was a CYP2C19 poor metabolizer. As expected, inclusion of the data from Subject 2003 did not have a large effect on the plasma concentration profile of clobazam. However, for N-CLB, the plasma concentration profile for Group 2 was substantially greater than that for Group 1 when Subject 2003 was included, and the two groups had comparable plasma N-CLB concentration profiles when data for Subject 2003 were excluded. Pharmacokinetic analyses were performed both including and excluding this subject; however, the primary pharmacokinetic results presented in this report are those excluding Subject 2003.

Clobazam was extensively metabolized, with 1% or less of the parent compound recovered in urine in 24 hours. N-CLB was also extensively metabolized as evidenced by the low 24-hour N-CLB urinary recovery. The primary analyte in plasma was N-CLB (the ratio of metabolite to the parent drug in plasma was 3-5).

Plasma concentration of Clobazam (Group 1, Period 1)



Plasma concentration of Clobazam (Group 2, Period 1)

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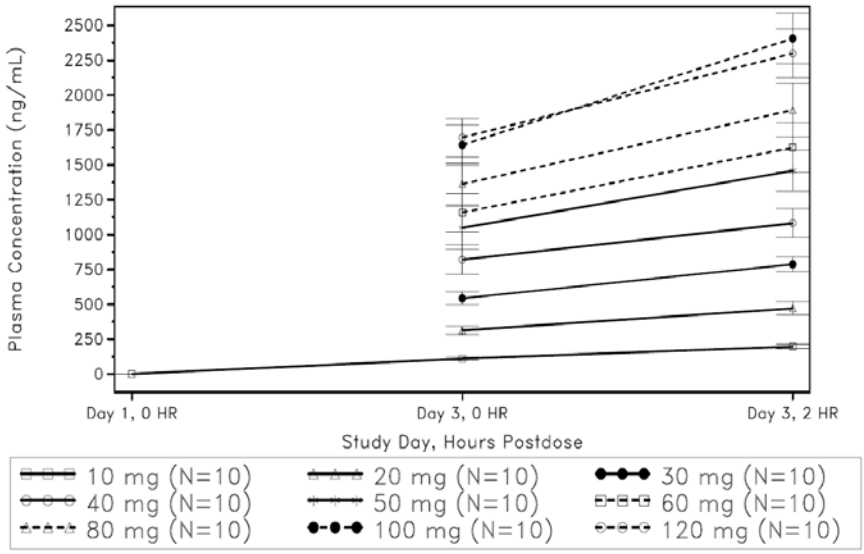

Table 13. Mean (%CV) Period 3 Clobazam and N-CLB Plasma and Urine Pharmacokinetic Parameters in Groups 1 and 2

	Period 3			
	Group 1 Clobazam 160 mg TDD PK Population N = 11		Group 2 Clobazam 120 mg TDD Steady-State Subject 2003 Excluded (a) N = 9	
Clobazam	Mean	(%CV)	Mean	(%CV)
$AUC_{0\text{-}168}$ (ng•hr/mL)	99,466	(31%)	75,031	(35%)
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	103,642	(34%)	78,374	(37%)
$AUC_{0\text{-}tau}$ (ng•hr/mL)	26,092	(13%)	19,867	(19%)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	104,184	(35%)	78,608	(37%)
C_{max} (ng/mL)	3,091	(10%)	2,629	(17%)
t_{max} (hr) (b)	2.00 (1.0 – 2.5)		1.50 (0.5 – 2.5)	
C_{min} (ng/mL)	NA		1,318	(21%)
C_{ave} (ng/mL)	NA		1,656	(19%)
CL/F (L/hr)	3.12	(13%)	3.12	(20%)
Vd/F (L)	165.96	(23%)	166.78	(23%)
λ_z (1/hr)	0.02	(29%)	0.02	(28%)
$t_{1/2}$ (hr)	37.98	(32%)	37.94	(26%)
$XU_{0\text{-}24}$ (ng)	610,662	(33%)	740,340	(31%)
$f_{e\ 0\text{-}24}$ (%)	0.76	(33%)	1.23	(31%)
CL_R (L/hr)	0.01	(38%)	0.02	(33%)
N-CLB				
$AUC_{0\text{-}168}$ (ng•hr/mL)	803,246	(45%)	850,298	(50%)
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	1,037,163	(56%)	1,139,771	(60%)
$AUC_{0\text{-}tau}$ (ng•hr/mL)	84,401	(29%)	89,539	(39%)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	1,127,815	(61%)	1,260,368	(68%)
C_{max} (ng/mL)	7,361	(30%)	8,090	(38%)
t_{max} (hr) (b)	3.00 (0.0 – 12.0)		2.50 (1.0 – 4.0)	
C_{min} (ng/mL)	NA		7,140	(38%)
C_{ave} (ng/mL)	NA		7,462	(39%)
λ_z (1/hr)	0.01	(40%)	0.01	(36%)
$t_{1/2}$ (hr)	71.37	(39%)	81.88	(42%)
Metabolic Ratio $AUC_{0\text{-}tau}$	3.39	(27%)	4.77	(35%)
$XU_{0\text{-}24}$ (ng)	5,755,975	(44%)	8,966,660	(41%)
CL_R (L/hr)	0.03	(40%)	0.04	(22%)

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In order to assess steady-state concentrations, Group 2 subjects received clobazam 120 mg TDD for a total of 11.5 days after being titrated from 10 mg TDD to 120 mg TDD, and daily predose blood samples were collected beginning on Day 9 of 120 mg TDD dosing. From Day 9 of Period 2 through Day 1 of Period 3, predose plasma concentrations of clobazam and N-CLB differed by <11% and 4 %, respectively, suggesting that steady-state concentrations were achieved by Day 9.

Mean (±SD) Predose Plasma Concentrations for Clobazam and N-CLB in Periods 2 and 3

Analyte Day	Group 2, Periods 2 and 3 Plasma Concentration Mean ± SD
Clobazam	
Day 9 (Period 2)	1475.00 ± 290.32
Day 10 (Period 2)	1429.78 ± 297.83
Day 11 (Period 2)	1397.89 ± 256.72
Day 1 (Period 3)	1317.56 ± 279.83
N-CLB	
Day 9 (Period 2)	7413.33 ± 2944.71
Day 10 (Period 2)	7132.22 ± 2639.57
Day 11 (Period 2)	7293.33 ± 2704.22
Day 1 (Period 3)	7140.00 ± 2718.77

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Reviewer's note: *Pre-dose plasma concentrations of clobazam on day 3 of 120 mg TDD are 1439.27 ng/mL in Group 1 and 1695 ng/mL in Group 2, which are similar to pre-dose clobazam concentrations on Days 9, 10 and 11 (steady-state). It suggests that the steady-state of clobazam may have been reached by 3 days of treatment, although the terminal elimination half-life of clobazm is estimated as 38 hrs.*

Urine concentrations of clobazam were low and the primary analyte in urine was N-CLB.

Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☑ No ☐ NA

Twenty-two (92%) of the 24 enrolled subjects reported at least 1 adverse event. Adverse events that were reported for 3 or more subjects included contact dermatitis (10 subjects), constipation (9 subjects), headache (8 subjects), dizziness (5 subjects), somnolence and upper respiratory tract infection (4 subjects each), and anxiety and withdrawal syndrome (3 subjects each).
In both groups 1 and 2, the incidences of adverse events were greatest during Period 3 due to withdrawal effects. Abrupt discontinuation or rapid reduction of benzodiazepines can result in benzodiazepine withdrawal syndrome. In order to assess the pharmacokinetic profile of the 120 and 160 mg TDD doses, clobazam dosing had to be abruptly discontinued at the highest doses in this study. Therefore, it was not unexpected that some subjects experienced withdrawal symptoms.
Subject 2003 was a poor CYP2C19 metabolizer, and on the 11th day of 120 mg TDD dosing, developed moderate delirium. On Day 11, the subject's predose plasma concentration of N-CLB

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was 26,700 ng/mL, which was approximately 4-fold higher than the mean C_{max} value for Group 2 (8090 ng/mL).

Conclusion

- Clobazam was extensively metabolized, with 1% or less of the parent compound recovered in urine.
- Following a dose-escalated titration phase, steady-state concentrations of clobazam and N-CLB were reached after 9 days of 120 mg TDD.
- At steady-state, plasma exposure to N-CLB was 5-fold greater than that to the parent drug. Plasma elimination half-lives were 38 hours for clobazam and 70-80 hours for N-CLB.
- The CYP2C19 PM had significantly elevated concentrations of N-CLB, but relatively equivalent concentrations of clobazam.

Additional Comments

To evaluate the dose linearity, mean plasma concentrations of clobazam before and 2 hours after each dose on Day 3 were compared by the reviewer.

Plasma Concentrations - Clobazam (ng/mL)

	Day 3, Predose		Day 3, 2 hours Postdose	
TDD	Group 1	Group 2	Group 1	Group 2
10 mg	95.12	100.22	175.55	184.89
20 mg	259.73	284.78	402.18	426.11
30 mg	452.00	499.44	673.18	739.56
40 mg	654.27	719.00	881.55	986.44
50 mg	805.45	897.89	1078.45	1337.67
60 mg	899.18	1025.56	1160.45	1469.89
80 mg	1096.73	1224.78	1434.55	1738.89
100 mg	1266.45	1508.89	1722.73	2280.00

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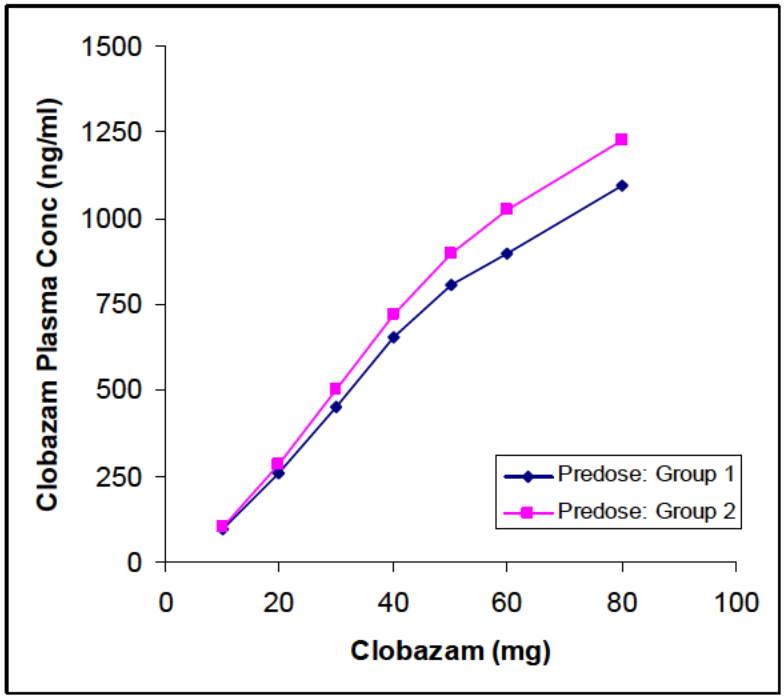

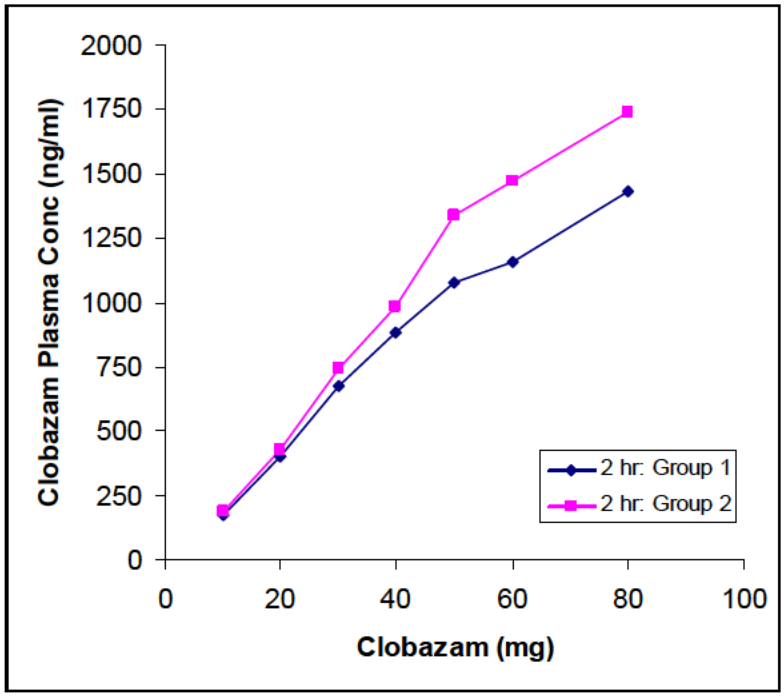

Comments: The incremental dose was given every 3 days and whether it has reached to the steady state before the next dose level was given can not be definitely ascertained. Nonetheless, based on Ctrough concentrations on Day 3, the PK of clobazam appears to be linear in the range of 10 mg to 60~80 mg TDD.

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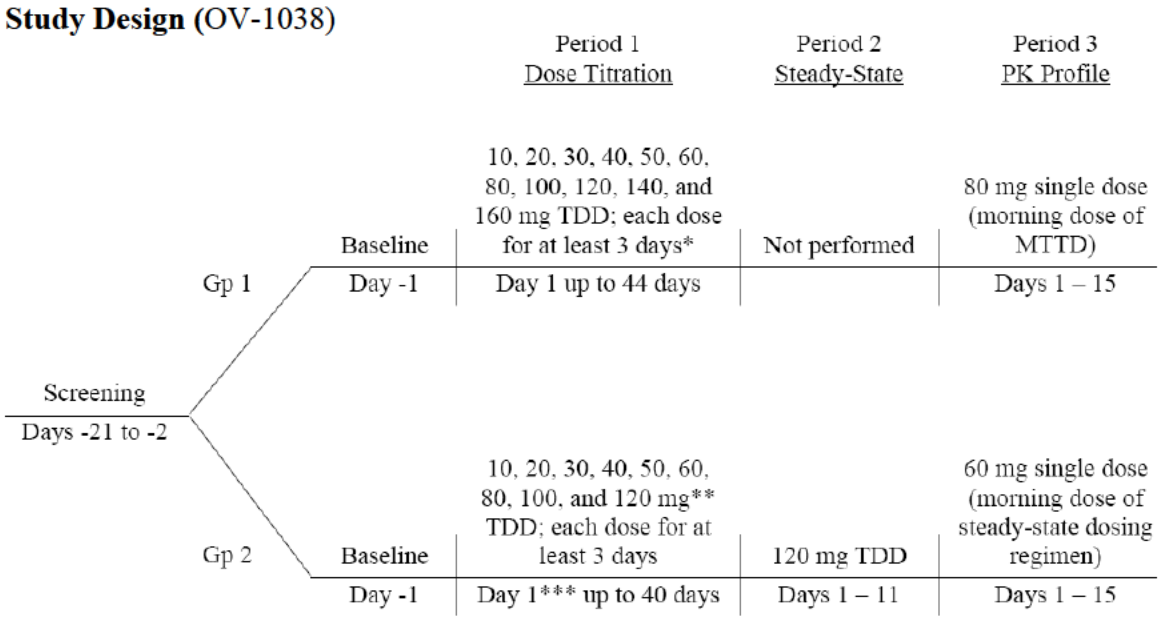
Report # 7802-135	**Study Period**: 02/04/09 to 10/11/10	
Title	Identification of Clobazam and Metabolites of Clobazam in Selected Human Plasma and Urine Samples Collected from Clinical Study OV-1038	
Study Design open-label, single-center, titrated, multiple-ascending-dose study		
☐ Bioequivalence	☐ Bioavailability	
Multiple-Dose Randomized Open-Label Single-Center 1-Peiod Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** N/A	

Study Objectives: To assess the presence of Clobazam and its metabolites in selected human plasma and urine samples collected from clinical study OV-1038

Study Design (OV-1038)



Treatments: (clobazam tablets manufactured by Catalent Pharma Solutions)

Sampling Times (plasma and urine)
Plasma and urine samples were collected from 12 subjects from Group 2 dosed with 60 mg of Clobazam in the morning following eleven days of Clobazam administration at 60 mg BID (120 mg total daily dose [TDD]). Plasma samples collected from subjects with wild type CYP2C19 genotype, i.e. Subject Nos. 2001, 2002, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, and 2012 at 2, 4, 12, 24, and 48 hours postdose, were pooled across subjects by time point. Urine samples collected from subjects with wild type CYP2C19 genotype were pooled (0.1% by weight) from 0-24, 24-48, 48-96, 96-120, 120-144, and 144-168 hours postdose.
Plasma samples collected from Subject No. 2003, a CYP2C19 PM, at 2, 4, 12, 24, and 48 hours postdose were analyzed individually.
Urine from Subject No. 2003 collected at 0-4, 4-8, 8-12, and 12-24 hours postdose was pooled to generate a single 0- to 24-hour pooled urine sample. Urine collected at 48-72 and 72-96 hours postdose was pooled to generate a single 48- to 96-hour urine sample. Samples collected from 24-48, 96-120, 120-144, and 144-168 hours postdose were analyzed individually.

Analytical Method: LC/MS/MS
The performance of the analytical method is acceptable. Yes ☑ No ☐

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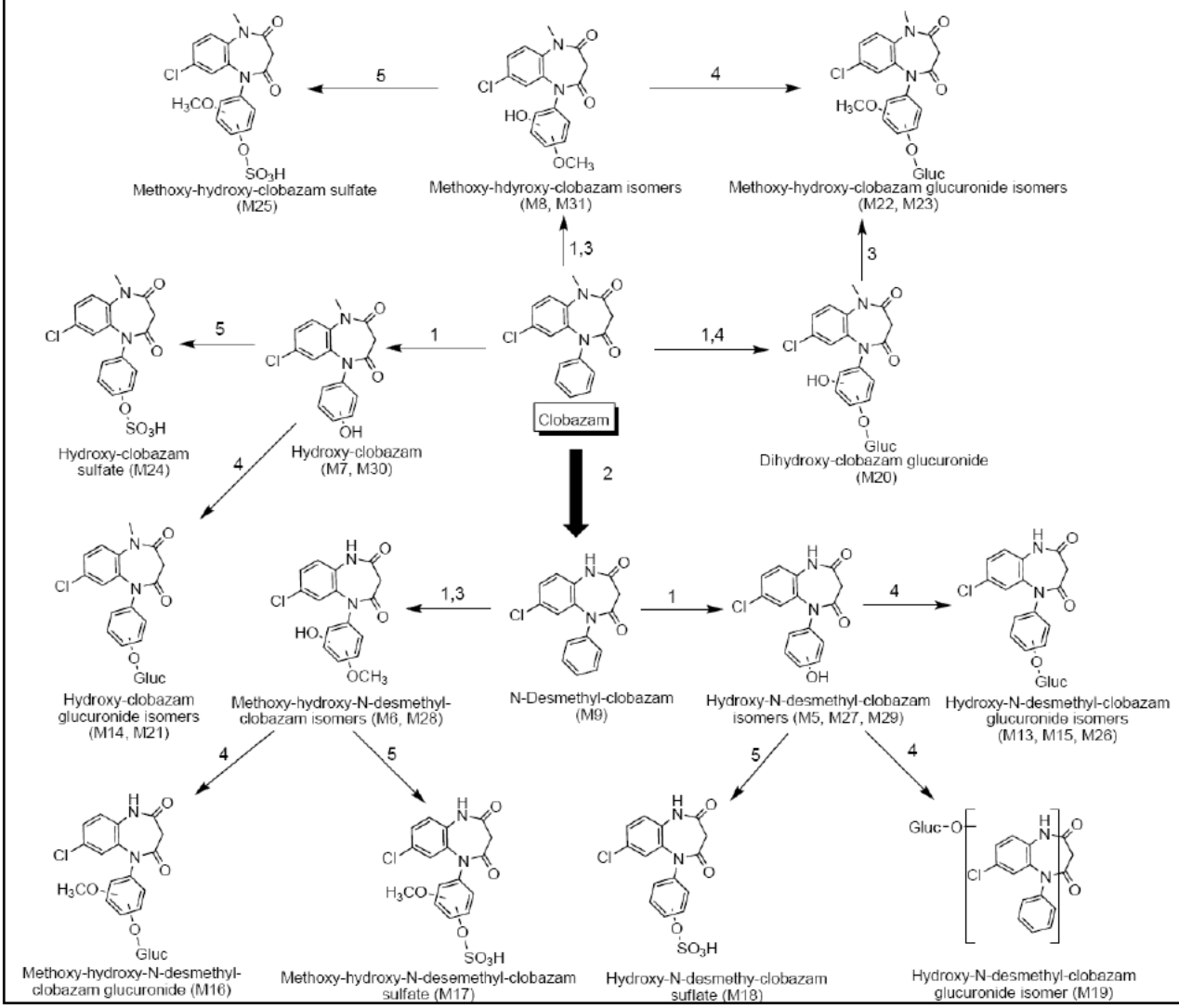
Metabolite percentages were calculated based on estimated multiple reaction monitoring (MRM) area counts for each metabolite, therefore, the analyses are of semi-quantitative nature.

Results

Following 11 days of Clobazam administrations at 60 mg BID, Clobazam and N-desmethyl Clobazam were the only major drug-related components in plasma. The ratio of N-CLB to Clobazam increased from 1.92 to 6.00 between the 2 hour and 48 hour postdose time interval in subjects with wild type CYP2C19 activity, and from 5.06 to 24.7 between the 2 hour and 48 hour postdose time interval in a CYP2C19 poor metabolizer. Clobazam was extensively metabolized and represented a minimal amount (0.11 to 6.51% for all subjects) of the drug-related material in urine. In human urine, N-CLB plus the sum of subsequent metabolites, comprised >80% of the drug-related components in urine.

Metabolic Pathway of Clobazam in human



Percentages of peak areas from MRM analysis of pooled plasma samples collected at specified times after dosing with Clobazam from human subjects (Group 2)

Final Metabolite Designation	Analyte	Retention Time (Minutes)	Percent[a] Time Point (Hours Postdose) 2	4	12	24	48
M13	M479A	8.40	0.00	0.00	0.00	0.00	0.00
M27	M303A	9.77	0.30	0.19	0.23	0.26	0.26
M14	M493A	9.96	0.01	0.01	0.01	0.01	0.01
M15	M479B	10.58	0.03	0.02	0.02	0.03	0.03
M16	M509A	10.72	0.02	0.02	0.01	0.02	0.02
M7	M317A	11.47	0.04	0.02	0.02	0.01	0.01
M17	M413	11.62	0.01	0.01	0.01	0.01	0.01
M18	M383	11.63	0.07	0.05	0.06	0.07	0.08
M19	M479C	NA	ND	ND	ND	ND	ND
M20	M509B	NA	ND	ND	ND	ND	ND
M21	M493B	12.27	0.01	0.01	0.01	0.01	0.01
M22	M523A	12.42	0.01	0.01	0.01	0.01	0.01
M23	M523B	13.01	0.00	0.00	0.00	0.00	ND
M8	M347A	13.14	0.02	0.01	0.01	0.01	0.01
M24	M397	NA	ND	ND	ND	ND	ND
M25	M427	NA	ND	ND	ND	ND	ND
M26	M479D	14.27	0.02	0.01	0.02	0.01	0.02
M5[b]	M303B	15.51	3.54	3.55	3.52	3.88	4.63
M6	M333A	15.63	0.07	0.07	0.08	0.07	0.07
M28	M333B	16.40	0.02	0.01	0.02	0.02	0.02
M29	M303C	NA	ND	ND	ND	ND	ND
M30	M317B	17.81	0.35	0.41	0.43	0.36	0.27
M31	M347B	18.05	0.02	0.01	0.01	0.01	0.01
M9	DCLB	20.58	62.7	68.3	70.5	74.8	81.1
M0	CLB	22.55	32.7	27.3	24.9	20.5	13.5

Reference ID: 3032655

Percentages of peak areas from MRM analysis of pooled urine samples collected a specified times after dosing with Clobazam from human subjects (Group 2)

Final Metabolite Designation	Analyte	Retention Time (Minutes)	Percent[a] Collection Interval (Hours Postdose) 0-24	24-48	48-96	96-120	120-144	144-168
M13	M479A	8.21	0.30	0.37	0.36	0.53	0.39	0.45
M27	M303A	9.70	23.2	24.9	24.8	23.5	22.4	22.4
M14	M493A[b]	9.90	1.40	1.07	0.63	0.35	0.34	0.27
M15	M479B[b]	10.43	4.34	5.90	6.95	6.74	7.89	8.81
M16	M509A[b]	10.59	0.68	0.89	0.98	0.91	0.89	1.05
M7	M317A	11.40	1.74	1.11	0.55	0.29	0.23	0.18
M17	M413[b]	11.55	2.46	2.75	2.65	2.73	2.26	2.41
M18	M383[b]	11.58	3.62	4.46	4.97	5.28	5.00	5.11
M19	M479C[b]	11.78	0.26	0.34	0.31	0.35	0.37	0.40
M20	M509B[b]	11.95	0.09	0.08	0.06	0.04	0.04	0.03
M21	M493B[b]	12.18	1.45	1.44	1.11	0.70	0.61	0.54
M22	M523A[b]	12.33	0.39	0.38	0.28	0.21	0.16	0.13
M23	M523B[b]	12.97	0.20	0.14	0.09	0.05	0.02	0.02
M8	M347A	13.05	0.75	0.58	0.35	0.20	0.17	0.13
M24	M397[b]	13.22	0.13	0.13	0.08	0.05	0.04	0.03
M25	M427[b]	13.24	0.25	0.20	0.13	0.09	0.06	0.05
M26	M479D[b]	14.35	2.89	3.54	3.15	3.81	3.42	3.41
M5	M303B	15.63	17.4	21.0	21.5	23.8	26.1	26.4
M6	M333A	15.77	1.88	1.70	1.99	1.70	1.61	1.34
M28	M333B	16.51	0.03	0.03	0.03	0.04	0.03	0.03
M29	M303C	16.52	0.55	0.67	0.61	0.56	0.53	0.51
M30	M317B	17.91	0.55	0.41	0.26	0.14	0.15	0.10
M31	M347B	18.12	0.06	0.03	0.03	0.01	0.02	0.01
M9	DCLB	20.64	28.9	24.9	26.5	27.0	26.3	25.6
M0	CLB	22.55	6.51	3.01	1.66	0.91	1.00	0.71
		Total*:	18.2	21.3	21.4	21.3	21.1	22.3

Conclusions from this semi-quantitative assessment are consistent with those derived for the clinical study (OV-1038) after quantitation of Clobazam and N-CLB using a validated LC-MS/MS method. The primary analyte in plasma was N-CLB, and $AUC_{0\text{-}tau}$ ratios indicated the plasma exposure to the metabolite was 3- to 5-fold greater than the exposure to the parent compound.

Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☐ No ☑ NA

Conclusion

- Clobazam was extensively metabolized, with ~2% of the parent compound recovered in urine. N-CLB was also extensively metabolized as evidenced by the low N-CLB urinary recovery.
- Conclusions from this semi-quantitative assessment are consistent with those derived for the clinical study (OV-1038).

Reference ID: 3032655

Report # LC-004	**Study Period**:	
Title	STUPY OF THE METABOLISM OF 14C-CARBONYL-LABELED CLOBAZAM (HR 376, RU 4723, ^{14}C-Clobazam) IN MAN, MONKEY, DOG , AND RAT (metabolite profiling of samples from LC-006)	
Study Design open-label, single-center, Single-dose study		
☐ Bioequivalence	☐ Bioavailability	
Single-Dose Randomized Open-Label Single-Center 1-Peiod Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** N/A	

Study Objectives: to study the metabolic behavior of clobazam in man, monkeys, dogs and rats

Study Design
3 healthy male subjects were enrolled in the study (43-46 years). They were fasted over night (no food, smoking, or alcoholic beverages for 11 h). At the start of the trial, they had a breakfast consisting of 2 slices of dark bread, 20 g of butter, 2 slices of cheese and 1 cup of mint tea with some sugar. Medication was given after the first slice of bread had been eaten. The lunch was given 4 h after drug intake.

Treatments: Clobazam hard gelatin capsules
The specific radioactivity of the HR376-14C (^{14}C-Clobazam) was 2.8 mCi/g (10.4 x 107 sec-1g-1, batch No, 3107 III). The content calculated radiochemioally was 39 mg.

Sampling Times (plasma and urine)
Serum samples for determination of total radioactivity and profiling were collected at pre-dose and at 1.5, 3.5, 5, 8 and 24 hr post-administration.

Urine and feces were collected during the 24 hr pre-dose interval and at 24 hr interval periods through 21-days post-administration
Urine: U3= 4-6 h after administration, U7 = 12-24 h after administration, U11= 96-120 h after administration; separate samples from each of three subjects
Feces: K1 and K2 = 1st and 2nd day post-dose

Analytical Method:
The performance of the analytical method is acceptable. Yes ☐ No ☐
Radiolabeled components in biological matrices (blood, plasma, urine and feces) were separated by 1- or 2-dimensional thin layer chromatography. Quantitation of 14C-containing material was performed by autoradiography. Radiolabeled material separated by TLC was eluted for further elucidation. The chemical structures of metabolites were elucidated by a combination of mass spectrometry, retention time compared against that of synthetic standards and/or nuclear magnetic resonance spectrometry.

The concentrations of total 14C-radioactivity in human serum, blood and urine were determined directly by liquid scintillation counting.

Results

Following a single oral dose at 39 mg of 14C-clobazam, four radiolabeled components were identified in serum: 4'hydroxy-*N*-CLB (M5), 4'-hydroxy clobazam (M7), *N*-CLB (M9), and

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CLB. Only clobazam and *N*-CLB were found in serum in significant amounts at any time point. 4'hydroxy-*N*-CLB (M5) represented <3% of the total radioactivity in a pooled sample (N=3) obtained at 24 hr postdose. 4'-hydroxy clobazam (M7), represented <5% of the total radioactivity at any time point.

Table 2. Separation and Identification of ^{14}C-Clobazam and Related Metabolites in Selected Serum Samples from Normal Volunteers after a Single Dose of ^{14}C-Clobazam (39 mg, N=3)

Sample time	Total Serum Radioactivity (ng eq./mL)	Percent (%) of Total Serum Radioactivity (Analyte Concentration, ng eq./mL)		
		4'-Hydroxy clobazam (M7)*	*N*-CLB (M9)*	Clobazam*
1.5 hours	513± 151	ND	5.0 ± 3.6 (25.7 ± 18.5)	95.0 ± 3.6 (487.7 ± 18.5)
3.5 hours	647 ±142	1.7 ± 1.2 (10.8 ± 7.5)	8.7 ± 2.5 (56.0 ± 16.3)	89.7 ± 2.9 (579.8 ± 18.7)
5.0 hours	577 ± 159	2.7 ± 2.1 (15.4 ± 12.0)	11.3 ± 0.6 (65.4 ± 3.3)	86.0 ± 2.0 (495.9 ± 11.5)
8.0 hours	497 ± 116	3.7 ± 1.2 (18.2 ± 5.7)	17.0 ± 4.6 (84.4 ± 22.8)	79.3 ± 4.9 (394.0 ± 24.5)
24.0 hours (pool of 3 subjects)	430 ± 101	0.5 # (2.15)	32 (137.6)	65 (279.5)

Table 3. Mean AUC0-24 of '*C-Clobazam and Related Metabolites in Human Serum Following a Single Oral Administration of ^{14}C-Clobazam (39 mg, N=3)

	AUC_{0-24} # ng•hr/mL	% Clobazam AUC
Clobazam	8903	100
4'-hydroxyclobazam (M7)	201	2.3
N-CLB (M9)	2193	25*

Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☐ No ☑ NA

Conclusion

After a single oral administration of 14C- clobazam (39 mg), *N*-CLB is the only human circulating metabolite that represents >10% of the clobazam AUC0-24, thus, the only major metabolite.

Comments

The mean exposures to clobazam and N-CLB in this legacy study are comparable to those observed in Study OV-1038 at a similar dose (40 mg).
Serum samples in this study were collected only up to 24 hr post-dose. The results of this study, therefore, are likely to underestimate the extent of production of N-CLB and its subsequent metabolites.

Reference ID: 3032655

Report # LC-006	**Study Period**:	
Title	Human trials with HR 376 (^{14}C-Clobazam) Pharmacokinetics after oral administration of 39 mg of a compound labeled in the carbonyl group.	
Study Design open-label, single-center, Single-dose study		
☐ Bioequivalence	☐ Bioavailability	
Single-Dose Randomized Open-Label Single-Center 1-Peiod Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** N/A	

Study Objectives: PK and metabolism to be examined in 3 healthy subjects after administration of 40 mg of HR 376-14C (^{14}C-Clobazam). Comparative measurements in serum are also to be performed with two nonradiochemioal methods.

Study Design
3 healthy male subjects were enrolled in the study (43-46 years). They were fasted over night (no food, smoking, or alcoholic beverages for 11 h). At the start of the trial, they had a breakfast consisting of 2 slices of dark bread, 20 g of butter, 2 slices of cheese and 1 cup of mint tea with some sugar. Medication was given after the first slice of bread had been eaten. The lunch was given 4 h after drug intake.

Treatments: Clobazam hard gelatin capsules
The specific radioactivity of the HR376-14C (^{14}C-Clobazam) was 2.8 mCi/g (10.4 x 107 sec-1g-1, batch No, 3107 III). The content calculated radiochemioally was 39 mg

Sampling Times (plasma and urine)
Serum samples for determination of total radioactivity and profiling were collected at pre-dose and at 1.5, 3.5, 5, 8 and 24 hr post-administration. Urine and feces were collected during the 24 hr pre-dose interval and at 24 hr interval periods through 21-days post-administration

Analytical Method:
The concentrations of total 14C-radioactivity in human serum, blood and urine were determined directly by liquid scintillation counting. In feces, it was determined by liquid scintillation counting following combustion of aliquots of fecal homogenates.
Radiolabeled components in biological matrices (blood, plasma, urine and feces) were separated by 1- or 2-dimensional thin layer chromatography. Quantitation of 14C-containing material was performed by autoradiography. Radiolabeled material separated by TLC was eluted for further elucidation. The chemical structures of metabolites were elucidated by a combination of mass spectrometry, retention time compared against that of synthetic standards and/or nuclear magnetic resonance spectrometry.
No formal bioanalytical report is available for this study.

Results

Following a single oral dose at 39 mg of 14C-clobazam with breakfast to three healthy volunteers, a mean of 93% of the dose was recovered. Elimination of 14C-clobazam and related metabolites was slow and significant amounts of radioactivity were recovered through 21-days post-dose. During this 21 d, 81 to 84 % of the radioactivity administered was recovered in urine and 7 to 13 % in feces (either unabsorbed radioactivity and/or biliary clearance).

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The metabolism of the substance was not considered in this analysis.
Half lives for three subjects

	Half-life (d)		
	Z_5	Z_6	Z_7
serum	2.5	4.2	3.3
urine	2.7	4.8	3.4
feces	2.8	5.5	3.9

Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☐ No ☑ NA

Conclusion

- After a single oral administration of 14C- clobazam (39 mg, N=3, fed), 93% of the dose recovered. The drug-related material was well absorbed and primarily eliminated in the urine (82%), with a small percentage eliminated in the feces (11%).

4.4.2 Intrinsic Factors

Report # Literature	**Study Period**
Title	**Pharmacokinetics of a Single Oral Dose of Clobazam in Patients with Liver Disease.** Monjanel-Mouterde et al., *Pharmacology & Toxicology* 1994, 74, 345-350.

Study Design

Single-Dose	Non-Randomized	Open-Label	Parallel	2-center
No. of Groups	☑Normal	☑Mild or Moderate	☑Severe	Total
No. of Subject	6	5	4	19
Age (range)	24-29	34-73		NA
Dose	20	20	20	NA

Reviewer's note: *While the study included mild, moderate and severe hepatic impairment subjects per Child-Pugh score, no subject-based assignment can be made with regards to the severity as there is no information on the Child-Pugh classification for each subject.*

- **Dosing**: single oral dose, 20 mg
- **Sampling Times** (PK, plasma): post-dose, 0.5, 1, 2, 3, 6, 9, 12 and 24 hr post-dose, then once a day till complete elimination
- **Protein Binding**: ☐All ☐Limited ☑Not Determined
- **Classification of hepatic function:**
  - Hepatic function was determined via Child-Pugh classification ☑ Yes ☐ No

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- Hepatic function was determined at: ☑ Screening ☑Baseline
- The groups are matched by ☐Age ☑ Body Weight ☑ Race and Sex Not Known
- The selected dose is acceptable ☑ Yes ☐ No
- Dosing is long enough to obtain steady state ☐ Yes ☐ No ☑ Not Applicable
- Sample size was determined based on statistical analysis ☐Yes ☐ No ☑ Not Known

- **Analytical Method**
  - Gas liquid chromatography with electron capture detection
  - Linearity of the assay for clobazam (CLB) and N-CLB: 1 to 4000 ng/ml.
  - Correlation coefficients were in the range of 0.9848 to 0.9998
  - Recovery rate: 80 ±4%.
  - Limit of quantification: 1 ng/ml

Pharmacokinetics

	Hepatic Function		
	Normal	**Mild, Moderate, Severe impairment**	**t-test**
N	6	9	
CLB C_{max} (ng/mL)	350 (18)	240 (47)	S
N-CLB C_{max} (ng/mL)	96 (21)	84 (22)	NS
CLB T_{max} (h)	1.6 (50)	2.5 (44)	NS
N-CLB T_{max} (h)	48 (40)	88 (22)	S
CLB $AUC_{0-\infty}$ (ng h/mL)	NA	NA	
CLB $t_{1/2}$ (h)	22 (26)	51 (39)	S
CLB CLt (L/hr)	2.8 (14)	2.7 (40)	NS
CLB Vd (L)	81 (25)	178 (40)	S
CLB kel (/hr)	0.066 (36)	0.061 (47)	NS
%Fu	NA	NA	

Values represent mean [%CV]
CLB – Clobazam; N-CLB – demethyl clobazam
S – significant; NS – not significant

Safety

Was there any death or serious adverse events? ☐ Yes ☐ No ☑ NA

Conclusions

Should the dose be adjusted in subjects with hepatic impairment? ☑ Yes ☐No

Comments

Since the hepatic impairment status of each subject was not provided in the literature, no evaluation can be made per the impairment categories to assess potential correlations between hepatic impairment and the effects on PK of clobazam.

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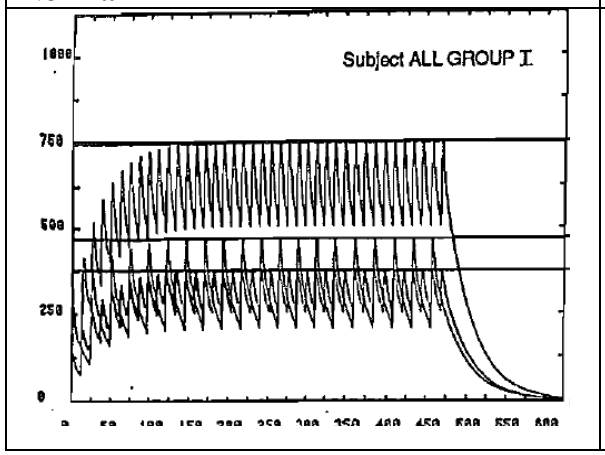
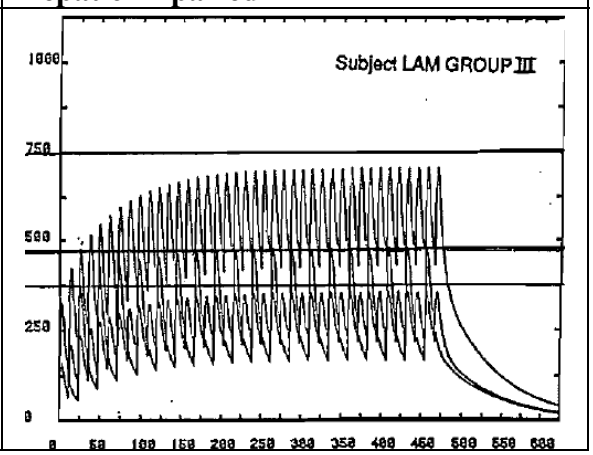
Hepatic impairment did not result in increases of Cmax of either clobasam or N-CLB. Clobasam Cmax was in fact lower in patients with liver disease (by 31 %) compared to the normal volunteers, while there were no statistical differences in total plasma clearance of clobazam between two groups, which may indicate similar clobazam plasma exposure (AUC) between normal and hepatic impaired subjects. No significant differences were reported in Cmax of N-CLB. To note, equivalence determination in this study was made using t-test.

Tmax of N-CLB was prolonged in patients with liver disease, suggesting liver disease may have altered the desmethylation of clobazam. To assess if there is an accumulation of clobazam following multiple dose administration, the authors fitted clobazam pharmacokinetics to a two-compartment model and performed a modeling simulation for the three typical subjects from each group using 3 putative therapeutic regimens: 10 mg bid, 20 mg qd and 20 mg bid for 20 days. Based on the visual inspection of the simulated graphs, plasma clobazam concentrations at the steady-state appear to be comparable between the normal and the hepatic impaired subjects in all dosing regimen scenarios. On face, results of simulation seem reasonable; however an internal validation of the simulation could not be conducted since no individual data exist.

Multiple dose simulation

Normal	**Hepatic Impaired**
	

Simulation of Clobazam plasma concentrations following repeated administration of clobazam for 20 day (doses: -10 mg bid, -20 mg qd, -20 mg bid)

Clobazam tablet used in this study is not the TBM formulation and thus the absolute values of Cmax and Tmax in this study are not relevant in the assessment of PK of the TBM product. Nonetheless, the results of this study provide supportive information regarding the effect of hepatic impairment on PK of clobazam.

Collectively, there are limited data to characterize the effect of hepatic impairment on the PK of clobazam or N-CLB. In addition, the active metabolite N-CLB was not determined in this study. There is inadequate information about metabolism of clobazam in patients with severe hepatic impairment. For these reasons, the maximum tolerated daily doses may remain the same for patients with mild to moderate hepatic impairment, but with a reduced initial doses and a slower titration. There is no dosing information recommended for patients with severe hepatic impairment.

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According to the label for Frisium® 10 (clobazam) marketing outside of U.S.:

- Frisium 10 is contraindicated with severe impairment of liver function (risk of precipitating a certain disease of the brain [encephalopathy]).
- "Patients with impairment of renal or hepatic function have an increased response to Frisium 10 and a higher susceptibility to its adverse effects; in such patients, a dose reduction may be necessary. In long-term treatment, renal and hepatic function must be checked regularly.'

However, no study information or data available to in this submission to support similar labeling recommendation for use of Onfi in LGS patients with hepatic dysfunction.

Report # OV-1032	**Study Period** 09 June - 04 November 2009
Title	The Effect of Renal Impairment on the Pharmacokinetics of Clobazam

Study Objectives:

To determine the pharmacokinetic profile of clobazam and N-CLB following single and multiple doses of clobazam in subjects with impaired renal function relative to matched control subjects with normal renal function.

Study Design

Multiple-Dose	Non-Randomized	Open-Label	Parallel	Multi-Center	
No. of Groups	☑Normal	☑Mild	☑Moderate	☐Sever	☐ESRD
No. of Subject /Completed	7/7 (per each group)	7/7	6/6	NA	NA
Males	4 for mild 6 for moderate	4	6	-	-
Age, Mean(range)	60.6 (54.5 - 67.2)	65.1 (52.1 - 74.5)	63.1 (49.7 - 72.6)	-	-

Treatment: A single 20 mg dose of clobazam on Day 1, followed by clobazam 20 mg QD on Days 5 through 11.

Sampling Times:

- Serial blood samples and pooled urine specimens were collected over 96 hours postdose relative to dosing on Days 1 and 11, and predose (trough) were collected on Days 8, 9, and 10
- Analyte; clobazam and N-desmethylclobazam (N-CLB)
- Blood samples for cytochrome P450 2C19 (CYP2C19) genotyping were collected prior to dosing on Day 1.

Classification of renal function is consistent with the FDA Guidance Recommendations:
☑ Yes ☐ No

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- Renal function was determined via ☑ G-C formula ☐ MDRD formula
- Renal function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☑ Smoking Status ☑ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Protein Binding: ☐All ☑Selected (in all subjects)
  Sampling Times: predose and at 2, 12, and 24 hours post dose on Day 1 and Day 11
  Method: Equilibrium Dialysis
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☑ Yes ☐ No
- The overall study design acceptable: ☑ Yes ☐ No (see Comments)

Analytical Method (Study Samples Analysis)

- Study samples were analyzed within the established stability period: ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No
  ☑ Yes ☐ No

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Analyte		Clobazam/N-CLB
Method		LC/MS/MS
Matrix		Plasma
Calibration	Range	1.00 -1000 ng/mL
	N	14
	%CV ≤	7.4
	%Bias	-2.0 - 1.5
Quality Control	%CV ≤	5.4
	%RE =	-0.8 - 2.9

Results

Pharmacokinetics:

Effect of Mild Renal Impairment on Multiple-Dose Pharmacokinetics:

For clobazam, the geometric mean ratio indicated 12% and 13% increases in AUC0-24 and AUC0-96, respectively, and a 24% increase in Cmax in subjects with mild renal impairment relative to control subjects.

For N-CLB, the geometric mean ratios indicated increases of 31% in AUC0-24, 36% in AUC0-96, and 34% in Cmax among subjects with mild renal impairment relative to matched controls. Renal clearance was comparable between the 2 groups (0.02 vs. 0.03 L/hr).

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	Day 11 Arithmetic Mean (%CV)		Geometric Mean Ratio (Mild/ Control)	90% CI (a) for Ratio
	Mild Impairment Clobazam 20 mg QD N = 6	Matched Controls Clobazam 20 mg QD N = 6		
Clobazam				
$AUC_{0\text{-}24}$ (ng•hr/mL)	13,864 (24%)	12,891 (29%)	1.12	(0.8304, 1.5114)
$AUC_{0\text{-}96}$ (ng•hr/mL)	38,769 (34%)	38,551 (41%)	1.13	(0.7595, 1.6674)
C_{max} (ng/mL)	902 (34%)	723 (25%)	1.24	(0.9104, 1.6911)
t_{max} (hr) (b)	1.00 (0.50 – 1.50)	2.25 (2.00 – 4.00)	n/a	n/a
C_{min} (ng/mL)	454 (24%)	425 (35%)	1.16	(0.8359, 1.6056)
CL/F (L/hr)	1.51 (24%)	1.68 (31%)	0.89	(0.6616, 1.2043)
CL/F/70 kg (L/hr)	1.47 (35%)	1.51 (45%)	0.90	(0.6682, 1.2206)
$XU_{0\text{-}96}$ (ng)	336,880 (32%)	503,942 (38%)	0.71	(0.4989, 1.0144)
$CL_{R\ 0\text{-}96}$ (L/hr)	0.01 (20%)	0.01 (32%)	0.63	(0.4710, 0.8485)
N-CLB				
$AUC_{0\text{-}24}$ (ng•hr/mL)	16,133 (23%)	11,964 (34%)	1.31	(0.9941, 1.7208)
$AUC_{0\text{-}96}$ (ng•hr/mL)	68,614 (15%)	51,646 (36%)	1.36	(1.0267, 1.8120)
C_{max} (ng/mL)	836 (14%)	641 (37%)	1.34	(0.9986, 1.8075)
t_{max} (hr) (b)	96.0 (2.5 – 96.0)	96.0 (6.0 – 96.0)	n/a	n/a
C_{min} (ng/mL)	588 (22%)	436 (34%)	1.31	(0.9913, 1.7399)
$XU_{0\text{-}96}$ (ng)	1,102,138 (30%)	1,426,088 (44%)	0.78	(0.5399, 1.1315)
$CL_{R\ 0\text{-}96}$ (L/hr)	0.02 (20%)	0.03 (15%)	0.57	(0.4648, 0.7065)

Effect of Moderate Renal Impairment on Multiple-Dose Pharmacokinetics:

For clobazam, the geometric mean ratios indicated a <1% change in AUC values, and a 3% increase in Cmax in subjects with moderate renal impairment relative to control subjects. Clobazam CL/F and CL/F/70 kg differed by <1%.

For N-CLB, the geometric mean ratios indicated increases of 11% in AUC0-24, 13% in AUC0-96, and 12% in Cmax among subjects with moderate renal impairment relative to matched controls. Renal clearance values for N-CLB were not different between the 2 groups (0.02 L/hr for both).

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	Day 11 Arithmetic Mean (%CV)		Geometric Mean Ratio (Moderate/ Control)	90% CI (a) for Ratio
	Moderate Impairment Clobazam 20 mg QD N = 6	Matched Controls Clobazam 20 mg QD N = 6		
Clobazam				
AUC_{0-24} (ng•hr/mL)	11,995 (26%)	12,521 (25%)	1.00	(0.7799, 1.2926)
AUC_{0-96} (ng•hr/mL)	32,926 (28%)	35,003 (35%)	1.00	(0.7103, 1.3941)
C_{max} (ng/mL)	726 (23%)	737 (23%)	1.03	(0.8324, 1.2860)
t_{max} (hr) (b)	1.25 (0.50 – 6.00)	1.50 (0.50 – 4.00)	n/a	n/a
C_{min} (ng/mL)	395 (29%)	412 (27%)	1.01	(0.7772, 1.3182)
CL/F (L/hr)	1.78 (29%)	1.67 (23%)	1.00	(0.7737, 1.2822)
CL/F/70 kg (L/hr)	1.54 (23%)	1.53 (22%)	1.00	(0.7807, 1.2907)
XU_{0-96} (ng)	417,421 (41%)	361,583 (37%)	1.23	(0.8158, 1.8603)
$CL_{R\ 0-96}$ (L/hr)	0.01 (23%)	0.01 (35%)	1.24	(0.8407, 1.8231)
N-CLB				
AUC_{0-24} (ng•hr/mL)	13,513 (53%)	12,332 (16%)	1.11	(0.8299, 1.4779)
AUC_{0-96} (ng•hr/mL)	59,071 (57%)	52,281 (19%)	1.13	(0.8100, 1.5812)
C_{max} (ng/mL)	685 (56%)	614 (19%)	1.12	(0.8079, 1.5562)
t_{max} (hr) (b)	78.0 (47.0 – 96.0)	78.0 (23.0 – 96.0)	n/a	n/a
C_{min} (ng/mL)	513 (56%)	456 (12%)	1.13	(0.8479, 1.4953)
XU_{0-96} (ng)	1,231,917 (57%)	1,148,776 (30%)	1.13	(0.7144, 1.7844)
$CL_{R\ 0-96}$ (L/hr)	0.02 (26%)	0.02 (36%)	1.00	(0.6820, 1.4595)

1. Is there a relationship between creatinine clearance and AUC? ☐ Yes ☑ No, if yes explain
2. Is there a relationship between creatinine clearance and C_{max}? ☐ Yes ☑ No, if yes explain

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

No adverse events causing withdrawal, SAEs, or deaths were reported.
There were no clinically important findings noted in the physical examination, vital sign, clinical laboratory, ECG, or OAAS data.

Conclusions:

Is there is a need to adjust the dose in patients with renal impairment? ☐ Yes ☑ No

The higher mean Cmax and AUC values observed in mild renal impairment group is mainly driven by one subject (#2008). Plasma protein binding of clobazam or N-CLB was comparable between the subjects with mild or moderate renal impairment and healthy control. No correlation was observed between creatinine clearance and clobazam plasma clearance in similar patient population, according to results of population PK analysis. Collectively, the small increases in the exposure of clobazam and N-C LB are not considered clinically meaningful and no dosage adjustment is recommended for subjects with mild or moderate renal impairment.

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Comments:

This study did not include subjects with severe renal impairment or end-stage renal disease (ESRD). Upon request during the review cycle, the sponsor provided a case report in the literature that showed dose-adjusted serum concentrations of clobazam and N-CLB in one subject with ESRD were comparable to those in renally healthy subjects both during the normal dosing interval and in hemodialysis (see comment below). With such limited experience with clobazam in those patients, in patients with severe renal impairment, doses should be titrated slowly in those patients with close monitoring for adverse events. It is not conclusive if clobazam or its active metabolite, N-clobazam, is dialyzable based on the limited available information.

One publication was provided by the sponsor during review cycle:

> *"Clobazam and N-desmethylclobazam serum concentrations in endstage renal failure and hemodialysis. Roberts GW and Zoanetti.GD. The Annals of Pharmacotherapy 2004; 28: 966-967."*

This is a case report of an 18 year old male patient with ESRD (GFR < 10 mL/min) on hemodialysis who has been taking clobazam 5 mg po bid. The patient's hepatic function was normal. Serum concentrations of clobazam and N-CLB were measured before and 3.5 hours after the dialysis and results were compared to those with normal renal function in literature on chronic clobazam therapy. The authors found that dose-adjusted serum concentrations of clobazam and N-CLB were comparable between renally healthy subjects and subjects with ESRD during the normal dosing interval and in hemodialysis.

Effect of dialysis for clobazam or N-CLB in ESRD patients was not evaluated in this study, therefore, it is not known based on this study if clobazam or N-CLB is dialyzable. However, considering the physico-chemical property and the disposition of clobazam, we do not anticipate a significant effect of dialysis procedure to help remove the accumulated of clobazam from the body.

4.4.3 Extrinsic Factors

Report # OV-1021	**Study Period** Nov 16, 2008 - Dec 23, 2008	**EDR Link**
Title	The Effect of Multiple Doses of Ketoconazole or Omeprazole on the Single Dose Pharmacokinetic Profile of Clobazam in Healthy Adult Subjects	
Study Design		
Rationale: Clobazam is metabolized to N-desmethylclobazam (N-CLB, M9) primarily via CYP3A4, and also to a lesser extent via CYP2C19. N-CLB is then further biotransoformed via CYP2C19 to 4'-hydroxy-N-CLB. Because of the potential for drug interactions with CYP3A4 and CYP2C19 inhibitors, this study was conducted to determine the effects of ketoconazole (CYP3A4) and omeprazole (CYP2C19) on the single dose PK of clobazam.		

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Single-Dose Randomized Open-Label Parallel Single-Center 1-Peiod Healthy Vonuteers

Sequence	**A**	**B**
	Clobazam alone	Ketoconazole or omeprazole and clobazam

Study Design

Screening	Check-in/ Baseline	Clobazam 10 mg Single Dose/PK	In-Patient PK/ Washout	Out-Patient PK/ Washout	Re-admission	Ketoconazole/ Omeprazole Dosing (a)	Ketoconazole/ Omeprazole & Clobazam Dosing (b)	In-Patient PK	Out-Patient PK	End of study/ Early Term
Days –21 to –2	Day -1	Day 1	Days 2-6	Days 7-15	Day 16	Days 17-21	Day 22	Days 23-27	Days 28-36	Day 37
	< ------Confinement to Clinic --->				< ---------- Confinement to Clinic ---------- -->					

(a) Either ketoconazole 400 mg QD (Group 1) or omeprazole 40 mg QD (Group 2) on mornings of Days 17-21.
(b) Clobazam 10 mg coadministered with either ketoconazole 400 mg (Group 1) or omeprazole 40 mg (Group 2).

Drug Treatments:
Single dose of clobazam 10 mg [1 x 10 mg tablet] administered on Days 1 and 22.
Ketoconazole 400 mg QD or omeprazole 40 mg QD on Days 17-22
Clobazam doses were administered under fasting conditions (Days 1 and 22). Food and water were allowed 2 hours following clobazam, ketoconazole, or omeprazole administration on Day 1 and Days 17 through 22.

- **Sampling Times**

Clobazam pharmacokinetic blood collection on Days 1 and 22: Predose (0 hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 312 and 360 hours postdose.
Ketoconazole/omeprazole collections: predose on Days 19, 20 and 21, and at predose (0 hour), 0.5, 1, 2, 3, 4, 8, 12 and 24 hours postdose on Day 22.
Clobazam urine collections: Day 1 predose (-10 to 0 hour) and on Days 1 and 22 at 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose.
Blood samples for possible genotyping pre-dose on Day 1.

Analytical Method:

Analyte		Clobazam/N-CLB
Method		HPLC/MS/MS
Matrix		Plasma
Calibration	Range	1.00 -1000 ng/mL
	N	24
	%CV ≤	7.0
	Accuracy(%)	95.8 - 104.5
Quality Control	%CV ≤	6.1
	Accuracy(%)	98.3 - 100.0

Statistical Method: A paired t-test was performed on the natural logarithms of C_{max}, $AUC_{0\text{-}lqc}$, and $AUC_{0\text{-}inf}$ for clobazam and N-CLB. Point estimates and 90% confidence intervals for the ratio of the geometric means of the test treatment (clobazam + ketoconazole or clobazam + omeprazole on Day 22) compared to the reference treatment (clobazam alone on Day 1) were obtained.

Study Population :

Randomized/Completed/ Discontinued Due to AE	36/35/0

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Age [Median (range)]	31.88 (19.0 – 44.8)
Male/Female	17/19
Race (Caucasian/Black/Asian)	25/10/1

No CYP2C19 poor metabolizer

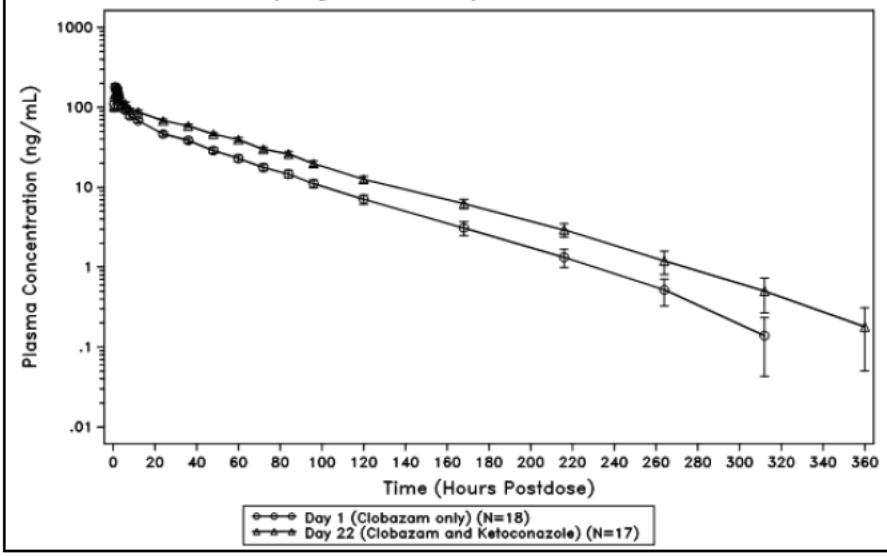
Results

I. Effect of Ketoconazole Coadministration

- Coadministration of ketoconazole and clobazam resulted in 53-54% increases in clobazam AUC values, and a 15% decrease in clobazam Cmax.
- Coadministration resulted in 15-18% increases in N-CLB AUC and a 1% decrease in N-CLB Cmax.
- Urinary excretion of clobazam was minimally increased, and N-CLB was minimally decreased, with coadministration.

	Mean (%CV)		Geometric Mean Ratio (Coadmin/ clobazam alone)	90% CI (a) for Ratio
	Clobazam 10 mg + Ketoconazole 400 mg N=17	Clobazam 10 mg N=18		
Clobazam				
$AUC_{0\text{-}lqc}$ (ng·hr/mL)	6,332 (19)	4,275 (30)	1.539	(1.424, 1.663)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6,432 (19)	4,360 (29)	1.529	(1.418, 1.648)
C_{max} (ng/mL)	190.1 (21)	223.7 (18)	0.855	(0.790, 0.926)
t_{max} (hr) (b)	2.00 (0.5, 2.5)	1.00 (0.5, 2.6)		
$t_{1/2}$ (hr)	41.7 (32)	37.5 (34)	n/a	n/a
N-CLB				
$AUC_{0\text{-}lqc}$ (ng·hr/mL)	7,106 (54)	6,433 (60)	1.154	(1.075, 1.238)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	7,851 (61)	6,987 (70)	1.175	(1.098, 1.257)
C_{max} (ng/mL)	37.5 (43)	37.8 (37)	0.986	(0.931, 1.045)
t_{max} (hr) (b)	84.0 (48.0, 120.0)	60.0 (36.0, 84.0)		
$t_{1/2}$ (hr)	74.0 (44)	67.5 (36)	n/a	n/a

Mean Plasma Concentrations of Clobazam With and Without Ketoconazole Coadministration (Days 1 and 22)



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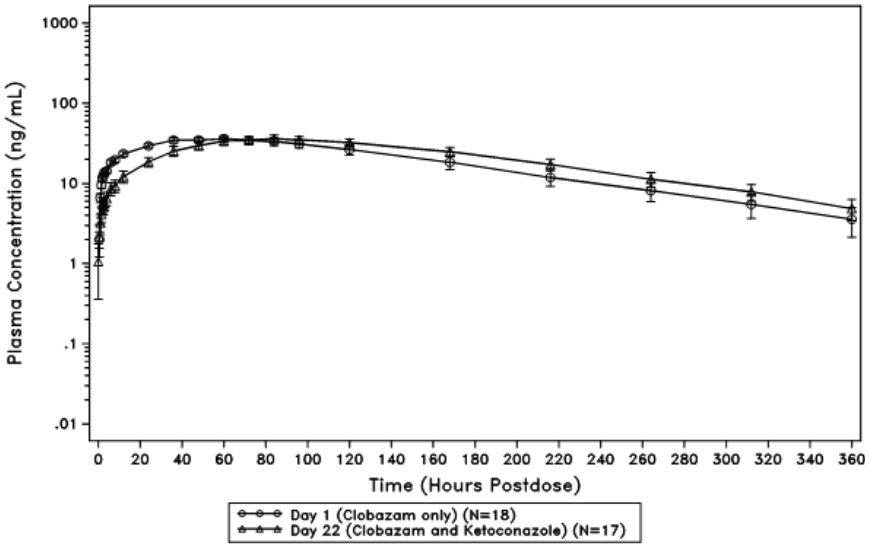
Mean Plasma Concentrations of N-CLB With and Without Ketoconazole Coadministration (Days 1 and 22)



II. Effect of Omeprazole Coadministration

- Coadministration of omeprazole and clobazam resulted in a 30% increase in clobazam AUC values, and a 4% decrease in clobazam Cmax.
- Coadministration resulted in increases of 36-37% in N-CLB AUC and 15% in N-CLB Cmax relative to clobazam alone.
- There were no significant changes in the urinary excretion of clobazam and N-CLB with coadministration.

	Mean (%CV)		Geometric Mean Ratio (Coadmin/ clobazam alone)	90% CI (a) for Ratio
	Clobazam 10 mg + Omeprazole 40 mg N=18 (a)	Clobazam 10 mg N=18		
Clobazam				
$AUC_{0\text{-}lqc}$ (ng·hr/mL)	5,311 (21)	4,142 (31)	1.304	(1.230, 1.383)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	5,398 (21)	4,239 (31)	1.304	(1.229, 1.384)
C_{max} (ng/mL)	210.6 (21)	218.2 (15)	0.956	(0.873, 1.047)
t_{max} (hr) (c)	1.25 (0.5, 4.0)	1.00 (0.5, 4.0)	n/a	n/a
$t_{1/2}$ (hr)	36.7 (32)	31.8 (37)	n/a	n/a
N-CLB				
$AUC_{0\text{-}lqc}$ (ng·hr/mL)	8,000 (59)	5,838 (58)	1.368	(1.294, 1.446)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	9,176 (85)	5,549 (50)	1.358	(1.277, 1.444)
C_{max} (ng/mL)	46.3 (34)	39.2 (24)	1.154	(1.094, 1.217)
t_{max} (hr) (c)	60.0 (48.0, 84.0)	42.0 (24.0, 84.0)	n/a	n/a
$t_{1/2}$ (hr)	66.7 (83)	54.4 (38)	n/a	n/a

Mean Plasma Concentrations of Clobazam With and WithoutOmeprazole Coadministration (Days 1 and 22)

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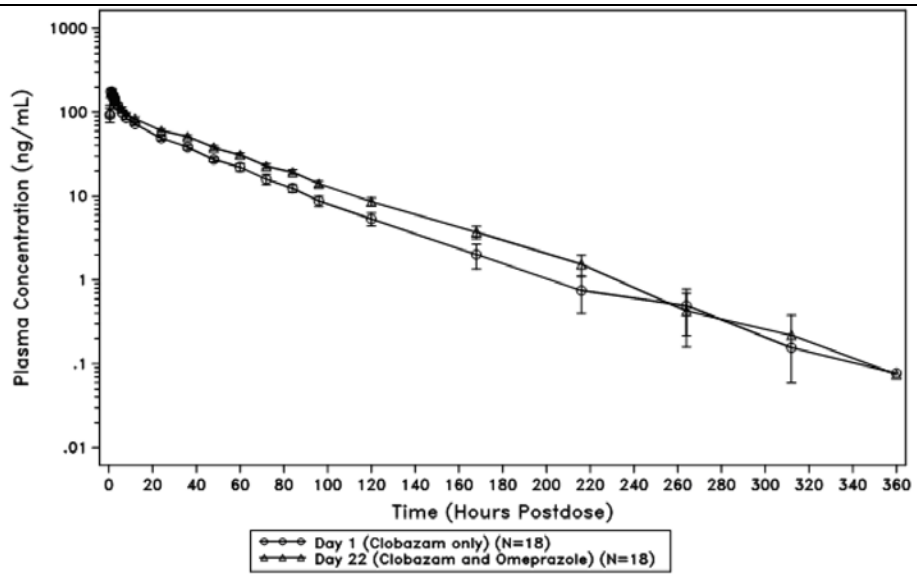
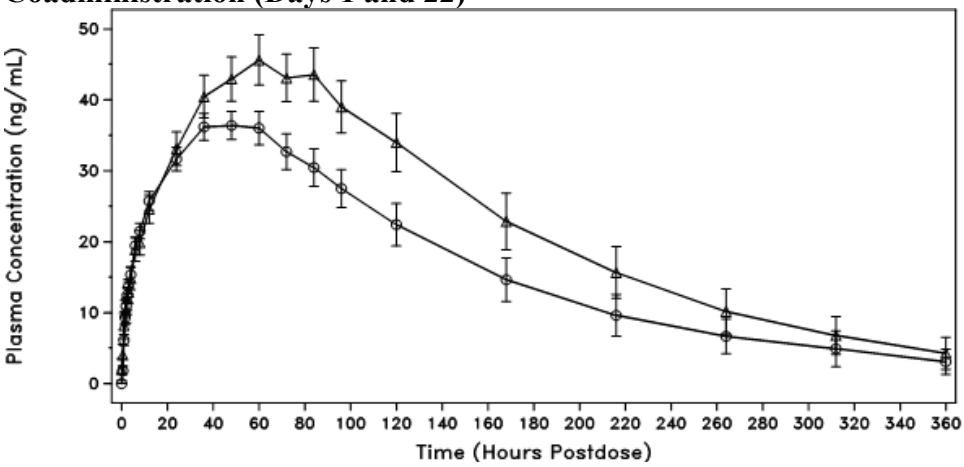


Mean Plasma Concentrations of N-CLB With and Without Omeprazole Coadministration (Days 1 and 22)



Summary

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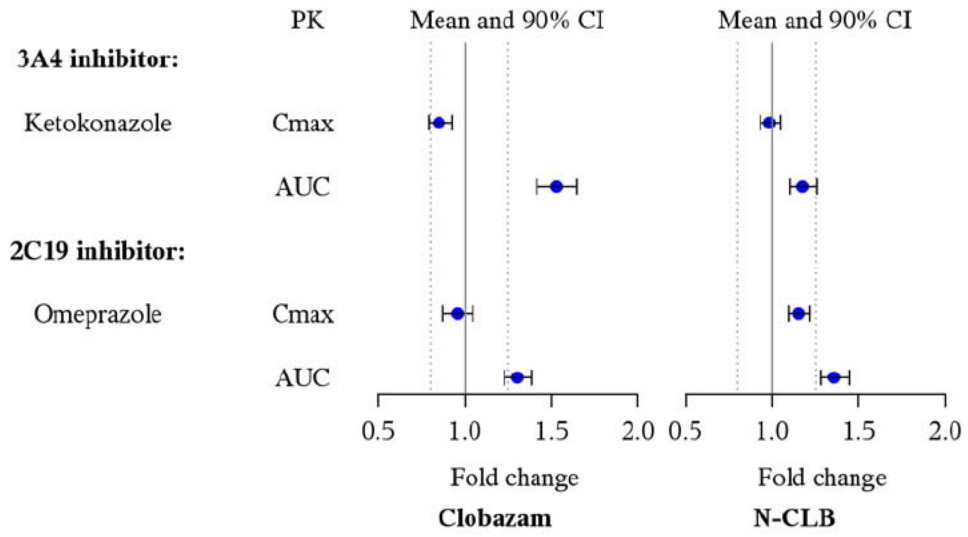

Assessments of Ketoconazole and Omeprazole

Table 9. Mean (±SD) Predose Plasma Concentrations for Ketoconazole and Omeprazole

Analyte / Day	Mean (ng/mL) ± SD: Ketoconazole N = 17	Mean (ng/mL) ± SD: Omeprazole N = 18
Day 19, predose	231.9 ± 213.20	0.03 ± 0.14
Day 20, predose	325.5 ± 255.7	0.09 ± 0.27
Day 21, predose	339.4 ± 257.9	0.03 ± 0.15
Day 22, predose	378.5 ± 277.8	0.10 ± 0.24

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- Administration of ketoconazole (a potent CYP3A inhibitor) 400 mg QD with a single dose of clobazam 10 mg did not have a clinically meaningful effect on plasma exposures to clobazam or N-CLB.
- Administration of omeprazole (a moderateCYP2C19 inhibitor) 40 mg QD with a single dose of clobazam 10 mg did not have a clinically significant effect on the plasma exposures to clobazam or NCLB based on the Sponsor's study design.

Comments

- For the drug-interaction study with omeprazole, considering the rapid absorption and short elimination half-life of omeprazole, and slow formation of N-CLB from clobazam and its long elimination t1/2, the inhibitory effect of omeprazole on CYP2C19 observed in this study is not considered definitive.
- Clobazam was shown to be a P-gp substrate based on the results from in vitro studies. However, the impact of co-administrated P-gp inhibitors on clobazam plasma exposure in vivo is unknown. Per Clinical Pharmacology review of Pre-NDA submission (meeting date August 31, 2010), the Agency agreed to the Sponsor's proposal to

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conduct the in vivo drug-drug interaction study between clobazam and a pure, strong P-gp inhibitor as a PMC/PMR at the NDA stage.

- During the review cycle, we noted that a dedicated drug-drug interaction study between clobazam and ketoconazole, a duel inhibitor for CYP3A4 and P-gp, exerted a combined effect of clobazam AUC increase by 54%. Results of this study suggest that the P-gp inhibition in humans will unlikely to exceed the observed exposure increase from this study and, therefore, an additional in-vivo study as PMR is not necessary.
- The Frisium label approved in Canada states that patients should not drink alcohol during treatment with Frisium 10 because of an increased risk of sedation and other adverse effects.
- Concomitant CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital) in clinical studies likely contributed to altered pharmacokinetic properties of CLB and N-CLB, noticeably the higher N-CLB exposure in patients than in healthy volunteers. It was reported that the antiepileptic effect of orally administered CLB in long-term therapy is predominantly due to its N-CLB metabolite. The need for dosage adjustment has not been suggested in literature or prescription information when patients are on CLB and concomitant enzyme-inducing AEDs.

Report # OV-1023	**Study Period** August 5, 2009 to August 30, 2009	**EDR Link**
Title	An Open-Label, Multiple-Dose Study to Assess the Effects of Clobazam on the Pharmacokinetics of Midazolam, Caffeine, Tolbutamide, and Dextromethorphan in Healthy Subjects	

Study Design

Study Rationale: In vitro metabolism studies have shown that clobazam and N-CLB are not significant inducers or inhibitors of the major CYP isozyme. This study is to confirm the in vitro results on 4 CYP P450 substrates in vivo: midazolam (CYP3A4), caffeine (CYP1A2), tolbutamide (CYP2C9), and dextromethorphan (CYP2D6).

Multiple-Dose Randomized Open-Label Parallel Single-Center 1-Peiod Healthy Vonuteers

Screening	Baseline	Treatment		Treatment			Final Visit/ Early Termin-ation
		Drug Cocktail (a) Single Dose	PK/ Washout	Clobazam 40 mg QD	Clobazam 40 mg + Drug Cocktail (a) Single Dose	PK	
Days -21 to -2	Day -1	Day 1	Days 2-3	Days 4-18	Day 19	Days 20-25	Day 26

Clobazam dose administration: 40 mg (20mg tablet x 2) on Days 4 through 19.
Drug cocktail dose administration: caffeine 200 mg (1 x 200 mg tablet), tolbutamide 500 mg (1 x 500 mg tablet), dextromethorphan 30 mg (2 x 15 mg gel capsule), and midazolam 2 mL syrup on Days 1 and 19.

Subjects abstained from all food and drink (except water) at least 8 hours prior to dosing

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on Days 1 and on Days 4 through 19.

- **Sampling Times**

Clobazam pharmacokinetic blood collections: predose (0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose relative to dosing on Day 4; predose (0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72 hours postdose relative to dosing on Day 19; and predose (0 hour) on Days 16 through 18.
Drug cocktail pharmacokinetic blood collections: predose (0 hour) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose relative to dosing on Days 1 and 19.
Drug cocktail pharmacokinetic urine collections: predose (-10 to 0 hour) on Day 1, and 0-12, 12-24, 24-36, 36-48, 48-60, and 60-72 hours postdose relative to dosing on Days 1 and 19.

Analytical Method:

Analyte		Clobazam/N-CLB
Method		HPLC/MS/MS
Matrix		Plasma
Calibration	Range	1.00 -1000 ng/mL
	N	50
	%CV ≤	6.0
	%Bias	-2.5- 3
Quality Control	%CV ≤	6.1
	%Bias	98.3 - 100.0

Statistical Method: With the ANOVA analysis using the natural logarithms of C_{max}, $AUC_{0\text{-}lqc}$, and $AUC_{0\text{-}inf}$, point estimates and 90% CIs for the ratio of the geometric least squares means of the test treatment (clobazam + drug cocktail, Day 19) compared to the reference treatment (drug cocktail, Day 1) were obtained.

Study Population :

Randomized/Completed/ Discontinued Due to AE	18/18/0
Age [Median (range)]	31.4 (18.2 – 45.5)
Male/Female	18/0
Race (Caucasian/Black/Asian)	8/10/0

Results

<u>I. Effect of Clobazam Co-administration on PK of Caffeine (CYP1A2 Probe)</u>

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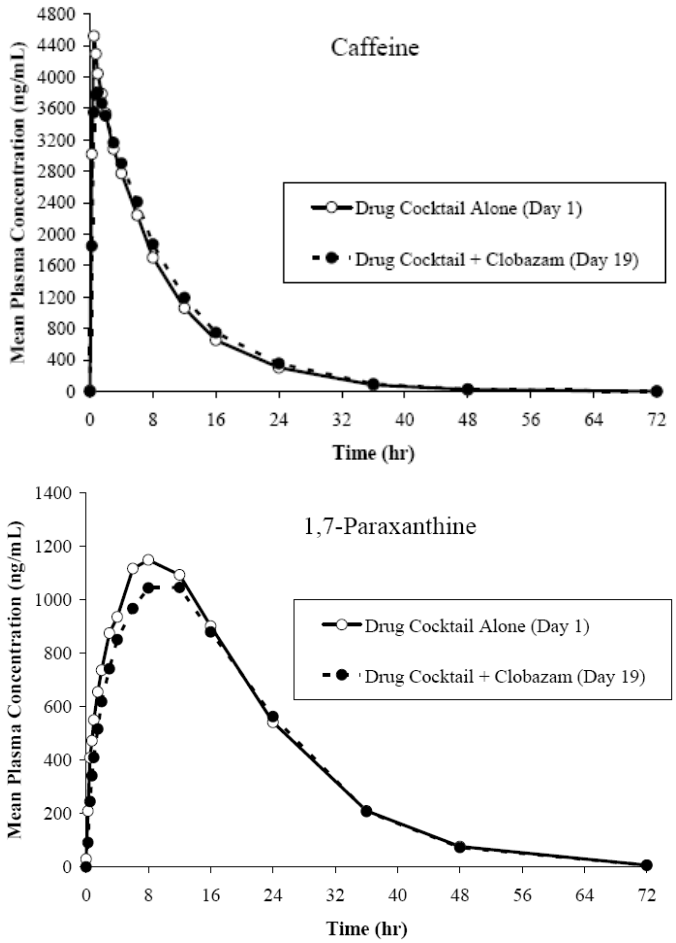
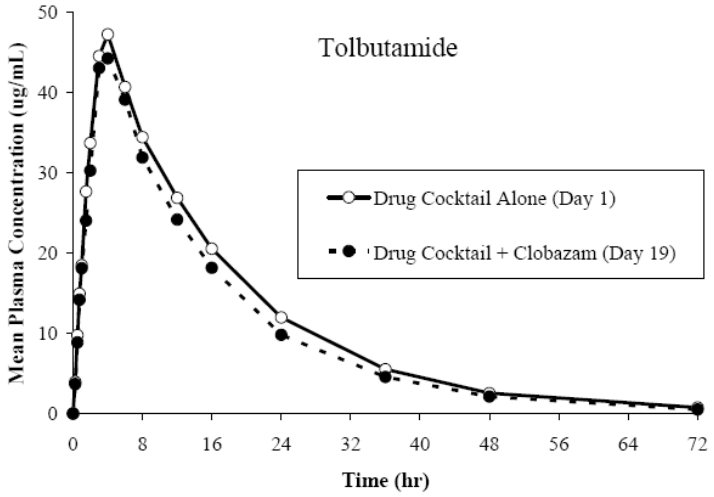


	Arithmetic Mean (%CV)		Geometric Mean Ratio (Coadmin/ Drug Cocktail alone)	90% CI (c) for Ratio
	Drug Cocktail (a) + Clobazam Day 19 N = 18 (b)	Drug Cocktail Alone (a) Day 1 N = 18		
Caffeine				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	40,028 (29%)	38,038 (33%)	1.06	(0.99, 1.14)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	40,622 (29%)	38,528 (33%)	1.06	(0.99, 1.14)
C_{max} (ng/mL)	4,676 (24%)	5,486 (24%)	0.85	(0.76, 0.95)
t_{max} (hr) (d)	0.75 (0.25 – 2.02)	0.50 (0.25 – 1.50)	n/a	n/a
CL/F (L/hr)	5.36 (31%)	5.73 (32%)	n/a	n/a
Vd/F (L)	45.98 (17%)	45.91 (18%)	n/a	n/a
$t_{1/2}$ (hr)	6.25 (20%)	5.92 (26%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	4,500 (37%)	4,812 (35%)	n/a	n/a
$f_{e\ 0\text{-}72}$ (%)	2.25 (37%)	2.41 (35%)	n/a	n/a
1,7-Paraxanthine				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	26,430 (24%)	27,836 (27%)	0.96	(0.91, 1.02)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	27,274 (23%)	28,626 (28%)	0.96	(0.91, 1.01)
C_{max} (ng/mL)	1,103 (14%)	1,213 (15%)	0.91	(0.89, 0.93)
t_{max} (hr) (d)	8.00 (6.00 – 12.03)	8.00 (6.00 – 12.00)	n/a	n/a
$t_{1/2}$ (hr)	8.04 (19%)	7.65 (23%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	14,336 (28%)	17,159 (23%)	n/a	n/a

Reference ID: 3032655

- For caffeine, the geometric mean ratios for coadministration of clobazam with drug cocktail relative to drug cocktail alone were 1.06 for $AUC_{0\text{-}lqc}$ and $AUC_{0\text{-}inf}$, and 0.85 for C_{max} . The 90% CIs for AUC were within the (0.80, 1.25), while those for Cmax were slightly below the lower limit of 0.8 (0.76, 0.95).
- For 1,7-paraxanthine, the 90% CIs for AUC and Cmax ratios were within the (0.80, 1.25) no-effect range.

II. Effect of Clobazam Coadministration on the PK of Tolbutamide (CYP2C9 Probe)



Reference ID: 3032655

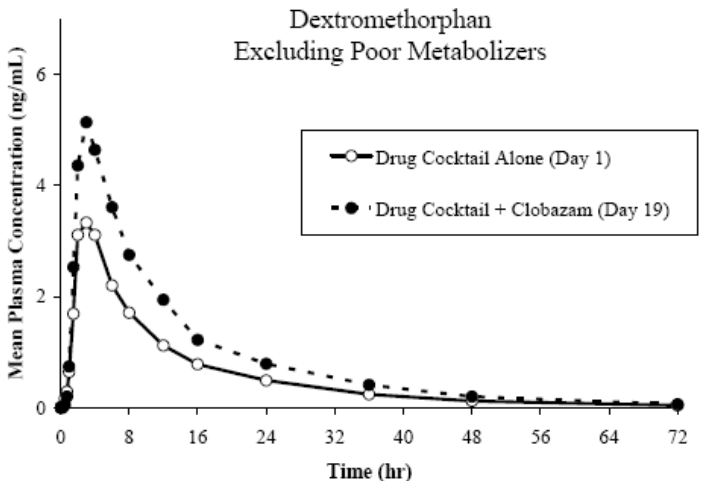
	Arithmetic Mean (%CV)		Geometric Mean Ratio (Coadmin/ Drug Cocktail alone)	90% CI (c) for Ratio
	Drug Cocktail (a) + Clobazam Day 19 N = 18 (b)	Drug Cocktail Alone (a) Day 1 N = 18		
Tolbutamide				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	730,541 (33%)	823,116 (32%)	0.89	(0.85, 0.93)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	746,043 (35%)	841,599 (35%)	0.89	(0.85, 0.93)
C_{max} (ng/mL)	47,511 (13%)	50,806 (12%)	0.93	(0.88, 0.99)
t_{max} (hr) (d)	3.53 (2.00 – 6.00)	3.50 (1.50 – 6.00)	n/a	n/a
CL/F (L/hr)	0.73 (27%)	0.65 (28%)	n/a	n/a
Vd/F (L)	9.02 (14%)	8.67 (16%)	n/a	n/a
$t_{1/2}$ (hr)	9.28 (37%)	10.02 (36%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	487 (45%)	595 (38%)	n/a	n/a
$f_{e\ 0\text{-}72}$ (%)	0.10 (45%)	0.12 (38%)	n/a	n/a
4-Hydroxytolbutamide				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	9,241 (32%)	8,282 (26%)	1.10	(1.05, 1.16)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	9,439 (32%)	8,461 (26%)	1.11	(1.05, 1.16)
C_{max} (ng/mL)	650 (31%)	504 (28%)	1.27	(1.19, 1.35)
t_{max} (hr) (d)	6.00 (3.05 – 6.05)	4.00 (2.00 – 6.00)	n/a	n/a
$t_{1/2}$ (hr)	9.66 (32%)	10.24 (30%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	79,104 (25%)	69,015 (20%)	n/a	n/a
Carboxytolbutamide				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	30,883 (24%)	30,844 (27%)	1.01	(0.98, 1.03)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	31,320 (23%)	31,314 (27%)	1.01	(0.98, 1.04)
C_{max} (ng/mL)	2,208 (35%)	1,908 (41%)	1.17	(1.08, 1.27)
t_{max} (hr) (d)	4.00 (3.00 – 8.00)	5.00 (2.00 – 8.00)	n/a	n/a
$t_{1/2}$ (hr)	9.37 (33%)	9.76 (33%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	490,979 (8%)	493,861 (8%)	n/a	n/a

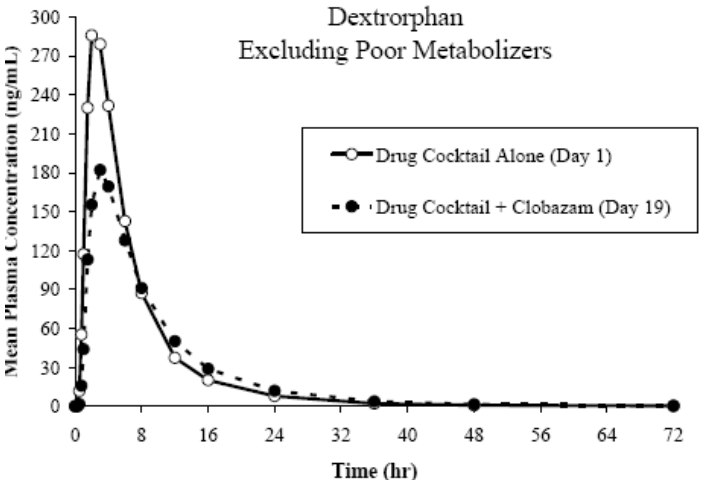
- For tolbutamide, the 90% CIs for AUC and C_{max} geometric mean ratios were within the (0.80, 1.25) no-effect range.
- For 4-hydroxytolbutamide and carboxytolbutamide, 90% CIs for AUC geometric mean ratios were within the (0.80, 1.25) no-effect range, while the upper ranges of 90% CIs for C_{max} were slightly above 1.25 (1.35 and 1.27, respectively). There were no statistically significant differences in median t_{max} values.

III. Effect of Clobazam Coadministration on PK of Dextromethorphan (CYP2D6 Probe)

Two subjects (1008 and 1015) were poor CYP2D6 metabolizers, and these subjects had overall dextromethorphan plasma exposures at least 5-fold greater, and overall dextrorphan exposures at least 6-fold lower, than the remaining subjects. PK analyses for dextromethorphan and dextrorphan were performed both including and excluding these subjects; however, the primary pharmacokinetic results for dextromethorphan are considered to be those excluding Subjects 1008 and 1015.

Reference ID: 3032655





	Arithmetic Mean (%CV)			
	Clobazam 40 mg + Drug Cocktail (a) Day 19 N=18 for All Subjects N = 16 for Excluding Poor Metabolizers (b)	Drug Cocktail (a) Day 1 N=18 for All Subjects N = 16 for Excluding Poor Metabolizers (b)	Geometric Mean Ratio (Coadmin/ Drug Cocktail alone)	90% CI (c) for Ratio
Dextromethorphan – Excluding Poor Metabolizers				
$AUC_{0\text{-}lqe}$ (ng•hr/mL)	64.1 (136%)	39.9 (156%)	1.90	(1.56, 2.32)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	66.6 (136%)	41.6 (155%)	1.95	(1.59, 2.39)
C_{max} (ng/mL)	5.65 (83%)	3.93 (101%)	1.59	(1.31, 1.93)
t_{max} (hr) (e)	3.00 (2.00 – 4.02)	2.00 (1.00 – 4.00)	n/a	n/a
CL/F (L/hr)	1,103 (81%)	2,407 (95%)	n/a	n/a
Vd/F (L)	11, 450 (66%)	21,953 (65%)	n/a	n/a
$t_{1/2}$ (hr)	8.67 (36%)	8.48 (38%)	n/a	n/a
$XU_{0\text{-}72}$ (µg) (f)	189 (146%)	118 (138%)	n/a	n/a
Dextrorphan – Excluding Poor Metabolizers				
$AUC_{0\text{-}lqe}$ (ng•hr/mL)	1,714 (21%)	1,939 (20%)	0.88	(0.85, 0.92)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	1,731 (21%)	1,958 (20%)	0.88	(0.85, 0.92)
C_{max} (ng/mL)	187 (29%)	308 (24%)	0.59	(0.56, 0.63)
t_{max} (hr) (e)	3.00 (2.00 – 4.02)	2.00 (1.50 – 4.00)	n/a	n/a
$t_{1/2}$ (hr)	6.93 (46%)	6.47 (60%)	n/a	n/a
$XU_{0\text{-}72}$ (µg) (f)	8,698 (17%)	9,998 (13%)	n/a	n/a

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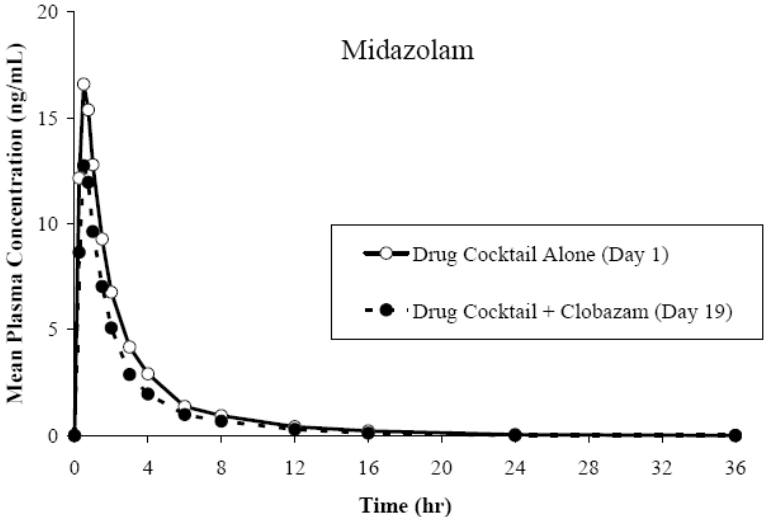
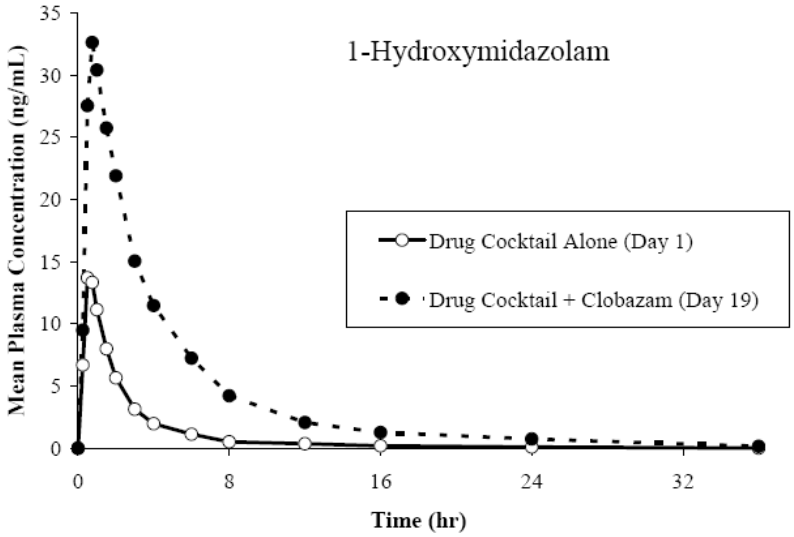
- Clobazam coadministration resulted in increases of 90-95% in AUC and 59% in Cmax for dextromethorphan, and decreases of 12% and 41% in AUC and Cmax for dextrorphan. Coadministration resulted in a delay in t_{max} for dextrophan compared to drug cocktail alone (3.00 vs. 2.00 hours, p=0.0176).

IV. Effect of Clobazam Coadministration on PK of Midazolam (CYP3A4 Probe)





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	Arithmetic Mean (%CV)		Geometric Mean Ratio (Coadmin/ Drug Cocktail alone)	90% CI (c) for Ratio
	Drug Cocktail (a) + Clobazam Day 19 N = 17 (b)	Drug Cocktail Alone (a) Day 1 N = 18		
Midazolam				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	30.6 (38%)	42.3 (45%)	0.73	(0.66, 0.81)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	31.4 (37%)	43.2 (44%)	0.73	(0.65, 0.80)
C_{max} (ng/mL)	15.2 (41%)	20.2 (53%)	0.76	(0.67, 0.88)
t_{max} (hr) (c)	0.50 (0.25 – 1.00)	0.50 (0.25 – 1.00)	n/a	n/a
CL/F (L/hr)	140.5 (29%)	106.5 (36%)	n/a	n/a
Vd/F (L)	687 (33%)	581 (43%)	n/a	n/a
$t_{1/2}$ (hr)	3.45 (25%)	3.93 (37%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	5.14 (43%)	7.86 (25%)	n/a	n/a
$f_{e\ 0\text{-}72}$ (%)	0.13 (43%)	0.20 (25%)	n/a	n/a
1-Hydroxymidazolam				
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	142.5 (45%)	33.5 (57%)	3.91	(3.30, 4.62)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	144.3 (45%)	37.3 (58%)	4.32	(3.78, 4.94)
C_{max} (ng/mL)	34.9 (37%)	16.3 (69%)	2.32	(1.91, 2.82)
t_{max} (hr) (c)	0.75 (0.27 – 2.00)	0.50 (0.25 – 1.00)	n/a	n/a
$t_{1/2}$ (hr)	7.18 (27%)	5.48 (58%)	n/a	n/a
$XU_{0\text{-}72}$ (µg)	2,816 (12%)	3,017 (7%)	n/a	n/a

- Coadministration of clobazam resulted in 27% and 24% decreases in AUC and Cmax for midazolam, and 4-fold and 2-fold increases in AUC and Cmax for 1-hydroxymidazolam.

Pharmacokinetic Profile of Clobazam

	Drug Cocktail (a) + Clobazam 40 mg QD Day 19 N = 18 (b)	Clobazam Alone 40 mg Single Dose Day 4 N = 18
Clobazam	Mean (%CV)	Mean (%CV)
$AUC_{0\text{-}24}$ (ng•hr/mL)	21,203 (29%)	8,783 (19%)
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	39,932 (34%)	8,783 (19%)
C_{max} (ng/mL)	1,373 (25%)	848 (25%)
C_{min} (ng/mL)	584 (37%)	n/a
t_{max} (hr) (c)	2.00 (0.75 – 5.98)	1.51 (0.50 – 6.00)
CL/F (L/hr)	2.05 (30%)	n/a
Vd/F (L)	90.6 (25%)	n/a
N-CLB		
$AUC_{0\text{-}24}$ (ng•hr/mL)	51,721 (47%)	2,363 (25%)
$AUC_{0\text{-}lqc}$ (ng•hr/mL)	147,459 (52%)	2,363 (25%)
C_{max} (ng/mL)	2,566 (43%)	141 (27%)
C_{min} (ng/mL)	2,031 (51%)	n/a
t_{max} (hr) (c)	7.00 (0.00 – 48.00)	24.00 (16.00 – 24.03)

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

The majority of the subjects (83%) experienced only mild adverse events.

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No adverse events causing study discontinuation, SAEs, or deaths were reported. There were no clinically significant findings noted in the physical examination, vital sign, clinical laboratory, ECG, SSS, or CIWA-B data.
Conclusion
• No clinically meaningful effects were observed on the CYP1A2-mediated metabolism of caffeine or the CYP2C9-mediated metabolism of tolbutamide following administration of clobazam 40 mg QD for 15 days. • Coadministration of clobazam resulted in a 95% increase of AUC and 59% increase of Cmax for dextromethorphan, compared to administration of drug cocktail alone. • Coadministration of clobazam resulted in decreases in AUC and Cmax of midazolam by 27% and 24%, respectively, and increases in AUC and Cmax of the metabolite 1´-hydroxymidazolam by 4-fold and 2-fold, respectively.
Comments
• Clobazam is an inhibitor of CYP2D6 in vivo. Therefore, narrow therapeutic index drugs that are metabolized by CYP2D6 may require dose reduction when used with Onfi. The use of other concomitant medications that are primarily metabolized by CYP2D6 should be monitored closely. • Clobazam can induce CYP3A4 activity in humans. However, this CYP3A4 induction is considered to be relatively mild. Consequently, doses adjustment for concomitant drugs primarily metabolized by CYP3A4 is not necessary.

4.4.4 *In-Vitro* Studies

Report # OVNC-9006	
Title: In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of Clobazam and N-Desmethylclobazam	
Objectives: To assess the potential of clobazam and N-desmethylclobazam to inhibit the catalytic activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 (midazolam), CYP3A4 (testosterone), UGT1A1, UGT1A6 and UGT2B4	
Study Design: • Cytochrome P450-specific probe substrates were incubated with pooled human liver microsomes in the presence and absence of standard inhibitors or clobazam (0, 0.04, 0.2, 1, 5 and 25 µM) or N-desmethylclobazam (0, 0.2, 1, 5, 25 and 125 µM). • Clobazam and N-desmethylclobazam (at concentrations as previously noted) were pre-incubated for 30 minutes with pooled human liver microsomes before the addition of the CYP-specific probe substrate to assess potential time-dependent inhibition. • Inhibition of UGT1A1, UGT1A6 and UGT2B4 by clobazam and N-desmethylclobazam was analyzed using commercially available recombinantly-expressed enzymes and appropriate substrates.	

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Isoform Monitored	Marker Substrate	Substrate Conc. (μM)	Incubation Time (min)	Protein Conc. (mg/mL)	Metabolite	Positive Control Inhibitor	Inhibitor Conc. (μM)
CYP1A2	Phenacetin	50	30	0.1	Acetaminophen	Furafylline	50
CYP2B6	Bupropion	125	20	0.25	Hydroxybupropion	ThioTEPA	25
CYP2C8	Paclitaxel	5	10	0.075	6α-Hydroxypaclitaxel	Quercetin	3
CYP2C9	Diclofenac	5	4	0.05	4'-Hydroxydiclofenac	Sulfaphenazole	20
CYP2C19	(*S*) Mephenytoin	50	30	0.1	4'-Hydroxymephenytoin	Ticlopidine	1
CYP2D6	Dextromethorphan	5	15	0.2	Dextrorphan	Quinidine	10
CYP3A4†	Midazolam	5	4	0.025	1'-Hydroxymidazolam	Ketoconazole	1
CYP3A4†	Testosterone	50	7	0.05	6ß-Hydroxytestosterone	Ketoconazole	1
UGT1A1	Estradiol	25	30	0.5	Estradiol-3-glucuronide	None available	
UGT1A6	4-Trifluoromethyl-7-hydroxycoumarin	50	20	0.05	4-Trifluoromethyl-7-hydroxycoumarin glucuronide	None available	
UGT2B4	4-Trifluoromethyl-7-hydroxycoumarin	50	20	0.25	4-Trifluoromethyl-7-hydroxycoumarin glucuronide	None available	

Results:

CYP450 inhibition by clobazam

	***Estimated IC_{50}* (μM)**	
P450 Isoform	**Direct Inhibition**	**Time-dependent (MBI) Inhibition**
CYP1A2	>25	>25
CYP2B6	>25	>25
CYP2C8	>25	>25
CYP2C9	>25	>25
CYP2C19	>25	>25
CYP2D6	>25	>25
CYP3A4 (M)	>25	>25
CYP3A4 (T)	>25	>25
UGT1A1	>62.5	Not determined
UGT1A6	>62.5	Not determined
UGT2B4	>62.5	Not determined

- No inhibition was observed for clobazam at concentrations up to 25 μM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 (midazolam) or CYP3A4 (testosterone). Clobazam at concentrations up to 62.5 μM did not inhibit UGT1A1, UGT1A6 or UGT2B4.
- Upon pre-incubation of clobazam with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 (midazolam) and CYP3A4 (testosterone), no significant inhibition was observed.

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CYP450 inhibition of by N-desmethylclobazam

	Estimated IC_{50} (µM)	
P450 Isoform	**Direct Inhibition**	**Time-dependent (MBI) Inhibition**
CYP1A2	>125	>125
CYP2B6	>125	>125
CYP2C8	>125	>125
CYP2C9	71.7	103
CYP2C19	>125	>125
CYP2D6	>125	>125
CYP3A4 (M)	>125	>125
CYP3A4 (T)	>125	>125
UGT1A1	>312	Not determined
UGT1A6	210	Not determined
UGT2B4	111	Not determined

- No inhibition was observed for N-desmethylclobazam at concentrations up to 125 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A4 (midazolam) or CYP3A4 (testosterone). Inhibition of greater than 50% was observed for CYP2C9 at N-desmethylclobazam concentrations up to 125 µM with an estimated IC50 = 71.7 µM.
- N-desmethylclobazam at concentrations up to 312 µM did not inhibit UGT1A1. N-desmethylclobazam at concentrations up to 312 µM inhibited UGT1A6 and UGT2B4 with estimated IC50 values of 210 and 111 µM, respectively.

Ki value for N-desmethylclobazam inhibition of CYP2C9 and UGT2B4

P450 Isoform	***K_i (µM)***	***Inhibition Model***
CYP2C9	84.0	Linear-mixed
UGT2B4	73.0	Competitive

Conclusion

- In vitro studies in human liver microsomes or recombinant enzymes indicated that clobazam did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 (midazolam), 3A4 (testosterone), UGT1A1, UGT1A6, or UGT2B4.
- N-CLB did not inhibit CYP1A2, 2B6, 2C8, 2C19, 2D6, 3A4 (midazolam), 3A4 (testosterone), and UGT1A1. However, inhibition by N-CLB was shown for CYP2C9, and UGT1A6 and 2B4.
- When Clobazam was administered 40 mg QD (20 mg tablet x 2) for Days 4 through 19 in Study OV-1023, mean Cmax for N-CLB was 2,566 ng/ml (8.5 uM) on Day 19, resulting in [I]/Ki of 0.1 and 0.116 for CYP2C9 and UGT2B4. It should be noted that

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in this study, Clobazam 40 mg was given as once a day. Given that the proposed dosing regimen of the product is up to 20 mg BID (40 mg TDD), drug interaction potential for N-CLB with CYP2C9 or UGT2B4 substrate concomitant drugs is likely to be low.

Comments

Report # OVNC-9007

Title: *In Vitro* Assessment of Induction Potential of Clobazam and *N*-Desmethylclobazam in Primary Human Hepatocytes.

Objectives: To assess the potential of clobazam and N-desmethylclobazam to induce liver microsomal cytochrome P450 (CYP450) enzymes using primary cultures of human hepatocytes

Study Design:

- Clobazam (at concentrations of 0.1, 2.5 and 25 µM), N-Desmethylclobazam (at concentrations of 0.5, 25 and 250 µM), and known prototypical CYP450 inducers, 3-methylcholanthrene (3-MC), phenobarbital (PB) and rifampicin (RIF) were incubated with three separate preparations of primary human hepatocytes on three days. Cytotoxicity was evaluated by microscopic observations of the hepatocytes.
- After the incubation period, microsomes were isolated and the enzymatic activities of CYP1A2 (phenacetin O-deethylation), CYP2C19 (S-mephenytoin hydroxylation) and CYP3A4 (testosterone 6β-hydroxylation) were measured. Additionally, cells were harvested from each treatment group, and the mRNA encoding CYP1A2, 2C19, 3A4 and UGT1A1 was measured by TaqMan PCR to compare mRNA expression across each treatment group.

Results:

CYP Activity after Treatment with Clobazam and *N*-Desmethylclobazam

% of Positive Control Induction

	1A2			2C19			3A4		
	Hu488	Hu503	Hu504	Hu488	Hu503	Hu504	Hu488	Hu503	Hu504
Rifampicin (10 µM)	2.9	2.8	1.2	100	100	100	100	100	100
3-MC (2 µM)	100	100	100	11.6	19.2	23.5	-0.14	-7.7	-18.7
Phenobarbital (1000 µM)	9.0	5.6	4.3	49.5	18.4	30.5	131	118	145
Clobazam (0.1 µM)	1.4	0.52	2.2	-2.8	7.1	-2.7	0.72	-3.0	-0.16
Clobazam (2.5 µM)	1.6	0.51	1.8	4.4	5.3	5.0	14.6	9.6	25.2
Clobazam (25 µM)	0.78	0.15	0.09	0.43	-19.5	-9.1	**53.6**	**60.9**	**63.6**
N-Desmethylclobazam (0.5 µM)	1.2	0.90	2.4	2.7	5.1	-0.16	3.6	11.4	-2.2
N-Desmethylclobazam (25 µM)	1.7	1.3	3.7	2.6	-20.4	-7.0	**41.9**	**56.0**	**57.2**
N-Desmethylclobazam (250 µM)	2.0	0.85	4.6	0.75	-28.1	-8.2	34.1	**75.9**	**82.0**

Numbers highlighted in **BOLD** indicate induction >40% relative to positive control

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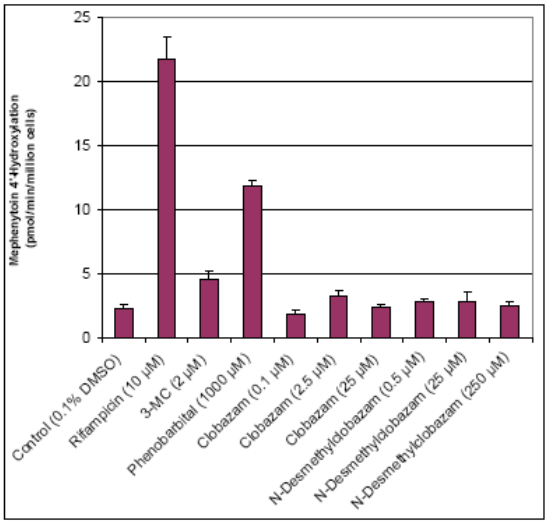
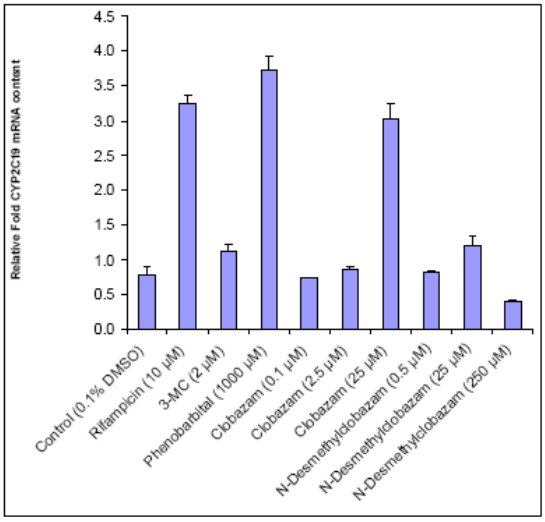
mRNA Levels after Treatment with Clobazam and *N*-Desmethylclobazam

% of Positive Control Induction

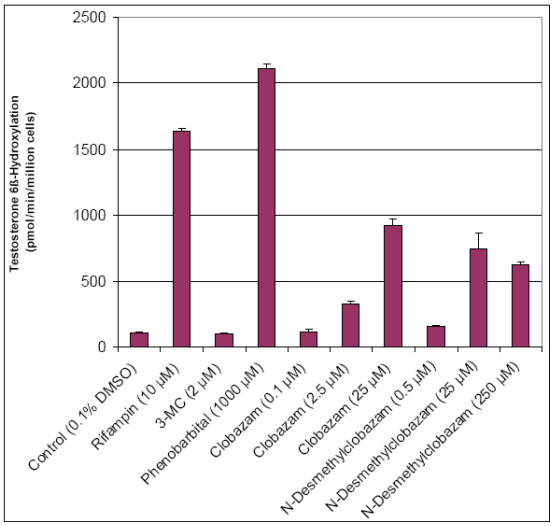
	1A2			2C19			3A4			UGT1A1		
	Hu488	Hu503	Hu504	Hu488	Hu503	Hu504	Hu488	Hu503	Hu504	Hu488	Hu503	Hu504
Rifampicin (10 μM)	0.19	0.66	1.4	100	100	100	100	100	100	100	100	100
3-MC (2 μM)	100	100	100	13.4	5.1	19.3	-3.4	-6.6	-4.4	172	31.4	71.0
Phenobarbital (1000 μM)	0.20	-0.38	0.06	119	96.0	118	99.5	71.6	89.5	137	96.9	138
Clobazam (0.1 μM)	0.10	0.08	0.86	-2.2	-2.0	3.5	-0.33	-4.6	-0.31	2.3	0.64	2.7
Clobazam (2.5 μM)	0.16	0.15	0.89	3.3	5.7	25.8	9.0	1.5	15.6	8.2	5.1	16.1
Clobazam (25 μM)	0.91	0.48	1.5	**91.2**	34.0	**60.4**	**68.9**	**42.8**	**65.7**	**91.2**	**55.5**	**90.1**
N-Desmethylclobazam (0.5 μM)	0.29	-0.11	1.3	0.98	-3.4	4.9	-0.41	-1.6	5.1	1.3	-0.18	2.5
N-Desmethylclobazam (25 μM)	0.48	1.0	2.1	17.0	9.8	29.3	35.0	16.6	28.3	31.0	15.2	37.3
N-Desmethylclobazam (250 μM)	0.15	-0.49	0.70	-15.8	1.1	13.9	9.1	12.4	27.0	26.2	20.0	**52.4**

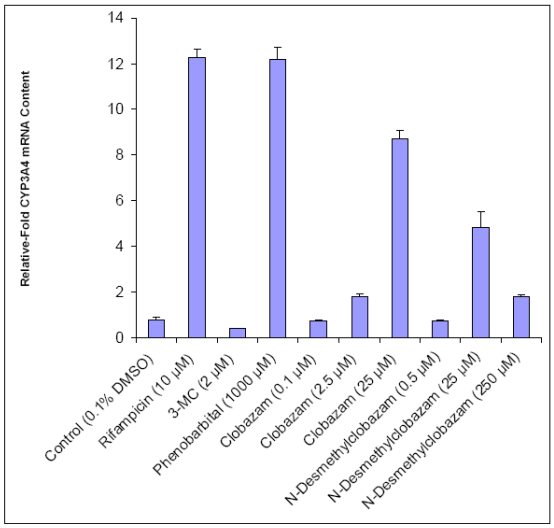
CYP2C19 Activity and mRNA Content in Human Hepatocytes (Hu488) Treated with Clobazam and N-Desmethylclobazam





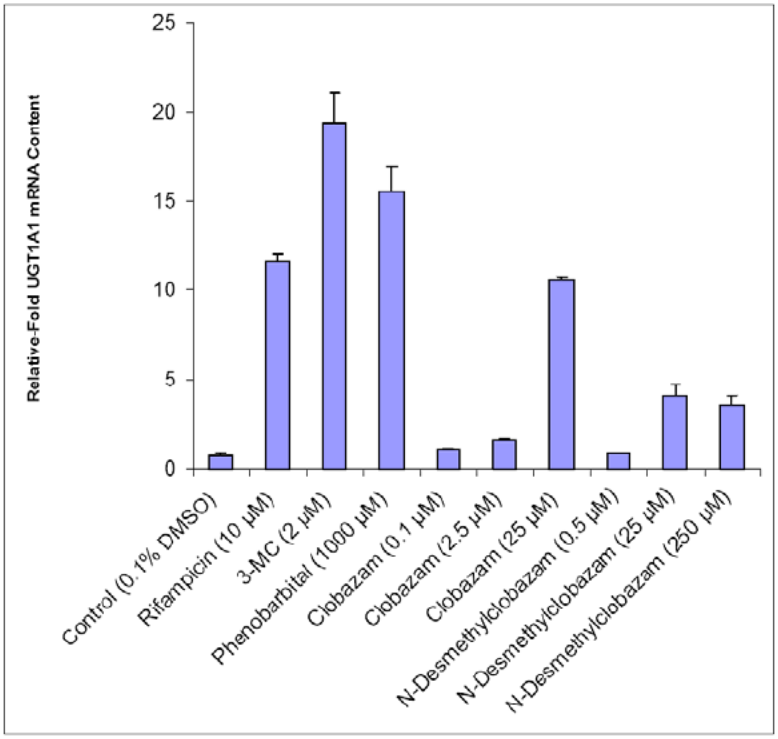
CYP3A4 Activity and mRNA Content in Human Hepatocytes (Hu488) Treated with Clobazam and N-Desmethylclobazam





UGT1A1 mRNA Content in Human Hepatocytes (Hu488) Treated with Clobazam and *N*-Desmethylclobazam

Reference ID: 3032655



Enzyme activity

- Clobazam and N-CLB did not significantly increase CYP1A2 or CYP2C19 activities. However, both clobazam and N-CLB caused concentration-dependent increases in CYP3A4 activity.

mRNA

- Clobazam at 25 µM (7,519 ng/mL) increased mRNA levels of CYP2C19, CYP3A4, and UGT1A1. However, there was no increase in CYP2C19 enzyme activity. NCLB at 250 µM (71,675 ng/mL) increased UGT1A1 in one donor.

Conclusion

- Clobazam and N-CLB induce CYP3A4 activities and expression in vitro, and as such may affect the metabolism of other concomitantly administered CYP3A4 substrates in vivo.
- Clobazam and N-CLB induce UGT1A1 mRNA in vitro. Increases in enzyme activities have not been evaluated.

Comments

Report # Literature report	**Study Period**:	
Title	IN VITRO CHARACTERIZATION OF CLOBAZAM METABOLISM BY	

Reference ID: 3032655

	RECOMBINANT CYTOCHROME P450 ENZYMES: IMPORTANCE OF CYP2C19 Giraud et al., *DRUG METABOLISM AND DISPOSITION* 32:1279–1286, 2004

Background

Studies to identify which CYP enzymes are responsible for clobazam and *N*-CLB metabolism were not conducted by the sponsor. In literature, the identification of the CYPs involved in metabolism was conducted by a combination of kinetic experiments (Vmax/km determinations) using cDNA-expressed CYPs and CYP-specific chemical inhibitors.

Study Objectives: to identify and kinetically characterize in vitro the P450 isoforms responsible for the metabolism of CLB and its metabolites.

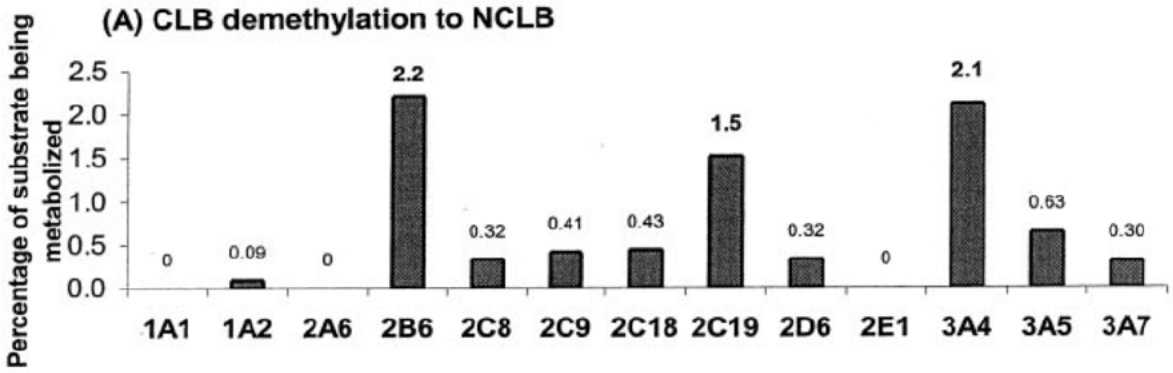
Method:
Human liver microsomes and specific human P450 enzymes (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, and 3A7) expressed in the Baculovirus- transfected insect cell system were used.
The P450-specific inhibitors used were 15 uM furafylline (CYP1A2 inhibitor), 10 uM thiotepa (CYP2B6 inhibitor), 1.5 uM sulfaphenazole (CYP2C9 inhibitor), 10 uM omeprazole (CYP2C19 inhibitor), 2 uM quinidine (CYP2D6 inhibitor), 5 uM chlorzoxazone (CYP2E1 inhibitor), and 1 uM ketoconazole (CYP3A4 inhibitor), at concentrations corresponding to 5 times the Ki values.

Analytical Method: HPLC

Results

Identification of the P450 Isoforms Involved in Clobazam Metabolism using cDNA-Expressed P450s.

Percentages of metabolism calculated after CLB incubation with the 13 different cDNA-expressed P450s suggested that CYP2B6 (2.2%), CYP3A4 (2.1%), and CYP2C19 (1.5%) mediated the formation of N-CLB. N-CLB was mainly metabolized by CYP2C19 (1.31%) and, at lower rates, by CYP2C18 (0.58%).



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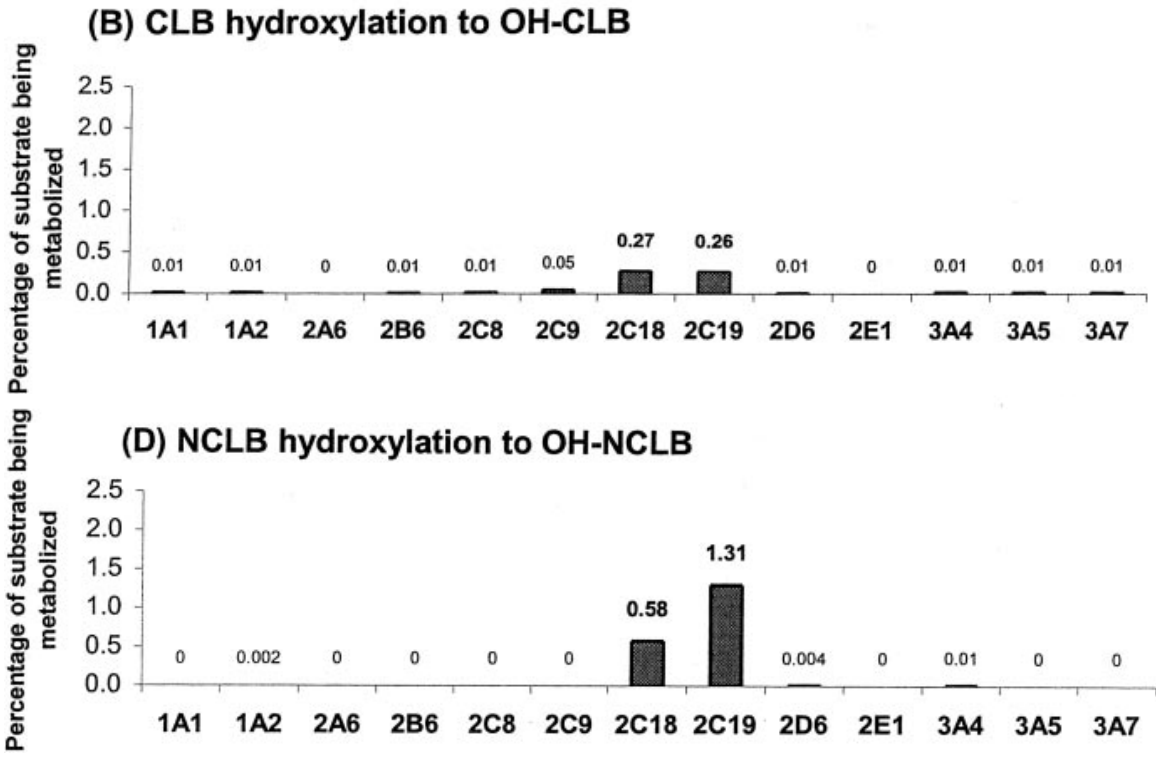

Kinetic Studies: Metabolism of CLB to NCLB

CYP3A4: Km of 29.0 uM and Vmax of 6.20 nmol/min/nmol.
CYP2C19: Km of 31.9 uM and Vmax of 1.15 nmol/min/nmol
CYP2B6: Km of 289 uM and Vmax of 5.70 nmol/ min/nmol

The intrinsic clearance (CLint) of CLB N-demethylation was 6 and 11 times higher for CYP3A4 than that for CYP2C19 and CYP2B6, respectively (214 versus 36.1 and 19.7 ul/min/nmol P450).

The hydroxylation of NCLB to OH-NCLB by cDNA-expressed CYP2C19: Km of 5.74 uM and Vmax of 0.219 nmol/min/nmol.

Chemical Inhibition Studies:
Ketoconazole decreased NCLB formation by 69.7%, and omeprazole and thiotepa reduced it by 18.7 % and 24.3 %, respectively.
NCLB hydroxylation was mainly inhibited by omeprazole (25.9 %).

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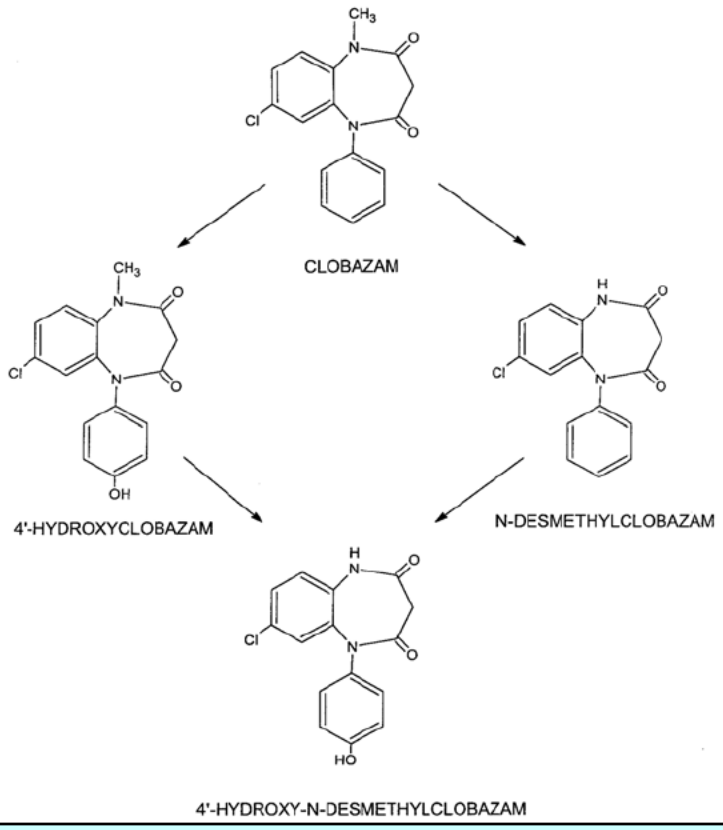
TABLE 2

Percentages of inhibition for CLB (2 μM) demethylation and NCLB (5 μM) hydroxylation measured in human liver microsomes in the presence of specific inhibitors.

Values are mean ± S.D.

Inhibitor	Inhibited P450	CLB Demethylation	NCLB Hydroxylation
Ketoconazole (1 μM)	CYP3A4	69.7 ± 6.6[a]	12.3 ± 2.8[a]
Omeprazole (10 μM)	CYP2C19	18.7 ± 8.8[a]	25.9 ± 1.5[a]
Thiotepa (10 μM)	CYP2B6	24.3 ± 8.0[a]	<5%
Furafylline (15 μM)	CYP1A2	<5%	<5%
Sulfaphenazole (1.5 μM)	CYP2C9	<5%	<5%
Chlorzoxazone (5 μM)	CYP2E	<5%	<5%
Quinidine (2 μM)	CYP2D6	<5%	<5%



Site Inspected	
Requested: Yes☐ No ☑	**Performed:** Yes☐ No ☐ N/A ☑
Safety: Was there any death or serious adverse events?	
☐ Yes ☐ No ☑ NA	
Conclusion	
CYP3A4 is the main enzymes involved in the N-demethylation of CLB to NCLB and CYP2C19 is the major contributor to the hydroxylation of NCLB.	

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Report # OVNC-9070	
Title: Characterization of N-Desmethyl Clobazam Metabolites by LC/MS/MS Following Incubations in Human Hepatocytes	
Objectives: To evaluate the metabolism of *N*-desmethyl clobazam in cryopreserved human hepatocytes	
Study Design: • Human hepatocytes were incubated with 100 µM N-desmethyl clobazam for 0, 60, 120 and 240 minutes and were analyzed for change in substrate concentration and for metabolite profiling and characterization. • As an amendment to the original protocol, incubations of *N*-desmethyl clobazam (10 µM) with NADPH- and UDP glucuronic acid-fortified human liver microsomes were performed and samples analyzed for change in substrate concentration and for metabolite profiling and characterization.	
Results: • Upon incubation with human hepatocytes, no loss of *N*-desmethyl clobazam was observed over the 240 min time course. The positive control data established that the human hepatocytes were metabolically competent in terms of CYP-dependent oxidation and sulfate and glucuronide conjugation. • In incubations with NADPH-fortified human liver microsomes, 15.6% loss of *N*-desmethyl clobazam was observed after 60 min. In UDP glucuronic acid-fortified human liver microsomal incubations, 11.4% loss of *N*-desmethyl clobazam was observed after 60 min. • Metabolite profiling analysis determined three components related to *N*-desmethyl clobazam metabolism, C1 through C3. Components C1 and C2 are proposed as hydroxylation metabolites, although specific sites of hydroxylation were not be determined. Component C3 is consistent with a glucuronide conjugate of *N*-CLB, possibly an *N*-glucuronide conjugate.	
Conclusion	
• No loss of N-CLB and no metabolites were found following the incubation of N-CLB with human hepatocytes. • Approximately 15.6% and 11.4% loss of N-CLB was determined after incubation with human liver microsomes fortified with NADPH and UDP glucuronic acid, respectively. Two hydroxylation metabolites and one direct glucuronide conjugate were formed from N-CLB.	
Comments	

Reference ID: 3032655

Report # OVNC-9024	

Title: In Vitro Assessment of Clobazam and N-Desmethylclobazam as a Substrate or Inhibitor of P-glycoprotein (P-glycoprotein/MDR1/ABCB1).

Objectives: To assess the potential of clobazam and N-desmethylclobazam to act as a substrate or inhibitor of the P-glycoprotein transporter.

Study Design:

- The potential of clobazam and N-desmethylclobazam to act as a substrate for P-gp was measured with monolayers of wild-type (WT) and Madin-Darby canine kidney (MDCK) cells. The apparent permeability (Papp) was determined for clobazam and N-desmethylclobazam at 0.1, 2.5, and 25 µM and 0.25, 12.5, and 62.5 µM, respectively, in the apical to basolateral (A→B) and the basolateral to apical (B→A) directions. The efflux ratio (RE = PB→A / PA→B) was calculated and the MDR1/WT ratio determined.
- Inhibition of P-gp transport was measured by determining 3H-digoxin Papp in both the A→B and B→A directions in the presence and absence of clobazam or N-desmethylclobazam at six concentrations (0, 0.04, 0.2, 1, 5, and 25 µM and 0, 0.2, 1, 5, 25, and 125 µM, respectively) or positive control inhibitor verapamil (0, 0.4, 2, 10, 50, and 250 µM).

Results:

Efflux Ratios of Clobazam with MDCK MDR1 and WT

A: MDCK MDR1 Monolayers

P_{app} (cm/s x 10^{-6})					
Clobazam (µM)	A → B	Standard Error	B → A	Standard Error	Efflux Ratio
0.1	23.2	0.0	24.0	2.5	1.03
2.5	4.19	0.36	22.0	1.2	5.25
25	5.93	0.16	20.3	1.4	3.43

Source: Appendix Tables 3.4–3.6

B: MDCK WT Monolayers

P_{app} (cm/s x 10^{-6})					
Clobazam (µM)	A → B	Standard Error	B → A	Standard Error	Efflux Ratio
0.1	23.2	0.0	19.4	0.0	0.833
2.5	9.42	0.72	7.54	0.47	0.801
25	4.60	4.24	12.9	1.6	2.80

Source: Appendix Tables 3.7–3.9

Efflux Ratios of N-CLB with MDCK MDR1 and WT

Reference ID: 3032655

A: MDCK MDR1 Monolayers

P_{app} (cm/s x 10^{-6})					
N-Desmethylclobazam (μM)	A → B	Standard Error	B → A	Standard Error	Efflux Ratio
0.25	10.9*	0.0	33.6	0.2	3.1
12.5	2.59	0.14	53.4	0.8	20.7
62.5	7.70	1.29	57.7	1.1	7.50

*LLOQ value used to calculate as original values were below LLOQ.
Source: Appendix Tables 3.10–3.12

B: MDCK WT Monolayers

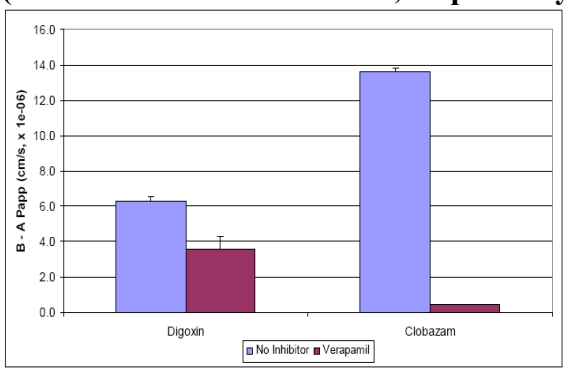
P_{app} (cm/s x 10^{-6})					
N-Desmethylclobazam (μM)	A → B	Standard Error	B → A	Standard Error	Efflux Ratio
0.25	22.0	9.9	17.5	0.6	0.77
12.5	14.1	7.7	30.9	0.1	2.2
62.5	89.1	35.8	66.8	0.9	0.75

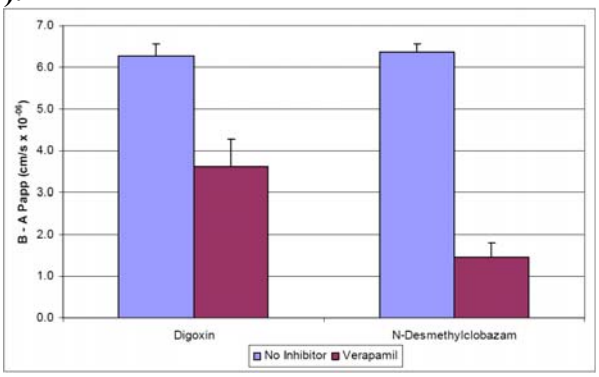
MDR1/WT Efflux Ratios for Clobazam and N-CLB

Clobazam (μM)	MDR1/WT Efflux Ratio
0.1	1.24
2.5	6.55
25	1.23

N-Desmethylclobazam (μM)	MDR1/WT Efflux Ratio
0.25	4.03
12.5	9.45
62.5	10.0

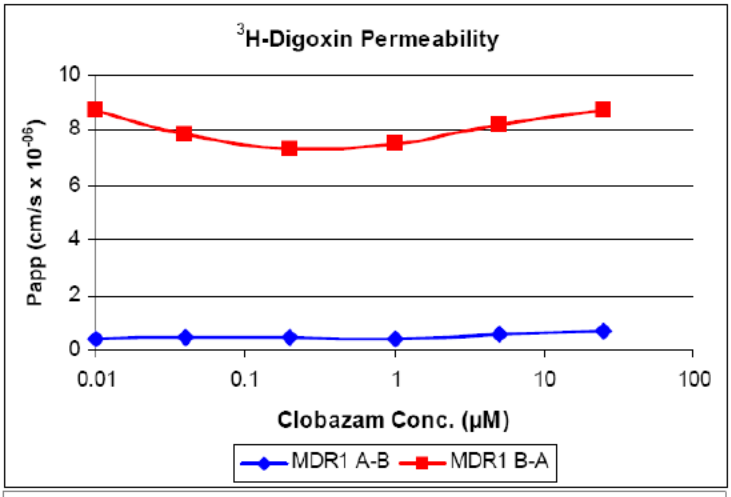
P(B→A) efflux of clobazam and N-CLB was significantly inhibited by verapamil (>96% and > 77% inhibition, respectively).

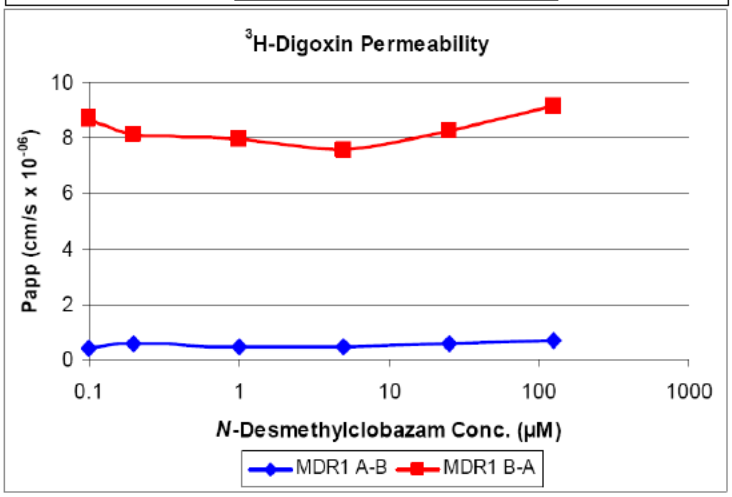




Effect of Clobazam and N-CLB on 3H-Digoxin Efflux

Reference ID: 3032655





Clobazam or N-CLB did not inhibit 3H-digoxin efflux in MDCK MDR1 cells by more than 50%.

Conclusion

- Clobazam and N-desmethylclobazam are substrates of P-gp.
- Clobazam and N-CLB do not appear to inhibit P-gp.

Comments

Report # OVNC-9015	
Title: In Vitro Assessment of Protein Binding for Clobazam and N-Desmethylclobazam in Human Plasma	
Objectives: To assess the extent of clobazam and N-desmethylclobazam to bind to plasma proteins in human plasma	

Reference ID: 3032655

Study Design:
Plasma protein binding of clobazam and N-desmethylclobazam in human plasma was determined by equilibrium dialysis. Clobazam, at 0, 12.0, 60.1, 300, 1500, and 7500 ng/m (0, 0.04, 0.2, 1.0, 5 and 25 μM) and N-CLB, at 0, 57.3, 290 1400, 7200 and 36,000 ng/ml (0, 0.2, 1.0, 5, 25 and 125 μM) were spiked into plasma and dialyzed against PBS at 37 °C for four hours. The effect of clobazam on N-CLB plasma binding and the effect of N-CLB on clobazam plasma binding were also evaluated.

Results:
- Mean clobazam binding to human plasma proteins is 78.5 ± 6.2%.
- Mean N-CLB binding to human plasma proteins was in the range of 72.5 ± 2.5 %.
- Clobazam plasma binding at 300 ng/ml (1 μM) was 72.6 ± 1.9% in the absence of N-desmethylclobazam and decreased to 67 % and 64 % in the presence of 290 ng/mL 7200 ng/mL of N-desmethylclobazam.
- N-CLB plasma binding at 2900 ng/mL (10 μM) was 72.7 % in the absence of clobazam and was not altered in the presence of 690 ng/mL clobazam.

Conclusion

- Clobazam and N-CLB are moderately bound to plasma proteins.
- Plasma protein binding of both compounds is concentration independent in the ranges evaluated. Similar results were observed in Study OVNC-9065.

Report # OVNC-9065	
Title: The Ex-Vivo Protein Binding of Clobazam and N-Desmethylclobazam in Human Plasma Collected from Subjects Enrolled in Clinical Study OV-1032	
Objectives: To determine, *ex-vivo*, the extent of protein binding of Clobazam and *N*-Desmethylclobazam, in human plasma obtained from normal and renally-impaired subjects enrolled in Clinical Study OV-1032	
Study Design: Study OV-1032 consisted of three groups of subjects (at least n = 6./group): Normal renal function (Creatinine Clearance (Clcr) > 80 mL/min), Moderate renal impairment (Clcr = 30 - 50 mL/min), and Mild renal impairment (Clcr = 50 - 80 mL/min). The protein binding of Clobazam and *N*-Desmethylclobazam in predose and 2-, 12-, and 24-hour post dose samples for Day 1 and Day 11 from 25 subjects was determined.	
Results: Mean percent protein binding of Clobazam and *N*-Desmethylclobazam	

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Condition of Renal Function	Clobazam (Mean ± SD) % Bound	Clobazam (Mean ± SD) % Unbound	*N*-desmethy Clobazam (Mean ± SD) % Bound	*N*-desmethy Clobazam (Mean ± SD) % Unbound
Mild	88.2 ± 1.7	11.8 ± 1.7	86.9 ± 1.7	13.1 ± 1.7
Moderate	87.9 ± 1.1	12.1 ± 1.1	86.5 ± 1.1	13.5 ± 1.1
Normal	89.0 ± 1.6	11.0 ± 1.6	87.7 ± 1.6	12.3 ± 1.6

Conclusion

- The protein binding of Clobazam and *N*-Desmethylclobazam was moderate. The protein binding did not appear to be concentration dependent.
- The *ex vivo* protein binding observed in plasma of subjects dosed with Clobazam was similar to that observed in *in vitro* study.
- The protein binding was not impacted by mild or moderate renal impairment.

Comments

Report # OVNC-9067

Title: In Vitro Evaluation of the Potential Effect of Clobazam and N-Desmethylclobazam on the Metabolic Activity of Human Recombinant Uridine Diphosphate Glucuronosyltransferase (UGT) Enzymes 1A4 and 2B4

Objectives: To evaluate the ability of Clobazam and N-Desmethylclobazam to inhibit select human recombinant uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A4 and UGT2B4)

Study Design:
Human rUGT1A4 (lot number: 21161) and human rUGT2B4 (lot number: 33191) expressed in insect cells (i.e., Supersomes) were used. The enzymes were characterized to measure the kinetic constants, Km and Vmax, for UGT1A4 and UGT2B4 activities.

Enzyme	Reagent use	Name
UGT1A4	Substrate	Trifluoperazine
	Substrate metabolite	Trifluoperazine glucuronide
	Internal standard	(b) (4)
	Direct inhibition positive control	Troglitazone
UGT2B4	Substrate	4-Trifluoromethyl-7-hydroxycoumarin
	Substrate metabolite	4-Trifluoromethyl-7-hydroxycoumarin glucuronide
	Internal standard	(b) (4)
	Direct inhibition positive control	Troglitazone

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Results:

- Clobazam inhibited the activity of rUGT2B4 with an IC50 value of 63 µM (18,944 ng/mL) - 66 µM (19,846 ng/mL).
- There was little inhibition of rUGT1A4 by Clobazam with approximately 11% inhibition observed at 100 µM.
- *N*-Desmethylclobazam inhibited human rUGT1A4 and rUGT2B4, with IC50 values of 110 µM (31,538 ng/mL) and 72 µM (20,643 ng/mL), respectively.

		Direct inhibition	
		Zero-minute preincubation	
Test article	Enzyme	IC_{50} (µM) [a]	Inhibition at 100 or 150 µM (%) [b]
Clobazam	UGT1A4	>100	11 [c]
	UGT2B4	63, 66	53 [c], 71 [d]
		IC_{50} (µM) [a]	Inhibition at 300 µM (%) [b]
N-Desmethylclobazam	UGT1A4	110	74
	UGT2B4	72	100

c The highest concentration of Clobazam evaluated was 100 µM.
d The highest concentration of Clobazam evaluated was 150 µM.

Conclusion

- Clobazam is a weak inhibitor of rUGT2B4 with IC50 values of 63 - 66 µM.
- Clobazam does not appear to inhibit human rUGT1A4.
- *N*-Desmethylclobazam is a weak inhibitor of human rUGT1A4 and rUGT2B4 with IC50 values of 110 µM and 72 µM, respectively.

Comments

In a repeat-dose study OV-1023, the mean Cmax at steady-state after 19 days of dosing of Clobazam (40 mg/day, QD) were 4.6 and 9 µM for Clobazam and N-desmethylclobazam, respectively. In this same study, the maximum individual concentrations observed were 6.9 and 15.7 µM for Clobazam and N-desmethylclobazam, respectively. These values are much lower than the lowest IC50 for UGT inhibition (63 µM for Clobazam with human rUGT2B4 and 72 µM for N-desmethylclobazam with human rUGT2B4) observed in this *in vitro* study.

Report # OVNC-9068

Title: *In vitro* evaluation of the potential effect of clobazam and *N*-desmethylclobazam on the glucuronidation of 1′-hydroxymidazolam in human liver and intestinal microsomes

Objectives: To evaluate if clobazam (CLB) or its major and active metabolite N-desmethyl clobazam (NCLB) have the potential to affect the glucuronidation of 1′-

Reference ID: 3032655

hydroxymidazolam in human liver and intestinal microsomes.

Study Design:
O- glucuronide and the N- glucuronide of 1′-hydroxymidazolam are generated by UGT2B4/UGT2B7 and UGT1A4, respectively.
1′-hydroxymidazolam (1, 10 and 100 µM) was incubated with human liver and intestinal microsomes in the presence of CLB or NCLB (0, 0.3, 1, 3, 10, 30, 100 and 300 µM). When 50% or more inhibition was observed, IC50 values were determined by nonlinear regression.

Substrate	Substrate (µM)	Inhibitor (µM)	Test system
1′-OH midazolam	10	CLB 0.3, 1, 3, 10, 30, 100, 300 µM and SC	HIM and HLM
	1, 10, 100	NCLB 0.3, 1, 3, 10, 30, 100, 300 µM and SC	HIM and HLM
	1, 10, 100	Hecogenin [a], 10 and 50 µM	HLM
	1, 10, 100	Diclofenac [b], 50 and 500 µM	HLM
	1, 10, 100	Fluconazole [c], 1 mM	HIM

Hecogenin was used as a positive control for UGT1A4 inhibition.
Diclofenac was used as a positive control for UGT2B4/2B7 inhibition.
Fluconazole was used as a positive control for UGT2B7 inhibition.

Results:

- The rate of 1′-hydroxymidazolam glucuronidation in liver was 2 -10 fold greater than in intestinal microsomes in this study. In the liver, N-glucuronide was the major conjugate, whereas in the intestine the N- and O-glucuronides were formed at similar levels.
- CLB resulted in concentration-dependent inhibition of the O-glucuronide in both human liver and intestinal microsomes, but with IC50 >300 µM. No significant inhibition of the N-glucuronide by CLB was detected in either human liver or intestinal microsomes.
- Concentration-dependent inhibition of the *O*-glucuronide and *N*-glucuronide by N-CLB was observed in both human liver and intestinal microsomes.
- In human liver microsomes, IC50 values for inhibition of the *O*-glucuronide by N-CLB were 109, 210 and 236 µM, when incubated with 1, 10 and 100 µM 1′-hydroxymidazolam, respectively. IC50 values for inhibition of the *N*-glucuronide were 96.6 and 175 µM at 1 and 10 µM 1′-hydroxymidazolam, respectively.

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Inhibitor	[Substrate] (µM)	Human liver microsomes		Human intestinal microsomes	
		O-glucuronide (IC_{50})	*N*-glucuronide (IC_{50})	*O*-glucuronide (IC_{50})	*N*-glucuronide (IC_{50})
CLB	10	> 300 µM	No inhibition	> 300 µM	No inhibition
NCLB	1	109 µM	96.6 µM	251 µM	> 300 µM
	10	210 µM	175 µM	> 300 µM	> 300 µM
	100	236 µM	> 300 µM	> 300 µM	> 300 µM

Conclusion

Concentration-dependent inhibition of the *O*-glucuronidation of 1′-hydroxymidazolam (via UGT2B4) by CLB and NCLB was observed in human liver and intestinal microsomes. NCLB also inhibited the *N*-glucuronidation of 1′-hydroxymidazolam (via UGT1A4) in a concentration-dependent manner in both human liver and intestinal microsomes, while CLB had no inhibitory effect on the *N*-glucuronidation. The lowest IC50 observed was > 96 µM.

Comments

In Study OVNC-9067 evaluating the ability of CLB and N-CLB to inhibit recombinant human UGT1A4 and UGT2B4, CLB was an inhibitor of UGT2B4 with an IC50 value of 63 – 66 µM, but not of UGT1A4, while NCLB was an inhibitor of both UGT1A4 and UGT2B4, with IC50 values of 110 µM and 72 µM, respectively.

In study OV-1023, the mean Cmax at steady-state after administration of Clobazam (40 mg/day, QD) from Day 4 through 19 were 4.6 (1,373 ng/mL) and 9.0 µM (2,566 ng/mL) for Clobazam and N-Desmethylclobazam, respectively. In this same study, the maximum individual concentrations observed were 6.9 (2.060 ng/mL) and 15.7 µM (4,500 ng/mL) for Clobazam and N-Desmethylclobazam, respectively.

The lowest IC50 value observed in this in vitro study was 96.6 µM. This is 10.7- and 6.2-fold higher than the highest mean and individual N-CLB plasma Cmax values observed in Study OV-1023 (9.0 µM and 15.7 µM, respectively).

4.4.5 General Biopharmaceutics

Report # OV1017	**Study Period**: 02/29/2008 (date of Period 1 dose) to 03/27/2008 (last subject visit)	
Title	Evaluation of the Relative Bioavailability of Oral Clobazam Tablets and Oral Clobazam Solution Following 20 mg Doses in Healthy Subjects	
Study Design single-dose, 2-way crossover, single-center, randomized, open-label study		
☐ Bioequivalence	☑ Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** 13 days, outpatient	

Reference ID: 3032655

Period 1/2	10 days, Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: clobazam)

	Test	**Reference**
Dosage Form	tablet	oral solution
Dosage Strength	1 × 20 mg	20 mg
Batch #.	Catalent Pharma API lot: 499841 [Catalent]; N002 [redacted] (b) (4)	API lot number: 499841 [Catalent], N002 [redacted] (b) (4)
Administration	oral	oral

Sampling Times (PK, plasma)

Screening	Baseline	Dosing and Pharmacokinetic Collection	Washout and Pharmacokinetic Collection
Days –21 to –2	Day –1	Period 1 (Day 1)	Days 1-3 *(confinement)* Days 4, 6, 8, and 10 *(outpatient)* Days 5, 7, 9, 11, and 12 *(outpatient-no pharmacokinetic collection)*
		Period 2 (Day 14)	Days 13-16 *(confinement)* Days 17, 19, 21, and 23 *(outpatient)* Days 18, 20, and 22 *(outpatient-no pharmacokinetic collection)*

Pharmacokinetic blood collection times: 0 (predose), 0.5, 1, 2, 3, 4, 8, 12, 24, 36, 48, 72, 120, 168, and 216 hours postdose.

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐

Statistical Method: Log-transformed AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F values of clobazam were evaluated by an analysis of variance (ANOVA) model using treatment, sequence, and period as fixed effects and subject within sequence as a random effect. A point estimate and a 90% confidence interval (CI) were obtained for the difference in means for the log-transformed values of AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F.

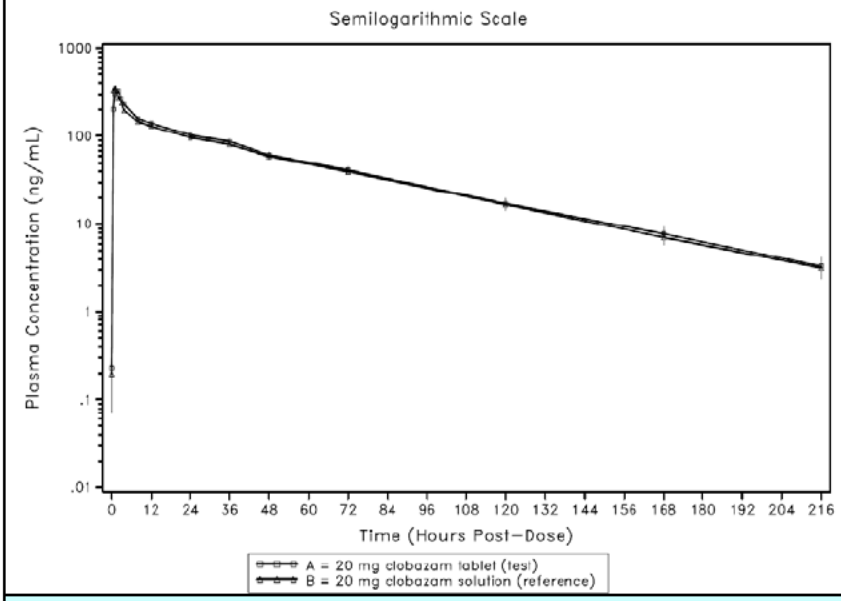
Study Population :

Randomized/Completed/ Discontinued Due to AE	18/18/0
Age [Median (range)]	35.25/37.15 (19.8 – 45.1)
Male/Female	11/7
Race (Caucasian/Black/Asian/other)	15/3/0/0

Results

Reference ID: 3032655

Ratios and 90% Confidence Intervals for Clobazam Pharmacokinetic Parameters				
Pharmacokinetic Parameter (units)	Geometric LSM		Ratio of Geometric LSM Test/Reference	90% CI of Ratio
	Tablet (Test)	Oral Solution (Reference)		
AUC0-lqc (hr•ng/mL)	9082.85	8656.69	1.0492	(0.9880, 1.1143)
AUC0-inf (hr•ng/mL)	9304.49	8878.98	1.0479	(0.9888, 1.1105)
Cmax (ng/mL)	381.19	367.94	1.0360	(0.9449, 1.1359)



Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☑ No ☐ NA

Conclusion

- With respect to AUC and Cmax, the 90% CIs for the tablet were contained within 80% to 125% relative to the oral solution.
- The mean Tmax values for clobazam tablet were 1.5 hours postdose, respectively. The mean t1/2 value was 36.5 hours for clobazam and 66.2 hours for N-desmethylclobazam following administration of clobazam tablet.
- Both clobazam 20 mg dose tablet and clobazam 20 mg dose oral solution formulations were well tolerated. The most frequently reported AE was somnolence. All AEs were mild in severity and no subject discontinued from the study because of an AE.

Report # OV1016	**Study Period**: 11/06/2007 to 01/07/2008	
Title	Bioequivalence Evaluation of Two Clobazam 5 mg Tablet Formulations	

Reference ID: 3032655

Study Design single-dose, 2-way crossover, single-center, randomized, open-label study

☑ Bioequivalence: To demonstrate bioequivalence between two 5 mg tablet formulations of clobazam that were manufactured at 2 different sites.	☐ Bioavailability

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers

Screening: ≤ 21 days	**Washout:** 13 days, outpatient
Period 1/2	10 days, Inpatient stay ☑Y ☐ N:

Treatments: (Active Ingredient: clobazam)
Drug was given after an overnight fast.

	Test	**Reference**
Dosage Form	tablet	tablet
Dosage Strength	4 x 5 mg	4 x 5 mg
Batch #.	manufactured by Catalent Pharma lot number: 0701322	manufactured by (b) (4)

Sampling Times (PK, plasma)
Pharmacokinetic blood sampling times were before dosing (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours after dosing.

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐

Statistical Method: Log-transformed AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F values of clobazam were evaluated by an analysis of variance (ANOVA) model using treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The test and reference treatments were considered bioequivalent if 90% confidence intervals (CI) for the ratio (test versus reference treatments) of the log-transformed averages of Cmax and AUC0-inf fell within the bioequivalence limit of 80% to 125%.

Study Population :

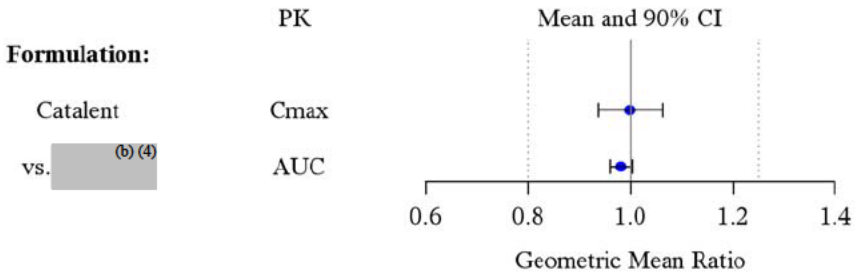
Randomized/Completed/ Discontinued Due to AE	40/39/0
Age [Median (range)]	35.03/34.25 (22.1-45.3)
Male/Female	26/14
Race (Caucasian/Black/Asian/other)	36/4/0/0

Results

Mean (%CV) of Plasma Pharmacokinetic Parameters of Clobazam

Pharmacokinetic Parameters (units)	Formulation Least Squares Mean: Catalent Test	Formulation Least Squares Mean: (b) (4) Reference	Ratio of Means Test/Reference	90% CI of Ratio
AUC0-lqc (h•ng/mL)	10261	10431	0.984	(0.965, 1.003)
AUC0-inf (h•ng/mL)	10635	10840	0.981	(0.961, 1.002)
Cmax (ng/mL)	357.7	358.5	0.998	(0.936, 1.063)

Reference ID: 3032655



Mean (%CV) of Plasma Pharmacokinetic Parameters of N-desmethylclobazam

Pharmacokinetic Parameters (units)	Test Clobazam 20 mg (Catalent Pharma Solutions) N = 40	Reference Clobazam 20 mg (b) (4) N = 39
AUC0-24 (h•ng/mL)	1122 (35)	1225 (61)
AUC0-lqc (h•ng/mL)	12731 (46)	13638 (73)
AUC0-inf (h•ng/mL)	11334 (21)[b]	12265 (35)[c]
Cmax (ng/mL)	87.2 (35)	91.9 (58)
Tmax (h)[a]	48.00 (24.0 – 216.0)	72.00 (36.0 – 168.0)
t1/2 (h)	58.6 (30)[b]	60.3 (29)[c]

Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☑ No ☐ NA

Conclusion

- A single 20 mg dose (4 × 5 mg tablets) of clobazam tablets manufactured by Catalent Pharma Solutions (test) was bioequivalent to a single 20 mg dose (4 × 5 mg tablets) of clobazam tablets manufactured by (b) (4) (reference).
- Overall, both test and reference clobazam tablets were well tolerated. No subject discontinued because of an AE and no SAE was reported.

Comments

Report # OV1018	**Study Period**: 02/19/08 (date of Period 1 dose) to 04/15/08 (last subject visit)	
Title	The Effect of Applesauce or a High Fat Meal on the Oral Bioavailability of Clobazam	
Study Design single-dose, 2-way crossover, single-center, randomized, open-label study		
☑ Bioequivalence	☐ Bioavailability	
Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy Vonuteers		
Screening: ≤ 21 days	**Washout:** 13 days, outpatient	
Period 1/2	Inpatient stay ☑Y ☐ N:	

Reference ID: 3032655

Treatments: (Active Ingredient: clobazam)

	Sequence	Dose Period 1	Dose Period 2
Group 1	1	A1 (4 × 5 mg)	B1 (4 × 5 mg)
	2	B1 (4 × 5 mg)	A1 (4 × 5 mg)
Group 2	1	A2 (1 × 20 mg)	B2 (1 × 20 mg)
	2	B2 (1 × 20 mg)	A2 (1 × 20 mg)
Group 3	1	A3 (1 × 20 mg)	B3 (1 × 20 mg)
	2	B3 (1 × 20 mg)	A3 (1 × 20 mg)

Treatment A1 4 × 5 mg tablets crushed with applesauce
Treatment B1 4 × 5 mg intact tablets without applesauce
Treatment A2 1 × 20 mg tablet crushed with applesauce
Treatment B2 1 × 20 mg intact tablet without applesauce
Treatment A3 1 × 20 mg intact tablet with a high-fat meal
Treatment B3 1 × 20 mg intact tablet in the fasted state

After an overnight fast, subjects received a single dose of 20 mg clobazam (4 × 5 mg or 1 × 20 mg tablets) on Day 1 of Period 1 and Day 14 of Period 2, except for those subjects assigned to the high-fat meal treatment.

Investigational Products:
Clobazam, 5 mg tablet, manufactured by Catalent Pharma Solutions, LLC, lot number 0701322 (API lot: 499841 [Catalent]; N002 [redacted] (b) (4).
Clobazam, 20 mg tablet, manufactured by Catalent Pharma Solutions, LLC, lot number 0701324 (API lot: 499841 [Catalent]; N002 [redacted] (b) (4)

Sampling Times (PK, plasma)

Screening	Baseline	Dosing and Pharmacokinetic Collection	Washout and Pharmacokinetic Collection
Days –21 to –2	Day –1	Period 1 (Day 1)	Days 1-3 *(confinement)* Days 4, 6, 8, and 10 *(outpatient)* Days 5, 7, 9, 11, and 12 *(outpatient-no pharmacokinetic collection)*
		Period 2 (Day 14)	Days 13-16 *(confinement)* Days 17, 19, 21, and 23 *(outpatient)* Days 18, 20, and 22 *(outpatient-no pharmacokinetic collection)*

Pharmacokinetic blood collection times were: 0 (predose) and 0.5, 1, 2, 3, 4, 8, 12, 24, 36, 48, 72, 120, 168, and 216 hours postdose.

Analytical Method: The performance of the analytical method is acceptable. Yes ☑ No ☐

Statistical Method: Log-transformed AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F values of clobazam were evaluated by an analysis of variance (ANOVA) model using treatment, sequence, and period as fixed effects and subject within sequence as a random effect. A point estimate and a 90% confidence interval (CI) were obtained for the difference in means for the log-transformed values of AUC0-24, AUC0-lqc, AUC0-inf, Cmax, CL/F, and Vd/F.

Study Population :

Reference ID: 3032655

Randomized/Completed/ Discontinued Due to AE (Reason for discontinuation: withdrew consent)	48/47/0
Age [(range)]	34.68 (21.1–45.7)
Male/Female	33/15
Race (Caucasian/Black/Asian/other)	37/11/0/0

Results

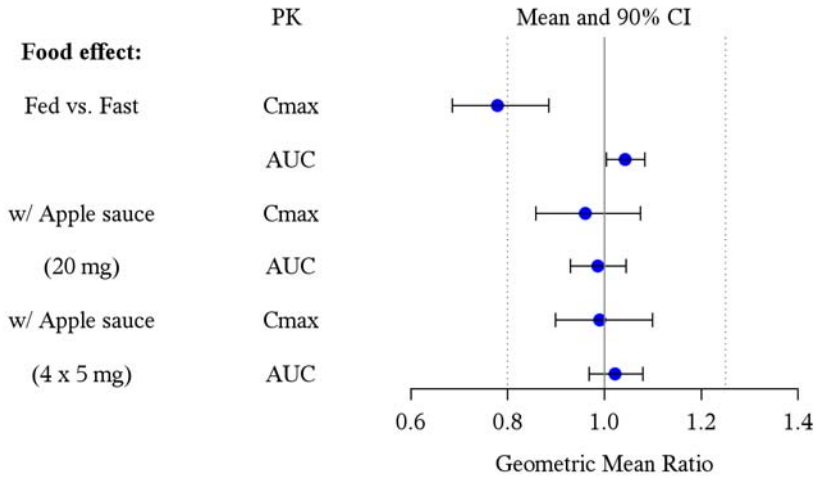
Table 7. Mean (%CV) Pharmacokinetic Parameters of Clobazam

Pharmacokinetic Parameter (unit)	Treatment[a]					
	A1 (N = 16)	B1 (N = 16)	A2 (N = 15)	B2 (N = 15)	A3 (N = 16)	B3 (N = 16)
AUC0-lqc (ng•h/mL)	9962 (30)	9771 (31)	10431 (23)	10589 (21)	9987 (17)	9579 (17)
AUC0-inf (ng•h/mL)	10278 (32)	10043 (31)	10822 (25)	10968 (23)	10202 (18)	9791 (18)
Cmax (ng/mL)	373 (24)	379 (30)	384 (23)	402 (22)	310 (30)	390 (21)
Tmax (h)[b]	2.00 (1.0-4.0)	2.00 (0.5-3.0)	2.00 (1.0-3.0)	1.00 (0.5-3.0)	3.00 (1.0-8.0)	2.00 (1.0-3.0)
t1/2 (h)	38.5 (28)	37.8 (27)	40.1 (36)	39.7 (34)	37.2 (26)	36.7 (30)
CL/F (L/h)	2.1 (28)	2.2 (27)	2.0 (23)	1.9 (23)	2.0 (21)	2.1 (22)
Vd/F (L)	111.6 (24)	113.2 (28)	108.8 (32)	105.1 (28)	108.3 (34)	112.0 (39)

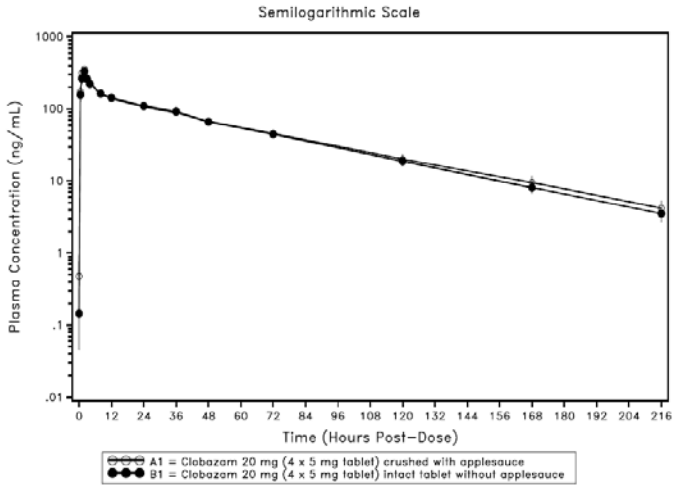
A1: 20 mg clobazam – 4 × 5 mg tablets crushed with applesauce; B1: 20 mg clobazam – 4 × 5 mg intact tablets without applesauce;
A2: 20mg clobazam – 1 × 20mg tablet crushed with applesauce; B2: 20mg clobazam – 1 × 20mg intact tablet without applesauce;
A3: 20 mg clobazam – 1 × 20mg intact tablet with a high-fat meal; B3: 20 mg clobazam – 1 × 20mg intact tablet in the fasted state

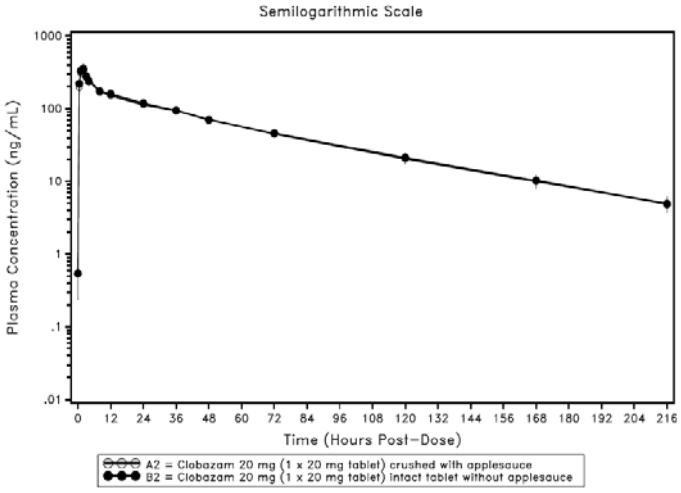
Table 8. Ratios and 90% Confidence Intervals for Clobazam Pharmacokinetic Parameters

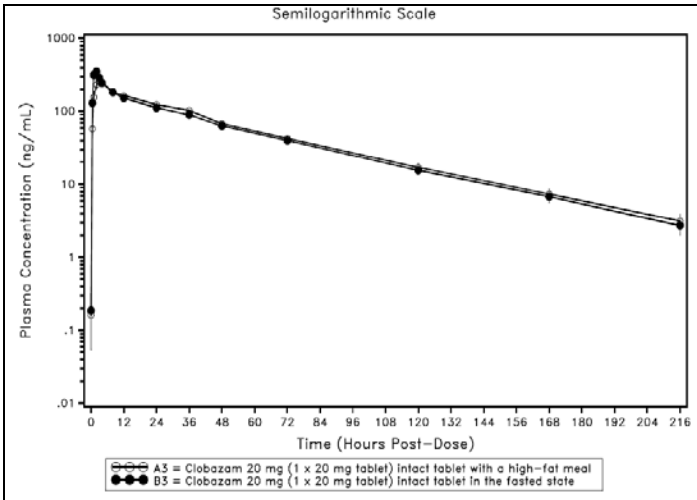
Pharmacokinetic Parameter (unit)	Treatment Comparison	n[a]	Geometric LSM		Ratio of Geometric LSM	90% CI of the Ratio
			A1, A2, or A3	B1, B2, or B3	A1/B1, A2/B2, or A3/B3	
AUC0-lqc (ng•h/mL)	(A1) 4 × 5 mg tablets crushed with applesauce (B1) 4 × 5 mg intact tablets without applesauce	16–16	9578.00	9385.25	1.0205	(0.969, 1.075)
	(A2) 1 × 20 mg tablet crushed with applesauce (B2) 1 × 20 mg intact tablet without applesauce	15–15	10237.11	10399.02	0.9844	(0.929, 1.044)
	(A3) 1 × 20 mg intact tablet with a high-fat meal (B3) 1 × 20 mg intact tablet in the fasted state	16–16	9837.60	9427.85	1.0435	(1.005, 1.083)
AUC0-inf (ng•h/mL)	(A1) 4 × 5 mg tablets crushed with applesauce (B1) 4 × 5 mg intact tablets without applesauce	16–16	9848.28	9634.70	1.0222	(0.968, 1.079)
	(A2) 1 × 20 mg tablet crushed with applesauce (B2) 1 × 20 mg intact tablet without applesauce	15–15	10580.39	10733.26	0.9858	(0.930, 1.045)
	(A3) 1 × 20 mg intact tablet with a high-fat meal (B3) 1 × 20 mg intact tablet in the fasted state	16–16	10040.67	9627.52	1.0429	(1.004, 1.083)
Cmax (ng/mL)	(A1) 4 × 5 mg tablets crushed with applesauce (B1) 4 × 5 mg intact tablets without applesauce	16–16	361.86	364.04	0.9940	(0.899, 1.099)
	(A2) 1 × 20 mg tablet crushed with applesauce (B2) 1 × 20 mg intact tablet without applesauce	15–15	376.94	392.82	0.9596	(0.858, 1.074)
	(A3) 1 × 20 mg intact tablet with a high-fat meal (B3) 1 × 20 mg intact tablet in the fasted state	16–16	297.41	381.97	0.7786	(0.685, 0.885)



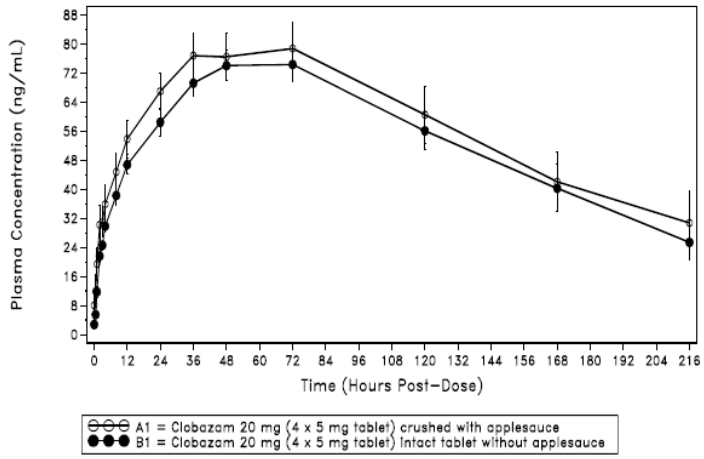
Mean (± SE) Plasma Concentration of Clobazam Versus Time

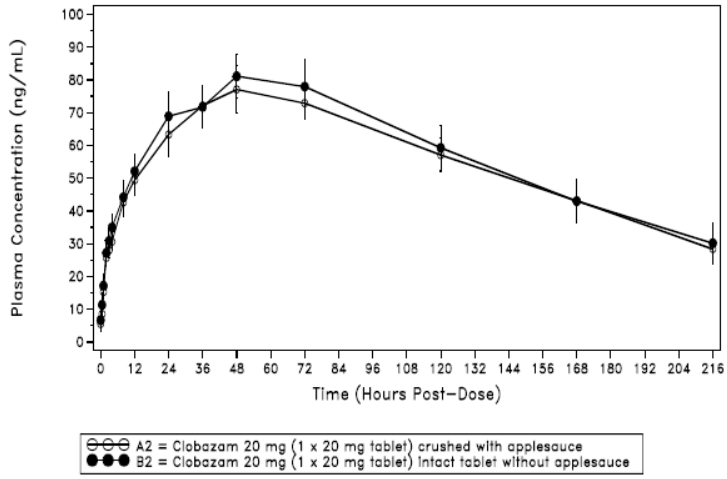


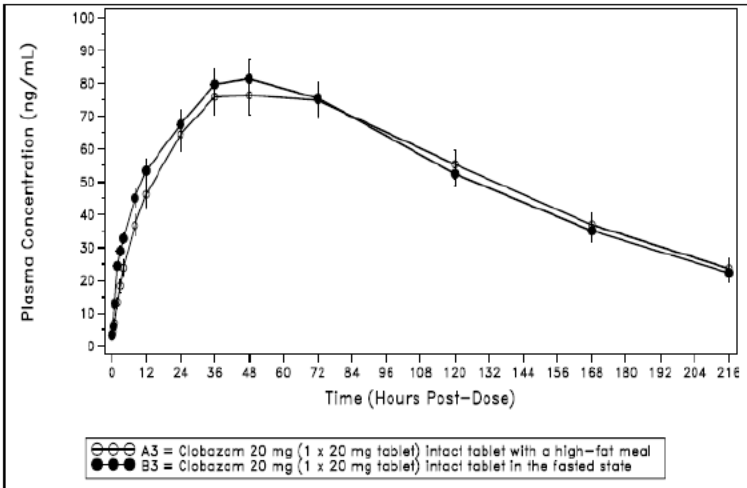




Mean (± SE) Plasma Concentration of N-desmethylclobazam Versus Time







Site Inspected

Requested: Yes☐ No ☑ | **Performed:** Yes☐ No ☐ N/A ☑

Safety: Was there any death or serious adverse events?

☐ Yes ☑ No ☐ NA

Conclusion

- Administration of clobazam tablets with applesauce did not have a significant effect on maximum and overall plasma exposures of clobazam or N-desmethylclobazam; the 90% CIs for the ratios were contained within 80% to 125%. Therefore, clobazam tablets can be given crushed with applesauce.
- Administration of clobazam with a high-fat meal did not affect clobazam exposure. High-fat meal delayed clobazam median Tmax 1 hour and reduced clobazam Cmax by 22%. However, these changes are not considered clinically significant and clobazam can be given without regard to meals.

Comments

Comparison of AUC and Cmax B1 vs. B2 and B1 vs. B3

	B1	**B2**	**B3**
AUC0-inf (ng•h/mL)	10043 (31)	10968 (23)	9791 (18)
Cmax (ng/mL)	379 (30)	402 (22)	390 (21)
CL/F (L/h)	2.2 (27)	1.9 (23)	2.1 (22)

B1: 4 × 5 mg intact tablets without applesauce;
B2: 1 × 20mg intact tablet without applesauce (fasted)
B3: 1 × 20mg intact tablet in the fasted state

Conclusions: AUC0-inf and Cmax following the intake of 4 × 5 mg tablets or 1 × 20mg tablet are comparable.

Reference ID: 3032655

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/s/

TA-CHEN WU
10/21/2011

SEONGEUN CHO
10/23/2011

YUXIN MEN
10/23/2011

CLINICAL PHARMACOLOGY REVIEW

NDA:	**202067**
Brand Name:	Onfi®
Generic Name:	Clobazam
Dosage Form & Strength:	Immediate Release Tablet (5, 10 and 20 mg)
Indication:	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients ≥2 years of age
Applicant:	Lundbeck Inc.
Submission:	505(b)(1), Standard
Submission Dates:	12/23/2010, 02/07/2011, 02/10/2011, 04/01/2011, 05/10/2011, 06/10/2011, 09/02/2011
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewers:	Seongeun Julia Cho, Ph.D., Ta-Chen Wu, Ph.D.
Team Leader:	Angela Yuxin Men, M.D., Ph.D.
Pharmacometrics Reviewer:	Joo-Yeon Lee, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer:	Hobart Rogers, Pharm.D., Ph.D.
Pharmacogenomics Team Leader:	Michael Pacanowski, Pharm.D., M.P.H.

The OCP office level briefing was held on August 16, 2011.

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Reference ID: 3026076

1. Executive Summary

The sponsor is seeking approval of Onfi (clobazam) as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥2 years of age. Clobazam belongs to the class of benzodiazepine, approved in other countries since late 1970's, and received Orphan drug designation granted on December 18, 2007 for the treatment of LGS. The proposed dosing regimen is (1) 5 mg QD with weekly dose titration up to 10–20 mg/day in children over 2 years of age and ≤ 30 kg body weight, or (2) 10 mg QD with weekly dose titration up to 20–40 mg/day in patients > 30 kg. Doses above 5 mg/day should be administered as BID.

To support the approval of the application, one Phase 2 and one pivotal placebo-controlled Phase 3 trial were conducted to demonstrate the safety and efficacy of Onfi. Clinical pharmacology program consists of single and multiple-dose studies evaluating pharmacokinetics (PK) of clobazam and its active metabolite, N-desmethylclobazam (N-CLB), examining the metabolic profiles, dose proportionality, effects of food, potential for drug-drug interactions, and bridging the to-be-marketed formulation and the one used in the Phase 2 study. Impact of mild and moderate renal impairment on PK of clobazam was studied, whereas literature information on impact of hepatic dysfunction was supplemented. Population PK analysis evaluated the key covariates in the target patient population, using the pooled data from healthy and patients in Phase 1~3 trials. Exposure-Response was also performed to evaluate the relationship between systemic exposure of clobazam and active metabolite and efficacy endpoint (percent reduction in the number of drop seizures) and safety endpoints (Sedation-related adverse events) using the data obtained from the Phase 3 study. In addition, the impact of CYP2C19 genetic polymorphism on pharmacokinetics of clobazam, as well as the need for any dose adjustment, was assessed.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds NDA 202067 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

1.2 Phase IV Commitment

No Post-Marketing Requirement or Commitment (PMR or PMC) was requested.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:
The PK of clobazam was dose-proportional over the range of 10 – 80 mg. Population pharmacokinetics analysis reveals that the pharmacokinetics of clobazam are linear from 5 mg/day to 160 mg/day.

Reference ID: 3026076

Absorption:
The relative bioavailability of clobazam tablets compared to a solution is approximately 100%. Clobazam absorption was at a fast to moderate rate, with T_{max} ranging from 0.5 to 4 hours after single- or multiple-dose administrations. High-fat meal reduced clobazam Cmax by 22% without affecting AUC. The changes are not clinically significant and clobazam can be given without regard to meals. When clobazam was administered as crushed tablets with applesauce, Cmax and AUC were bioequivalent to those following an administration of tablets.

Distribution:
Clobazam is widely distributed to peripheral tissues. The apparent volume of distribution in healthy volunteers and patients ranges 99-120L. Plasma protein binding of clobazam and its active metabolite, N-CLB, is moderate (88.9-77.7% and 74.1-69.1%, respectively) and is concentration independent in the therapeutic ranges. Mild or moderate renal impairment did not affect the extent of protein binding of clobazam or N-CLB.

Metabolism:
Clobazam is extensively metabolized, recovered approximately 2% of the dose as unchanged in urine. The major metabolic pathway of clobazam is N-demethylation to form N-CLB, the only pharmacologically active and major metabolite. The transformation is mediated mainly by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-CLB plus the sum of subsequent metabolites comprise ~94% of the total drug-related components in urine.

N-CLB is also extensively metabolized, mainly by CYP2C19. For CYP2C19 poor metabolizers, levels of N-CLB in plasma were much higher than those in the wild type subjects and represented 62.5-73.8 % of the total metabolic products in urine (total peak area). In CYP2C19 wild type subjects, N-CLB in urine ranged 25-29%.

Elimination:
Clobazam is cleared mainly by metabolism with subsequent renal elimination of metabolites. In a mass balance study, 82% of the dose administered was recovered in the urine and 11% in the feces. Clobazam represents ~2 % of the dose recovered in urine. In healthy adults and patients, clobazam oral clearance (CL/F) ranges from 1.94 to 2.5 L/hr and the mean terminal half-life of clobazam is 36-42 hr. The mean steady-state half-life of N-CLB is 71-82 hr.

Dose/Exposure-Response relationships:
There were clear exposure-response relationships for both efficacy and safety, and the relationship supports the sponsor's proposed dosing regimen, which appears to be reasonable.

The primary efficacy analysis showed that the drop seizure rates (i.e., primary efficacy end point) appeared to decrease in dose-dependent manner, as the exposure increases, and it reaches a plateau at the highest maximum daily dose (40mg/day). All three dose

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groups (10 mg, 20 mg, and 40 mg per day) showed statistically significantly superior to the placebo groups

The sedation-related adverse events (sedation, somnolence, sleepiness, drowsiness, sleepy, lethargy and listlessness) were evaluated as safety endpoints. For light-weighted patients (≤ 30kg), clobazam seems to be safe across all dose levels, although the doses of 10-20 mg/day showed higher percentage of sedation-related AE than placebo or 5mg/day. For heavy patients (>30 kg), it appears to be dose-dependent increase in sedation-related AE but the difference between 20 mg/day and 40 mg/day is negligible.

Intrinsic factors:

Age, gender, race:

The population PK analysis showed that the clearance of clobazam appears to be lower in the elderly (≥ 65 years old) compared to that of adult patients (18 years older) and adolescents (12-17 years, 45 subjects). However, clinical studies did not include sufficient numbers of the elderly subjects to determine whether they respond to the clobazam treatment differently from the younger subjects. Initiating therapy at the lower dose (5 mg) should be considered in the elderly. Either race or gender did not influence PK of clobazam or N-CLB.

CYP2C19 genotypes:

N-CLB is mainly metabolized by CYP2C19. CYP2C19 genotype does not affect clobazam exposure. However, mean Cmax and AUC of N-CLB in CYP2C19 poor metabolizer were 3-5 fold higher than those in intermediate/extensive metabolizers (based on results from phase 1 studies and population PK analysis). Considering the higher exposures and prolonged half-life of N-CLB in CYP2C19 PMs, initiating therapy at the lower dose (5 mg) and slower titration based on tolerability should be considered.

Renal impairment:

Results from a dedicated PK study showed that the changes in clobazam Cmax and AUC in mild and moderate renal impairment subjects are small (3-24% increase in mean Cmax and 0-13% increase in mean AUC0-96 compared to healthy control) and likely clinically insignificant. No dose adjustment is recommended for subjects with mild to moderate renal impairment. This study did not include subjects with severe renal impairment or end-stage renal disease (ESRD), and there is essentially no experience with clobazam in those patients. (b) (4) (details in Section 2.3.1.4).

Hepatic impairment:

There are limited data to characterize the effect of hepatic impairment on the PK of clobazam. The effect of hepatic impairment on clobazam PK was evaluated in subjects with liver disease as reported in the literature. While the study comprised 5 subjects with mild or moderate hepatic impairment and 4 subjects with severe hepatic impairment, compared with 6 normal controls, individual subject data are not available, and therefore a quantitative relationship between the impairment severity and clobazam clearance could

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not be determined. Collectively, following a single dose administration of 20 mg clobazam, Cmax of clobazam or N-CLB was not increased in subjects with hepatic impairment compared to normal control. There was no statistical difference in total plasma CL of clobazam. Tmax of N-CLB and clobazam terminal half-life were prolonged. Due to the inadequate information about metabolism of clobazam and N-CLB exposure in patients with severe hepatic impairment, no dosing recommendation in those patients can be given (details in Section 2.3.1.5).

Extrinsic factors:
Drug-Drug Interaction (DDI)

In vitro studies:
Clobazam did not inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 in vitro. N-CLB showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4 with IC50 values of 71.7, 110, 210 and 111 uM, respectively, in vitro.

Clobazam and N-CLB induce CYP3A4 activity. Clobazam and N-CLB also induced UGT1A1 mRNA. However, the effects on UGT1A1 enzymatic activities are not known.

Clobazam and N-CLB do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

Effect of co-administered drugs on clobazam:
Co-administration of 400 mg ketoconazole (CYP3A4 inhibitor) increased clobazam AUC by 54 % with no effect on Cmax. Co-administration of 40 mg omeprazole (CYP2C19 inhibitor) increased AUC of clobazam and N-CLB by 30-36 % without any effect on Cmax. These changes are not considered clinically significant and thus no dose adjustment of clobazam is recommended.

The population PK analysis, which was included CYP3A4 inducer group (phenobarbital, phenytoin, and carbamazepine), CYP2C19 inducer group (valproic acid, phenobarbital, phenytoin, and carbamazepine) and CYP2C19 inhibitor group (felbamate and oxcarbazepine) as a binary covariate, showed that the fraction of N-CLB formed increased by 9.4% by CYP3A4 inducers whereas CYP2C19 inducers made elimination of N-CLB faster by 10.5%, which implies that the net change in PK of N-CLB may be negligible. Hence, no dose change may be required in the presence of the CYP3A4 inducers and CYP2C19 inducers together.

Effect of clobazam on co-administered drugs:
Clobazam co-administration increased dextromethorphan (CYP2D6 probe) AUC and Cmax by 90% and 59%, respectively. Narrow therapeutic index drugs that are metabolized by CYP2D6 may require dose reduction when used with Onfi. The use of other concomitant medications that are primarily metabolized by CYP2D6 should be monitored closely.

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Coadministration of clobazam resulted in decreases of midazolam (CYP3A4 probe) AUC and Cmax by 27% and 24%, respectively, and 4-fold and 2-fold increase in AUC and Cmax of the metabolite 1´-hydroxymidazolam. These results indicate that clobazam can induce CYP3A4 activity in humans. However, this CYP3A4 induction is considered to be relatively mild. Consequently, doses adjustment for concomitant drugs primarily metabolized by CYP3A4 is not necessary.

Population analysis showed that clobazam did not affect the exposure of valproate (CYP2C9 substrate) and lamotrigine (UGT substrate). No dose adjustment of lamotrigine or valproic acid is required when clobazam is co-administered.

Food effect
Food (high fat meal) reduced Clobazam C_{max} by 22% (90% CI: 68.5 – 88.5%) without having effect on clobazam AUC. Clobazam can be given without regard to meals.

When clobazam was administrated in applesauce, C_{max} and AUC of clobazam crushed tablet in applesauce were comparable to those of intact tablets, meeting BE criteria. No dose adjustment is required when clobazam tablet is given crushed with applesauce.

PK Comparison of TBM vs. Phase 2/Developmental Formulations
All clinical studies were conducted using to-be-marketed (TBM) formation, except for the Phase 2 efficacy study, OV-1002. Results from a comparative PK study evaluating the Phase 2 formulation (OV-1002) and TBM products showed that two formulations are bioequivalent.

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2. Question Based Review

2.1 General Attributes

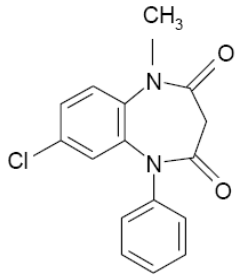
2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Onfi?

Onfi (clobazam) is proposed as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥2 years of age.

The exact mechanism of action for clobazam is not fully understood. The presumed major mechanism of action is as a positive allosteric modulator (PAM) at gamma containing GABA(A) receptors. Following binding to the GABA(A) receptor, clobazam enhances chloride currents mediated via the endogenous amino acid GABA.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Clobazam, the active ingredient of Onfi, is chemically known as 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4-(3H,5H)-dione, without chiral centers in the structure. Its molecular formula is $C_{16}H_{13}C_lN_2O_2$ and the molecular weight is 300.7. Clobazam is a white or almost white, crystalline powder that is slightly soluble in water, freely soluable in methylene chloride, and sparingly soluble in ethanol. The pH value for an aqueous solution is in the range of 5.5–7.5. The structure for carisbamate drug substance is provided in the Figure below. The available strengths of Onfi are 5, 10 and 20mg.



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

The sponsor proposes that the total daily dose of clobazam should be administered orally at the following proposed dosing regiments:

- Children over 2 years of age and ≤ 30 kg body weight should initiate therapy at 5 mg QD and doses titrated at weekly intervals to a target dose of 10–20 mg/day.
- Patients > 30 kg body weight should initiate therapy at 10 mg daily (5 mg BID) and doses titrated at weekly intervals to a target dose of 20–40 mg/day .
- In both cases, doses above 5 mg/day should be administered in two divided doses and the titration schedule and final dose should be determined based on response.

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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted 10 clinical pharmacology studies in healthy adults, one Phase 2 (OV-1002) and one pivotal Phase 3 clinical study (OV-1012) in patients with LGS. A Phase 2/3 open-label extension study is ongoing.

The drug-release profiles of clobazam tablets were assessed in the biopharmaceutics program. In the clinical pharmacology development program, the following single-dose studies assessed the biopharmaceutics/pharmacokinetics of clobazam in healthy volunteers:

- Study OV-1017 was conducted to determine the bioavailability of clobazam tablets relative to a solution.
- Study OV-1016 was conducted to determine the bioequivalence of 2 tablet formulations: one tablet formulation used in the Phase 2 clinical study (OV-1002) and the other tablet formulation used in the Phase 3 clinical study (OV-1012). The Phase 3 tablet formulation is the to-be-marketed (TBM) formulation.
- Study OV-1018 was conducted to assess the effects of administering crushed tablets in applesauce and of a high-fat meal on clobazam PK.
- Study LC-006 was conducted to determine mass-balance following single dose ^{14}C-clobazam
- Study LC-010 to evaluate PK of three dose levels of clobazam (10, 20 and 40 mg)

The sponsor also submitted three single-dose biopharmaceutical studies (Study LC-001, LC-002 and LC-003) conducted by the previous sponsor in the 1970s and data reported in the literature. However, the dosage forms evaluated in these studies are different from those used in Lundbeck's clinical development program and the results from these studies are only supportive in nature. These legacy studies are listed in Table below.

Healthy Subject Pharmacokinetic Studies	
Comparative bioavailability, single dose 40 mg, tablet, capsule, solution	LC-001
Bioequivalency, single dose 10 mg, capsules with/without starch	LC-002
Bioequivalency, single dose, 10 mg, tablets, capsules	LC-003
Multiple dose study of clobazam, 30 mg/day	LC-008
Dose proportionality, 10 mg, 20 mg and 40 mg	LC-010
Healthy Subject, Metabolism Studies	
Metabolite profiling, samples from LC-006	LC-004
Mass balance, single 39mg ^{14}C-clobazam (carboxyl label)	LC-006
Mass balance, single dose 20 mg ^{14}C-clobazam (methyl label)	LC-007

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In addition, clobazam has been studied in both single- and multiple-dose studies in healthy adult subjects and LGS patients to evaluate the potential impact of intrinsic and extrinsic factors, as listed below.

- Study OV-1032: To evaluate the effects of CLB 20 mg on PK, safety, and tolerability in subjects with impaired renal function and healthy matched control subjects with normal renal function
- Study OV-1021: To evaluate the PK, safety, and tolerability of CLB administered alone and following multiple doses of ketoconazole or omeprazole
- Study OV-1023: To evaluate the effects of CLB 40 mg on the multiple P450 substrates (cocktail)
- Study OV-1022: To evaluate the effect of CLB on PD (QT interval), PK, safety, and tolerability following multiple oral doses
- Study OV-1038: To evaluate the effects of CLB 10-160 mg/day on PK, safety, and tolerability
- The sponsor relies on a literature report of a clinical study evaluating the effect of hepatic impairment on PK of CLB and N-CLB.
- PK-MB-001: study report for metabolic profiling of clobazam following single- and multiple-dose administration.

The Phase 2 and Phase 3 studies in LGS patients include:

- Study OV-1012: Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to determine the efficacy of CLB in the reduction of drop seizures at 3 dose levels when compared to placebo during 12 weeks maintenance dosing in subjects with LGS
- Study OV-1002: Phase 2, randomized, double-blind, dose-ranging, parallel-group study to determine the safety and efficacy of low-dose and high-dose CLB in the treatment of seizures that lead to drop attacks in subjects with LGS
- Study OV-1004: Phase 2/3, ongoing, uncontrolled, open-label extension for subjects who participated in Studies OV-1002 and OV-1012 to evaluate the long-term safety and effectiveness of CLB in the treatment of drop seizures in subjects with LGS

Population PK analysis (PK-POP-001) was performed using the data in healthy subjects (five Phase 1 studies) and LGS patients (OV-1002 and OV-1012) to determine the exposure-response relationship with respect to efficacy and safety for clobazam and/or N-CLB.

2.2.2. What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Lennox-Gastaut syndrome is characterized by multiple seizure types, including the tonic-atonic seizures (drop attack/drop seizure) involving the entire body, trunk, or head.

The primary efficacy endpoint in the clobazam clinical program was a percent reduction in drop seizures (average per week) from the 4-week baseline period to the 4-week (for

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Phase 2 study) or 12-week (for Phase 3 study) maintenance period. The weekly number of drop seizures during baseline was the number of drop seizures reported during baseline divided by the number of days recorded during baseline multiplied by 7. Similarly, the weekly number of drop seizures during maintenance was the number of drop seizures reported during the maintenance period divided by the number of days during the maintenance period multiplied by 7.

The sponsor conducted a Phase 2, multicenter, randomized, double-blind, dose-ranging study (OV-1002), assessing the safety and efficacy of clobazam as adjunctive therapy in subjects with LGS. Comparing the high-dose and low-dose groups in this study, a statistically significantly greater percent reduction from baseline in drop seizures for subjects in the high-dose group was observed compared to subjects in the low-dose group.

The pivotal Phase 3 trial (OV-1012) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of clobazam at three dose levels as adjunctive therapy for LGS. In addition to the primary end point (ie., percent reduction in the average weekly rate of drop seizures from the 4-week baseline to 12-week maintenance period), several secondary variables were assessed, including;

- percentage of responders, defined as those with ≥ 25%/≥ 50%/≥ 75%/100% reduction in drop seizures from baseline compared to the maintenance period
- percent reduction in the average weekly rate of total (drop and non-drop) seizures combined from baseline compared to the maintenance period
- percent reduction in the average weekly rate of non-drop seizures from baseline compared to the maintenance period

In both Phase 2 and Phase 3 studies, sparse blood samples were collected and population PK analyses were performed to assess the influence of subject covariates on the PK of clobazam and N-CLB. These covariates included gender, age, race, weight, genotype, anti-epileptic co-medications, etc.

2.2.3 Exposure-Response

2.2.3.1. Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?

Yes, it shows a clear exposure-response relationship for both efficacy and safety, and the relationship supports the sponsor's proposed dosing regimen.

The data from one phase III study (OV-1012: multicenter, randomized, double-blinded, placebo-controlled, parallel study) was used for exposure-response analysis. The study OV-1012 had a 4-week baseline period, a 3-week titration period and a 12-week maintenance period, followed by a 2- or 3-week taper period for subjects not continuing into the open-label extension study.

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In the study of OV-1012, subjects were stratified into 1 of 2 pre-specified weight groups (≤ 30 kg and > 30 kg) and randomly assigned to placebo or a low (target dose of 0.25 mg/kg: a maximum daily dose of 10 mg), medium (target dose of 0.5 mg/kg: a maximum daily dose of 20 mg), or high (target dose of 1.0 mg/kg: a maximum daily dose of 40 mg) dose of clobazam. Subjects who could not tolerate the target dose or the decreased dose were to be discontinued from the study and may have been eligible to enter into the open-label extension study.

The primary efficacy end point was the percent reduction in the number of drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period. The primary efficacy analysis showed that the drop seizure rates appeared to decrease in dose-dependent manner, and all three dose groups showed statistically significantly superior to the placebo groups (p-value: 0.012, 0.0015, <0.0001 for low, med, high dose groups, respectively).

The sponsor proposes the dosing regimen as follows;

- Children over 2 years of age and ≤30 kg body weight should initiate therapy at 5 mg QD and doses titrated at weekly intervals to a target dose of 10-20 mg/day.
- Patients >30 kg body weight should initiate therapy at 10 mg daily (5 mg BID) and doses titrated at weekly intervals to a target dose of 20-40 mg/day.

In the reviewer's exposure-efficacy analysis, the subject-specific average steady state concentrations of clobazam (Cavg,p) and N-CLB (Cavg,m) obtained from the results of the population PK analysis were used as an exposure, and the same primary endpoint was used for the efficacy endpoint. Figure below presents the model-predicted relationship between average concentration for both clobazam and N-CLB and the primary endpoint from the reviewer's analysis. The drop seizure rates appears to be decreasing as the exposure increases, and it reaches a plateau at the highest maximum daily dose (40mg / day), which is consistent with the sponsor's analyses results. However, it also should be noticed that there is a substantial overlap in Cavg,m between doses.

Figure. Model-predicted relationship between Cavg and % reduction in drop seizure during maintenance period from the baseline for clobazam (left) and N-CLB (right). The dots represent the observed % reduction at octile of Cavg, and the solid line is the model-predicted relationship with 95 % prediction interval (blue shade). The four boxplots on the bottom represent the distribution of Cavg at actual dose received during maintenance period (15 mg and 35 mg were combined with 20 mg and 40mg, respectively due to completely overlap in the distribution and small sample size).

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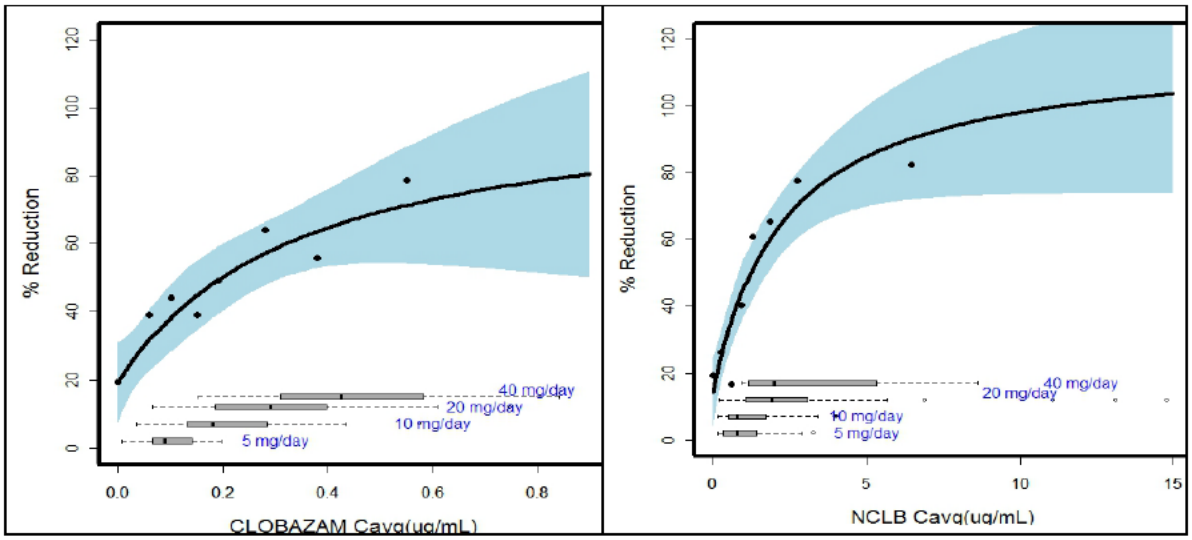
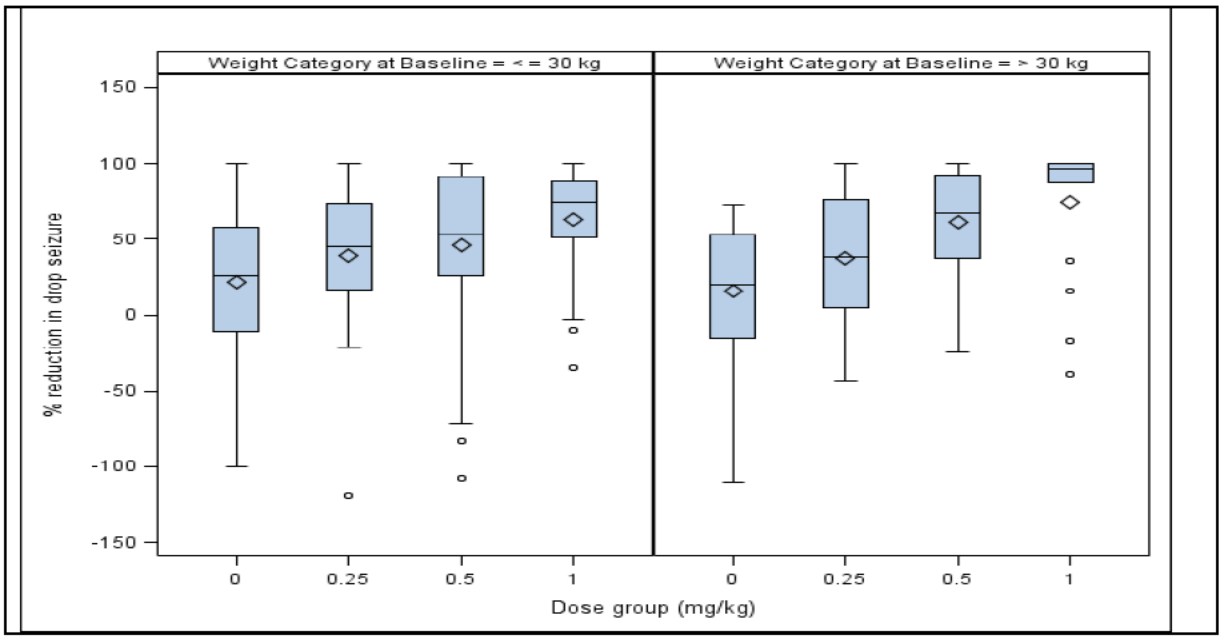


In order to evaluate the sponsor's proposed dosing regimen, the reviewer looked at the dose-response (% reduction in drop seizure) relationship by each weight category, which is shown in Figure below. For both weight categories it shows clear dose-response relationship, although there appears to be large variability.

Figure. Dose-Response relationship by weight category:



In terms of safety analysis, the sedation-related adverse events (sedation, somnolence, sleepiness, drowsiness, sleepy, lethargy and listlessness) were evaluated as an endpoint. Figure below shows the dropout-adjusted time profile of percent of patients having at least 1 sedation-related adverse event at each day from observed data by weight category. For light-weighted patients (≤ 30kg), clobazam seems to be safe across all dose levels, although the doses of 10-20 mg/day showed higher percentage of sedation-related AE

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(b) (4)

negligible.

Figure. The percent of patients having at least 1 sedation-related adverse event – time profile from observed data: dropout-adjusted.

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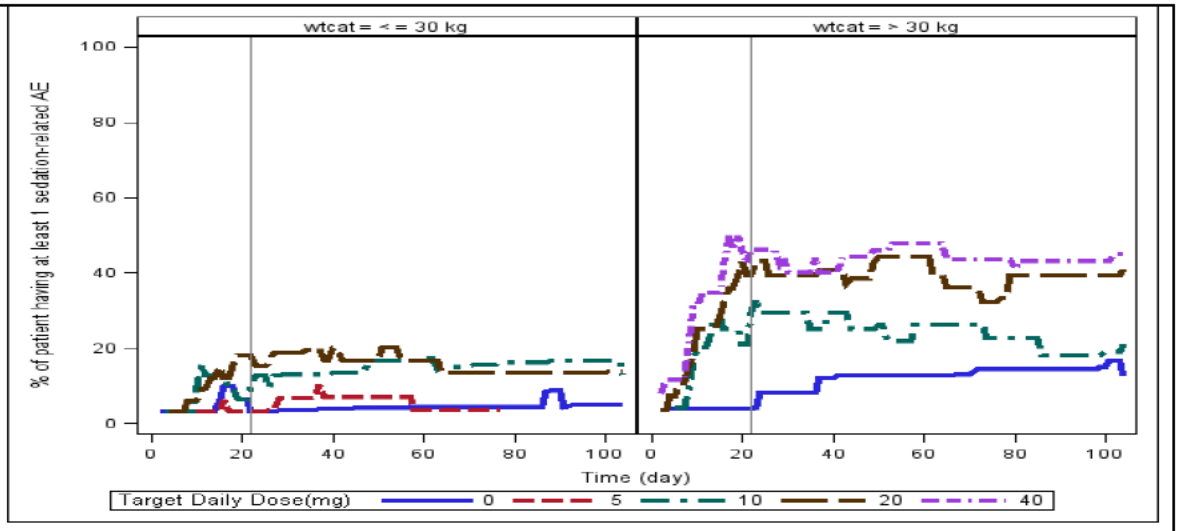

Given efficacy and safety profiles, the sponsor's proposed dosing regimen is considered reasonable.

2.2.3.2 Does this drug prolong the QT or QTc interval?

No, clobazam did not produce a significant QTc prolongation effect in healthy subjects who received clobazam 40 mg and 160 mg (supratherapeutic dose). The supratherapeutic dose (160 mg) produced mean clobazam Cmax values 2.7-fold and N-CLB Cmax values 3.9-fold the mean Cmax for the 40-mg dose. The exposures observed in this study following the 160-mg dose covered the scenarios as the results of drug-drug interaction. Details are available in review for thorough QT study conducted by Dr. Joanne Zhang of the QT-IRT review team.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

2.2.4.1 What are the single and multiple dose PK parameters?

Single and multiple dose PK characteristics of clobazam were evaluated in several studies OV-1016, OV-1017, and OV-1038. Clobazam dose-linearity was demonstrated in the 10–40 mg range following single dose administration and in the 10–80 mg range following multiple dose administrations (LC-010, OV-1038). Dose-proportionality of N-desmethylclobazam (N-CLB) could not definitely be determined due to the limited available data. The elimination half-lives ($t_{1/2}$) of clobazam and N-CLB are 36-42 hrs and

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59-82 hrs, respectively. Following multiple daily oral doses, steady-state of clobazam and N-CLB was attained by 11-14 days. The accumulation factor for clobazam is 2-3, while that for N-CLB is approximately 20. At the steady-state, the exposure of N-CLB was 3-5 time higher than that of clobazam.

2.2.4.2 What are the characteristics of drug absorption?

The relative bioavailability of clobazam tablets when compared to oral solution was approximately 100%. Clobazam absorption was at a fast to moderate rate, with T_{max} ranging from 0.5 to 4 hours after single or multiple administrations. Administration of crushed clobazam tablets with applesauce did not have a significant effect on the bioavailability of clobazam. High-fat meal reduced clobazam Cmax by 22%. However, the overall clobazam plasma exposure (AUC) was not altered by a high-fat meal.

2.2.4.3 What are the characteristics of drug distribution?

Clobazam is widely distributed to peripheral tissues. Following oral administration, clobazam concentration was declined in bi-exponential fashion after reaching the peak. The apparent volume of distribution across the single and multiple dose PK studies up to 40 mg TID and from population PK analysis was 99-120 L. Plasma protein binding of clobazam and N-CLB was moderate (78.5 % and 72.5 % mean plasma protein binding, respectively), independent of concentrations in the therapeutic range. The *ex vivo* protein binding study showed that the protein binding of clobazam or N-CLB was not affected by mild or moderate renal impairment.

2.2.4.4 What are the characteristics of drug metabolism?

Clobazam is extensively metabolized, recovered approximately 2% of the dose as unchanged in urine. Approximately 25 drug-related species were identified in human plasma and/or urine (OV-7802-135).

The major metabolic pathway of clobazam is N-demethylation to form N-CLB, the major and the only pharmacologically active metabolite. The transformation is mediated mainly by CYP3A4 and to a lesser extent by 2C19 and 2B6. N-CLB is also extensively metabolized (~25% of the dose recovered in urine), mainly by CYP2C19. N-CLB plus the sum of subsequent metabolites comprise >80% of the total drug-related components in urine. In CYP2C19 poor metabolizers (PMs), levels of N-CLB in plasma were much higher than in the wild type subjects and represented 62.5-73.8 % of the total metabolic products in urine (total peak area, PK-MB-001). Hydroxylation of clobazam is a minor metabolic path in human both *in vitro* and *in vivo* and is mediated via CYP2C19 and CYP2C18. No direct conjugation of Clobazam and N-CLB was observed. The major metabolic pathways of clobazam are illustrated in the Figure below.

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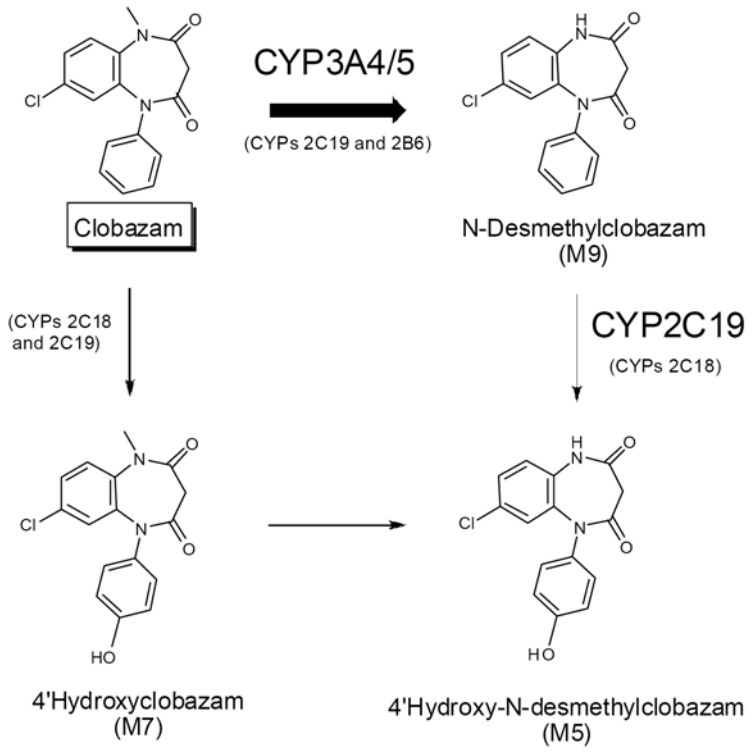

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

In a mass balance study with single dose (39 mg) of ^{14}C-clobazam, a total recovery of radioactivity was ~93% through 21 days post dose, of which 82% were recovered in the urine and 11% in feces. Clobazam is extensively metabolized and subsequently eliminated in urine. Overall, ~2% of the dose was recovered intact in urine (3.01-0.7% over 24-168 hours period, OV-7802-135).

2.2.4.6 What are the characteristics of drug elimination?

Clobazam is cleared mainly by metabolism with subsequent renal elimination of metabolites. In a mass balance study, among approximately 93% of the radioactivity recovered, 82% of the dose was found in the urine and 11% in the feces.

Across the single and multiple dose studies in healthy volunteers, clobazam oral clearance (CL/F) was 1.94 to 2.3 L/hr. In the population PK analysis the estimated CL/F for clobazam was 2.5 L/hr. Following single and multiple dose studies, the mean terminal half-life of clobazam was 36-42 hours. In the population PK analysis the median terminal t½ of clobazam was estimated to 36 hours. The mean t½ of N-CLB following single and multiple doses were 59-75 hours and 71-82 hours, respectively. The median terminal t½ of N-CLB estimated by population PK analysis was 79 hours.

2.2.4.7 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

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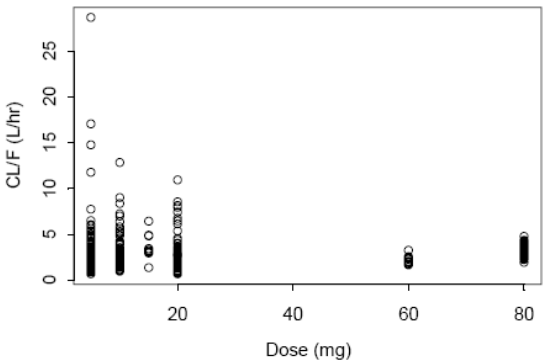
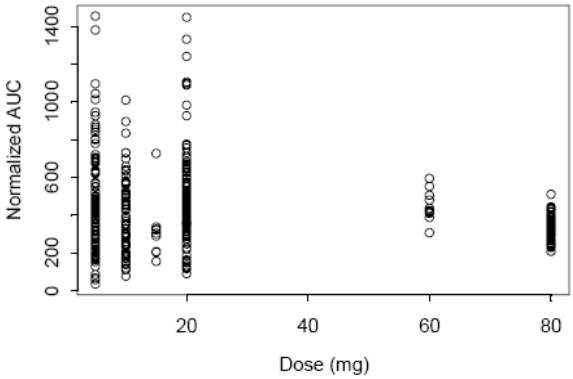
Clobazam dose proportionality was evaluated in a multiple dose study (OV-1032) and in the population PK analysis. The PK of clobazam was dose-proportional over the range of 10–80 mg.

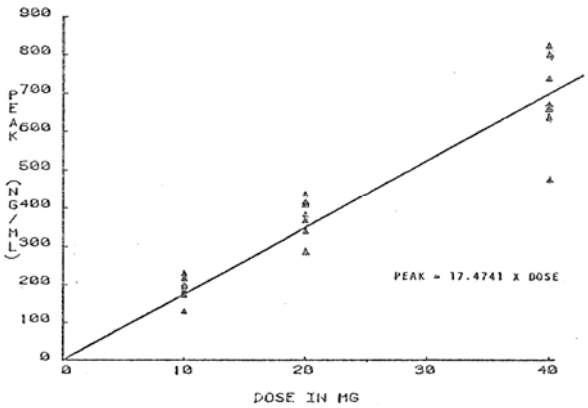
The following plots show the relationship depicting clobazam elimination and AUC over a dose range obtained from the population PK analysis. Clobazam CL/F was independent of dose and the slope of the dose-normalized AUC vs. dose, estimated using the power model, yielded an approximate slope of 1, suggesting dose-proportionality.



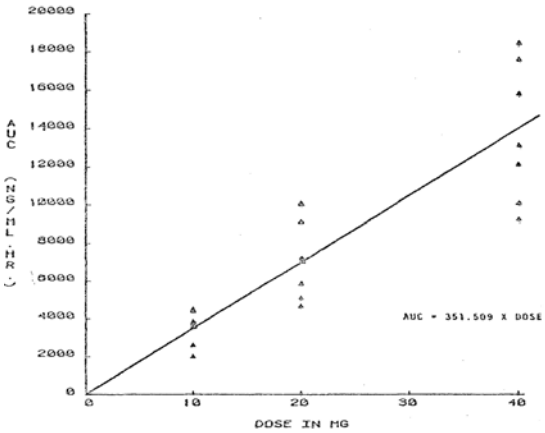


Dose-proportionality was also demonstrated in a legacy single dose study in which clobazam doses of 10, 20 and 40 mg were administered. The plasma levels of clobazam increased with increasing doses from 10 mg to 40 mg and linear relationships for Cmax and AUC0-144 were observed.

Cmax



AUC



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Population pharmacokinetics analysis reveals that the pharmacokinetics of clobazam are linear from 5 mg/day to 160 mg/day.

<u>Reviewer's comment</u>:
The single ascending dose study above was conducted in 1970's using a different formulation than the current commercial formulation. Nonetheless, data collectively from

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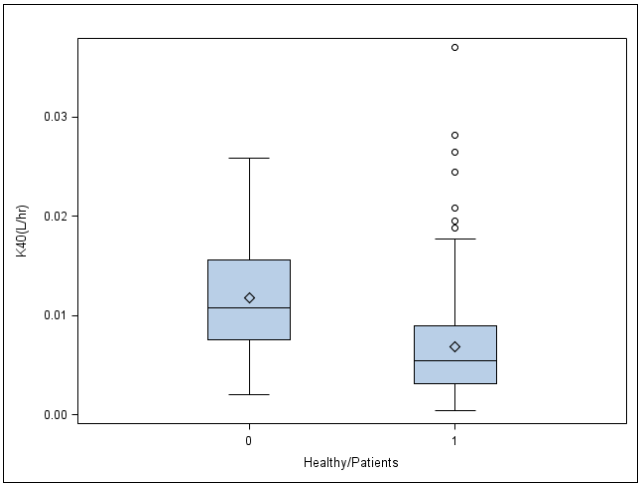
a single and multiple dose studies and the population PK analysis support dose-proportionality of oral clobazam in the therapeutic dose range. To note, the Cmax and AUC values in this single dose study were comparable to those observed in recent Phase 1 studies, further implicating the relevance of the data in supporting the conclusion.

2.2.4.8 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?

The intensive PK was only collected from the healthy subjects. For LGS patients, sparse PK was obtained from Phase 2 and 3 studies. The sponsor did not examine the difference in PK between healthy subjects and patients. However, the reviewer's independent assessment showed that patients appear to eliminate N-CLB slower than healthy subjects (see Figure below), and the difference was found out to be statistically significant.

Figure. The distribution of individual estimate for K40 (elimination of N-CLB) between patients and healthy subjects.



Reviewer's comment:
The difference in disposition of N-CLB reported in population PK analysis may be attributed to the stable concomitant CYP3A4 inducers (e.g., phenytoin, carbamazepine) in Phase 2/3 clinical trials. The pharmacokinetic differences in CLB and to a greater extent in N-CLB exposure between healthy subjects and patients with epilepsy has been reported in literature [Br. J Clin. Pharmac. 24:793-797, 1987; Br. J Clin. Pharmac. 18:873-877, 1984; Epilepsia 39(suppl 1):S15-S23, 1998]. The observed lower CLB levels and higher N-CLB levels in patients in these reports, compared to that in healthy subjects, were attributed to the concomitant enzyme-inducing phenytoin and carbamazepine.

2.2.4.9 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The mean inter-subject variability of CL/F and V/F in single and multiple dose studies in healthy subjects was approximately 20-30%. The mean estimate of inter-subject

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variability of CL/F and V/F in patients based on population PK analysis was 52% and 59%, respectively.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Intrinsic factors, such as age, gender, race, hepatic impairment, and renal impairment, were studied in Phase 1 trials and via population PK analysis, as described in the following Sections. The potential impact of CYP2C19 genotypes on metabolism and systemic exposure of clobazam was evaluated using available data obtained from PM, compared to intermediate (IM) or extensive metabolizers (EM), in Phase 1 studies and in population PK analysis (refer to Genomic Review in Section 4.3 of Appendix for details). The potential significant covariate which may affect the clobazam PK was evaluated in population PK analysis (refer to Pharmacometrics Review in Section 4.2 of Appendix for details).

2.3.1.1 Elderly

The population PK analysis showed that the clearance of clobazam appears to decrease in adult patients (18 years older) compared to children (2-11 years, 130 subjects) and adolescents (12-17 years, 45 subjects) (see Figure below). Results are consistent with the finding reported by *Greenblatt et al*. (refer to Reviewer's comments below). It appears, however, that there is a greater variability in the clobazam clearance in children and adolescents compared to adults, based on a visual inspection of the plot. (Refer to Pharmacometrics Review in Section 4.2 of Appendix for details)

Figure. The relationship between age and individual estimates for CL. The left panel shows the relationship with loess curve, and the right graph is the same relationship when age is grouped into three categories: children (2-11 years), adolescent (12-17 years) and adults (18-60 years, ≥ 60 years)

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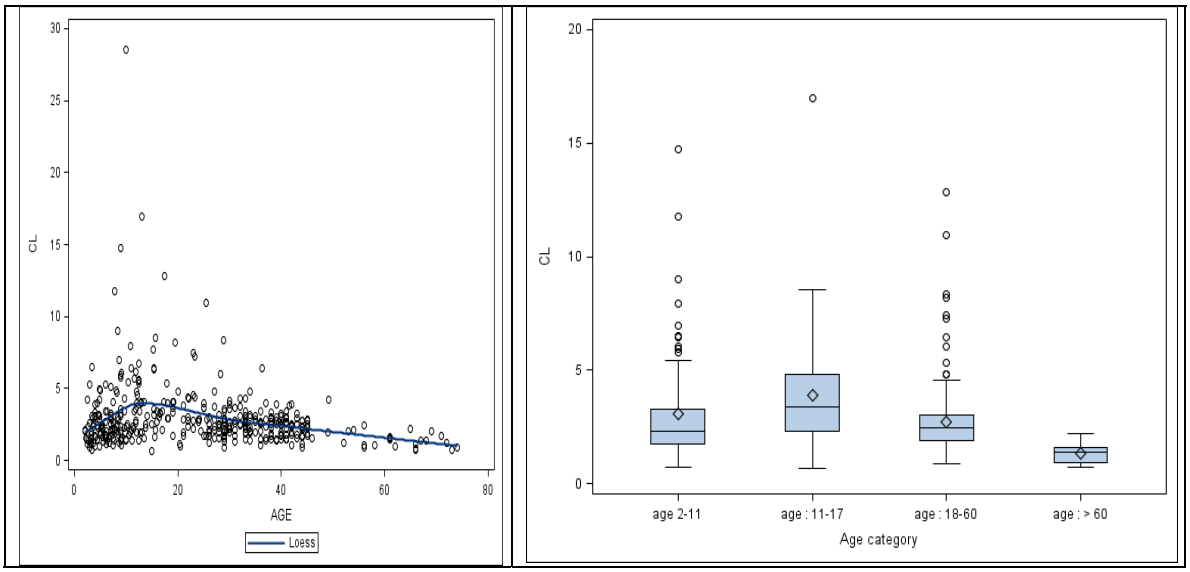

It is noted that clinical studies of Onfi did not include sufficient numbers of subjects ≥ 65 years old (N=11) to determine whether they respond differently from younger subjects. For these reasons, dosing should be adjusted in the elderly with the initial dose being 5 mg/day. Patients should be titrated initially to 10-20 mg/day and may be titrated further to a maximum daily dose of 40 mg if tolerated (refer to Proposed Labeling in Section 4.1 of Appendix).

Reviewer's comments:

- *According to information available for Frisium® (clobazam) marketed outside the U.S.A., aging can reduce the clearance, increase the Vd, and prolong the terminal t1/2 of CLB and N-CLB significantly. Further, the use of clobazam in the elderly can cause significant CNS depressant effect even at low doses.*
- *The effects of age (and gender) on the disposition of clobazam were reported by Greenblatt et al. [Br. J. Clin. Pharmac. (1981), 12, 631-636]. In this study, 20-mg oral clobazam dose was administered to four approximately equally sized groups (aged 18-72) of young male (N=8), young female (N=8), elderly male (N=7), and elderly female (N=6) subjects. The authors reported that age and gender did not affect the absorption kinetics, however, these factors significantly prolonged the elimination half-life in elderly vs. young males (48 vs. 17 h, P < 0.01). In women, half-life also increased with age, but with smaller differences between young and elderly women (31 vs. 49 h, P < 0.05). Among other findings are significantly decreased unbound clearance of clobazam with age in men (but not in women), and age-related increase in mean free fraction of plasma protein binding. In a separate report [Clin Pharmacokinet. 1983 Jan-Feb;8(1):83-94], subjects received single 10mg doses of clobazam daily for 22 consecutive days. Compared with the young male subjects, elderly males had slower rates of clobazam accumulation and washout, higher steady-state plasma levels, and lower steady-state clearance. Accumulation of N-CLB was slower and more extensive in the elderly male group. Among females, however, age-related kinetic differences did not approach significance.*

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2.3.1.2 Gender/ Race

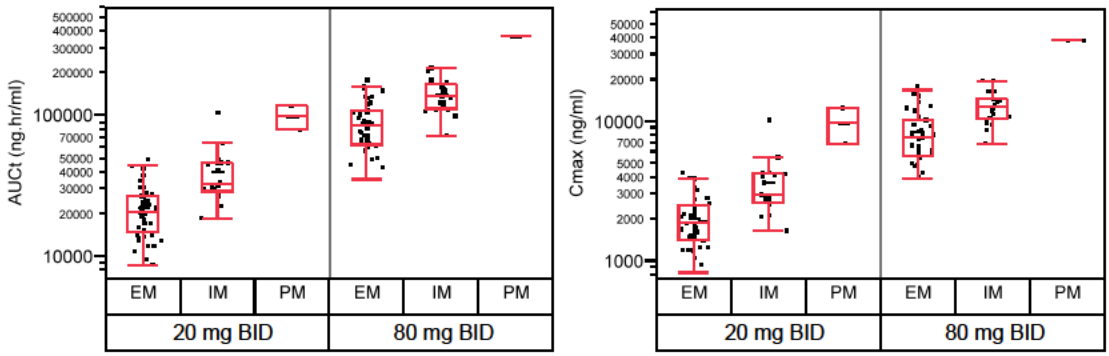
The population PK analysis showed that either race or gender does not influence PK of clobazam /N-CLB. (Refer to Pharmacometrics Review in Section 4.2 of Appendix for details)

2.3.1.3 CYP2C19 genotypes

CYP2C19 polymorphisms can influence the exposures to the active metabolite N-CLB. CYP2C19*2 and *3 alleles were genotyped in 418 clobazam-treated subjects across 7 studies. A total of 12 CYP2C19 PMs (*2/*2) were included in these Phase 1 studies, of which 6 subjects were dosed with clobazam.

In the densely sampled multiple dose study (OV-1022), as expected, steady-state exposures ($AUC_{0\text{-}tau}$) of clobazam did not differ with regard to CYP2C19 genotype status. However, mean exposure (Cmax and AUC) of N-CLB in CYP2C19 PM subjects were 3-4-fold higher than pooled IM/EM subjects, and were approximately 5-fold higher in CYP2C19 PMs compared to EMs (see Figure below). Despite potential higher N-CLB exposures, CYP2C19 PMs did not demonstrate consistently higher response rates or adverse events rates in the pivotal efficacy trial OV-1012.

Figure. N-CLB AUC_{τ} (left) and $C_{max,\ ss}$ (right) by CYP2C19 genotype and dose



In the study population included in population PK analysis, there were 8 CYP2C19 PMs, of which 7 were dosed clobazam. The following are plots showing the relationship between CYP2C19 genotype and clobazam clearance and N-CLB clearance rate constant from the population analysis. These Figures illustrate that CYP2C19 PMs have approximately 4-5-fold decrease in clearance of N-CLB compared to EMs, supporting the finding for the increase in exposure in PMs as shown in the above Figures.

Clobazam clearance N-CLB clearance rate constant

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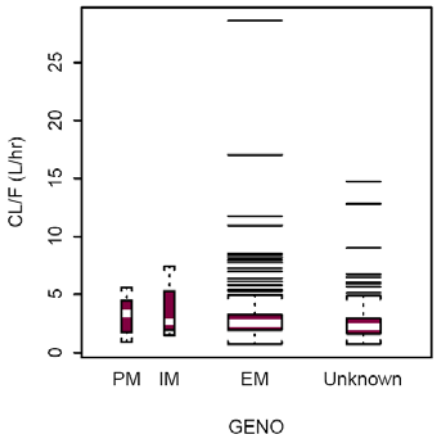

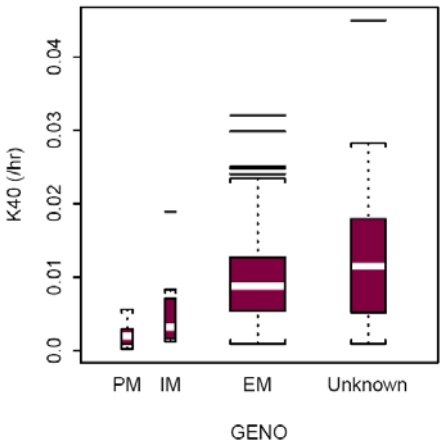

(PM: N=12, IM: N=11 and EM: N=299)

Published literature was also evaluated to supplement the limited safety database in CYP2C19 PMs. A retrospective study of 110 Japanese patients with epilepsy, which contained 23% CYP2C19 PMs, found no significant difference in terms of adverse effects across EMs, IMs, and PMs. There was a higher frequency (40%) of drowsiness in the CYP2C19 PMs compared to (32%) in the EMs. This same study found significant differences in the efficacy in the reduction of seizures from clobazam in the CYP2C19 PMs compared to the EMs. (Seo T, 2008 PMID: 1846600). (Refer to Genomics Group Review in Section 4.2 of Appendix for details)

Despite the wide therapeutic index for clobazam and the main adverse effect being limited to sedation/somnolence, caution should still be exercised when administering clobazam to patients who are known CYP2C19 PMs. Due to the degree of exposure increase of the active metabolite (N-CLB) in CYP2C19 PMs, consider starting at the minimal dose and extending the titration interval in these patients.

2.3.1.4 Renal impairment

The effect of renal impairment was assessed in Study OV-1032, following administration of multiple doses of clobazam, 20 mg/day, in subjects with mild (CL_{CR} > 50~80 mL/min; N=6) or moderate (CL_{CR} = 30~50 mL/min; N=6) renal impairment, with matching healthy controls (N=6). There were small increases in mean Cmax and AUC values in mild and moderate renal impairment subjects compared to healthy control (3-24% and 0-13% increases of Cmax and AUC0-96 of clobazam, respectively) after single dose administration. Similar results were observed following multiple doses on Day 11, although greater increase in N-CLB levels was observed for the mildly impaired patients. Graphical presentation of the clobazam exposure and 90% confidence intervals comparing renally impaired subjects to healthy volunteers following single- and multiple-doses are shown below.

Single dose (on Day 1):

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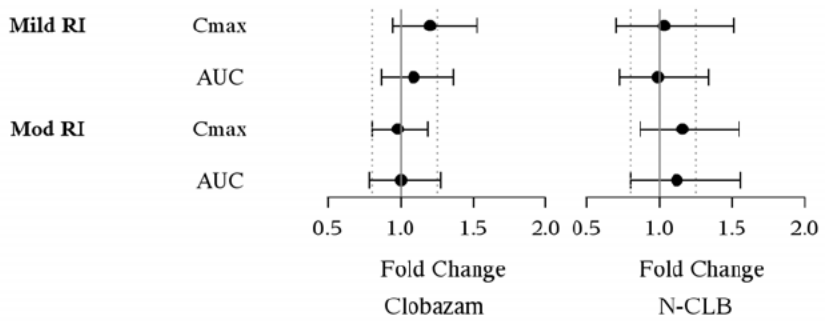
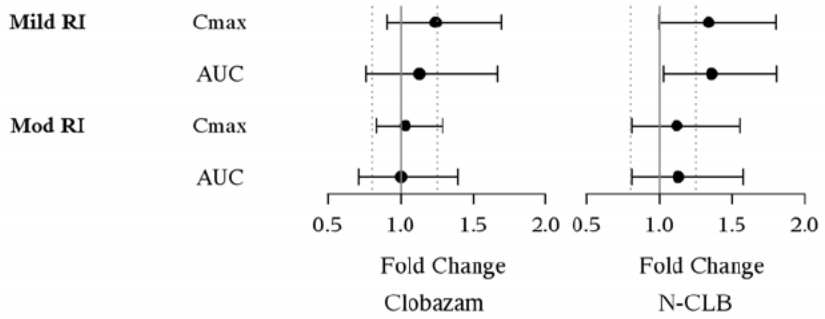


Multiple dose (on Day 11):



The higher mean Cmax and AUC values observed in mild renal impairment group is mainly driven by one subject (#2008). Plasma protein binding of clobazam or N-CLB was comparable between the subjects with mild or moderate renal impairment and healthy control. No correlation was observed between creatinine clearance and clobazam plasma clearance in similar patient population, according to results of population PK analysis. Collectively, the small increases in the exposure of clobazam and N-CLB are not considered clinically meaningful and no dosage adjustment is recommended for subjects with mild or moderate renal impairment.

This study did not include subjects with severe renal impairment or end-stage renal disease (ESRD). Upon request during the review cycle, the sponsor provided a case report in the literature that showed dose-adjusted serum concentrations of clobazam and N-CLB in one subject with ESRD were comparable to those in renally healthy subjects both during the normal dosing interval and in hemodialysis (see Reviewer's comments in this section). (b) (4) It is not conclusive if clobazam or its active metabolite, N-clobazam, is dialyzable based on the limited available information.

Reviewer's comments:

1. The reviewer requested the sponsor to provide available data either from their internal source or from the literature inclusive of other indications as well that have addressed the impact of severe renal impairment/ESRD on clobazam PK and/or a safety profile. One relevant publication was identified as follows:

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"Clobazam and N-desmethylclobazam serum concentrations in endstage renal failure and hemodialysis. Roberts GW and Zoanetti.GD. The Annals of Pharmacotherapy 2004; 28: 966-967."

This is a case report of an 18 year old male patient with ESRD (GFR < 10 mL/min) on hemodialysis who has been taking clobazam 5 mg po bid. The patient's hepatic function was normal. Serum concentrations of clobazam and N-CLB were measured before and 3.5 hours after the dialysis and results were compared to those with normal renal function in literature on chronic clobazam therapy. The authors found that dose-adjusted serum concentrations of clobazam and N-CLB were comparable between renally healthy subjects and subjects with ESRD during the normal dosing interval and in hemodialysis.

2. *Effect of dialysis for clobazam or N-CLB in ESRD patients was not evaluated in this study. However, considering the physico-chemical property and the disposition of clobazam, we do not anticipate a significant effect of dialysis procedure to help remove the accumulated of these circulating moieties from the body.*

2.3.1.5 Hepatic impairment

The effect of hepatic impairment on clobazam PK was assessed based on a literature report [*Pharmacokinetics of a Single Oral Dose of Clobazam in Patients with Liver Disease. Monjanel-Mouterde et al., Pharmacology & Toxicology 1994, 74, 345-350*], following a single dose administration of 20 mg clobazam in subjects with liver disease and healthy controls. The study was conducted in 6 normal control and 9 hepatic impairment subjects, ranging from mild to severe per Child-Pugh score (N=5 for mild or moderate impairment and N=4 for severe impairment). However, no quantitative correlation between the disease severity and clobazam clearance can be made as individual subject data are not available.

Cmax values of clobasam or N-CLB were not increased in subjects with hepatic impairment compared to normal control and there were no statistical differences in total plasma clearance of clobazam, which may indicate similar clobazam plasma exposure (AUC) between two groups. The authors reported that clobazam terminal half-life was prolonged, which may suggest effects of hepatic impairment on the terminal elimination phase.

However, a multiple dose simulation analysis conducted by the authors showed that there was no difference in the accumulation or steady-state concentrations of clobazam following multiple dose administration. Given the lack of changes in clobazam clearance and Cmax, on face the results of simulation seems reasonable; however an internal validation of the simulation could not be conducted since individual data were not available.

Summary of the PK parameters:

	Hepatic Function		
	Normal	**Mild, Moderate, Severe**	**t-test**

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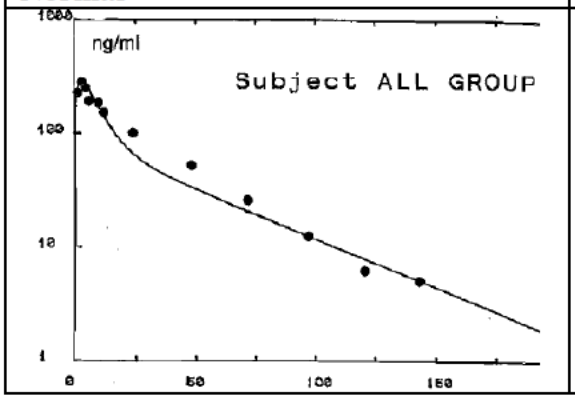
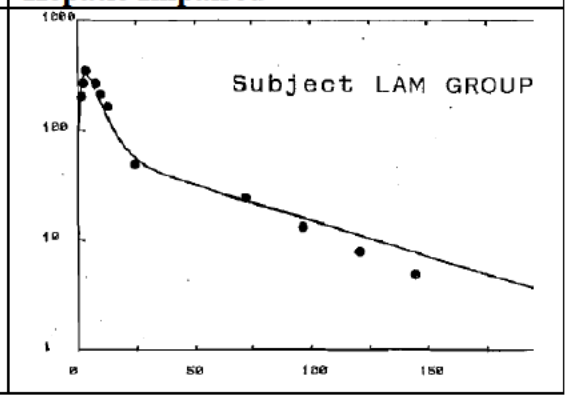
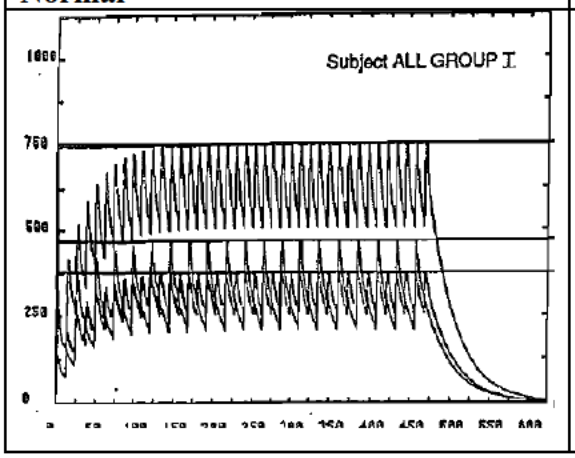
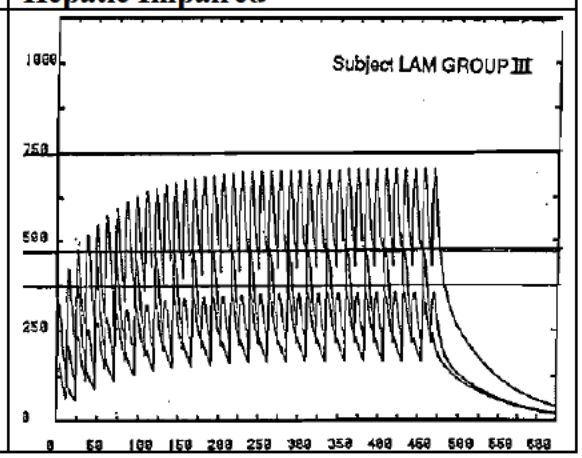
		impairment	
N	6	9	
CLB C_{max} (ng/mL)	350 (18)	240 (47)	S
N-CLB C_{max} (ng/mL)	96 (21)	84 (22)	NS
CLB CLt (L/hr)	2.8 (14)	2.7 (40)	NS
CLB T_{max} (h)	1.6 (50)	2.5 (44)	NS
N-CLB T_{max} (h)	48 (40)	88 (22)	S
CLB $t_{1/2}$ (h)	22 (26)	51 (39)	S
CLB kel (/hr)	0.066 (36)	0.061 (47)	NS
Values represent mean (%CV) S – significant; NS – not significant			

Examples of PK profiles in each group:

Normal	Hepatic Impaired
	

Multiple-dose simulation:

Normal	Hepatic Impaired
	

Simulation of Clobazam plasma concentrations following repeated administration of clobazam for 20 day (doses: -10 mg bid, -20 mg qd, -20 mg bid)

Collectively, clobazam is primarily metabolized in liver; however, there are limited data to characterize the effect of hepatic impairment on the PK of clobazam or N-CLB. Further, there is inadequate information about metabolism of clobazam in patients with severe hepatic impairment. For these reasons, the maximum tolerated daily doses may

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remain the same for patients with mild to moderate hepatic impairment, but with a reduced initial doses and a slower titration.

***Reviewer's comments*:**
According to the label for Frisium® 10 (clobazam) marketing outside of U.S.:

- *Frisium 10 is contraindicated with severe impairment of liver function (risk of precipitating a certain disease of the brain [encephalopathy]).*
- *"Patients with impairment of renal or hepatic function have an increased response to Frisium 10 and a higher susceptibility to its adverse effects; in such patients, a dose reduction may be necessary. In long-term treatment, renal and hepatic function must be checked regularly.'*

However, no study information or data available to in this submission to support similar labeling recommendation for use of Onfi in LGS patients with hepatic dysfunction.

2.4 Extrinsic Factors

2.4.1 Is the drug and/or the major metabolite a substrate, inhibitor or inducer of CYP enzymes on an in vitro basis?

Metabolism by CYP: CYP3A4 is the major contributor to the elimination of clobazam via N-demethylation to form N-CLB. The polymorphic CYP2C19 is primarily responsible for the further metabolism of N-CLB.

Inhibition potential: Clobazam did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 in vitro. N-CLB did not inhibit CYP1A2, 2B6, 2C8, 2C19, 2D6, 3A4 and UGT1A1. However, N-CLB showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and 2B4 with IC_{50} values of 71.7, 110, 210 and 111 μM, respectively, in vitro.

Induction potential:
Clobazam and N-CLB did not significantly increase CYP1A2 or CYP2C19 activities, but did increase CYP3A4 activity in a concentration-dependent manner. Clobazam and N-CLB also induced UGT1A1 mRNA in vitro but at much higher concentration than therapeutic levels. Effects on UGT1A1 enzymatic activities were not evaluated. Clobazam increased CYP2C19 mRNA but did not increase the enzymatic activity. Induction potential for CYP2B6 and CYP2C8 by clobazam and N-CLB has not been evaluated (see Section 2.4.3.2).

2.4.2 Is the drug and/or the major metabolite a substrate and/or an inhibitor of P-glycoprotein transport processes or any other transporter system?

Clobazam and N-CLB are both substrates for P-glycoprotein (P-gp). Verapamil (inhibitor for P-gp) reduced the transport of clobazam and N-CLB in MDCK MDR1 cells by >96% and 77%, respectively, suggesting that P-gp is the major transporter of clobazam and N-CLB efflux. Clobazam and N-CLB do not inhibit P-gp. Clobazam and N-CLB were not

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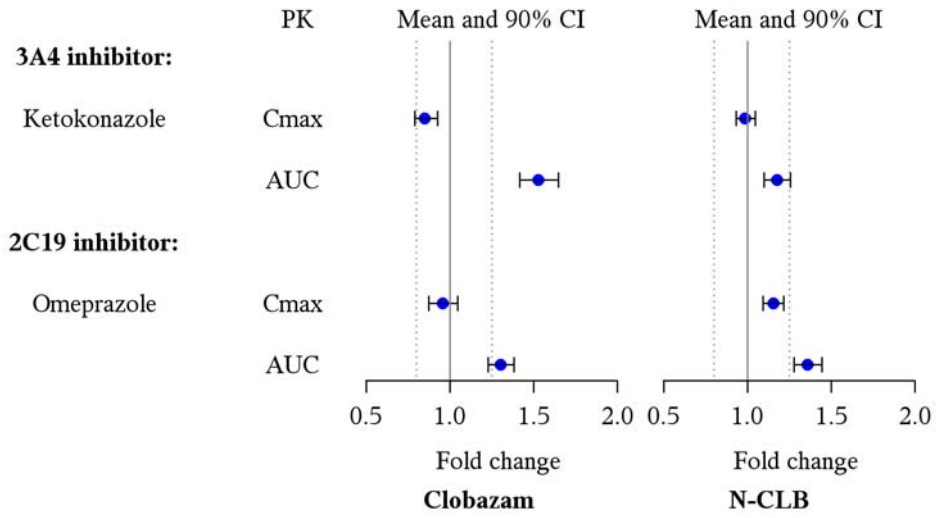
reported to be substrates for other transporters such as OCT (organic cation transporter) and OAT (organic anion transporter).

2.4.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered? If yes, is there a need for dosage adjustment?

2.4.3.1 Effect of co-administered drugs on clobazam



Study OV-1021 (N=18) was conducted to examine the effect of multiple doses of ketoconazole (strong CYP3A4 inhibitor) or omeprazole (moderate CYP2C19 inhibitor) on the pharmacokinetic profile of single-dose clobazam. As illustrated in the above Figure, co-administration of ketoconazole 400 mg QD for 5 days increased clobazam AUC by 54 %, with no effect on Cmax. There is no significant change on AUC and Cmax of N-CLB. Results of the study indicated the in-vivo CYP3A4 inhibition by clobazam. However, the magnitude of exposure increase for clobazam is not considered clinically significance in view of the safety profile observed for the CYP2C19 poor metabolizers. Therefore, no dose adjustment is recommended for clobazam in the presence of co-medications that are CYP3A4 inhibitor.

Co-administration of omeprazole 40-mg QD for 5 days increased AUC of clobazam and N-CLB by 30-36 % without having effect on Cmax. The magnitude of these exposure increases is not considered clinically significant to warrant a dosage adjustment for the same reason for concomitant CYP3A4 substrates.

In addition, the effect of the presence of other antiepileptic drugs (AEDs, 2C19 inhibitors and inducers of 3A4 and 2C19) on clobazam PK was evaluated using a population PK approach to provide supporting evidence for a lack of clinically significant drug-interactions involving these mechanisms. The drugs that constituted the CYP3A4 inducer group (18 subjects) were phenobarbital, phenytoin, and carbamazepine. CYP2C19 inducer group (77 subjects) comprised valproic acid, phenobarbital, phenytoin, and

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carbamazepine, and the CYP2C19 inhibitor group (17 subjects) included felbamate and oxcarbazepine. The sponsor's analysis showed that the fraction of N-CLB formed increased by 9.4% by CYP3A4 inducers whereas CYP2C19 inducers made elimination of N-CLB faster by 10.5%, which implies that the net change in PK of N-CLB may be negligible. Hence, no dose change may be required in the presence of the CYP3A4 inducers and CYP2C19 inducers together.

As described in the proposed labeling, alcohol has been reported in literature to increase the maximum plasma exposure by approximately 50%.

Reviewer's comments:

1. *For the drug-interaction study with omeprazole, considering the rapid absorption and short elimination half-life of omeprazole, and slow formation of N-CLB from clobazam and its long elimination t1/2, the inhibitory effect of omeprazole on CYP2C19 observed in this study is not considered definitive.*
2. *Clobazam was shown to be a P-gp substrate based on the results from in vitro studies. However, the impact of co-administrated P-gp inhibitors on clobazam plasma exposure in vivo is unknown. Per Clinical Pharmacology review of Pre-NDA submission (meeting date August 31, 2010), the Agency agreed to the Sponsor's proposal to conduct the in vivo drug-drug interaction study between clobazam and a pure, strong P-gp inhibitor as a PMC/PMR at the NDA stage.*
   During the review cycle, we noted that a dedicated drug-drug interaction study between clobazam and ketoconazole, a duel inhibitor for CYP3A4 and P-gp, exerted a combined effect of clobazam AUC increase by 54%. Results of this study suggest that the P-gp inhibition in humans will unlikely to exceed the observed exposure increase from this study and, therefore, an additional in-vivo study as PMR is not necessary.
3. *The Frisium label approved in Canada states that patients should not drink alcohol during treatment with Frisium 10 because of an increased risk of sedation and other adverse effects.*
4. *As commented in Section 2.2.4.8, concomitant CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital) in clinical studies likely contributed to altered pharmacokinetic properties of CLB and N-CLB, noticeably the higher N-CLB exposure in patients than in healthy volunteers. It was reported that the antiepileptic effect of orally administered CLB in long-term therapy is predominantly due to its N-CLB metabolite. The need for dosage adjustment has not been suggested in literature or prescription information when patients are on CLB and concomitant enzyme-inducing AEDs.*

2.4.3.2 Effect of clobazam on co-administered drugs

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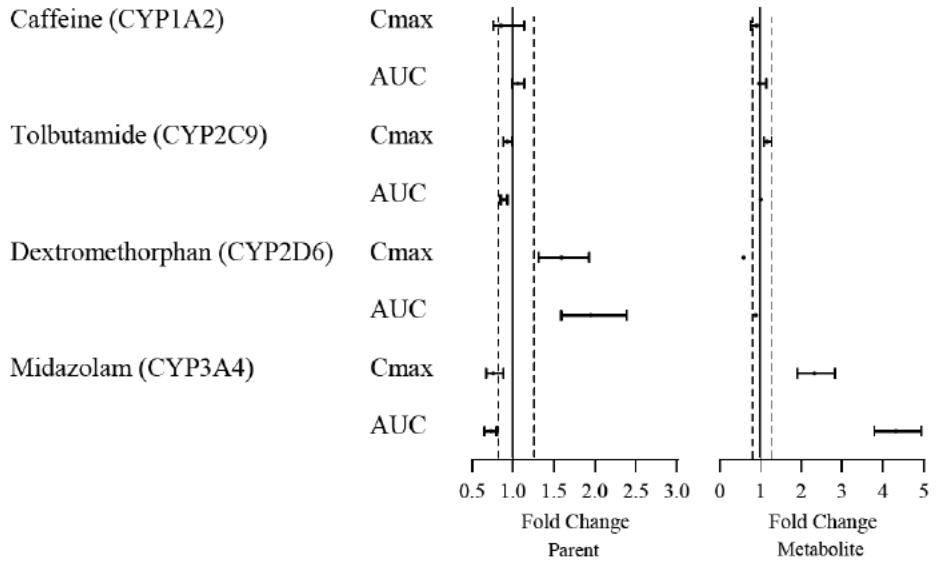

Study OV-1023 was conducted to examine the effect of repeat 40-mg QD doses of clobazam on the pharmacokinetic profiles of single-dose midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate), and dextromethorphan (CYP2D6 substrate) given as drug cocktail (N=18).

As illustrated in the above Figure, repeated clobazam doses had no impact on caffeine and tobutamine, hence 5, 10, 20On the other hand, clobazam increased AUC and Cmax of dextromethorphan (CYP2D6 probe) by 90% and 59%, respectively, indicating that clobazam is an inhibitor of CYP2D6 in vivo. Narrow therapeutic index drugs that are metabolized by CYP2D6 may require dose reduction when used with Onfi. The use of other concomitant medications that are primarily metabolized by CYP2D6 should be monitored closely. Coadministration of clobazam resulted in decreases in AUC and Cmax of midazolam by 27% and 24%, respectively, and increases in AUC and Cmax of the metabolite 1´-hydroxymidazolam by 4-fold and 2-fold, respectively. These results indicate that clobazam can induce CYP3A4 activity in humans. However, this CYP3A4 induction is considered to be relatively mild. Consequently, doses adjustment for concomitant drugs primarily metabolized by CYP3A4 is not necessary.

Population analysis of data from the Phase 3 study comparing the plasma concentrations of AEDs, valproic acid (CYP2C9 substrate) and lamotrigine (UGT substrate, primarily UGT1A4), prior to and following clobazam therapy indicated that clobazam did not affect the exposure of valproate and lamotrigine. (b) (4)

Reviewer's comment:
In view of the CYP3A4 induction by clobazam for metabolism of midazolam (CYP3A4 probe), the induction potential for CYP2B6 and CYP2C8 cannot be ruled out. Since AEDs may not be the only concomitant medications that the intended patients will be taking, it is necessary to screen for the induction potential for these two CYP isozymes. The Agency's recommendation has been conveyed to the Sponsor during the review

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cycle (b) (4)

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

A formal BCS classification for clobazam has not been determined.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Two formulations were used during clinical studies. In the Phase 2 study, clobazam tablets were manufactured by (b) (4). The Phase 3 clinical supplies using the proposed commercial formulation were manufactured by Catalent Pharma Solutions, in Winchester, Kentucky. (b) (4) only manufactured a 5-mg strength, but Catalent manufactured 5, 10, and 20 mg strengths.

Comparison of the (b) (4) and Catalent formulations:

(b) (4)			Catalent (Phase 3)		
Ingredient	**Amount, %**	**Amount, mg/tablet**	**Ingredient**	**Amount, %**	**Amount, mg/tablet[2]**
(b) (4)	(b) (4)	5.00	Clobazam	(b) (4)	5.00
Lactose, (b) (4) NF		(b) (4)	Lactose monohydrate, NF/EP		(b) (4)
Starch (corn) NF			Corn starch, NF/EP		
(b) (4)			---		
(b) (4) silicon dioxide, NF			Silicon Dioxide, NF		
Magnesium Stearate, NF			Magnesium Stearate, NF/EP		
Talc, USP			Talc, USP/EP		
(b) (4)	---	---	(b) (4)		
Total	(b) (4)	(b) (4)			

Clobazam Tablets Used in Clinical Studies:

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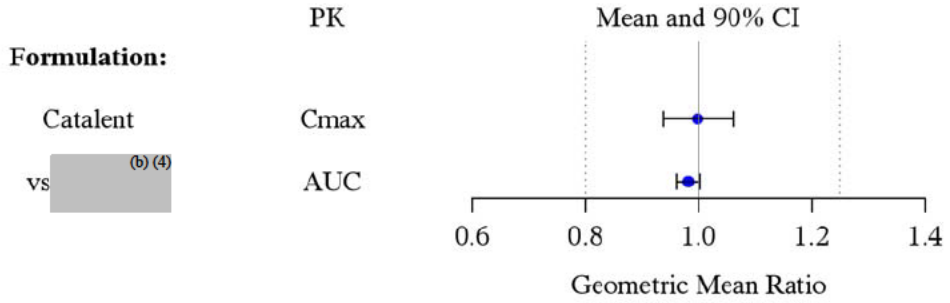
Study Number	Strength	Manufacturer[1]
		Phase I Clinical Studies
OV-1016	5 mg tablet	Catalent
	5 mg tablet	(b) (4)
OV-1017	20 mg tablet	Catalent
OV-1018	5 mg tablet	Catalent
	20 mg tablet	Catalent
OV-1021	10 mg tablet	Catalent
OV-1022	20 mg tablet	Catalent
OV-1023	20 mg tablet	Catalent
OV-1032	20 mg tablet	Catalent
OV-1038	5 mg tablet	Catalent
	10 mg tablet	Catalent
	20 mg tablet	Catalent
		Phase II & III Clinical Studies
OV-1002	5 mg tablet	(b) (4)
OV-1004	5 mg tablet	
	5 mg tablet	Catalent
	10 mg tablet	Catalent
	20 mg tablet	Catalent
OV-1012	5 mg tablet	Catalent
	Placebo	Catalent

All clinical studies in this submission sponsored by Lundbeck were conducted using to-be-marketed (TBM) formation manufactured by Catalent Pharma Solutions, in Winchester, Kentucky, except for the Phase 2 study, OV-1002, in which clobazam tablets were manufactured by (b) (4) Study OV-1016 evaluated the bioequivalence between the tablet formulation used in the study OV-1002 and TBM formulation (N=40). An analysis of the 90% CI for the geometric mean ratios of AUC and Cmax for the two formulations showed that they are bioequivalent.

Formulation	TBM	Phase 2
Dosage Form	Tablet	Tablet
Manufacturer	Catalent	(b) (4)
Dose	4 x 5 mg	4 x 5 mg



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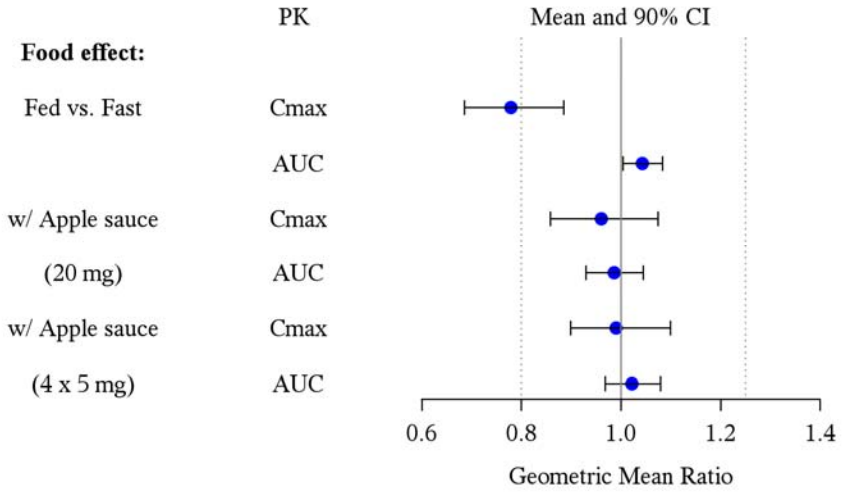
2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

When clobazam tablets were administered with a high fat meal (approximately 1000 kcal), there was a 22% reduction in C_{max} (90% CI 68.5 – 88.5%) without any changes in clobazam AUC. These effects are clinically insignificant and clobazam can be given without regard to meals.

Clobazam bioavailability was also evaluated following an administration of crushed clobazam tablets in applesauce. The C_{max} and AUC of clobazam was comparable between administrations as intact tablets and crushed in applesauce with the 90% confidence intervals for C_{max} and $AUC_{0\text{-}inf}$ ratio were within the BE limits. No dose adjustment is needed when clobazam is given crushed with applesauce.



2.6 Analytical section

2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. Both the parent compound and an active metabolite were measured in all studies.

2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

A validated LC/MS/MS method was used to quantitate clobazam and N-CLB in plasma and urine. Summary of bioanalytical assay for clobazam and N-CLB is provided in the Table below.

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Plasma analysis (6657-210):

Parameter	Clobazam	N-CLB
Matrix	Plasma	Plasma
Method	LC/MS/MS	LC/MS/MS
LLOQ	1.00 ng/mL	1.00 ng/mL
Linear range	1.00-1000 ng/mL	1.00-1250 ng/mL
QC samples	1.00, 3.00, 80.0, 800	1.00, 3.00, 80.0, 800
Accuracy	92.1% - 105.6%	94.5% - 104.8%
Precision	0.6% - 6.3%	1.4% - 8.8%
Freeze-thaw stability	6 cycles; Precision = 2.8% - 8.5% Accuracy = 97.0% - 103.0%	6 cycles; Precision = 1.3% - 9.6% Accuracy = 97.1% - 100.3%

Urine analysis (8203- 833):

Parameter	Clobazam	N-CLB
Matrix	Urine	Urine
Method	LC/MS/MS	LC/MS/MS
LLOQ	1.00 ng/mL	2.50 ng/mL
Linear range	1.00-500 ng/mL	2.50 -1250 ng/mL
QC samples	3.00, 40.0, 400	7.50, 100, 1000
Accuracy	98.7% - 109.0%	96.0% - 105.0%
Precision	1.4% - 5.6%	0.0% - 6.0%
Freeze-thaw stability	5 cycles; Precision = 4.4 - 5.2% Accuracy = 101.3 - 102.7 %	5 cycles; Precision = 3.2 - 3.6% Accuracy = 98.1 - 98.5%

3. Detailed Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for Onfi (clobazam) immediate release oral tablets and found it acceptable provided that the recommended revisions are made to the labeling language.

Labeling recommendation to be sent to the Sponsor:

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The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~Strikethrough text~~ is recommendation for deletion from the perspective of OCP.

4. Appendices

4.1 Proposed labeling

APPEARS THIS WAY
ON ORIGINAL

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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4.2 Consult Reviews

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there any covariate which affects clobazam and metabolige N-desmethylclobazam (N-CLB) PK?

Yes, The sponsor's analysis showed that CYP2C19 genotype status (poor metabolizer (PM)/intermediate metabolizer IM)/extensive metabolizer(EM)) and ethnicity (Hispanic vs. Non-Hispanic) were found to be significant covariate for N-CLB elimination. Also the reviewer's assessment showed that elimination of clearance of clobazam appeared to be slower as patients get older.

Population PK analyses included data from a total of seven studies; 5 healthy volunteer studies (OV-1016, OV-1017, OV-1022, OV-1032, OV-1038) and 2 studies (OV-1002 and OV-1012) in Lennox-Gastaut syndrome (LGS) patients.

Covariates considered in the sponsor's population model are CYP 2C19 genotype information (-1:PM/0:IM/1:EM), weight (kg), age (yrs), sex (1=Male, 2=Female), Creatinine Clearance (CLCR), alanine aminotransferase (ALT), total bilirubin (TBIL), aspartate aminotransferase (AST), food effect (fed/fasted), formulation, ethnicity (Hispanic / Non-hispanic) and race (Caucasian/Black/Asian/other). The sponsor's population PK analysis showed that race, gender, age, and renal function (CRCL) were not found to influence either clobazam PK or N-CLB PK. However, age was found to influence elimination of clobazam (CL/F) based on the reviewer's reassessment (Figure 6).

Extensive metabolizers and Hispanic (or Latino) subjects appeared to clear N-CLB faster than poor metabolizers and non-Hispanic subjects (Figure 2).

The sponsor evaluated the effect of antiepileptic drugs (AEDs) on clobazam using data from the studies of OV-1017 and OV-1012. AEDs were classified into three sub groups; CYP3A4 inducers, CYP2C19 inducers, and CYP2C19 inhibitors. The drugs that constituted the CYP3A4 inducer group (18 subjects) were phenobarbital, phenytoin, and carbamazepine. CYP2C19 inducer group (77 subjects) comprised valproic acid, phenobarbital, phenytoin, and carbamazepine, while the CYP2C19 inhibitor group (17

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subjects) comprised felbamate and oxcarbazepine. These covariates were treated as binary covariates taking on a value of 1 (presence) or 0 (absence) of the AED interactors. The sponsor's analysis showed that the fraction of N-CLB formed increased by 9.4% by CYP3A4 inducers whereas CYP2C19 inducers made elimination of N-CLB faster by 10.5%, which implies that the net change in PK of N-CLB may be negligible. Hence, no dose change may be required in the presence of the CYP3A4 inducers and CYP2C19 inducers together.

1.1.2 Is there any significant exposure-response relationship? And does the relationship support the proposed dosing regimen?

Yes, it shows a clear exposure-response relationship for both efficacy and safety, and the relationship supports the sponsor's proposed dosing regimen.

The data from one phase III study (OV-1012: multicenter, randomized, double-blinded, placebo-controlled, parallel study) was used for exposure-response analysis. The study OV-1012 had a 4-week baseline period, a 3-week titration period and a 12-week maintenance period, followed by a 2- or 3-week taper period for subjects not continuing into the open-label extension study.

In the study of OV-1012, subjects were stratified into 1 of 2 pre-specified weight groups (≤ 30 kg and > 30 kg) and randomly assigned to placebo or a low (target dose of 0.25 mg/kg: a maximum daily dose of 10 mg), medium (target dose of 0.5 mg/kg: a maximum daily dose of 20 mg), or high (target dose of 1.0 mg/kg: a maximum daily dose of 40 mg) dose of clobazam.

The primary efficacy end point was the percent reduction in the number of drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period. The primary efficacy analysis showed that the drop seizure rates appeared to decrease in dose-dependent manner, and all three dose groups showed statistically significantly superior to the placebo groups (p-value : 0.012, 0.0015, <0.0001 for low, med, high dose groups, respectively).

The sponsor proposes the dosing regimen as follows;

- Children over 2 years of age and ≤30 kg body weight should initiate therapy at 5 mg QD and doses titrated at weekly intervals to a target dose of 10-20 mg/day.
- Patients >30 kg body weight should initiate therapy at 10 mg daily (5 mg BID) and doses titrated at weekly intervals to a target dose of 20-40 mg/day.

In the reviewer's exposure-efficacy analysis, the subject-specific average steady state concentrations of clobazam (Cavg,p) and N-CLB (Cavg,m) obtained from the results of the population PK analysis were used as an exposure, and the same primary endpoint was used for the efficacy endpoint. Figure 10 presents the model-predicted relationship between average concentration for both clobazam and N-CLB and the primary endpoint

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from the reviewer's analysis. The drop seizure rates appears to be decreasing as the exposure increases, and it reaches a plateau at the highest maximum daily dose (40mg / day), which is consistent with the sponsor's analyses results (see section 3). However, it also should be noticed that there is a substantial overlap in Cavg,m between doses.

In order to evaluate the sponsor's proposed dosing regimen, the reviewer looked at the dose-response (% reduction in drop seizure) relationship by each weight category, which is shown in Figure 11. For both weight categories it shows clear dose-response relationship, although there appears to be large variability.

In terms of safety analysis, the sedation-related adverse events (sedation, somnolence, sleepiness, drowsiness, sleepy, lethargy and listlessness) were evaluated as an endpoint. Figure 14 shows the dropout-adjusted time profile of percent of patients having at least 1 sedation-related adverse event at each day from observed data by weight category. For light-weighted patients (≤ 30kg), clobazam seems to be safe across all dose levels, although the doses of 10-20 mg/day showed higher percentage of sedation-related AE than placebo or 5mg/day. For heavy patients (>30 kg), it appears to be dose-dependent increase in sedation-related AE but the difference between 20 mg/day and 40 mg/day is negligible.

The sponsor's exposure-safety analysis predicted that probabilities for the first occurrence of sedation were similar between 20mg and 40 mg doses (42.5%: 20mg/day, 45.2%: 40mg/day). However, it was observed that there was large variability around model-predicted relationship as well as substantial overlap in N-CLB Cavg (see Figure 5).

Given efficacy and safety profiles, the sponsor's proposed dosing regimen seems to be reasonable.

1.2 Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 202067) and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

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2 PERTINENT REGULATORY BACKGROUND

The sponsor is seeking the approval for clobazam for a adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age. Clobazam is a 1,5–benzodiazepine approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide. FDA agreed that one phase III study (OV-1012) and one phase II study (OV-1002) are adequate to demonstrate the effectiveness of clobazam in the patients with LGS.
The sponsor proposed the following dosing regimen;

- Children over 2 years of age and ≤30 kg body weight should initiate therapy at 5 mg QD and doses titrated at weekly intervals to a target dose of 10-20 mg/day.
- Patients >30 kg body weight should initiate therapy at 10 mg daily (5 mg BID) and doses titrated at weekly intervals to a target dose of 20-40 mg/day.
- Doses above 5 mg/day should be administered in two divided doses.
- The titration schedule and final dose should be based on response.

3 RESULTS OF SPONSOR'S ANALYSIS

PK analyses

Population PK analyses included data from a total of seven studies; 5 healthy volunteer studies (OV-1016, OV-1017, OV-1022, OV-1032, OV-1038) and 2 studies (OV-1002 and OV-1012) in Lennox-Gastaut syndrome (LGS) patients. Altogether there were 439 pharmacokinetic evaluable subjects who contributed pharmacokinetic data for the development of PK model. Table 1 summarizes the 7 studies with sampling scheme.

Table 1. Summary of studies included in population PK analyses and sampling scheme.

Sampling Design	Sampling Scheme (Time after dose)	Comment	Study	Development Phase
Sparse	1.63, 2.27	Sampling at 2 dosing intervals	OV-1002	Phase 2
Less Sparse	1.08, 2.25, 4.75	Sampling many dosing intervals	OV-1012	Phase 3
Intensive	0.5, 1,2, 3, 4, 5, 6, 8, 12, 6, 24, 36, 48, 72, 96, 120, 144	After after 2 dosing occasions	OV-1016	Phase 1
Intensive	0.5, 1,2, 3, 4, 5, 6, 8, 12, 6, 24, 36, 48, 72, 96, 120, 168, 217	After after 2 dosing occasions	OV-1017	Phase 1
Mixed design Sparse (trough) Intensive	 11.92 0.62, 1.12, 1.62, 2.12, 3.12, 4.12, 6.12, 8.12, 12.12, 16.12, 23.62, 48 72	After many dosing occasions	OV-1022 OV-1032	Phase 1 Phase 1
Mixed design Sparse (trough) Intensive	 11.92 0.5, 1, 2, 2.5, 3, 4, 8, 12, 36, 48, 60, 72, 84, 96, 120, 168, 216, 264, 312, 360	After many dosing occasions	OV-1038	Phase 1

Source: the sponsor's pop pk report, page 25.

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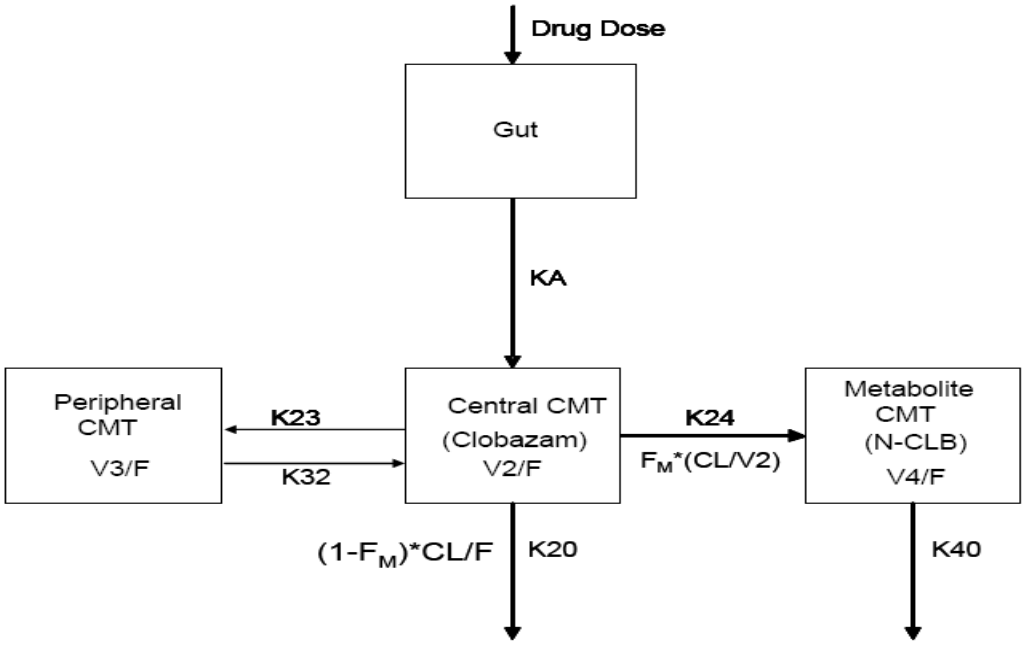
Figure 1 presents PK model for both clobazam and metabolite N-CLB. Clobazam and N-CLB were modeled sequentially. PK parameters for clobazam were estimated first with clobazam data alone. These parameters were fixed in the subsequent analysis. The apparent volume of distribution of the metabolite was also fixed at 1 L in order to make the fraction of metabolite formed (Fm) estimable. Two compartment pharmacokinetics with first order absorption was tested for clobazam, and one compartment described N-CLB. Specifically, the model for N-CLB was parameterized in terms of its formation (Fm) and metabolite clearance rate (K40). The fraction of metabolite formed was parameterized using a logistic function to constrain the range between 0 and 1 as follows,

$$PM = e^{\theta_i + \eta_{F_{Mi}}}$$

$$F_M = \left(PM / \left(1 + PM\right)\right)$$

where PM is a scalar quantity initially defined to allow the quantification of the fraction of the metabolite to be defined in the patient i (logit of Fm). As shown in Figure 1, formation rate was computed as the product of the fraction of the metabolite formed and the apparent elimination rate of the parent drug.

Figure 1. Schematic of the Pharmacokinetic Model for Clobazam and N-CLB.



*Note: there appears to be error in this flow chart in the sponsor's report: (1-Fm)*CL/F should be changed to (1-Fm)*CL/V2.*
Source: the sponsor's pop pk report, page 39.

The parameters of KA and K20 are the first order rate constants of clobazam absorption into and elimination from the central compartment, respectively; K23 and K32 are the

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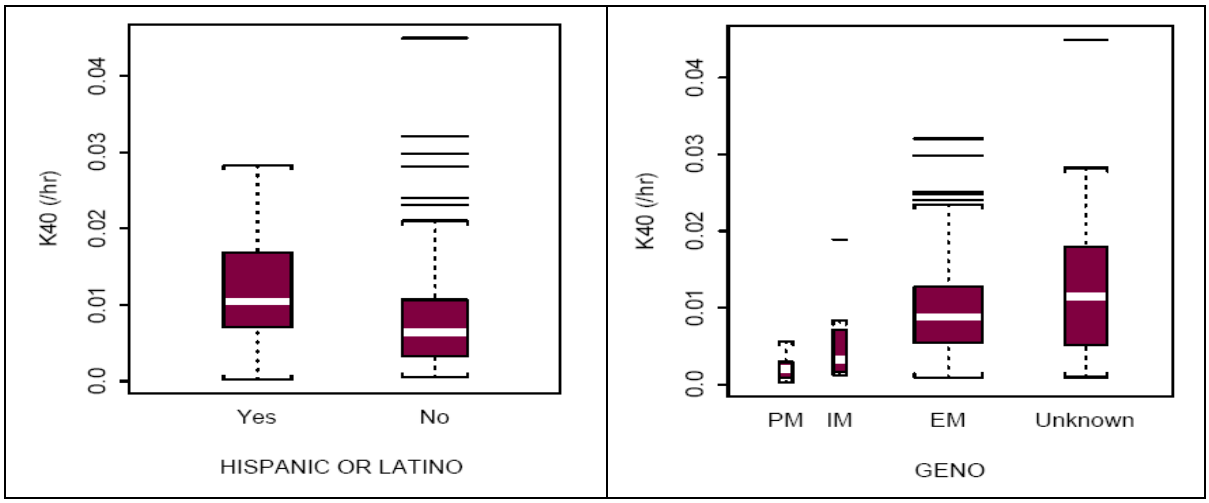
respective transfer rate constants of clobazam from the central compartment to the peripheral compartment and vice versa; F_M is the fraction of N-CLB formed; K24 is N-CLB formation rate constant, and K40 the N-CLB clearance rate constant.

Covariates considered in the sponsor's population model are CYP 2C19 genotype information (-1:PM/0:IM/1:EM), weight (kg), age (yrs), sex (1=Male, 2=Female), Creatinine Clearance (CLCR), alanine aminotransferase (ALT), total bilirubin (TBIL), aspartate aminotransferase (AST), food effect (fed/fasted), formulation, ethnicity (Hispanic / Non-hispanic) and race (Caucasian/Black/Asian/other).
The sponsor's population PK analysis showed that race, gender, age, and renal function (CRCL) were not found to influence either clobazam PK or N-CLB PK. However, CYP2C19 genotype and ethnicity were found to be significant covariate for N-CLB elimination (**Figure 2**). The parameter estimates and covariates effects from the sponsor's final model are presented in the appendix.

Figure 2. The effect of CYP2C19 genotype and Ethinicity on K40 (elimination rate constant of N-CLB).



source: the sponsor's pop pk report, page 74.

Drug-Drug interaction

The sponsor evaluated the effect of antiepileptic drugs (AEDs) on clobazam using data from the studies of OV-1017 and OV-1012. AEDs were classified into three sub groups; CYP3A4 inducers, CYP2C19 inducers, and CYP2C19 inhibitors. The drugs that constituted the CYP3A4 inducer group (18 subjects) were phenobarbital, phenytoin, and carbamazepine. CYP2C19 inducer group (77 subjects) comprised valproic acid, phenobarbital, phenytoin, and carbamazepine, while the CYP2C19 inhibitor group (17 subjects) comprised felbamate and oxcarbazepine. These covariates were treated as binary covariates taking on a value of 1 (presence) or 0 (absence) of the AED interactors.

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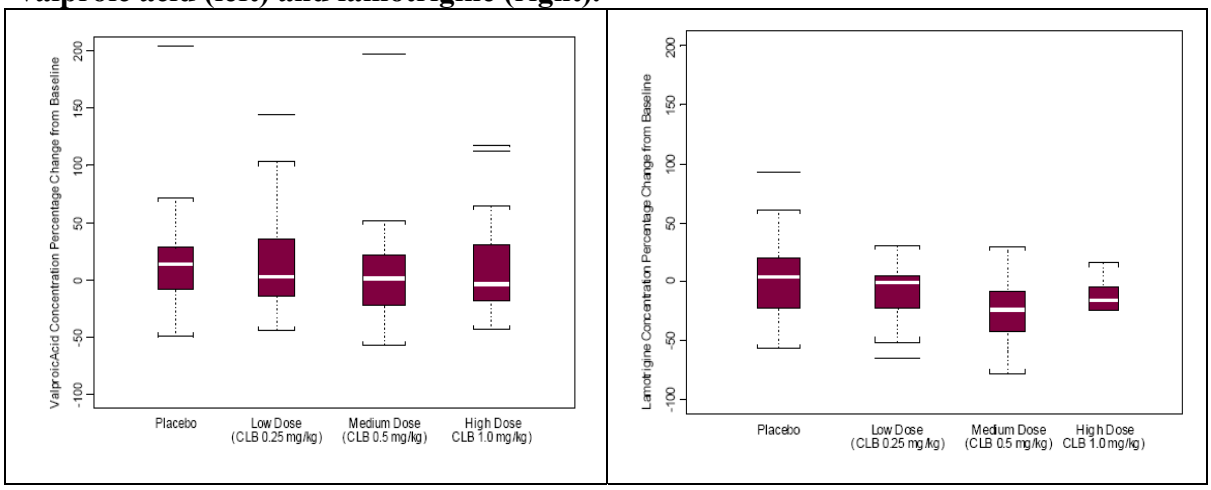
The effect of CYP3A4 inducers was tested on the formation of N-CLB from clobazam (Fm), and the effect of CYP2C19 inducers and inhibitors were tested on N-CLB elimination (K40). This was based on knowledge that clobazam is metabolized by CYP3A4 to N-CLB and the conversion to 4'-hydroxynorclobazam is catalyzed by CYP2C19.

The effects of AEDs were tested based on objective function (OFV) using NONMEM. The sponsor's analysis showed that CYP3A4 inducers and CYP2C19 inducers were found to influence the formation of N-CLB (Fm) and the elimination of N-CLB (K40), respectively. However, CYP2C19 inhibitors did not have an effect on the elimination of N-CLB (K40) when the effect of CYP2C19 inducers was accounted for. It is also important to note that there were only two drugs (felbamate and oxcarbazepine) included in the CYP2C19 inhibitors. The fraction of N-CLB formed increased by 9.4% ($\exp(\theta_{PM,3A4inducer}) / \exp(\theta_{PM})$, in the Appendix 2) by CYP3A4 inducers whereas CYP2C19 inducers made elimination of N-CLB faster by 10.5% ($\theta_{k40,c19inducer} / \theta_{K40}$, in the Appendix 2) which implies that the net change in PK of N-CLB may be negligible. Hence, no dose change may be required in the presence of the CYP3A4 inducers and CYP2C19 inducers together.

Also, the effect of clobazam on the trough levels of valproic acid and lamotrigine was investigated. Only data from subjects who had both nominal sampling times (baseline and week 5 pre-dose data) were included in the comparison of concentrations of valproic acid and lamotrigine prior to and following clobazam administration. 88 subjects on valproic acid and 48 subjects on lamotrigine were included the analysis subject pool. The comparison was based on percent change in valproic acid and lamotrigine concentrations from baseline in clobazam trough concentration. Also, the Kruskal-Wallis test was used for the statistical comparison. Clobazam was found not to affect the exposure of valproic acid and lamotrigine (Figure 3).

Figure 3. Percent change in trough concentration in week 5 from the baseline for valproic acid (left) and lamotrigine (right).



Source : the sponsor's pop pk report, page 115, 120.

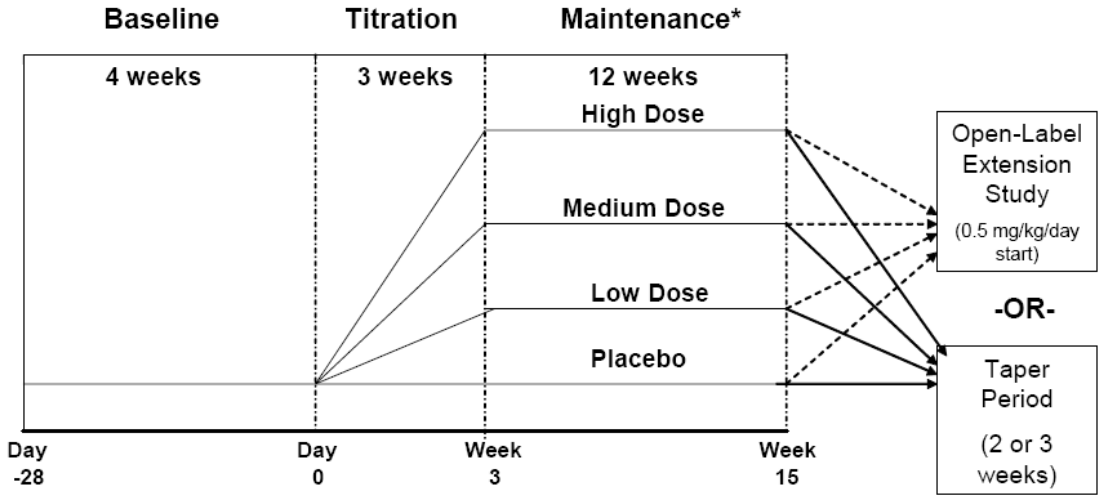
Reference ID: 3026076

Exposure-Efficacy analyses

The data from one phase III study (OV-1012, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study) was used for exposure-response analysis. The study OV-1012 had a 4-week baseline period, a 3-week titration period and a 12-week maintenance period, followed by a 2- or 3-week taper period for subjects not continuing into the open-label extension study (Figure 4).

In the study of OV-1012, subjects were stratified into 1 of 2 pre-specified weight groups (≤ 30 kg and > 30 kg) and randomly assigned to placebo or a low (target dose of 0.25 mg/kg: a maximum daily dose of 10 mg), medium (target dose of 0.5 mg/kg: a maximum daily dose of 20 mg), or high (target dose of 1.0 mg/kg: a maximum daily dose of 40 mg) dose of clobazam.

Figure 4. Summary of study design for OV-1012.



Source: the sponsor's clinical study report : OV-1012, page 17.

The primary efficacy endpoint in the study of OV-1012 was the percent reduction in the number of drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period. The weekly number of seizures during baseline was the number of seizures reported during 4-week baseline period divided by the number of days recorded during 4-week baseline period multiplied by 7. The weekly number of seizures during maintenance period was calculated similarly.

A drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in chair, or head hitting surface or that could have led to a fall or injury, depending on the position of the subject at the time of the attack or spell.

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The reduction in drop seizures was calculated as the average weekly number of drop seizures during baseline minus the average weekly number of drop seizures during the maintenance period. Percent reduction in drop seizures was calculated as: (reduction in drop seizures divided by baseline drop seizures) x 100. A positive value indicated a reduction in the number of drop seizures from baseline.

Table 2 summarizes the results from the primary analysis, which shows that all three dose groups were statistically significantly superior to the placebo group.

Table 2. Primary analysis result: Percent Reduction in Average Weekly Rate of Drop Seizures (Baseline to Maintenance Period) – MITT Population

	Dose Level			
Parameter	**Placebo N = 57**	**Low (0.25 mg/kg) N = 53**	**Medium (0.5 mg/kg) N = 58**	**High (1.0 mg/kg) N = 49**
Baseline mean seizure rate	97.8	99.6	60.5	105.2
Baseline median seizure rate (range)	35.5 (2, 920)	29.2 (2, 1077)	22.5 (2, 798)	46.4 (2, 856)
Maintenance mean seizure rate	71.4	70.2	23.6	30.2
Maintenance median seizure rate (range)	26.0 (0, 676)	16.3 (0, 927)	6.9 (0, 173)	5.1 (0, 276)
Mean percent reduction in seizure rate	12.1	41.2	49.4	68.3
Median percent reduction in seizure rate (range)	23.2 (-374, 100)	46.7 (-119, 100)	57.9 (-262, 100)	86.5 (-39, 100)
Mean difference from placebo (95% CI)		29.1 (6.45, 51.73)	37.3 (14.38, 60.13)	56.1 (33.38, 78.88)
p-value: comparison to placebo[1]		0.0120	0.0015	< 0.0001
p-value: comparison to placebo[2]		0.0170	0.0002	< 0.0001
p-value: linear trend		< 0.0001		

Source: the sponsor's clinical study report : OV-1012, page 66.

In the sponsor's exposure-efficacy analysis, the slightly different endpoint was used — the fraction of baseline drop seizure frequency. Specifically, the average daily seizure count, calculated for weekly (7-day) intervals following administration of the first clobazam dose, was divided by the average daily seizure count during the baseline (pre-treatment) period. Thus, all subjects began with a fraction of baseline value of 1.0 at Week 0 (start of treatment) and would subsequently have values ranging from 0.0 (representing complete elimination of recorded seizures) to values greater than 1.0 if the average daily seizure rate during a week was greater than baseline.

The subject-specific average steady state concentrations of clobazam (Cavg,p) and N-CLB (Cavg,m) obtained from the results of the population PK analysis were used as an exposure. Specifically, Cavg,p and Cavg,m were calculated for each study day using following equations;

Cavg,p = Dose /(CL/F X 24),
Cavg,m=(Fm X Dose)/(K40 X 24)

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where Dose is the total daily dose, CL/F is the individual estimate of apparent total clobazam clearance, Fm is the individual estimate of the fraction of clobazam metabolized to NCLB and K40 is the "clearance" of N-CLB (the apparent volume of distribution of the metabolite was fixed at 1).

The sponsor's exposure-efficacy analysis was conducted in two major stages:
1) The first stage was to model the time course of fraction of baseline data for placebo group; only data from patients in the placebo arm of the study were used for this analysis.
2) The second stage was to develop a model describing the time course and exposure dependence of the fraction of baseline data for patients given clobazam conditioned on the population model for the placebo group; the dataset for this analysis stage excluded placebo data, and the parameters from placebo model were fixed at population mean estimates.

A model for the time course of placebo response was developed first as follows;

$$\hat{R}_{ij} = 1 - \frac{Asym_i \times Week_{ij}^{\gamma_i}}{T50_i^{\gamma_i} + Week_{ij}^{\gamma_i}}$$

$$Asym_i = Asym_{pop} + \eta_i$$

$$T50_i = T50_{pop} \times e^{\eta_i}$$

$$\gamma_i = \gamma_{pop} \times e^{\eta_i}$$

$$y_{ij} = R_{ij} \times \left(1 + \varepsilon 1_{ij}\right) + \varepsilon 2_{ij}$$

---

where R_{ij} is the predicted fractional change from baseline in the ith patient at the jth week, $Asym_i$ is the patient-specific empirical Bayesian estimate of the asymptote (the maximum change from baseline), $Week_{ij}$ is the jth week in the ith patient, $T50_i$ is the patient-specific empirical Bayesian estimate of the Week at which 50 percent of $Asym_i$ is realized, γ_i is the patient-specific empirical Bayesian estimate of the sigmoidal (steepness) parameter. $Asym_{pop}$, $T50_{pop}$ and γ_{pop} are the population estimates of the parameters. The ηs have estimated variances, ω^2. The ε have estimated variances σ^2.

Table 3 presents the parameter estimates from placebo effect model.

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Table 3. Parameter estimates for Placebo effect

Parameter	Estimate	Relative Standard Error
$Asym_{pop}$	0.269	31%
ω^2_{Asym}	0.319	21%
$T50_{pop}$	0.613	62%
ω^2_{T50}	7.61	36%
γ_{pop}	5.23	36%
ω^2_{γ}	1.31	47%
$\sigma 1^2$	0.289	7%
$\sigma 2^2$	~0[a]	NA

Source: the sponsor's pop pk report, page 154.

The exposure-response model was developed to quantify the relationship between clobazam and the fractional change from the baseline in drop seizure. The parameter estimates from the placebo model were fixed and the patients assigned to placebo group were excluded from the analyses. In order to do this, the probabilities of being responder and non-responsder were estimated using $MIX in NONMEM as the first step. The purpose of this was to consider some of patients who did not show specific pattern of improvement. The allocation of a patient to responder/non-responder was based on the estimation algorithm determining whether the drug effect model is the more probable description of a patient's profile.
As the next step, the exposure-response model for the responders was developed after accounting for competitive agonism between clobazam and N-CLB (clobazam and N-CLB interact to the same set of receptors). For the non-responders, a non-specific change from baseline was estimated. Overall drug effect was estimated after integrating each component. Each component of model was estimated simultaneously, and the model for the each component is displayed below.

Responder model:

$$D\max_{pop} = 1 - PBO_{pop}$$

$$R_{ij\,pop} = D\max_{pop} \times \left(\frac{Cavg, p_{ij}}{EC50, p \times \left(1 + \frac{Cavg, m_{ij}}{EC50, m}\right) + Cavg, p_{ij}} + \frac{Cavg, m_{ij}}{EC50, m \times \left(1 + \frac{Cavg, p_{ij}}{EC50, p}\right) + Cavg, m_{ij}} \right)$$

$$R_{ij} = R_{pop} + \eta_i$$

$Dmax_{pop}$ is the maximum achievable effect attributable to drug, PBO_{pop} is the population placebo response calculated using the population parameter estimates from the placebo effect model. $R_{ij,pop}$ is the population response at the jth time point given the subject- and time-specific average concentrations of clobazam and N-CLB. The variance of the

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random variable η is ω_2. The interindividual variability in R was assumed to be approximately normally distributed based on graphical evaluation.

Non-Responder model:

$$NR_i = NR_{pop} \times e^{\eta_i}$$

where NRi and NR pop are the individual estimates and population mean for the change from baseline in the non-responder group.

Overall drug effect model:

$$Eff = PBO_{pop} + R_{ij}$$
$$Neff = PBO_{pop} - NR_i$$
$$F_{ij} = 1 - Eff \times I_{Resp} - Neff \times (1 - I_{resp})$$
$$y_{ij} = F_{ij} \times (1 + \varepsilon_{ij})$$

where Eff and Neff are the magnitude of change from baseline for patients in the responder and non-responder groups, respectively, F_{ij} is the predicted change from baseline, I_{Resp} is an indicator variable defined by 0 (non-responder) and 1 (responder), ε_{ij} is residual error.

The parameter estimates from each component are presented in Table 4 and Table 5. The results from the exposure-response model for the responders shows that N-CLB (EC50 = 0.9 μg/mL) has about one-third the potency of clobazam (EC50 = 0.303 μg/mL).

Table 4. Parameter estimates for responder model.

Parameter	Estimate	Relative Standard Error
$Dmax_{pop}$*	0.731	NA
$EC50,p_{pop}$ (μg/mL)	0.303	**
$EC50,m_{pop}$ (μg/mL)	0.899	**
ω^2	0.0563	18%

*Parameter is mathematically derived, not estimated
**Standard error estimates were infinitely small.

Source: the sponsor's pop pk report, page 161.

Table 5. Parameter estimates for non-responder model.

Parameter	Estimate	Relative Standard Error
NR_{pop}*	0.383	33%
ω^2	0.582	43%

Source: the sponsor's pop pk report, page 161.

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Table 6 presents the predicted median percent change from the baseline; placebo caused an approximate 27% reduction in drop seizure frequency; clobazam administration in the presence of placebo caused an additional maximal reduction in drop seizure frequency of approximately 73%. Overall, a near maximal reduction in seizure frequency occurs with the 20 mg dose at an EC50 multiple of 1 – 2 times for clobazam and 2 times for N-CLB, while maximal benefit occurs at a dose of 40 mg.

Table 6. Median predicted percent change in daily seizure rate from baseline by clobazam dose and multiples of clobazam and N-CLB EC50.

		Clobazam Dose							
EC_{50} Multiple		5 mg		10 mg		20 mg		40 mg	
Clobazam	*N-CLB*	*Frequency*	*Response*	*Frequency*	*Response*	*Frequency*	*Response*	*Frequency*	*Response*
<1x EC_{50}	<1x EC_{50}	55	43.9	52	51.0	12	32.3	0	--
	1-2x EC_{50}	28	64.4	11	62.7	18	74.7	6	58.1
	>2x EC_{50}	17	72.2	17	68.9	25	63.9	18	100
1-2x EC_{50}	<1x EC_{50}	0	--	4	29.2	4	67.2	0	
	1-2x EC_{50}	0	--	7	69.0	16	70.0	24	74.9
	>2x EC_{50}	0	--	9	65.5	22	85.5	29	97.5
>2x EC_{50}	<1x EC_{50}	0	--	0	--	0	--	0	--
	1-2x EC_{50}	0	--	0	--	0	--	12	37.4
	>2x EC_{50}	0	--	0	--	4	74.0	12	96.9

Frequency is the percent of subjects with Cavg for clobazam and N-clobazam contained in the indicated EC_{50} multiple range. Columns many not sum to 100% due to rounding.
Response is the median of the individual predicted percent change from baseline for subjects contained in the EC_{50} multiple range indicated.

Source: the sponsor's pop pk report, page 171.

Exposure-Safety Analyses

Sedation-related adverse events (sedation, somnolence, sleepiness, drowsiness, sleepy, lethargy and listlessness) were evaluated as a safety endpoint. The same exposure metrics (Cavg,p and Cavg,m) in the efficacy analysis were related to the safety endpoint.
The logistic regression analysis was employed for the probability of having any sedation-related adverse event during treatment period. In the sponsor's analysis, concentration for clobazam could not be related to sedation-related adverse event so N-CLB concentration (Cavg,m) was used for exposure-safety analysis.

Figure 5 present the sponsor's exposure-safety analysis results. The sponsor's analysis showed that the median probability of having an incidence of sedation in the lower doses (5 mg and 10 mg) was predicted to be about 10% higher than that for the placebo group, and about 28% higher than the placebo group for the higher doses (20 mg and 40 mg). There was similarity in the predicted incidence of sedation between the 20 mg and the 40 mg doses.

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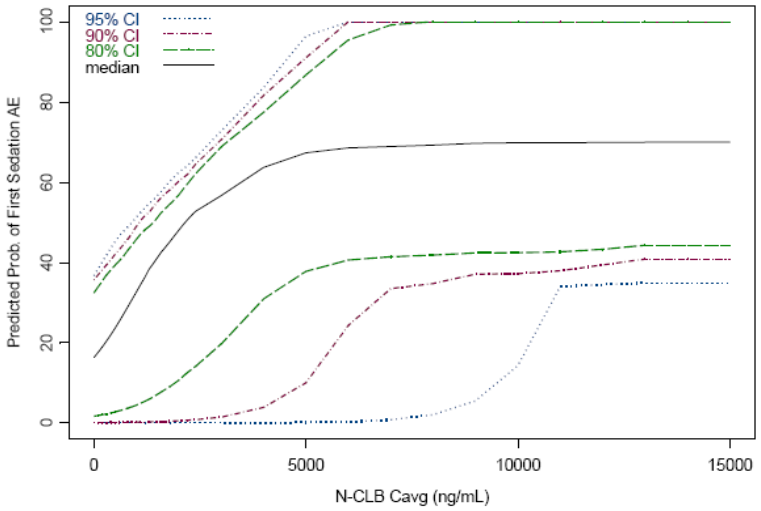
Figure 5. Predicted probability of sedation-related adverse event from the sponsor's logistic regression.



Source: the sponsor's pop pk report, page 137.

Reviewer's comments:

- *For the sponsor's population PK analyses.*
  - *The reviewer found out coding errors in some of covariates in the dataset.*
    - *Those errors have been fixed and conclusions remained same.*
  - *Non-significant effect of CYP2C19 inhibitors on PK of N-CLB seems to be counterintuitive as CYP2C19 poor metabolizers were found to strongly influence elimination of N-CLB. However, this may be explained by the fact that both felbamate and oxcarbazepine are known to be weak CYP2C19 inhibitors.*
  - *The sponsor did not evaluate the difference in PK between patients and healthy subjects.*
    - *The reviewer observed that there appeared to be different in elimination of N-CLB (see the section 4).*
  - *The effect of age on clobazam clearance was observed based on the reviewer's assessment unlike the sponsor's claim (see the section 4).*

- *The sponsor's exposure-response analyses are acceptable. The reviewer has the following minor comments:*
  - *Based on the reviewer's observation and the sponsor's report, the fraction of baseline appears to reach steady-state quickly (see* Figure 8 *in the reviewer's analysis and Figures 75 and 80 in the sponsor's report) so it is not necessary to account for time-course in the E-R model.*
  - *Based on the sponsor's estimate, there was only 7.5% of non-responder and the sponsor's model did not describe the observed data well for non-responder (Figure 81 in the sponsor's report). Thus, the reviewer did not*

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see the benefit from modeling by considering two different populations (responder/non-responder).

- *The sponsor used sedation-related adverse events during titration period as well as maintenance period.*
    - *Based on the reviewer's observation (AE-time profile), it would be more appropriate to see the relationship for maintenance period only.*
- *The sponsor's model-predicted probability for sedation-related AEs may not be reliable due to large variability.*

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4 REVIEWER'S ANALYSES

4.1 Introduction

The sponsor did not claim the effect of any covariate on clearance of clobazam. However, the reviewer observed the effect of age on elimination of clobazam which was based on finding from one of literatures (Greenblatt et al. Br.J. clin.Pharmac, 1981). Hence, the reviewer attempted to reassess the effect of age on clearance of clobazam to confirm finding from the paper. Also the difference in PK between patient and healthy population was evaluated as the sponsor has not done it.

In addition to that, the reviewer saw the sponsor's model unnecessarily complicated, which resulted in poor performance of model prediction in the certain population such as non-responder group. Therefore, the reviewer performed the independent analyses to confirm the sponsor's main conclusions from the exposure-response analyses by rather simple approach and to address whether the sponsor's proposed dosing regimen seems to be reasonable.

4.2 Objectives

- To reassess the effect of age on elimination of clobazam
- To investigate whether there is difference in PK between patient and healthy population
- To perform the independent exposure-response analyses to confirm the sponsor's main conclusions by simpler method

4.3 Methods

4.3.1 Data Sets

The reviewer took individual estimate for CL from the sponsor's base model for the effect of age on CL of clobazam, and the dataset for the sponsor's population PK analyses was used for the evaluation of difference in PK between patient and healthy population.
For the exposure-response analyses, the data from the study of OV-1012 was combined with the dataset for the sponsor' exposure-response analysis to incorporate concentration measurements.

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4.3.2 Software

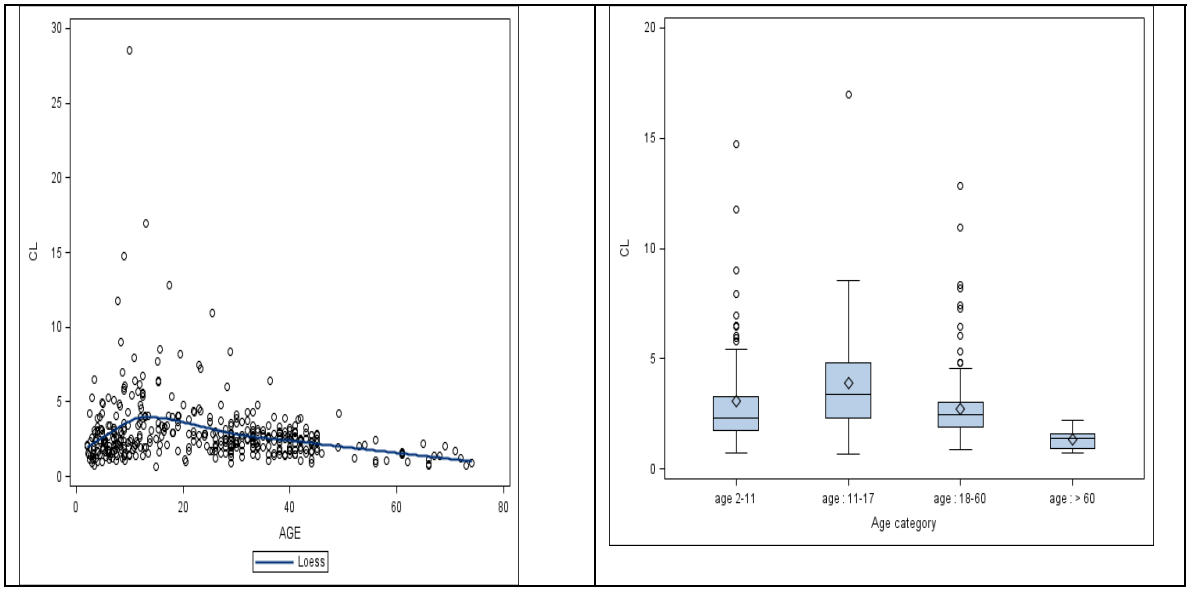
SAS 9.2 and R 2.5 were used for the analysis.

4.3.3 Model Results

<u>The effect of age on clearance of clobazam</u>

The sponsor assumed linear relationship between the effect of age and CL of clobazam. However, as shown in Figure 6 the assumption of linearity may not appear to be correct: CL increases as a patient gets older until about 18 years old, then slightly decreases in adult population.

Figure 6. The relationship between age and individual estimates for CL. The left panel shows the relationship with loess curve, and the right graph is the same relationship when age is grouped into four categories: children (2-11 years), adolescent (12-17 years), adults (18-60 years) and elderly patients (≥ 60 years)



<u>The difference in PK between patients and healthy population.</u>

A patient variable (1: patients, 0: healthy subjects) was created in the population PK dataset; the healthy population came from 5 Phase I studies, and the subjects from the studies of OV-1002 and OV-1012 comprised of the patients population.

As shown in Figure 7, the reviewer observed that there appeared to be different in elimination of N- CLB between two populations. Hence, for more formal approach, the effect of different population on K40 parameter was added to the sponsor's final

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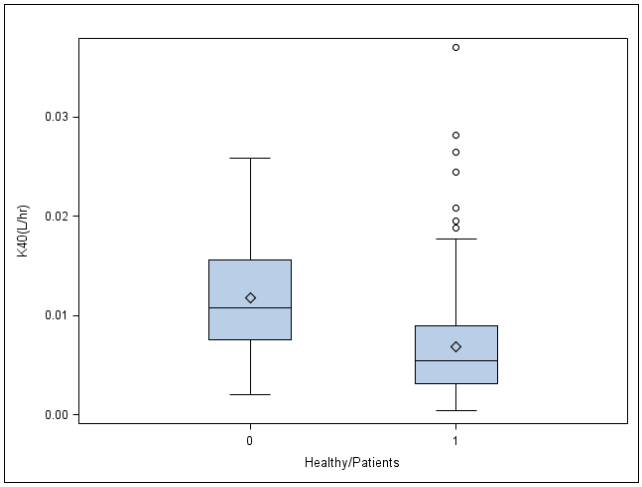
population PK model as one more covariate. OFV changed from 22916.3 to 22955.5, meaning statistically significant difference in elimination of N-CLB.

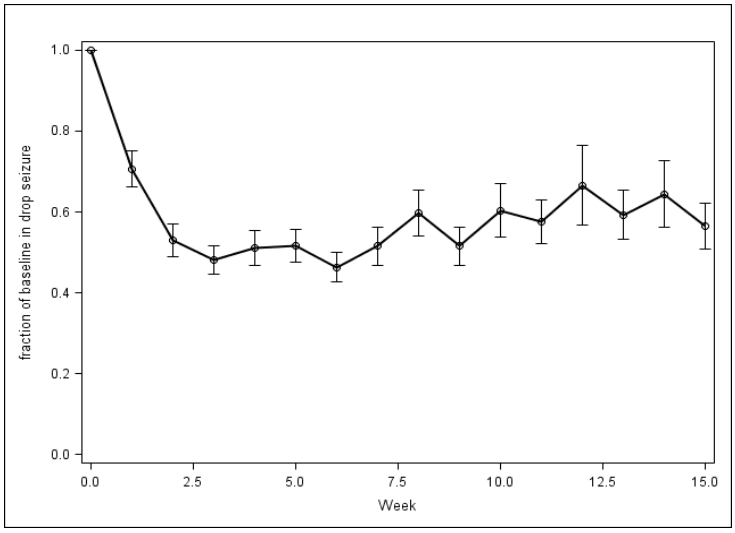
Figure 7. The distribution of individual estimate for K40 (elimination of N-CLB) between patients and healthy subjects.



Exposure-Response Relationship

As shown in Figure 8, the fraction of baseline in drop seizure at each time point (the sponsor's endpoint) appears to be stable during the maintenance period. Thus, the same primary efficacy endpoint (the percent reduction in drop seizures during maintenance period from baseline) rather than weekly fraction from the baseline was used for the reviewer's exposure-efficacy analysis. The endpoint was log-transformed to ensure normality assumption.

Figure 8. Fraction of baseline drop seizure at each week.



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In the study of OV-1012, subjects were stratified into 1 of 2 pre-specified weight groups (≤ 30 kg and > 30 kg) and randomly assigned to placebo or a low (target dose of 0.25 mg/kg, a maximum daily dose of 10 mg), medium (target dose of 0.5 mg/kg, a maximum daily dose of 20 mg), or high (target dose of 1.0 mg/kg, a maximum daily dose of 40 mg) dose of clobazam. **Table 7** presents the number of patients in each dose group by actually received dose (mg/day) during maintenance period stratified weight category. Notice that the maximum daily doses are different by weight category. Figure 9 displays the distribution of Cavg for clobazam and N-CLB by weight category and actual dose received, which shows substantial overlap between 15mg and 20mg, and between 35mg and 40mg.

Table 7. The number of patients who received actual dose (mg/day) during maintenance period in each dose group (There were 217 patients in MITT population. However, 15 patients not having PK and 1 patient having extreme value in the percent reduction (-374 %) were excluded in the analyses.

	ACTUAL DOSE (MG/DAY) RECEIVED DURING MAINTENANCE PERIOD													
	Weight ≤ 30 kg							Weight > 30 kg						
	0	5	10	15	20	35	40	0	5	10	15	20	35	40
Placebo	31							25						
Low (0.25mg/kg)		24							2	19				
Med (0.5mg/kg)		3	28								3	21		
High (1.0mg/kg)				3	25								9	8

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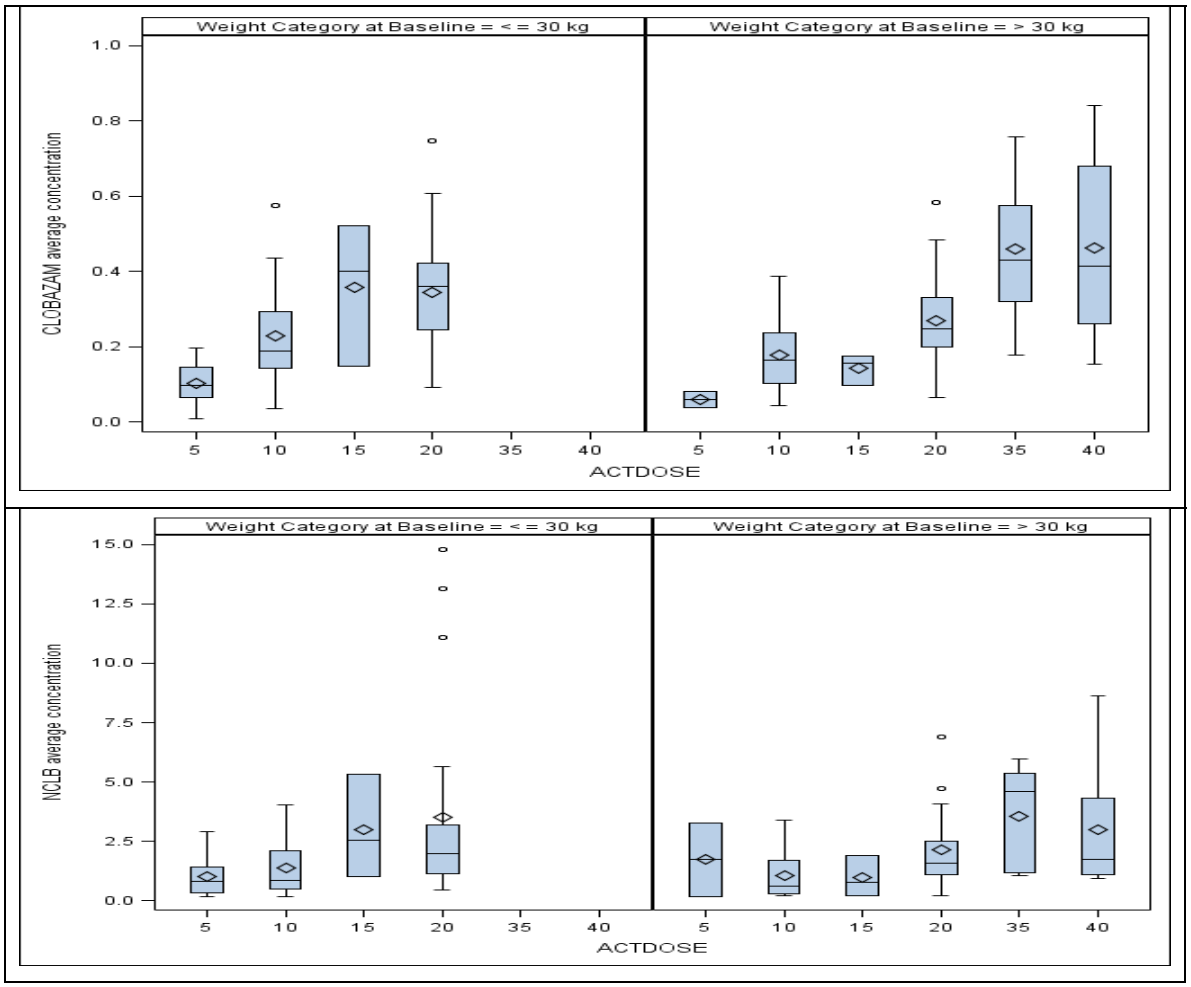
Figure 9. The distribution of Cavg for clobazam (top) and N-CLB (bottom) by weight category and actual dose received during maintenance period.



Unlike the sponsor's approach, Emax model was fitted for clobazam and N-CLB separately as a sensitivity analysis. However, the reviewer agrees that it is more reasonable to model clobazam and N-CLB simultaneously than separately because of pharmacologic activity as addressed before.

As consistent with the sponsor's result, clobazam showed larger potency than N-CLB (EC50=0.3 for clobazam and 2.1 for N-CLB). Figure 10 presents the results from the reviewer's exposure-efficacy analyses. The drop seizures rates appear to be decreasing in concentration-dependent manner for both clobazam and N-CLB, and it reaches a plateau at 40mg / day, which is consistent with the sponsor's analyses results. The predicted % reduction from the reviewer's analysis should be explained in a qualitative and relative sense (the higher the exposure, the more % reduction) in that both clobazam and N-CLB contributed to the overall % reduction in drop seizure.

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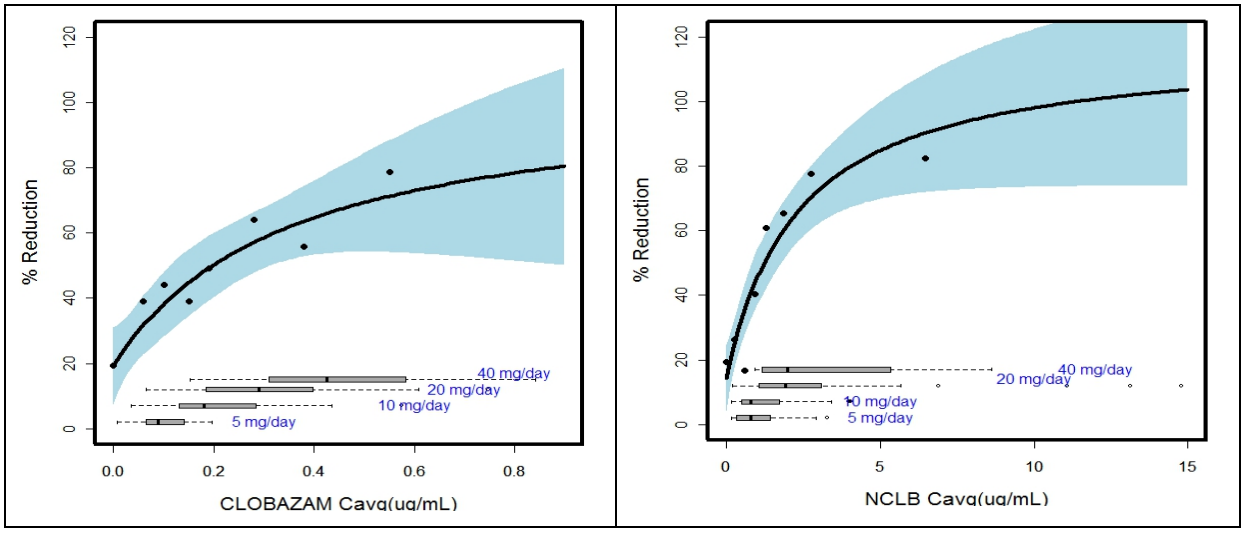
Figure 10. Model-predicted relationship between Cavg and % reduction in drop seizure during maintenance period from the baseline for clobazam (left) and N-CLB (right). The dots represent the observed % reduction at octile of Cavg, and the solid line is the model-predicted relationship with 95 % prediction interval (blue shade). The four boxplots on the bottom represent the distribution of Cavg at actual dose received during maintenance period (15 mg and 35 mg were combined with 20 mg and 40mg, respectively due to completely overlap in the distribution and the small sample size).



In order to evaluate the sponsor's proposed dosing regimen, the reviewer looked at the dose-response (% reduction in drop seizure) relationship by each weight category, which is shown in Figure 11. For both weight categories it shows clear dose-response relationship, although there appears to be large variability.

Figure 11. Dose-Response relationship by weight category

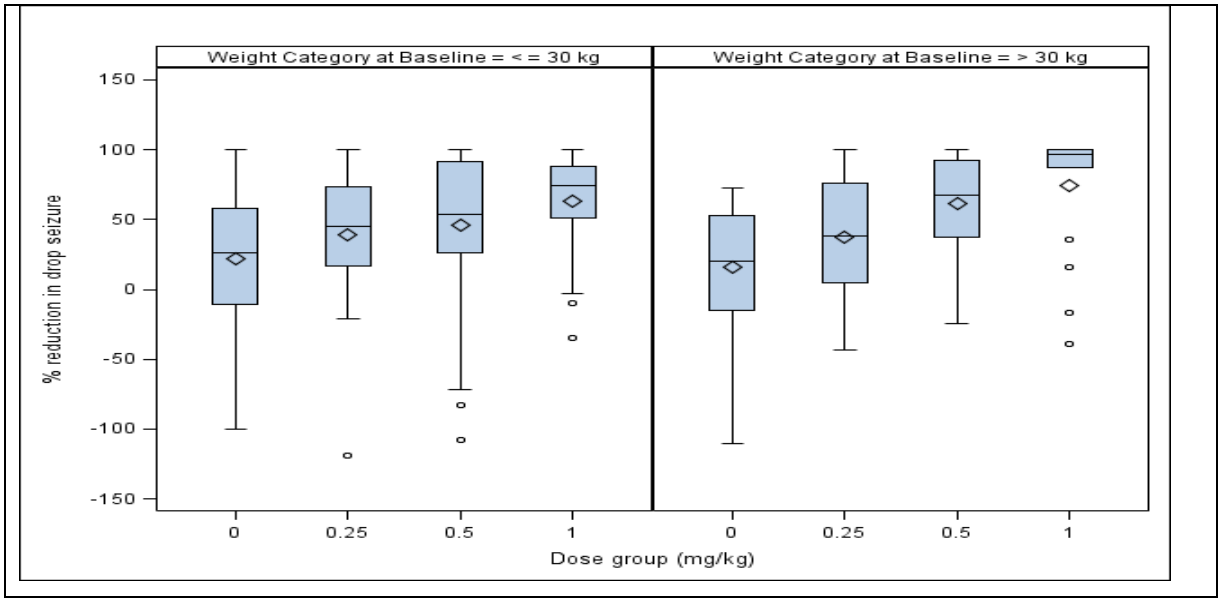


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Figure 12 displays the time profile of the percent of patients having at least one sedation-related AEs by weight category. The adverse event rate at the dose of 40 mg went up and dropped dramatically after titration phase ended, which made the dose of 20 mg worse in this safety-time profile. One of reasons for this pattern could be higher drop rate at the highest dose. Hence, the reviewer looked at the dropout rate at each dose level and Figure 13 shows that actually the highest dropout rate occurred at the dose of 40 mg. If dropout is related to sedation-related AE, the probability of sedation-related AE needs to be adjusted. According to the sponsor's report, the number of patients who dropped out the study due to sedation-related AE was 1, 3, 4 and 6 patients at placebo, 10 mg, 20 mg and 40 mg, respectively. Those patients were taken into consideration in a safety-time profile, and Figure 14 presents the dropout-adjusted sedation-related AE-time profile. For light-weighted patients (≤ 30kg), clobazam seems to be safe across all dose levels, although the doses of 10-20 mg/day showed higher percentage of sedation-related AE than placebo or 5mg/day. For heavy patients (>30 kg), it appears to be dose-dependent increase in sedation-related AE but the difference between 20 mg/day and 40 mg/day is negligible.

Figure 12. The percent of patients having at least 1 sedation-related adverse events – time profile by weight category.

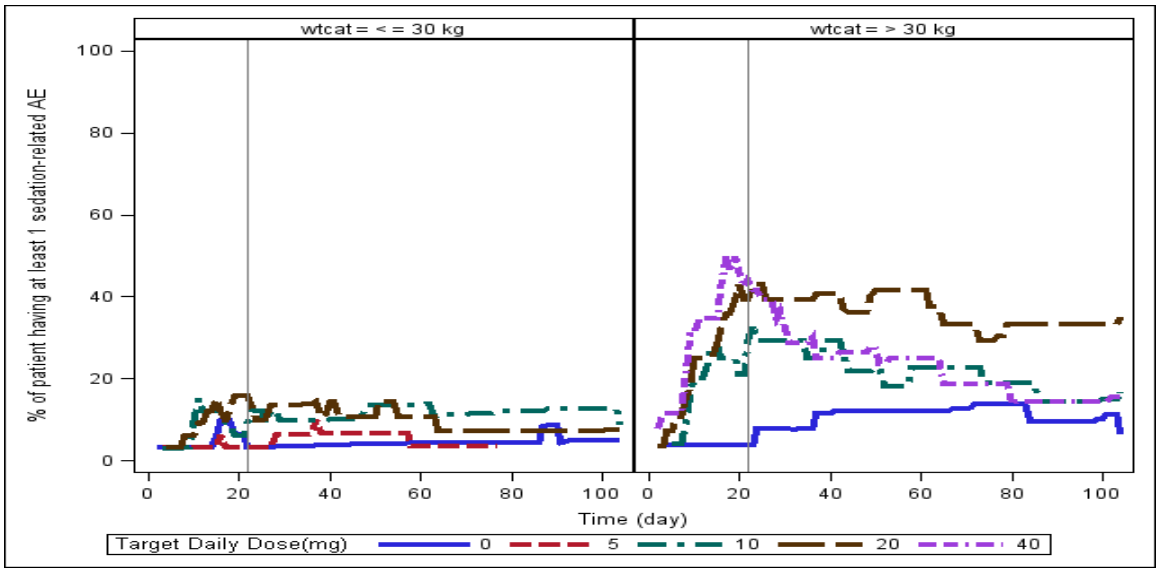

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Figure 13. Dropout rate due to any reason by weight category.

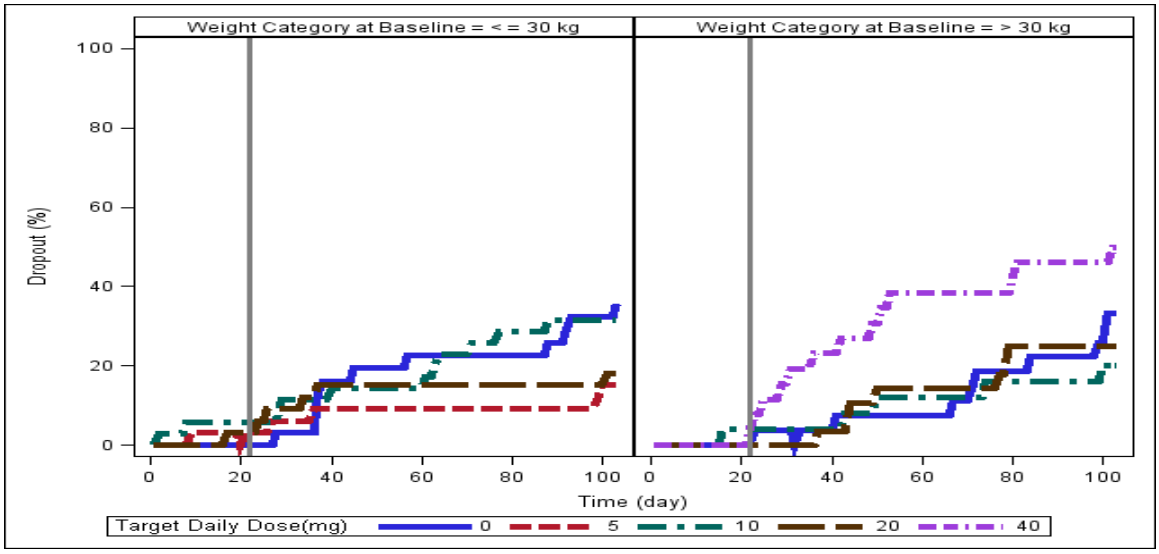
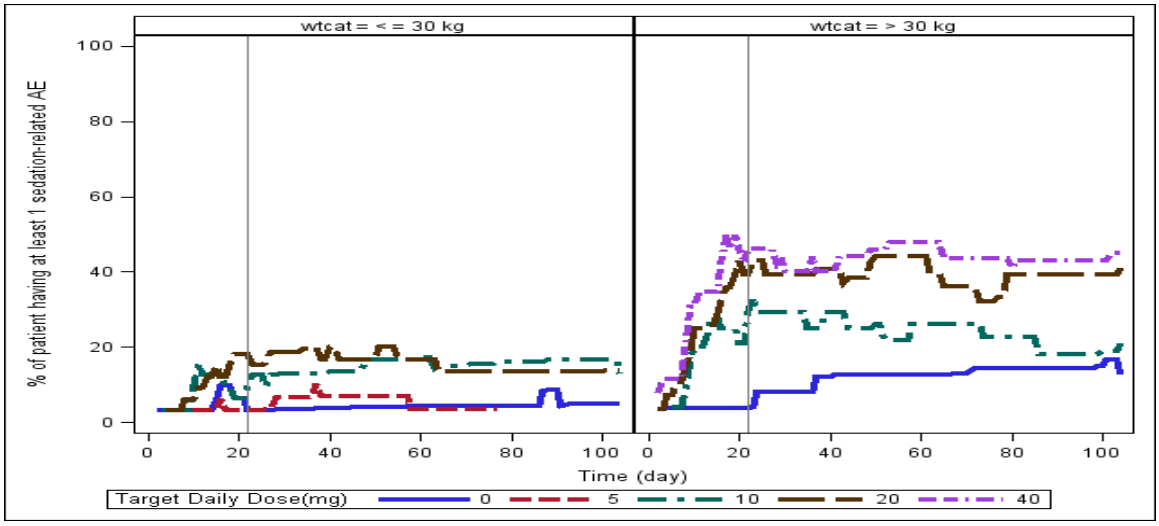


Figure 14. Dropout-adjusted sedation-related AE-time profile.



In conclusion, the sponsor's conclusions from exposure-response analyses for both efficacy and safety can be supported by the reviewer's assessment also.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ER_analysis.sas AE analysis_imputed.sas	The reviewer's exposure-efficacy analysis The reviewer's exposure-safety analysis	

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APPENDIX

Appendix 1: The parameter estimates from the sponsor's final population PK model.

Parameter	Units	Estimate	SE	%RSE
$\theta_{CL/F}$	L/hr	2.49	0.063	2.53
$\theta_{V2/F}$	L	54.7	2.84	5.19
θ_{KA}	hr^{-1}	1.05	0.091	8.67
$\theta_{Q/F}$	L/hr	4.55	0.863	19.0
$\theta_{V3/F}$	L	47.1	3.08	6.54
$\theta_{STD,Res,CLB}$		0.193	0.008	4.15
$\theta_{STD,Res,N\text{-}CLB}$		0.206	0.009	4.37
θ_{FM}		-4.42	0.028	0.633
θ_9	hr^{-1}	0.002	0.0005	25.0
θ_{10}	hr^{-1}	0.010	0.0005	5.00
θ_{11}	hr^{-1}	0.575	0.043	7.48
$\omega^2_{CL/F}$		0.268	0.028	10.4
$\omega^2_{CL/F_V2/F}$		0.109	0.031	28.4
$\omega^2_{V2/F}$		0.345	0.087	25.2
ω^2_{KA}		0.878	0.164	18.7
$\omega^2_{Q/F}$		1.08	0.168	15.6
$\omega^2_{V3/F}$		0.216	0.048	22.2
ω^2_{FM}		0.064	0.009	14.1
ω^2_{K40}		0.510	0.043	8.43

The θ's are the estimated fixed parameters which are appropriately subscripted, except $\theta_{STD,Res,CLB}$ and $\theta_{STD,Res,N\text{-}CLB}$ which estimates of the standard deviations of the residual error for clobazam and N-CLB, respectively. The η's are the estimated fixed parameters which are appropriately subscripted. θ_9 to θ_{11} have the same meaning as in Table 5.

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Note: θ_9, θ_{10} are typical value of N-CLB clearance for PM(poor metabolizer), non-PM; θ_{11} is a scaling parameter for non-Hispanics. $\theta_{Fm\,1}$ is a parameter estimate for logit of Fm (PM in the previous description).

Source: *the sponsor's pop pk report, page 79.*

Appendix 2: The parameter estimates from population PK model for DDI.

Parameter	Units	Estimate	SE	%RSE
$\theta_{CL/F}$	L/hr	2.8	0.137	4.89
$\theta_{V2/F}$	L	51.4	8.99	17.49
θ_{KA}	hr^{-1}	1.19	0.557	46.81
$\theta_{Q/F}$	L/hr	6.48	1.51	23.30
$\theta_{V3/F}$	L	53.2	6.9	12.97
$\theta_{SD,Res,CLB}$		0.311	0.018	5.79
$\theta_{SD,Res,N\text{-}CLB}$		0.340	0.024	7.06
θ_{PM}		-3.15	0.092	2.92
$\theta_{PM,3A4Inducer}$		-3.06	0.125	4.08
θ_{K40}	hr^{-1}	0.019	0.0001	0.526
$\theta_{K40,C19Inducer}$	hr^{-1}	0.021	0.0015	7.14
ω^2_{CL}		0.361	0.049	13.57
$\omega^2_{CL_V2/F}$		0.181	0.088	48.62
$\omega^2_{V2/F}$		0.861	0.344	39.95
ω^2_{KA}		1.13	0.626	55.4
ω^2_{Q}		0.020	-	-
$\omega^2_{V3/F}$		0.021	0.02	95.2
ω^2_{FM}		1.00	0.105	10.50
ω^2_{K40}		0.021	0.016	76.19

The θ's are the estimated fixed parameters which are appropriately subscripted, except $\theta_{SD,Res,CLB}$ and $\theta_{SD,Res,N\text{-}CLB}$ which estimates of the standard deviations of the residual error for clobazam and N-CLB, respectively. The η's are the estimated fixed parameters which are appropriately subscripted.

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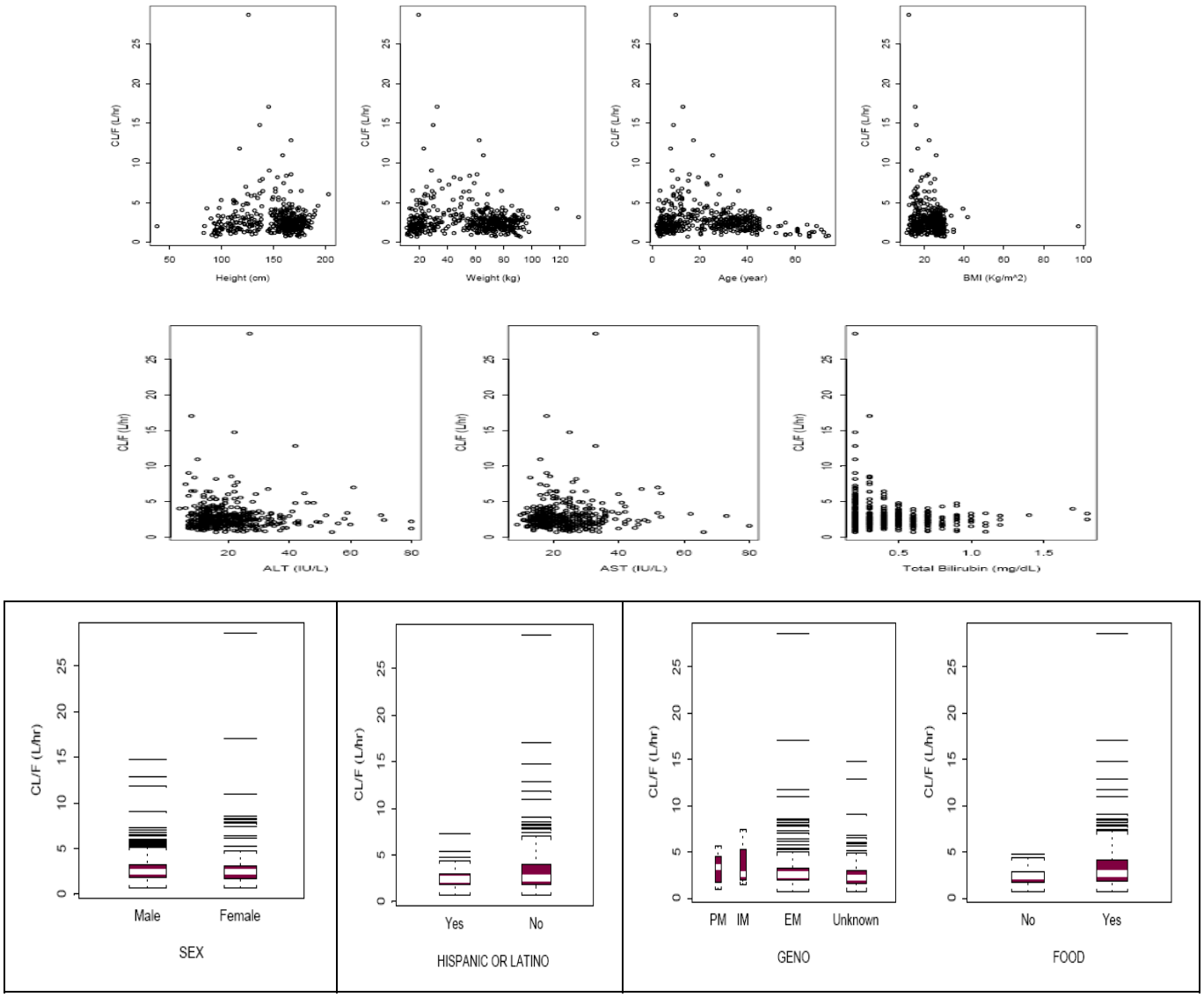
Source: *the sponsor's pop pk report, page 97.*

Reference ID: 3026076

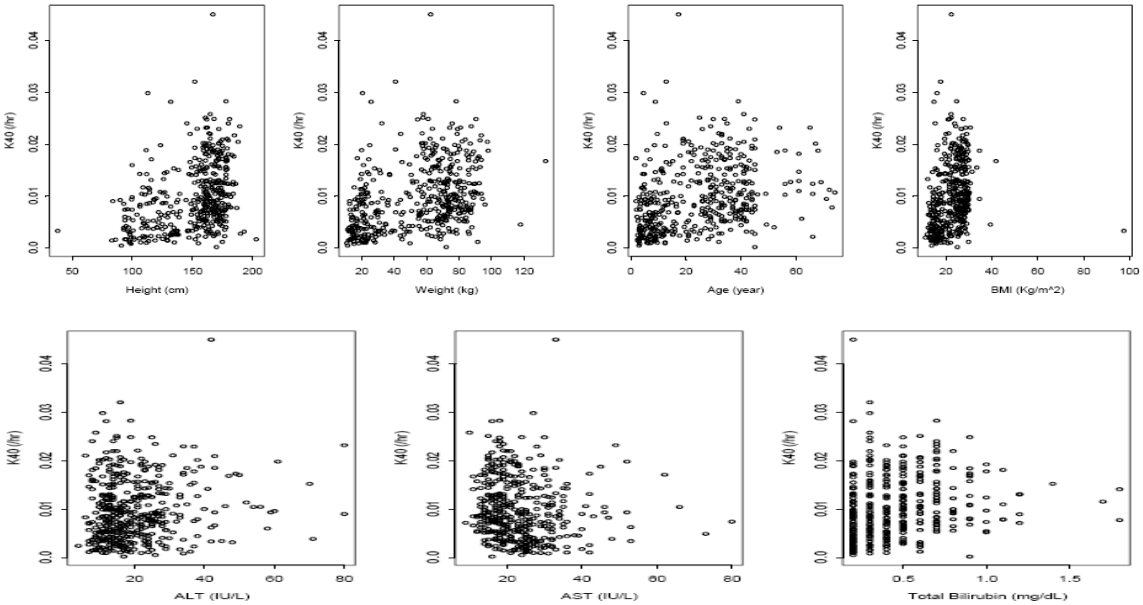
Appendix 3. The relationship between clobazam CL/F and covariates

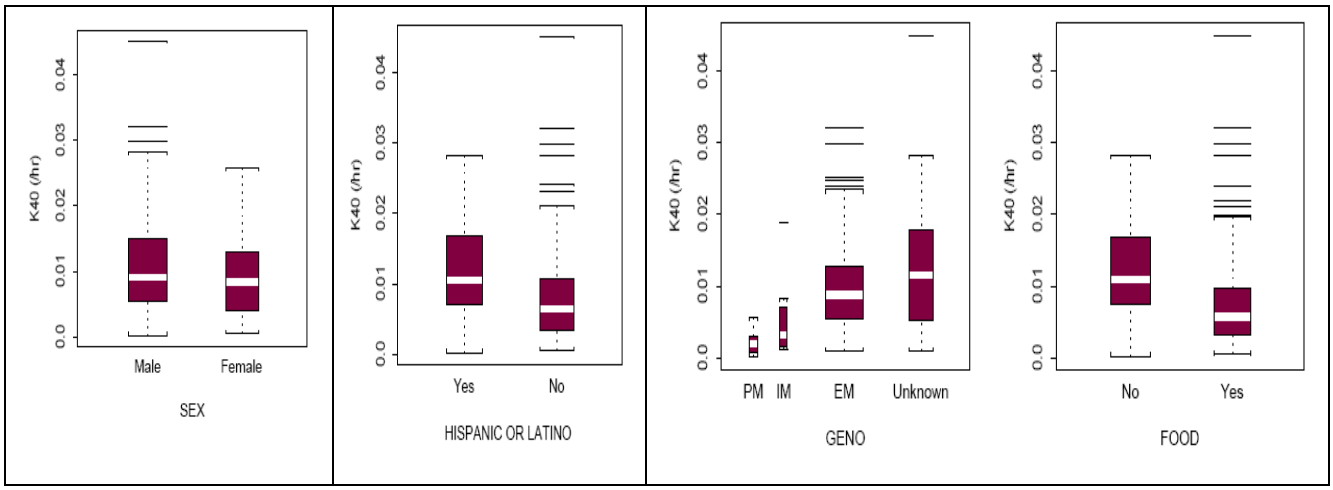


Source: the sponsor's report, page 62-63

Reference ID: 3026076

Appendix 4: The relationship between N-CLB clearance (K40) and covariates

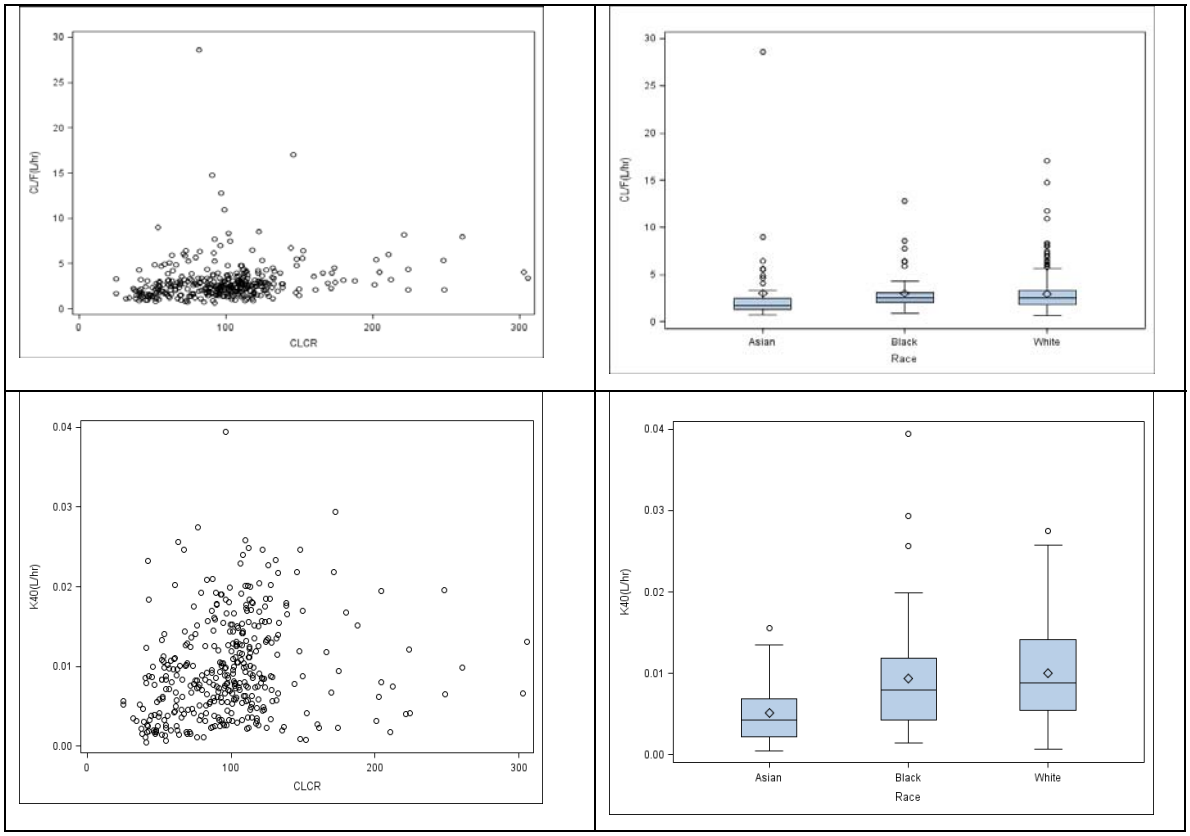




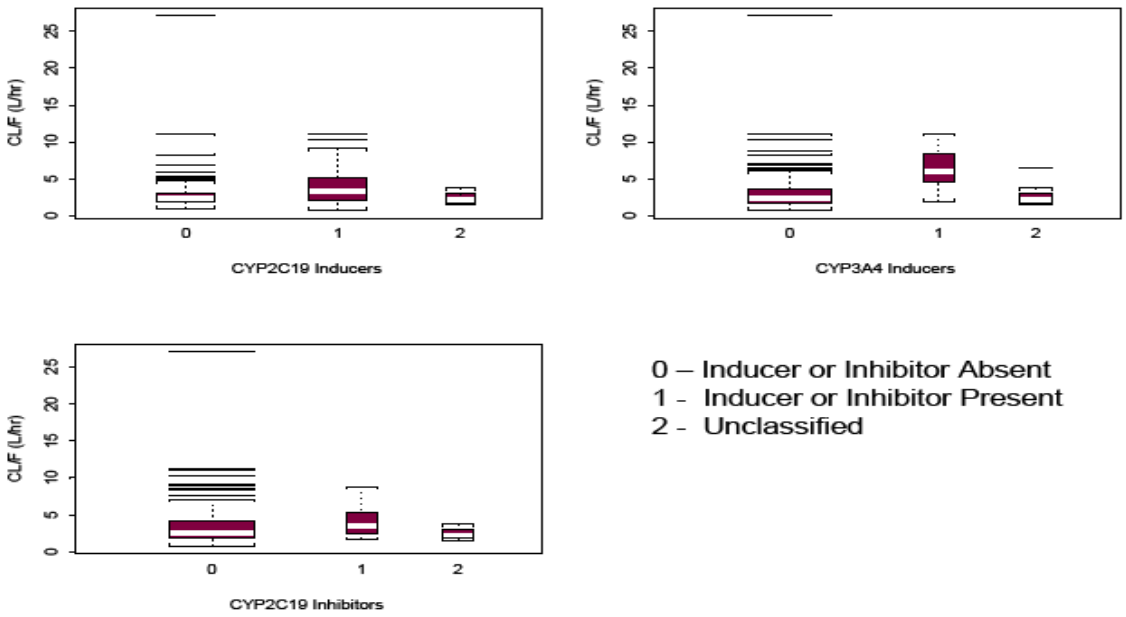
Source: the sponsor's report, page 73-74.

Reference ID: 3026076

Appendix 5: Corrected data – CLCR and Race effects on PK of clobazam and N-CLB



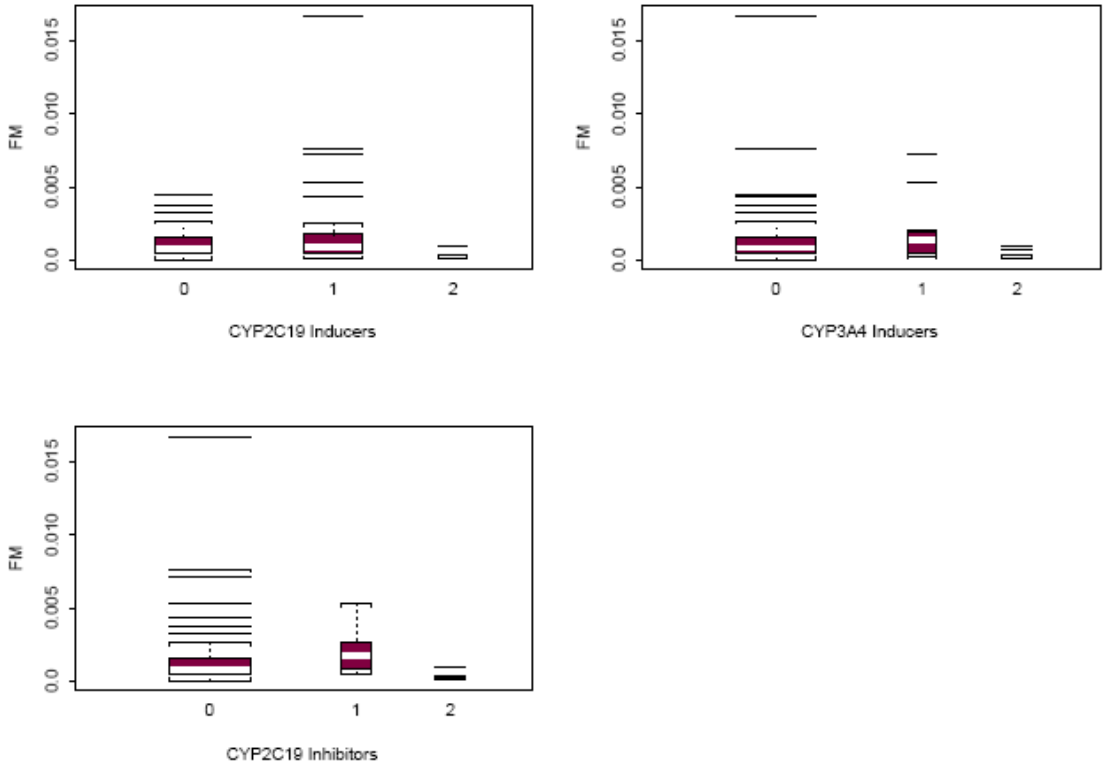
Appendix 6: Relationship between clobazam clearance (CL/F) and AEDs.



Source: the sponsor's report, page 90.

Reference ID: 3026076

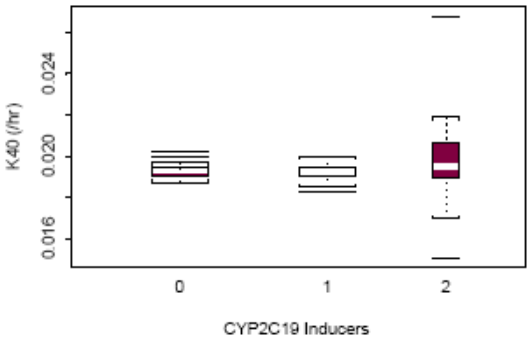
Appendix 7: Relationship between the formation of N-CLB (Fm) and AEDs.

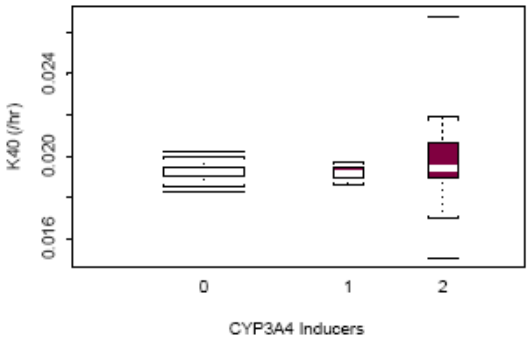


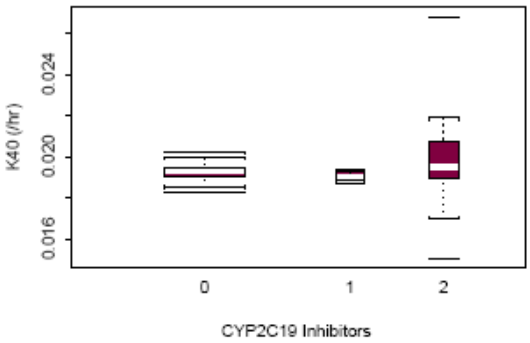
Source: the sponsor's report, page 91.

Reference ID: 3026076

Relationship between N-CLB (K40) and AEDs.







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OFFICE OF CLINICAL PHARMACOLOGY

GENOMICS GROUP REVIEW

NDA Number	202067
Submission Date	23 Dec 2010 (SDN 1), 7 Feb 2011 (SDN 4)
Drug Name	Clobazam
Sponsor	Lundbeck Inc
Primary Reviewer	Hobart L. Rogers, Pharm.D., Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

Executive Summary

Clobazam is a benzodiazepine that purportedly acts as a positive allosteric modulator at gamma containing GABA(A) receptors. The proposed indication for clobazam in this NDA submission is for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age. Clobazam is extensively metabolized in the liver primarily by CYP3A4 to an active metabolite, N-desmethylclobazam (N-CLB), which in turn is metabolized extensively by CYP2C19. Pharmacogenetic studies of CYP2C19 included in the submission indicate that subjects who are CYP2C19 poor metabolizers (~3% prevalence), based on genotype, have approximately a 3-5 fold increase in exposure to N-CLB compared to extensive metabolizers; intermediate metabolizers (~30% prevalence) also have higher exposures but not to the extent of poor metabolizers. While exposure correlates with both efficacy and adverse effects, intermediate or poor metabolizers did not consistently have better efficacy or worse safety than extensive metabolizers. Since clobazam appears to be tolerated across a wide range of doses, including doses higher than that being submitted for approval and that doses are titrated to tolerability and effect, prospective genotyping of patients is not indicated. However, information related to the high exposures in CYP2C19 poor metabolizers should be included in labeling. (b) (4)

1 Background

The current submission is a New Drug Application for clobazam, a benzodiazepine derivative. The proposed indication is for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome. Clobazam is approved in Europe, Japan, Canada, India, and New Zealand for various seizure disorders and anxiety.

Clobazam is thought to be a positive allosteric modulator at GABA-A receptors. Clobazam is primarily metabolized by the CYP3A4 system in the liver to an active metabolite N-desmethylclobazam (N-CLB). N-CLB is then metabolized by the polymorphic CYP2C19. The applicant reports that N-CLB concentrations are higher in CYP2C19 poor metabolizers, and

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proposes descriptive labeling language to describe this pharmacogenetic interaction (but is not proposing use of testing to guide treatment decisions).

For the current submission, the Division of Pharmacometrics review confirmed 1) a clear relationship between CLB and N-CLB concentrations and clobazam efficacy (number of drop seizures) and safety (sedation adverse events), and 2) that CYP2C19 and race/ethnicity are the main factors influencing N-CLB clearance. The purpose of this review is to evaluate the appropriateness of the applicant's proposed labeling and whether CYP2C19 genotyping is indicated for the appropriate use of clobazam.

2 Submission Contents Related to Genomics

The data for the population PK analysis were drawn from multiple studies, as summarized in the following table.

Table 1. CYP2C19 genotype data sources submitted for population PK analysis

Study	Study Phase	Purpose	Multiple Dose	Subjects*
OV-1002	2	Efficacy	Yes	64
OV-1012	3	Efficacy	Yes	174 (125)
OV-1021	2	DDI	No	36
OV-1022	2	QT	Yes	277 (138)
OV-1023	2	DDI	Yes	18
OV-1032	2	Renal impairment	Yes	24
OV-1038	2	Dosing Ranging	Yes	23

*includes subjects that received placebo or other control, number of clobazam-treated subjects noted in parentheses

3 Key Questions and Summary of Findings

3.1 Is CYP2C19 genotype a major determinant of N-CLB exposure?

3.1.1 Clobazam PK and pharmacogenetic interaction potential

Clobazam is metabolized primarily by CYP3A4 to an active metabolite N-desmethylclobazam (N-CLB). In turn, N-CLB is metabolized by CYP2C19. Based on exposure-response modeling, N-CLB is thought to have about one-third the potency of clobazam. N-CLB has been shown to have a much longer elimination phase compared to clobazam; the half-life of N-CLB is estimated to be 79 hours compared to 36 hours for its parent CLB. Exposure to both CLB and N-CLB is correlated with efficacy and safety, as reflected in the Division of Pharmacometrics review (Joo-Yeon Lee 2011).

CYP2C19, which is responsible for clearance of N-CLB is polymorphic. The two most common CYP2C19 polymorphisms are referred to as *2 and *3, both of which introduce a premature stop codon that results in a truncated, nonfunctional protein. Individuals with reduced CYP2C19 function would be expected to have higher exposures to N-CLB. The *2 and *3 variants are common in the population. In whites and blacks, approximately 30% of the population has at least one variant allele (intermediate metabolizers [IMs] while 2-4% have 2 variant alleles (poor

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metabolizers [PMs]. The variant genotypes are more common in Southeast Asian populations, with up to 13-20% being CYP2C19 PMs (Xie HG et al., PMID 11264478).

3.1.2 Applicant's pharmacogenetic analysis

The sponsor determined CYP2C19 genotype in seven clinical studies (see Section 2) to infer a CYP2C19 phenotype (EM, IM, PM). Subjects were genotyped for the *2, *3, *5, *6, and *7 alleles of CYP2C19 in OV-1002 using fluorescence primer extension methods; the alleles genotyped were otherwise not described. DNA was also collected in clinical studies for CYP2B6 genotyping. These results were not included in the current submission. Initially the sponsor's CRO used a fluorescent primer extension method (FPE) for the Phase 2 studies, and then switched to the xTAG CYP2C19 platform.

Comment: Bioanalytical reports for the genotyping assays were not included in the current submission. The distribution of the alleles is similar to what is expected based on the known distribution of CYP2C19 poor metabolizer alleles.

Key results from the applicant's population PK analysis of single- and multiple-dose PK studies (dense and sparse sampling) are summarized in the following figure. CLB clearance (left panel) was not significantly affected by CYP2C19 phenotype, whereas N-CLB clearance (right panel) was significantly lower in PMs. IMs had clearance values between those of PMs and EMs, as would be expected.

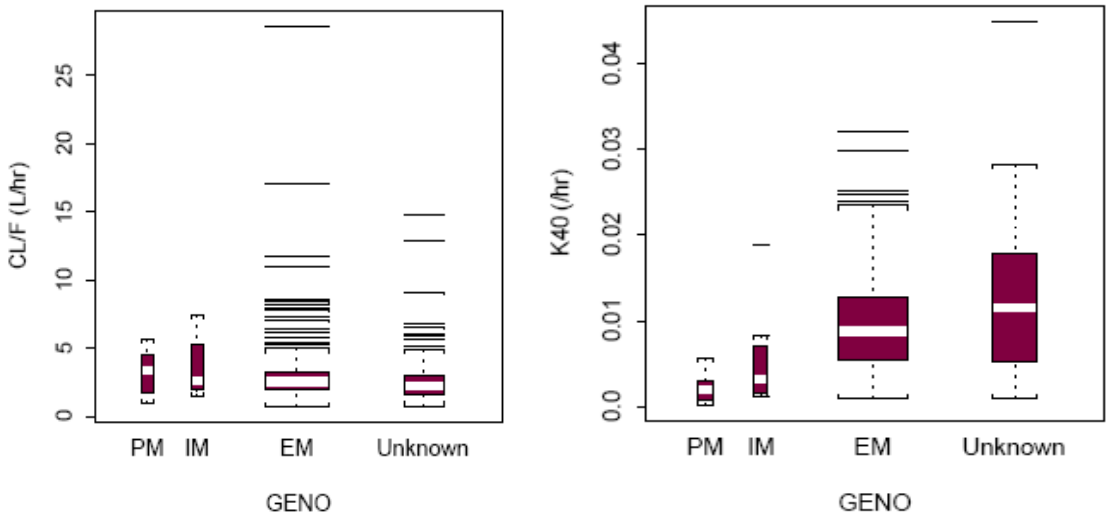

Figure 1. Clobazam clearance by CYP2C19 genotype (left) and N-CLB clearance by CYP2C19 genotype (right)

*Comment: Please see Division of Pharmacometrics review (Joo-Yeon Lee, 2011) for details on population PK analyses and results. Note that inconsistencies were found in assignment of genotype-derived phenotype. Specifically, in studies OV-1012, OV-1021, OV-1022, OV-1023, OV-1032, IMs (*1/*2, *1/*3) were categorized as EMs by the sponsor, but were categorized as IMs in other studies. Individual CYP2C19 genotypes were used to reassign phenotypes and the*

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data were reanalyzed (see section 3.1.3). Corrected phenotypes were used in the Pharmacometrics and Genomics Group analyses.

Analysis of PK studies OV-1022 and OV-1038 suggests that N-CLB concentrations are approximately 3-4 fold higher in CYPC19 PMs compared to EMs as shown in the following table. Study OV-1022 used supratherapeutic doses of clobazam to assess the ECG effects, while study OV-1038 was assessing the tolerability of clobazam (80 mg BID). These studies were multiple dose studies selected for their dense PK data, which was sufficient enough to include CYP2C19 PMs.

Table 2. CLB and N-CLB pharmacokinetic parameters by CYP2C19 and clobazam dose in OV-1022 and OV-1038

	Clobazam		N-CLB	
	$AUC_{0\text{-}tau}$ ng•hr/mL	C_{max} ng/mL	$AUC_{0\text{-}tau}$ ng•hr/mL	C_{max} ng/mL
20 mg BID EM/IM (N=64)	10394	1081	28285	2783
20 mg BID PM (N=2)	8933	916	100174	9830
60 mg BID EM/IM (N=11)	19867	2629	89539	8090
60 mg BID PM (N=1)	19973	2760	309500	32600
80 mg BID EM/IM (N=60)	25658	2902	108809	10084
80 mg BID PM (N=2)	19074	2900	375295	39100

3.1.3 Reviewer's pharmacogenetic analysis

Given the inconsistency in genotype-derived phenotype assignment, CYP2C19 phenotypes were reassigned by the reviewer as follows: *1/*1 = EM, *1/*2 or *3 = IM (one subject had *1/*4 genotype), *2 or*3/*2 or *3 = PM. In total, genotype data were available for 418 clobazam-treated subjects; 107 (25%) were IMs, 13 (3.1%) were PMs. To confirm the sponsor's analysis on the magnitude of effect of CYP2C19 genotype on N-CLB concentrations, data from multiple dose studies with dense PK sampling that included PMs were selected for re-analysis; only OV-1022 met these criteria.

Of the 138 subjects enrolled in OV-1022, 42 (30%) were IMs and 4 (2.9%) were PMs. N-CLB AUC_{τ} and $C_{max,\ ss}$ differed significantly by CYP2C19 genotype at the 40 mg/day and 160 mg/day doses (P<0.0001 for each dose stratum), as shown in the following figures. Both CYP2C19 IMs and PMs had significantly higher exposures to N-CLB compared EMs (P=0.02 for PMs vs. EMs, P<0.0001 for IMs vs. EMs). For both doses, the CYP2C19 PMs had 5-fold higher exposure to the active metabolite N-CLB compared to EMs, while IMs had exposures that were 1.9 times higher than EMs. Exposures to CLB did not differ by CYP2C19 genotype (not shown).

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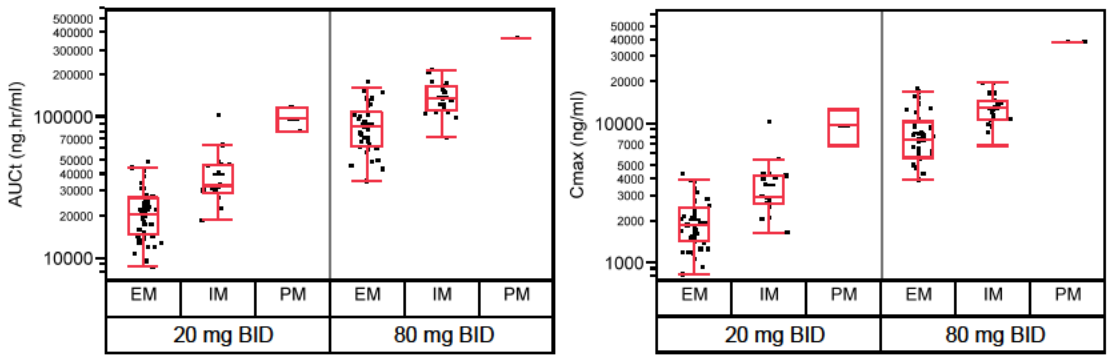

Figure 2. N-CLB AUC_{τ} (left) and $C_{max,\,ss}$ (right) by CYP2C19 genotype and dose

Comment: CYP2C19 genotype significantly affects exposure to N-CLB. The reviewer confirmed the applicant's analyses shown in Table 4, including lack of genotype effect on parent compound. Please see Joo-Yeon Lee's review for additional information on the population pharmacokinetic analyses of CYP2C19 effects on N-CLB clearance.

To evaluate whether PMs are at increased risk for adverse events as a result of the higher exposure, AE data from the pivotal efficacy trial, OV-1022, were analyzed according to CYP2C19 phenotype. AEs of interest were limited to those that were at least possibly related to study drug and were moderate or severe. As shown in the table below, AE rates were increased with higher doses, but did not follow consistent trends across CYP2C19 phenotype within the dose groups. When including mild adverse events, all clobazam-treated PMs experienced an adverse event, although none of these subjects discontinued treatment for toxicity (not shown). Considering that patients may be at highest risk during the early titration interval (i.e., first 3 weeks of the trial), AE rates in this phase were also reviewed. Again, no consistent trends for higher rates in IMs or PMs were noted. Three SAEs occurred in three subjects in the genotyped population, all of whom were EMs.

In a logistic regression model that adjusted for race, site, and baseline seizure rate, CYP2C19 phenotype was not a significant predictor of moderate/severe AEs (P=0.97) or mild/moderate/severe AEs (P=0.93). By contrast, the primary efficacy endpoint, percent reduction in weekly drop seizure rates, tended to be improved at higher doses, but again, no consistent effect of CYP2C19 phenotype on efficacy was observed. CYP2C19 phenotype was not a significant predictor of clobazam response in a multivariable general linear model that adjusted for race, site, and baseline seizure rate (P=0.51).

Table 3. Adverse effects of different doses of clobazam by CYP2C19 genotype

Event	Phenotype	N	Placebo	CLB-LO	CLB-MOD	CLB-HI	CLB-ALL
Percent	ALL	155	17 (75)	43 (65)	53 (61)	85 (51)	62 (71)
Reduction in DS	EM	115	34 (80)	38 (68)	58 (64)	75 (66)	59 (69)
Rate, median	IM	33	12 (25)	34 (40)	35 (47)	90 (17)	43 (56)
(IQR)	PM	7	-11	98 (3)		98 (20)	92 (4)
Mod-Sev	ALL	169	11 (23)	8 (22)	16 (37)	19 (45)	43 (36)
Treatment-	EM	126	9 (26)	6 (24)	12 (34)	15 (47)	33 (36)
Related AE, n	IM	36	2 (15)	2 (22)	4 (50)	2 (33)	8 (35)
(%)	PM	7	0	0	0	2 (50)	2 (33)

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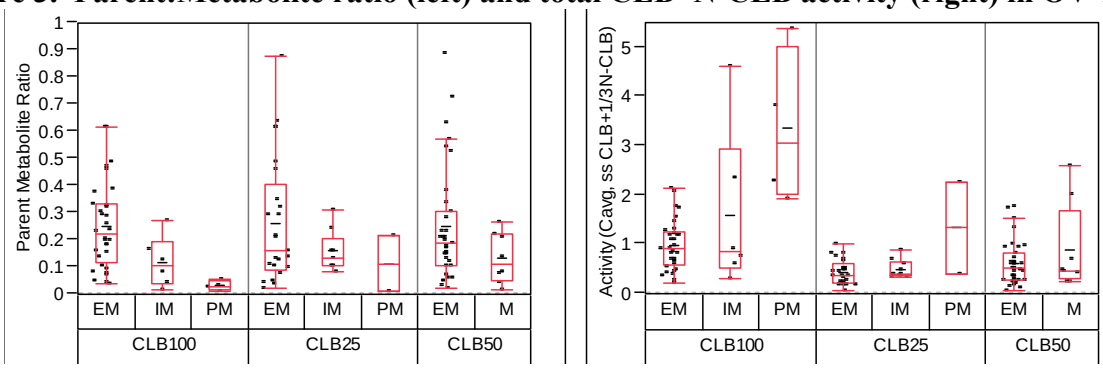
Event	Phenotype	N	Placebo	CLB-LO	CLB-MOD	CLB-HI	CLB-ALL
Mild-Mod-Sev	ALL	169					
Treatment-	EM	126	17 (50)	14 (56)	25 (71)	23 (72)	62 (67)
Related AE, n	IM	36	5 (38)	3 (33)	6 (75)	6 (100)	15 (65)
(%)	PM	7	0 (0)	2 (100)	0 (0)	4 (100)	6 (100)
Mod-Sev	ALL	169	4 (8)	5 (14)	13 (30)	15 (36)	33 (27)
Treatment-	EM	126	4 (12)	4 (16)	9 (26)	12 (38)	25 (27)
Related AE,	IM	36	0	1 (11)	4 (50)	1 (17)	6 (26)
Days 1-21, n (%)	PM	7	0	0	0	2 (50)	2 (33)
P-value based on Kruskal-Wallis or Fisher's exact test							

Comment: Efficacy and safety analyses in PMs are limited by a small number of patients. Consequently, conclusions regarding the effect of CYP2C19 phenotype on clobazam efficacy or safety are not definitive. Considering the drug is titrated to tolerability and effect, and that CLB concentrations also contribute to the efficacy and safety, it is reasonable to believe that CYP2C19 has a limited contribution to the efficacy or tolerability of clobazam. The results should be interpreted with caution because of the small sample size.

$C_{avg,ss}$ from OV-1022 was used to compute the ratio of parent to metabolite (left figure) and overall systemic active drug exposure (right figure). Poor metabolizers had consistently lower ratio of parent CLB to N-CLB, as would be expected given the very high exposure to the metabolite. Extending these findings, total active drug (CLB+1/3 N-CLB) was significantly higher in PMs compared to EMs and IMs.

Figure 3. Parent:Metabolite ratio (left) and total CLB+N-CLB activity (right) in OV-1022



Comment: Systemic exposure to active drug appears to be higher in CYP2C19 PMs, which is consistent with the lack of phenotypic effects on parent compound and 5-fold increase in N-CLB concentrations in CYP2C19 PMs. Despite the lack of differences in AE rates, exposure increases in this range may still warrant dose modification if CYP2C19 genotype is known.

3.1.4 Published information

The pharmacokinetics of clobazam and N-CLB were previously evaluated in a study of 16 Japanese patients between the ages of 1.5 and 33 years. All the patients in this study were concomitantly receiving other antiepileptic drugs. Of these 16 patients, 3 patients were classified as CYP2C19 PMs. The authors reported significant differences in the ratio of N-CLB to clobazam concentrations based upon CYP2C19 genotype. The ratio of N-CLB to clobazam was 6 times higher in patients with two copies of the CYP2C19 variant alleles. The authors

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concluded that CYP2C19 genotype was the major determinant of the steady-state concentration of N-CLB.(Kozaki K, 2004 PMID 15533655)

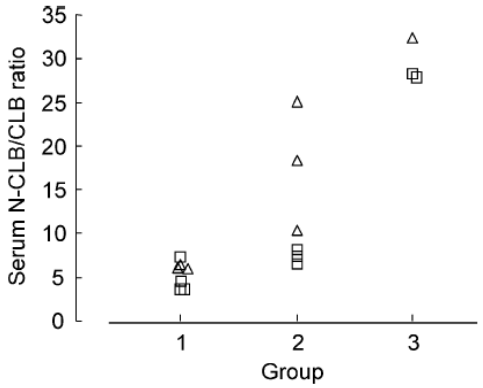

Figure 4. Gene-dose effect of CYP2C19 polymorphism on the serum N-CLB/Clobazam concentration ratio. Group 1 = CYP2C19 *1/*1, Group 2 = *1/*2 or *1/*3, Group 3 = *2/*2, *2/*3 or *3/*3

A retrospective study of 110 Japanese patients with epilepsy, which contained 23% CYP2C19 PMs, found no significant difference in terms of adverse effects across EMs, IMs, and PMs (Table 4 below). The duration of clobazam treatment ranged from 0.1 to 6.0 years. Patients with both generalized and partial seizures were included. However, this same study found significant differences in the efficacy in the reduction of seizure from clobazam based on CYP2C19 genotype (Table 5 below). (Seo T, 2008 PMID: 1846600).

Table 4. Association between CYP2C19 genotypes and adverse reactions

Adverse reaction	Homozygous EMs (n = 41)	Heterozygous EMs (n = 44)	PM (n = 25)	p-value
Drowsiness	13 (31.7%)	13 (29.5%)	10 (40.0%)	0.13
Dizziness	1 (2.4%)	4 (9.1%)	4 (16.0%)	0.12
Weight gain	1 (2.4%)	3 (6.8%)	4 (16.0%)	0.12
Hypersalivation	2 (4.9%)	3 (6.8%)	1 (4.0%)	1.00
Others*	3 (7.3%)	3 (6.8%)	3 (12.0%)	0.75

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Table 5. Association between CYP2C19 genotypes and responder rate for clobazam therapy

Characteristic	Observed (n [%])	Unadjusted ORs (95% CI)	p-value	Adjusted ORs* (95% CI)	p-value
≥50% reduction					
Homozygous EMs	13 (33.3)	1		1	
Heterozygous EMs	20 (47.6)	1.82 (0.74–4.47)	0.19	2.53 (0.88–7.29)	0.09
PM	15 (65.2)	3.75 (1.27–11.11)	0.02	9.88 (2.47–39.56)	0.001
≥75% reduction					
Homozygous EMs	12 (30.8)	1		1	
Heterozygous EMs	19 (45.2)	1.86 (0.74–4.62)	0.18	2.91 (0.98–8.60)	0.05
PM	14 (60.9)	3.50 (1.19–10.29)	0.02	7.70 (2.09–28.32)	0.002
Seizure freedom					
Homozygous EMs	3 (8.1)	1		1	
Heterozygous EMs	10 (23.8)	3.54 (0.89–14.04)	0.07	6.12 (1.05–35.73)	0.04
PM	5 (21.7)	3.15 (0.67–14.70)	0.15	7.83 (1.12–54.74)	0.04

Comment: Published literature is consistent with the data included in the applicant's submission.

4 Summary and Conclusions

4.1 CYP2C19 PMs have 3-5 times higher plasma exposures to the active metabolite of clobazam (N-CLB) compared to EMs. Some literature reports have found that CYP2C19 PMs may have upwards of a 6-fold increase in N-CLB when compared to CYP2C19 EMs (Kozaki K, 2004 PMID 15533655).

4.2 Available data seem to suggest that clobazam has a reasonably wide therapeutic margin considering the range of doses that have been tolerated in clinical trials. The most common adverse events are related to sedation/somnolence. These adverse events are related to both CLB and N-CLB exposure. The efficacy of clobazam is also related to CLB and N-CLB exposures.

4.3 Clobazam is titrated to effect, starting at 10 mg daily for subjects > 30 kg and 5 mg daily for < 30 kg. A 4-fold increase in exposure at this dose would still be within the range of exposures for the targeted dose range of 20-40 mg/d, which is lower than doses studied in clinical trials. High exposures might be expected to impact tolerability in the titration period. We found no evidence for such effect on AE rates or discontinuation in the pivotal efficacy and safety trial. However, the results should be viewed with caution because of the small sample size.

4.4 Poor metabolism is likely to represent the worst case scenario for N-CLB exposure changes. Despite the limited data available for CYP2C19 PMs, 5-fold higher N-CLB exposures in PMs did not appear to translate to significant untoward effects in the pivotal efficacy trial. However, given the increased exposure and half-life of N-CLB in CYP2C19 PMs, clobazam should be titrated cautiously in these patients.

4.5 Recommending dose adjustment based on genotype implies that patients are tested in advance of administering the drug. All patients would have to be genotyped to adjust

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doses for ~3% of the population. However, considering the magnitude of the exposure increase in PMs, starting at a lower dose and extending the titration interval should be considered in patients who are known to CYP2C19 PMs.

5 Recommendations

Despite the wide therapeutic index for clobazam and the main adverse effect being limited to sedation/somnolence, caution should still be exercised when administering clobazam to patients who are known CYP2C19 PMs. Due to the degree of exposure increase of the active metabolite (N-CLB) in CYP2C19 PMs, consider starting at the minimal dose and extending the titration interval in these patients. The label for Clobazam should contain the following updates based upon the current review.

5.1 Post-marketing Studies

None.

5.2 Labeling

Label recommendations are detailed below. Insertions are underlined, deletions are ~~strikethrough~~.

2.3 CYP2C19 Poor Metabolizers

(b) (4)

12.3 Pharmacokinetics

…

Metabolism and Excretion

(b) (4)

The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethylclobazam (See 12.5 Pharmacogenomics).

….

(b) (4)

…

12.5 Pharmacogenomics

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The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-CLB. Compared to extensive CYP2C19 metabolizers, N-CLB AUC and Cmax are approximately 3-5 times higher in poor metabolizers (e.g., subjects with (b) (4) 2 times higher in intermediate metabolizers (e.g., subjects with *1/*2 genotype; (b) (4) subjects studied). The prevalence of CYP2C19 poor metabolism differs depending on racial/ethnic background. The systemic exposure of clobazam is similar between CYP2C19 poor and extensive metabolizers.

Reference ID: 3026076

4.3 OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202067**	**Brand Name**	**Onfi**
OCP Division (I, II, III, IV, V)	**DCP-1**	**Generic Name**	**Clobazam**
Medical Division	**HFD-120**	**Drug Class**	**Anticonvulsant**
OCP Reviewer	**Seongeun (Julia) Cho Ph.D.**	**Indication(s)**	**Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥2 years of age**
OCP Team Leader	**Angela Yuxin Men, M.D., Ph.D.**	**Dosage Form**	**Tablet: 5, 10, or 20 mg**
Pharmacometrics Reviewer **PM Team Leader** **Pharmacogenomics Reviewer** **GG Team Leader**	**Joo-Yeon Lee, Ph.D.** **Yaning Wang, Ph.D.** **Hobart Rogers, Pharm.D., Ph.D.** **Michael Pacanowski, Pharm.D., M.P.H.**	**Dosing Regimen**	• **Children over 2 years of age and ≤30 kg body weight: 5 mg QD initially and doses titrated at weekly intervals to a target dose of 10-20 mg/day.** • **Patients >30 kg: 10 mg daily (5 mg BID) and doses titrated at weekly intervals to a target dose of 20-40 mg/day.** • **Doses above 5 mg/day to be administered in two divided doses.**
Date of Submission	**12/23/2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**8/16/11**	**Sponsor**	**Lundbeck Inc**
Medical Division Due Date	**8/23/2011**	**Priority Classification**	**S**
PDUFA Due Date	**10/23/2011**		

Clin. Pharm. and Biopharm. Information

Summary:
Clobazam, 1,5–benzodiazepine, is being currently pursued for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in US. It is approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide. Lennox-Gastaut

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syndrome is a severe childhood epileptic encephalopathy characterized by a slow spike and wave electroencephalogram (EEG), multiple seizure types (predominantly the tonic, atonic, and atypical absence variety), and usually an abnormal developmental state and behavioral disturbances. Onset of LGS generally occurs between 3 and 8 years of age, with peak occurrence between 3 and 5 years. Most patients continue to have refractory epilepsy and continued neurocognitive impairment that persists into adulthood. Orphan drug designation was granted for clobazam in 2007.

The current NDA submission consists of Lundbeck-sponsored nonclinical and clinical studies, including in vitro studies, clinical pharmacology studies, Phase 2, and Phase 3 studies. A Phase 2/3 open-label extension study is ongoing.

Efficacy Clinical Trials in the submission

- Phase 3, randomized, double-blind, placebo-controlled, parallel-group (Study OV-1012)
- Phase 2, randomized, double-blind, dose-ranging, parallel-group (Study OV-1002)
- Phase 2/3, ongoing, uncontrolled, open-label extension for subjects who participated in Studies OV-1002 and OV-1012 (Study OV-1004)

Clinical pharmacology development program

In vitro studies

Reference ID: 3026076

Study Type	Method of Administration	Species	Compound Administered	Reference
In vitro, plasma protein binding	In vitro, spiked plasma	Human plasma	Clobazam, N-CLB	OVNC-9015
Ex vivo, plasma protein binding	Plasma from subjects administered clobazam in Study OV-1032	Human plasma from healthy volunteers and renally impaired subjects	Clobazam, N-CLB	OVNC-9065
In vitro induction, human hepatocytes	In vitro, spiked primary cultured human hepatocytes	Human, (hepatocytes)	Clobazam, N-CLB	OVNC-9007
In vitro, inhibition, human liver microsomes	In vitro, spiked human microsomes	Human (liver microsomes)	Clobazam, N-CLB	OVNC-9006
In vitro metabolite profiling, cryopreserved human hepatocytes	In vitro human hepatocytes	In vitro human hepatocytes	N-CLB	OVNC-9070
In vitro, human liver and intestinal microsomes, glucuronidation of 1-OH midazolam	In vitro, spiked human microsomes	Human (liver and intestinal microsomes)	Clobazam, N-CLB	OVNC-9068
In vitro, P-gp	In vitro, spiked MDCK cells	Human MDR1 receptors in Maden-Darby Canine Kidney (MDCK) cells	Clobazam, N-CLB	OVNC-9024
Identification of clobazam and metabolites	Ex vivo, samples from Study OV-1038	Human plasma and urine	Clobazam, metabolites	7802-135
In vitro metabolism, human recombinant UGT enzymes	In vitro, recombinant human UGT enzymes	Human UGT enzymes	Clobazam, N-CLB	OVNC-9067

Clinical pharmacology studies

Study Type	Study Title	Reference
Single dose		
Bioequivalence	The bioequivalency evaluation of two clobazam 5 mg tablet formulations	OV-1016
Relative Bioavailability	Evaluation of the relative bioavailabilty of oral clobazam tablets and oral clobazam solution following 20 mg doses in healthy subjects	OV-1017
Food effect on absorption	The effects of applesauce or a high fat meal on the oral bioavailability of clobazam	OV-1018
Drug Interaction	The effect of multiple doses of ketoconazole or omeprazole on the single dose pharmacokinetic profile of clobazam in healthy adult subjects	OV-1021

Reference ID: 3026076

Multiple Dose		
Effect on cardiac function	A double-blind, double-dummy, randomized, parallel trial in healthy subjects assessing the ECG effects of clobazam following a therapeutic and supratherapeutic dose compared to placebo with moxifloxacin as the active control	OV-1022
Drug interaction: cocktail study	An open-label, multiple-dose study to assess the effects of clobazam on the pharmacokinetics of midazolam, caffeine, tolbutamide, and dextromethorphan in healthy volunteers	OV-1023
Tolerability and safety	The safety, tolerability, and pharmacokinetic evaluation of clobazam following administration of multiple ascending twice daily doses of clobazam tablets in healthy volunteers	OV-1038
Metabolism	Metabolism of clobazam in humans following single and multiple dose administration	PK-MB-001
Special population	The effect of renal impairment on the pharmacokinetics of clobazam	OV-1032

Additional Clinical Studies Performed by the Previous Sponsor (different formulations)

Healthy Subject Pharmacokinetic Studies	
Comparative bioavailability, single dose 40 mg, tablet, capsule, solution	LC-001
Bioequivalency, single dose 10 mg, capsules with/without starch	LC-002
Bioequivalency, single dose, 10 mg, tablets, capsules	LC-003
Multiple dose study of clobazam, 30 mg/day	LC-008
Dose proportionality, 10 mg, 20 mg and 40 mg	LC-010
Healthy Subject, Metabolism Studies	
Metabolite profiling, samples from LC-006	LC-004
Mass balance, single 39mg ^{14}C-clobazam (carboxyl label)	LC-006
Mass balance, single dose 20 mg ^{14}C-clobazam (methyl label)	LC-007

Reference ID: 3026076

Healthy Subjects, Pharmacodynamic Studies	
Effect on motor performance, single dose 30 mg	LC-005
CNS depressant effect and the effect on motor-coordination of the benzodiazepines clobazam and diazepam	LC-013
Effect on awake state EEG, single dose 20 mg and multiple dose 40 mg/day	LC-014
Effect on psychomotor performance, Critical Flicker Fusion and measures of anxiety, single dose 20 mg	LC-015
Anxiolytic and sedative effects, and effect on psychomotor performance and morning arousal after evening dose, 20 mg	LC-016
Effect on psychomotor performance, single dose 10 mg and multiple doses of 10 mg/kg	LC-017

Exposure-Response/ population PK analysis
Using efficacy data from Study OV-1012, Population PK analysis was conducted. A pharmacokinetic model was developed to determine the exposure-response relationship for clobazam and/or N-CLB and the primary endpoint of fractional reduction in number of drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period.

Formulations
The formulation used in the clinical development program are (b) (4) tablets containing 5, 10, or 20 mg clobazam manufactured in Winchester, Kentucky by Catalent Pharma Solutions with exception of a Phase 2 study. A Phase 2 study (OV-1002) used an (b) (4) tablet containing 5 mg clobazam manufactured in (b) (4) (b) (4)

Bioanalytical methods:
A validated LC/MS/MS method is used to quantitate clobazam and N-CLB in both plasma and urine.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Sponsor provided Word file and PDF file for labeling
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			LC-006: single 39mg 14C-clobazam
Isozyme characterization:	X			

Reference ID: 3026076

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Blood/plasma ratio:	-			
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			OV-1016 OV-1017 OV-1018 OV-1021
multiple dose:	X			OV-1022 OV-1023 OV-1038 OV-1032
Patients-				
single dose:				
multiple dose:	X			OV-1002 OV-1012
Dose proportionality -				OV-1018
fasting / non-fasting single dose:	X			LC-010
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			OV-1021 Ketoconazole, omeprazole,
In-vivo effects of primary drug:	X			OV-1023 drug cocktail
In-vitro:	X			9 studies (CYP, p-gp, UGT, protein binding)
Subpopulation studies -				
ethnicity:	X			Population PK
gender:	X			Population PK
pediatrics:	X			Population PK
geriatrics:				No specific assessment - population PK
renal impairment:	X			OV-1032 Single- and multiple dose, mild and moderate
hepatic impairment:	X			Literature report Mild and moderate (possible severe)
PD -				
Phase 2:	X			OV-1002
Phase 3:	X			OV-1012
PK/PD -				
Phase 1 and/or 2, proof of concept:				OV-1002
Phase 3 clinical trial:	X			OV-1012
Population Analyses -				
Data rich:	X			Rich data from Phase 1 studies
Data sparse:	X			Sparse data from Phase 2/3 study
II. Biopharmaceutics				
Absolute bioavailability				

Reference ID: 3026076

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Relative bioavailability -				
solution as reference:	X			
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies	X			OV-1018
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X			CYP2C19 Population analysis on Phase 3 data
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		39 study, validation, and literature reports submitted	40 reports reviewed, including 4 literature reports	9 in vitro 13 PK 2 PopPK 14 validation report (assays and metabolite ID) Literature (hepatic impairment)

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes			
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Yes			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Yes			
5	Has a rationale for dose selection been submitted?	Yes			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Yes			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Yes			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Yes			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	Yes			

Reference ID: 3026076

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	Yes			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	Yes			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	Yes			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		No		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Provide the QC validation reports for the legacy studies (e.g., LC-010). If they were submitted, please identify the location of the files.
- We request you to make reference to each statement/conclusion in the Clinical Pharmacology and Biopharmaceutics Review Aid with the study number and a link to the study report. For example, most statements in the sections of 2.4.2.1 Absorption and 2.4.3. Mass balance are missing study reference.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Reference ID: 3026076

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TA-CHEN WU
10/07/2011

YUXIN MEN on behalf of SEONGEUN CHO
10/07/2011

JOO YEON LEE
10/07/2011

YANING WANG
10/08/2011

HOBART ROGERS
10/08/2011

MICHAEL A PACANOWSKI
10/08/2011

YUXIN MEN
10/09/2011

MEHUL U MEHTA
10/09/2011

BIOPHARMACEUTICS REVIEW (Review # 2) Office of New Drugs Quality Assessment			
Application No.:	NDA 202-067	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	12/23/2010		
Division:	Division of Neurology Drug Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Lundbeck Inc. 4 Parkway North Suite 200, Deerfield, IL 60015	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	Onfi™	**Date Assigned:**	12/15/2010
Generic Name:	Clobazam	**Date of Review:**	08/01/2011
Indication:	Lennox Gastaut Syndrome (LGS)	**Type of Submission:** Original NDA 505(b)1	
Formulation/strengths	Tablet 5 mg, 10 mg and 20 mg		
Route of Administration	Oral		

HISTORY AND SUBMISSION:

Clobazam (Ph. Eur. BP) is an anti-convulsant currently marketed under the trade name of Frisium® (by Sanofi Aventis) in more than 80 countries (except in US) including Canada for the treatment of Lennox Gastaut Syndrome (LGS). The applicant has submitted this NDA under the 505 b (1) regulatory provision in order to manufacture (by Catalent Pharma Solutions in Winchester, Kentucky) and market in the US under the proposed trade name, Onfi™. The initial IND pertaining to this drug was submitted on 25th May, 2005 (IND # 70,125). (b) (4) (b) (4) Compendial pharmaceutical grade inactive ingredients such as corn starch, lactose monohydrate, magnesium stearate, talc and silicone dioxide were used in the formulation. During development, however, the applicant used a second tablet formulation for the Phase 2 studies. The Phase 2 product was manufactured by (b) (4) (b) (4) Phase 2 tablets were qualitatively and quantitatively different from the commercial formulation (b) (4) The applicant states that the Phase 2 and Phase 3 formulations are bioequivalent. However, the BE study was conducted using the 20 mg of the phase 3 formulation and 5 mg of the phase 2 formulation (4x5 mg tablets = 20 mg). (b) (4)

REVIEW:

The first biopharmaceutics review (dated 4/11/2011) was conducted on the sponsor's "report on the dissolution comparison of 5, 10 and 20 mg immediate-release clobazam

Reference ID: 2981859

tablets in three dissolution media at pH 1.0, pH 4.5 and pH 6.8". Based on the data provided, the reviewer concluded the dissolution specification as "not acceptable" and proposed a dissolution specification of (b) (4) The reviewer also asked for the submission of details of the dissolution method development. The following two questions were sent out on 12th April, 2011:

FDA Request No. 1
Provide details of the dissolution method development such as; justification of the apparatus, rotation speed, choice of volume and discriminating power (e.g. API particle size effect, effect of critical formulation and process parameters).

Sponsor Response:
The sponsor responded on 4/22/2011 and said that the already existing analytical methods were transferred and revalidated at (b) (4) (b) (4) in order to preserve the same testing regimen that had been historically used for the (b) (4) tablets in the rest of the world markets. Therefore, no formal method development was necessary for the dissolution method. The sponsor also mentioned that the dissolution method parameters such as apparatus type and paddle speed were not investigated because it was desired to minimize changes to the method in order to make meaningful comparisons between tablets manufactured at the proposed US manufacturing site and those manufactured at the (b) (4) the rest of the world markets. The volume of the method was investigated and the sponsor justified that since clobazam has ~0.1 mg/mL solubility, sink conditions are obtained for the 20 mg tablet in 900 mL of media. The effect of pH was found to be minimal and a report describing the effect of dissolution
media pH. The effect of API particle size was not investigated directly (b) (4) (b) (4)

The sponsor submitted the following dissolution summary in their response:

Table 1. Average dissolution data (75 rpm, 45 min in 0.1N HCl, n=6) for registration stability/clinical batches at release.

Tablet Batch Number - Strength	API batch number	(b) (4) Batch Number	% Dissolution Result at Release (b) (4)	Average % Dissolution, %RSD
0701322 – 5 mg	N002	0701317		92%, 1.0%
0701323 – 10 mg		0701318		90%, 3.2%
0701324 – 20 mg				92%, 1.5%
0800960 – 5 mg	B008	0800949		76%, 2.6%
0800959 – 10 mg				75%, 1.6%
0800957 – 20 mg	B008/B009	0800950		91%, 1.7%
0804077 – 5 mg	B007/B009	0804069		83%, 4.3%
0804076 – 10 mg	B007	0804070		87%, 3.5%
0804075 – 20 mg	B009	0804071		87%, 5.5%

Reference ID: 2981859

Table 2. Average Dissolution Results (75 rpm, 45 minutes in 0.1 N HCl, n=6) for Registration Stability/Clinical Batches Stored at 25°C/60% RH

Batch #	Time, months							
	0	3	6	9	12	18	24	36
0701322 (5 mg)	92%	93%	96%	97%	96%	93%	95%	95%
0701323 (10 mg)	91%	91%	90%	92%	92%	93%	91%	92%
0701324 (20 mg)	93%	91%	93%	94%	94%	91%	93%	90%
0800960 (5 mg)	76%	75%	75%	76%	75%	79%	76%	NR
0800959 (10 mg)	79%	78%	78%	78%	78%	80%	78%	NR
0800957 (20 mg)	94%	93%	94%	92%	94%	96%	92%	NR
0804077 (5 mg)	85%	83%	84%	84%	83%	82%	NR	NR
0804076 (10 mg)	90%	89%	91%	90%	91%	90%	NR	NR
0804075 (20 mg)	86%	86%	86%	88%	87%	85%	NR	NR

NR = not yet reported

Evaluation: Acceptable.

FDA Request No. 2

Based on the dissolution data provided, it is observed that almost (b) (4) of the active pharmaceutical ingredient is released from the tablets in less than 30 minutes. Therefore, tighten your dissolution limit from Q= (b) (4) to Q= (b) (4)% in 30 min.

Sponsor Response:

The sponsor responded on 4/22/2011 and said that for some batches they have observed (b) (4)% release in 30 min and therefore justifying their proposed dissolution limit as Q= (b) (4)% in (b) (4) The sponsor also has submitted the following data in support of their response:

Table 3. Average Dissolution Profile Results (n=6) for Engineering Batches 1002587 (5 mg) 1002588 (10 mg) and 1002589 (20 mg)

Tablet Strength	% dissolved			
	15 minutes	30 minutes	45 minutes	60 minutes
5 mg	72%	84%	90%	96%
10 mg	70%	82%	89%	94%
20 mg	76%	82%	88%	91%

Statistical treatment of the release results for all nine batches reveals the following:

Average dissolution result at release: 86%
Standard deviation: (b) (4)%
3 standard deviations: (b) (4)%

Based on this analysis, a reasonable lower limit would be (average – 3s) or (b) (4)%. This is equal to the stage 1 requirement for Q = (b) (4) which is lower than the currently proposed Q = (b) (4)%. The current limit of Q (b) (4) is therefore imposing a tighter limit that this analysis would suggest.

Evaluation: *The reviewer was in disagreement with the sponsor and sent out the following deficiency.*

Reference ID: 2981859

FDA Request No. 3

We do not agree to your proposed dissolution limit. Based on the data provided, the lowest average dissolution data was (b) (4) from batches # 0800959, 0800960 which were not used in clinical studies. Batches used for the clinical studies (e.g. # 0701322) showed faster dissolution profile (average of ~ (b) (4) %). Therefore your proposed dissolution limit of Q = (b) (4) is not acceptable. We suggest that you revise your dissolution limit based on the actual dissolution data used for clinical studies or provide in vivo PK data showing that lots with Q of (b) (4) % drug release in 45 min will be still bioequivalent to the clinical batches.

Sponsor Response:

On The sponsor responded to the agency and said that batches 0800959 and 0800960 were actually used in a currently ongoing clinical study OV-1004 which is an open label efficacy study. Based on the data of these clinical batches, the sponsor has revised the limit as follows:

Q= (b) (4)

Evaluation: *The sponsor's proposed dissolution limit of Q= (b) (4) covers the lower limit on the batches (0800959 and 0800960) used in clinical trials (OV-1004, efficacy trial).Therefore, this limit can be considered clinically relevant since it was based on the performance of the lots used in the pivotal clinical trials. Additionally, all the stability data of the registration batches meets the lower side of the proposed limit.*

OVERALL CONCLUSION:

- Proposed dissolution method: **Acceptable.**
- Proposed dissolution limit: **Acceptable.**

Akm Khairuzzaman, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick Marroum Ph.D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: Angelica Dorantes, Ph.D.

Reference ID: 2981859

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AKM KHAIRUZZAMAN
08/04/2011
Acceptable from Biopharmaceutics point of view

PATRICK J MARROUM
08/04/2011

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

Pharmacovigilance Review

Date:	August 2, 2011
Reviewer(s):	Kelley M. Simms, PharmD, BCPS Division of Pharmacovigilance I
Team Leader:	Cindy Kortepeter, PharmD Division of Pharmacovigilance I
Deputy Division Director:	Ann McMahon, MD, MS Division of Pharmacovigilance I
Drug Name(s):	Clobazam
Application Type/Number:	NDA: 202067
Applicant/sponsor:	Lundbeck Inc.
OSE RCM #:	2011-1800

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EXECUTIVE SUMMARY

The Controlled Substance Staff (CSS) requested that the Office of Surveillance and Epidemiology (OSE) review foreign databases regarding misuse, abuse and overdose associated with clobazam. The Division of Pharmacovigilance-I was tasked with assessing cases suggestive of abuse, misuse and overdoses reported in association with clobazam use from the Agency's Adverse Event Reporting System (AERS) database as well as the World Health Organization (WHO) VigiBase database. VigiBase contains individual safety case reports submitted from member countries in the WHO International Drug Monitoring Programme.

An extensive search of the AERS database captured only two cases of overdose reported in association with clobazam for hands-on review. There were no cases of abuse or misuse in AERS. The first overdose case occurred in a patient with renal insufficiency who presumably had higher than necessary serum concentrations of several drugs due to his declining renal function. The second overdose case occurred as a consequence of a medication administration error by a healthcare provider. The WHO VigiBase database provided a handful of cases of drug dependence, overdose, and abuse; however, without narratives, it is not possible to assess these cases. Based on the findings from these 2 databases, there does not appear to be overwhelming evidence of abuse, misuse, or overdose with clobazam.

Reference ID: 2982716

1 BACKGROUND

1.1 INTRODUCTION

The Controlled Substance Staff (CSS) requested that the Office of Surveillance and Epidemiology (OSE) review foreign databases regarding misuse, abuse and overdose associated with clobazam. The Division of Pharmacovigilance-I was tasked with assessing cases suggestive of abuse, misuse and overdoses reported in association with clobazam use from the Agency's Adverse Event Reporting System (AERS) database as well as the World Health Organization (WHO) VigiBase database.

VigiBase is the name of the WHO global individual case summary reports database. VigiBase contains individual safety case reports submitted from member countries in the WHO International Drug Monitoring Programme from 1968 until today. National and regional centers in all official and associate member countries can have free access to the data in VigiBase through the search tool VigiSearch, or by requesting special searches from the Uppsala Monitoring Centre (UMC). For national and regional center users no narratives or laboratory values are available. Only members of the UMC Signal Review panel and employees at the UMC have full access to the data, including report narratives and laboratory values.[1] To date, the database contains more than six million case reports.

According to the Federal Food, Drug, and Cosmetics Act (FDCA), if potential for abuse exists, the following abuse-related data must be included in the New Drug Application (NDA) for review:

- *All data pertinent to abuse of the drug*
- *Proposal for scheduling under the Controlled Substance Act (CSA)*
- *Data on overdose*

Because the evaluation of new drugs for abuse potential is based upon a comprehensive and interdisciplinary review, all postmarketing reports of abuse, misuse, overdose, and diversion related to the product should be reviewed.[2]

1.2 REGULATORY HISTORY

Clobazam is "used in treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide."[3] Clobazam has been marketed as an anxiolytic since 1975 and as an antiepileptic since 1984. As a benzodiazepine derivative, clobazam is considered a drug of significant abuse in some countries.[4] The current NDA is being

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[1] The Uppsala Monitoring Centre FAQs – The WHO Global ICSR database. [online] http://who-umc2010.phosdev.se/DynPage.aspx?id=101247&mn1=7347&mn2=7252&mn3=7258

[2] The Controlled Substance Staff: An Integral Part of the 21st Century Review Team. Regulatory Project Manager's Seminar. January 12, 2011.

[3] Summary of Clinical Safety. Clobazam. Lundbeck Inc. 12 November 2010.

[4] WHO Review Group (1983). Use and abuse of benzodiazepines. Bull World Health Organ (World Health Organisation) 61 (4): 551-562.

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reviewed by the FDA for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS). At this time, five antiepileptic drugs are approved by the FDA for treatment of seizures associated with LGS: clonazepam, felbamate, lamotrigine, topiramate, and rufinamide.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

We searched the Adverse Event Reporting System (AERS) database using the strategy in Table 1.

Table 1: AERS Search Strategy	
Date of search	May 26, 2011
Data lock date	April 30, 2011
Active ingredient	Clobazam
MedDRA PTs	Drug withdrawal syndrome, Dependence, Drug abuse, Drug abuser, Drug dependence, Drug diversion, Drug withdrawal syndrome neonate, Intentional overdose, Intentional drug misuse, Polysubstance abuse, Withdrawal syndrome, Multiple drug overdose, Substance abuse, Substance abuser, Drug tolerance, Drug tolerance increased, Tachyphylaxis, Overdoses, Neonatal complications of maternal substance abuse, Drug and chemical abuse, Poisoning deliberate, Euphoric mood, Agitation, Elevated mood, Feeling abnormal, Feeling drunk, Dizziness, Thinking abnormal, Hallucination, Inappropriate affect, Somnolence, Depersonalisation, Psychomotor hyperactivity, Affective disorder

2.2 WHO DATABASE

On May 4, 2011, the VigiBase database was searched for all PTs coded in reports possibly associated with clobazam. VigiBase is an adverse event report search tool utilized by the Uppsala Monitoring Centre in Sweden. Uppsala Monitoring Centre is an independent foundation providing International Drug Monitoring for the WHO.

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3 RESULTS

3.1 AERS CASES

The AERS search resulted in 106 reports coded with the MedDRA PTs from the search strategy described in Table 1. Only two cases remained for detailed analysis in this review after excluding reports for the following reasons:

- Duplicate reports (n=2)
- Misuse of multiple medications (n=20)
- No misuse, abuse, overdose or diversion of clobazam reported (n=82)

Case Descriptions (n=2)

ISR 5074834, Foreign: A 67-year-old male with epilepsy and chronic renal insufficiency "developed idiokinetic and speech slowing down with severe asthenia." At the time of event he was taking phenytoin, carbamazepine, clobazam, ramipril, nifedipine and pentoxifylline. He was hospitalized with a diagnosis of phenytoin, carbamazepine and clobazam overdosage. The dosages of phenytoin and carbamazepine were reduced, and unspecified potentially nephrotoxic drugs were discontinued. The patient's condition was improving at the time of reporting.

Reviewer comment: This patient with chronic renal insufficiency experienced a supratherapeutic level of clobazam presumably without overdose.

ISR 6296230, Foreign: A 40-year-old male was reportedly taking the following medications: lamotrigine, valproic acid, and omeprazole. One evening the nurse mistakenly administered oxcarbazepine, clobazam, hydroxyzine, risperidone, amoxicillin/clavulanic acid, and omeprazole to the patient in addition to his usual medications. The next morning, the patient experienced excessive sedation, arterial hypotension (80/55 mmHg), and hypothermia. The error was noted, and the patient was monitored the entire day. The following day, the patient fully recovered.

3.2 WHO DATABASE

Of approximately six million case reports in the database, there were (b) (4) reports retrieved from the VigiBase database, and (b) (4) PTs coded. As stated in the INTRODUCTION, none of the reports retrieved from the WHO database provided narratives. Appendix B contains a list of PTs coded in the clobazam reports and the number of reports associated with each PT.[5] The following PTs and counts (see Appendix B) may be of interest:

(b) (4)

[5] These data are crude data; therefore, duplicate reports may be included.

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(b) (4)

4 DISCUSSION

Drug abuse refers to a pattern of misuse or overuse of a drug without regard to health concerns. Drug misuse is the use of a drug for an unintended purpose or intended purposes, but in improper amounts. Drug overdose is an excess use of a drug beyond what is recommended. In the AERS case series, one case described a patient with chronic renal insufficiency who experienced a supratherapeutic level of clobazam presumably without overdose. The other case described a patient who was accidently administered clobazam by the nurse. Based on the AERS case series, there does not appear to be a consistent pattern of abuse associated with clobazam; however, clobazam is currently not approved in the United States (US), thus AERS reports with clobazam are of patients who used US-approved medications concomitantly.

Appendix A lists caveats of using the WHO database information. Of note, narratives from the WHO database cannot be viewed by those who are not members of the UMC Signal Review panel or employees at the UMC. Appendix B lists, alphabetically, PTs coded in clobazam reports and the number of reports associated with each PT. This data provides limited value as there is no certainty that clobazam caused the reported event. The event may have been related to the underlying disease being treated, may have been caused by some other drug/biologic product being used concomitantly, or simply may have occurred by chance while using clobazam. Finally, these data are crude data. Crude is a term used to describe reports that have not been de-duplicated, reviewed in detail for relevance or assessed for causal inference.

5 CONCLUSION

The AERS and WHO data that has been reviewed did not demonstrate unequivocal evidence of abuse potential associated with clobazam.

6 APPENDICES

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6.1 APPENDIX A: LIMITATIONS OF WHO (VIGIBASE) DATABASE DATA – CAVEAT DOCUMENT

CAVEAT DOCUMENT

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some national Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product.

Thus the sources of reports accepted by National Centres vary, as do the proportions. A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product caused the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO data base.

Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with

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respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i) of the source of the information,

(ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,

(iii) that the information does not represent the opinion of the World Health Organization.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

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6.2 APPENDIX B: WHO DATABASE (VIGIBASE) COUNT OF PTS REPORTED FOR CLOBAZAM TO DATA LOCK DATE MAY 4, 2011.

(b) (4)

7 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KELLEY M SIMMS
08/02/2011

CINDY M KORTEPETER
08/02/2011

ANN WARD W MCMAHON
08/03/2011
I concur.

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-067	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	12/23/2010		
Division:	Division of Neurology Drug Products	**Team Lead:** Angelica Dorantes, PhD	
Sponsor:	Lundbeck Inc. 4 Parkway North Suite 200, Deerfield, IL 60015	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	Onfi™	**Date Assigned:**	12/15/2010
Generic Name:	Clobazam	**Date of Review:**	04/06/2011
Indication:	Lennox Gastaut Syndrome (LGS)	**Type of Submission:** Original NDA 505(b)1	
Formulation/strengths	Tablet 5 mg, 10 mg and 20 mg		
Route of Administration	Oral		

HISTORY AND SUBMISSION:

Clobazam (Ph. Eur. BP) is an anti-convulsant currently marketed under the trade name of Frisium® (by Sanofi Aventis) in more than 80 countries (except in US) including Canada for the treatment of Lennox Gastaut Syndrome (LGS). The applicant has submitted this NDA under 505 b (1) regulatory provision in order to manufacture (by Catalent Pharma Solutions in Winchester, Kentucky) and market in US under the proposed trade name, Onfi™. The initial IND pertaining to this drug was submitted on 25th May, 2005 (IND # 70,125). (b) (4) (b) (4) Compendial pharmaceutical grade inactive ingredients such as corn starch, lactose monohydrate, magnesium stearate, talc and silicone dioxide were used in the formulation. During development, however, the applicant used a second tablet formulation for the Phase 2 studies. The Phase 2 product was manufactured by (b) (4) Phase 2 tablets were The applicant states that Phase 2 and Phase 3 formulations are bioequivalent. Ho wever, the BE study was conducted using the 20 mg of the phase 3 formulation and 5 mg of the phase 2 formulation (4x5 mg tablets = 20 mg). (b) (4)

BIOPHARMACEUTICS INFORMATION:

The solubility of clobazam in water is classified as "slightly soluble". Based on this information, the solubility/dose ratios values of all strengths of clobazam tablets (5 mg, 10

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mg and 20 mg) may result in drug dosage forms that could behave as a poorly soluble drug. The formulation composition is dose proportional across all the strengths. Since there was a formulation differences between the phase 2 and the commercial formulation (phase 2 formulation), the sponsor has conducted a BE study between the 20 mg tablet of the commercial formulation and the 5 mg phase 3 formulation (4x5 mg tablet). (b) (4)

Dissolution profiles were generated from twelve (12) tablets for the 5, 10, and 20 mg clobazam tablets at 5, 10, 15, 30, 45, and 60 minutes. Each tablet strength was run in each of the three dissolution media (0.1 N HCl for pH 1.0 medium, 0.1 M sodium acetate for the 4.5 pH, and 0.1 M sodium phosphate for the 6.8 pH), buffered to different pH, using USP <711> dissolution apparatus (b) (4) (b) (4) The results of the dissolution study were evaluated using a model independent approach such as similarity factor (f_2) and difference factor (f_1).

Dissolution development report:

The sponsor has identified dissolution as the product's target profile. The unit dose formulation (mg/tablet) is as follows:

Table 1. Clobazam Formulations Used in Clinical Trials

(b) (4) (Phase 2)			Catalent (Phase 3)		
Ingredient	**Amount, %**	**Amount, mg/tablet**	**Ingredient**	**Amount, %**	**Amount, mg/tablet[2]**
Clobazam	(b) (4)	5.00	Clobazam	(b) (4)	5.00
Lactose, (b) (4) NF		(b) (4)	Lactose monohydrate, NF/EP		(b) (4)
Starch (corn) NF			Corn starch, NF/EP		
(b) (4) (b) (4) NF			---		
(b) (4) silicon dioxide, NF			Silicon Dioxide, NF		
Magnesium Stearate, NF			Magnesium Stearate, NF/EP		
Talc, USP			Talc, USP/EP		
(b) (4)			(b) (4)		
Total					

[1] (b) (4)

[2] Amount shown in this table is for the 5 mg tablet. (b) (4) (b) (4)

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Commercial Formulation of all three strengths:

Table 1. Quantitative Composition of Clobazam Tablets

(b) (4)	Theoretical Quantity (mg/tablet)	Function	Quality Standard
Clobazam, (b) (4)	5.00 10.00 20.00 (b) (4)	(b) (4)	EP
Corn Starch			NF
Lactose Monohydrate (b) (4)			NF
Corn Starch (b) (4) (b) (4)			NF USP
Magnesium Stearate			NF
Talc			USP
Silicon Dioxide			NF
Total Tablet Weight:	(b) (4)		

(b) (4)

The proposed commercial formulation of Onfi® Tablets (phase 3 formulation (b) (4) All tablets proposed for commercialization will be (b) (4). During development, however, the applicant used a second tablet formulation for Phase 2 studies. As shown in the above table, Phase 2 tablets were qualitatively and quantitatively different from the commercial formulation (phase 3) (b) (4) (b) (4)

Proposed Dissolution Method:

(b) (4)

Dissolution test acceptance criteria:

TEST	METHOD	RELEASE SPECIFICATIONS
Dissolution	HPLC	Q(b) (4)%. For S1, 6 of 6 tablets NLT (b) (4) S2 and S3 as per USP.

Selection of the dissolution method and justification of the parameters:

Dissolution profiles were generated from twelve (12) tablets for the 5, 10, and 20 mg clobazam tablets at 5, 10, 15, 30, 45, and 60 minutes. Each tablet strength was run in each of the three dissolution media (b) (4)

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Dissolution data:
Dissolution data given by the sponsor is summarized below:

(b) (4)

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F & F comparison table.

(b) (4)

***Reviewer's comment*:**

(i) *Based on the dissolution data provided by the sponsor, it is observed that almost (b) (4) the drug had dissolved by 30 minutes time point from all strengths in all media. However, the 5 mg tablet curve was consistently higher (faster) than the 10 mg and 20 mg strength curves. But all dissolution curves beyond 30 minute time point appear to merge. On the other hand, the sponsor has set up a limit of not less than (NLT) (b) (4) % (Q) at time (b) (4) Such limit is not optimal due to the fact that the drug product releases of its active ingredients in less than 30 minutes.*

(ii) *There are no details of the dissolution method development found in the application. Following details need to be submitted by the applicant:*

Justification of apparatus
Justification of rotation speed
Justification for choice of volume
Discriminating power of the method

Evaluation: Not Acceptable.

Question to the sponsor:

(i) *Based on the dissolution data provided, it is observed that almost (b) (4) of the active pharmaceutical ingredient is released from the tablets in less than 30 minutes. Therefore, tighten your dissolution limit from Q (b) (4) % in (b) (4) min to Q (b) (4) % in 30 min.*

(ii) *Provide details of the dissolution method development such as; justification of apparatus, rotation speed, choice of volume and discriminating power (e.g. API particle size effect, effect of critical formulation and process parameters).*

Discriminatory potential of the proposed dissolution method:

The sponsor has not clarified whether the proposed dissolution method was optimal to distinguish critical formulation and process parameters. During technology transfer to Catalent Pharma Solutions in Winchester the process controls; both critical and noncritical parameters (b) (4) (b) (4) were derived from the data collected during manufacture of the nine registration batches of 5 mg, 10 mg and 20 mg clobazam tablets. However, no study on these parameters linking the proposed dissolution method was found in the application.

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Evaluation: Not Acceptable.
***Question to the reviewer**: See question # ii in previous page.*

Bio Waver: A bioequivalence study was conducted to evaluate two clobazam 5 mg tablet formulations (phase 2 vs. phase 3 formulations). Applicant concluded that a single 20 mg dose (4 × 5 mg tablets) of clobazam tablets manufactured by Catalent Pharma Solutions (test, phase 3 and commercial formulation) was bioequivalent to a single 20 mg dose (4 × 5 mg tablets) of clobazam tablets manufactured by (b) (4) (reference) (b) (4)

***Reviewer's evaluation:** Since the details of the dissolution method development was not submitted* (b) (4)

OVERALL CONCLUSION:

- Proposed dissolution method: **Not Acceptable.** Determination of the acceptability of the method will be made once the requested information is submitted and reviewed by the agency.
- Detailed information on the dissolution method development: **Not sufficient**.
- Dissolution specification: **Not acceptable**. Recommendation: Adopt a specification of Q= (b) (4)% in 30 minutes.

Questions need to be sent out to the sponsor:

1. *Provide details of the dissolution method development such as; justification of apparatus, rotation speed, choice of volume and discriminating power (e.g. API particle size effect, effect of critical formulation and process parameters).*
2. *Based on the dissolution data provided, it is observed that almost (b) (4) of the active pharmaceutical ingredient is released from the tablets in less than 30 minutes. Therefore, tighten your dissolution limit from Q= (b) (4)% in (b) (4) minutes to Q (b) (4)% in 30 min.*

Akm Khairuzzaman, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick Marroum Ph.D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: Angelica Dorantes, Ph.D.

Reference ID: 2928589

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AKM KHAIRUZZAMAN
04/11/2011
Not acceptable. Comments/deficiencies need to be communicated to the sponsor.

PATRICK J MARROUM
04/11/2011