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RESEARCH**

*APPLICATION NUMBER:*

**202067Orig1s000**

**SUMMARY REVIEW**

## MEMORANDUM

DATE: September 25, 2011

FROM: Director  
Division of Neurology Products/HFD-120

TO: File, NDA 202067

SUBJECT: Summary Memo for NDA 202067, for the use of ONFI (clobazam) Tablets, 5, 10, and 20 mg, for the adjunctive treatment of Lennox-Gastaut Syndrome (LGS) in patients 2 years of age and older

NDA 202067, for the use of ONFI (clobazam) Tablets, 5, 10, and 20 mg, for the adjunctive treatment of Lennox-Gastaut Syndrome (LGS) in patients 2 years of age and older, was submitted by Lundbeck, Inc. on 12/23/10. The application contains the results of two randomized controlled trials and safety data, as well as the requisite chemistry and manufacturing (CMC), pharmacology/toxicology, clinical pharmacology, and other data.

Clobazam is a 1,5 benzodiazepine that is currently approved for numerous indications, including epilepsy and anxiety disorders, in over 100 countries, first having been approved in 1970 in Australia. The current sponsor is Lundbeck, Inc., but much of the data (both safety and non-clinical) were generated by other sponsors many years ago. Considerable information is not available for some proportion of the safety and non-clinical data; this will have implications for our recommendations.

LGS is a severe form of childhood epilepsy, characterized by multiple seizure types, as well as abnormal development. It generally has an onset between the ages of 3 and 8 years, and can persist into adulthood. The most problematic seizure type are drop attacks, which may occur related to tonic, atonic, or myoclonic seizures, and may result in significant injury. For this reason, most clinical trials that evaluate treatments for LGS (including in this application) target drop attacks as their primary outcome.

The application has been reviewed by Dr. Philip Sheridan, medical reviewer, Dr. Ohidul Siddiqui, statistician, Dr. Gerard Boehm, safety reviewer, Dr. Sally Yasuda, safety team leader, the Interdisciplinary Review Team for QT Studies, Dr. Edward Fisher, pharmacologist, Dr. Lois Freed, pharmacology supervisor, Dr. Akm Khairuzzaman, chemistry reviewer, Drs. Seongeun Julia Cho and Ta-Chen Wu, clinical pharmacology reviewers, Dr. Hobart L. Rogers, genomics reviewer, Dr. Lubna Merchant, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Alicja Lerner, Controlled Substance Staff (CSS), Dr. Kelley Simms, Division of Pharmacovigilance I, Dr. Antoine El-Hage, Office of Scientific Investigations, and Dr. Norman Hershkowitz, neurology team leader and Cross

Discipline Team Leader (CDTL).

The clinical review team recommends that the application be approved. I will very briefly review the pertinent findings, and offer the division's recommendation for action on this application.

## **EFFECTIVENESS**

As noted above, the sponsor has submitted the results of two randomized controlled trials, OV-1012 and OV-1002.

### **OV-1012**

This was a randomized, double blind, parallel group trial in which patients 2-60 years old with LGS were randomized to receive one of three target doses (0.25 mg/kg/day [maximum daily dose of 10 mg], 0.5 mg/kg/day [maximum daily dose of 20 mg], or 1.0 mg/kg/day [maximum daily dose of 40 mg]). The doses were given in a BID dosing regimen. Patients were stratified according to their baseline weight: 12.5-30 kg or >30 kg.

Eligible patients entered a 4 week Baseline phase, a 3 week Titration Phase, and then a 12 Maintenance phase, followed by either a 2-3 week taper phase or entrance into a long-term, open-label extension. At the start of the Titration phase, all patients received a daily dose of 5 mg, which was increased every 7 days until the target dose was reached.

The primary outcome was the percent reduction in average weekly frequency of drop attacks during the Maintenance phase compared to the Baseline phase. Multiple secondary outcome measures were assessed, including:

- 1) change in weekly drop attacks between baseline and the last/first 4 weeks of the Maintenance phase
- 2) percent responders (>25%, >50%, >75%, 100% decrease in drop attacks)
- 3) percent responders during the last/first 4 weeks of Maintenance
- 4) change in total (drop and non-drop attacks) weekly seizure frequency
- 5) change in weekly frequency of non-drop attacks
- 6) an assessment of tolerance: a patient was considered a responder if he or she had at least a 50% reduction in drop attacks during the first 4 weeks of Maintenance compared to baseline. The number and percentage of responders who returned to their baseline seizure rate during the last 4 weeks of Maintenance, or those who discontinued for lack of efficacy were compared between groups. An analysis was also done using a definition of responder based on the first 8 weeks of Maintenance.
- 7) Physician, parent/caregiver globals

The primary analysis was to be an analysis of covariance (ANCOVA). According to the protocol, a hierarchical approach was to be taken, with the highest dose compared to placebo first, followed by comparisons of the mid- and low-doses, if each preceding comparison reached statistical significance. Each comparison to placebo was to be tested at alpha=1%, not the traditional 5%.

## Results

A total of 238 patients were randomized at 53 sites, primarily in the US (35 sites) and India (13 sites). The following table displays the disposition of patients in the study:

	Pla	LD	MD	HD
Randomized	59	58	62	59
Completed	41	50	45	41
D/C due to AE	2 (3%)	4 (7%)	8 (13%)	12 (20%)
D/C due to lack of effect	10	1	4	0

The majority of patients in each group were between the ages of 2 and 12 years (61%, 62%, 52%, and 58%, in the placebo, low-, mid-, and high-dose groups, respectively). The oldest patient was 59 years old; the next oldest was 49 years old.

The following table presents the results of the primary analyses for drop attacks:

	Pla	LD	MD	HD
N	57	53	58	49
Baseline				
Mean	97.8	99.6	60.5	105.2
Median	35.5	29.2	22.5	46.4
Percent Reduction				
Mean	12.5	41.6	47.8	69.5
Median	23.2	46.7	57.9	86.5
P-value		0.012	0.0015	<0.0001

Dr. Siddiqui presents the results of numerous sensitivity analyses accounting for multiple factors, including sites, missing data, etc. These results are presented in his Table 5, page 13 of his review. As can be seen there, the HD and MD are all significant at the 1% level for all analyses. The LD is nominally positive for numerous of the sensitivity analyses at, or close to, the 1% level, with several

more nominally positive at the 5% level, and not significant for several other analyses.

The following table presents the results of the analyses of the weekly frequency of the total (drop and non-drop) attacks:

	Pla	LD	MD	HD
N	57	53	58	49
Baseline				
Mean	117.1	131.1	111.5	128.7
Median	46.8	45.5	36.6	80.6
Percent Reduction				
Mean	10.1	36.8	42.2	66.2
Median	11.3	43.1	62.1	82.8
P-value		0.041	0.0044	<0.0001

There were no nominally statistically significant differences between any dose and placebo for the comparisons of weekly frequency of non-drop attacks for the primary ANCOVA analyses (though there were dose-related trends). However, there were nominally significant differences between HD and placebo when using a Wilcoxon rank-sum test ( $p=0.005$ ) and a rank ANCOVA analysis ( $p=0.007$ ).

The following table presents the results of analyses of the reduction in drop attacks between the first, middle, and last 4 weeks of Maintenance and Baseline for drug and placebo in completers:

	Pla	LD	MD	HD
Maintenance phase				
First 4 weeks				
N	57	53	58	49
Baseline median rate	35.5	29.2	22.5	46.4
Median % reduction	30.7	44.4	72.7	92.1
P-value		0.002	<0.001	<0.001
Middle 4 weeks				
N	47	52	53	44
Baseline median rate	25.8	28.9	23.5	45.4
Median % reduction	38.8	48.9	57.1	88.1
P-value		0.10	0.22	0.002
Last 4 weeks				
N	44	51	46	42
Baseline median rate	31.9	29.2	22.6	42.6
Median % reduction	35.6	46.8	69.2	89.0
P-value		0.15	0.016	0.002

At the request of Dr. Hershkowitz, the sponsor performed additional analyses of the time course of seizure response, utilizing the modified intent to treat population and last observation carried forward:

	Pla	LD	MD	HD
Maintenance phase				
First 4 weeks				
N	57	53	58	49
Baseline median rate	35.5	29.2	22.5	46.4
Median % reduction	30.7	44.4	72.7	90.7
P-value		0.003	0.0002	<0.0001
Middle 4 weeks				
Baseline median rate	35.5	29.2	22.5	46.4
Median % reduction	33.7	48.7	58.7	90.3
P-value		0.06	0.15	0.0003
Last 4 weeks				
Baseline median rate	35.5	29.2	22.5	46.4
Median % reduction	31.0	46.8	62.1	90.1
P-value		0.16	0.037	0.0003

The percentages of patients judged Much Improved or Very Much Improved on the Physician's Global rating were 23.6%, 46.2%, 64.9%, and 63.3% for the placebo, LD, MD, and HD groups, respectively.

## STUDY OV-1002

This was a randomized, double-blind parallel group trial in patients ages 2-30 years old with LGS on concomitant AEDs. In this study, patients were randomized to receive clobazam, either the low dose or the high dose (as in Study 1012); there was no placebo. In this trial, there was a 4 week Baseline phase, a 3 week Titration phase, a 4 week Maintenance phase, after which patients entered either a 3 week taper phase, or they entered long-term, open-label extension treatment.

In this study, patients were placed into one of 6 weight categories for purposes of stratification of the randomization. The outcome measures were essentially the same as for Study OV-1012; in particular, the primary outcome assessed the treatment effect on drop attacks. The hypotheses were tested at an alpha of 5%.

## Results

The study was performed entirely in the US.

The following table presents the disposition of patients in the study:

	LD	HD
Randomized	32	36
Completed	28	30
D/C due to AE	3 (9%)	6 (17%)

The oldest patient in this study was 26 years old.

The following table presents the results of the primary analysis for drop attacks:

	LD	HD
N	29	32
Baseline Rate		
Mean	142	209
Median	66	97
Percent Reduction		
Mean	10.1	85.2
Median	29	93
P-value		<0.0001

The following table presents the results of the primary analysis for total (non-drop and drop attacks) weekly seizure frequency:

	LD	HD
N	29	32
Baseline Rate		
Mean	153.3	216.6
Median	88.1	105.2
Percent Reduction		
Mean	19.1	85.2
Median	27.1	86.2
P-value		<0.0001

The results on the Physician's Global rating were similar to those seen in Study OV-1012.

## SAFETY

As noted above, numerous of the studies that the sponsor submitted to assess the safety of clobazam were performed by other sponsors in the past. As a result, we do not have as complete a dataset as we would expect if the studies had been done more recently. The current sponsor (Lundbeck, Inc.) has performed 8 Phase 1 and 3 Phase 2/3 studies, totaling 633 subjects exposed to at least one dose of clobazam. They have presented safety data for a total of 2236 subjects in clinical trials; the additional data is derived from numerous controlled trials performed in epilepsy (Study 301) and various psychiatric indications (so-called Legacy Psychiatry studies. The sponsor does not have complete exposure data for all of these Legacy Psychiatry studies.

Presented below is a table presenting the percent of available data in various categories available to the sponsor for the Legacy Psychiatry studies, taken from Dr. Boehm's table on page 13 of his review:

Assigned to CBZ	With start/stop dates	With exp data	Without Exp Data
1484	668 (45%)	427 (29%)	389 (26%)

Subtracting the 389 patients for whom the sponsor has no exposure data from the 2236 subjects the sponsor included safety data for yields 1847 patients/subjects for whom exposure data is available.

Of these 1847 subjects, 357 patients have received clobazam for at least 6 months, 243 have received clobazam for at least one year, and 100 patients have received clobazam for at least 2 years.

The following table presents the mean modal dose for the Phase 2/3 studies performed by Lundbeck (Studies 1002 and 1012 described above, and Study 1004, an open-label extension study):

	Days of Exposure				
	>90	>180	>360	>540	>720
N	264	253	197	137	100
Daily dose (m/k)					
Mean Modal	.9	.92	.96	.98	.98
Maximum Mean	1.17	1.19	1.24	1.27	1.29

#### Deaths

There were 9/2263 (0.4%) deaths in the clobazam-treated subjects for whom the sponsor has presented safety data. All of these deaths occurred in the open-label extension study 1004.

The most common cause was pneumonia (N=3). Another 3 patients had no identified cause of death, one patient died under hospice care of dehydration (and pneumonia), one died during a hospitalization for seizures and the cause of death was respiratory failure, and one died of urosepsis. These patients were treated with clobazam from 183-1318 days, with 5 treated for at least 500 days. All patients had significant neurologic illness and were taking numerous medications. Dr. Boehm has reviewed the available data for these patients. There is no clear or obvious link between these deaths and treatment with clobazam.

#### Serious Adverse Events (SAEs)

The following table presents the incidences of those SAEs that were reported in a total of more than one patient in either of the controlled trials 1002 and 1012:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59
Event						
Pneumonia	0	0	0	2	2	1
Constipation	0	1	0	0	1	1
Grand mal Sz	0	0	0	0	1	1

The following table presents the SAEs reported at >1% in the combined data for Studies 1002, 1012, and 1004 (N=300):

Event	Percent
Pneumonia	14% (N=43)
Convulsion	7% (N=21)
Status epilepticus	2% (N=6)
UTI	2% (N=6)
Grand mal sz	1.7% (N=5)
Pyrexia	1.7% (N=5)
Sleep apnea Syndrome	1.7% (N=5)
Constipation	1.3% (N=4)
Dehydration	1.3% (N=4)
Gastroenteritis	1.3% (N=4)
Vomiting	1.3% (N=4)

Dr. Boehm discusses several SAEs of interest.

#### Rash

A 3 year old boy experienced an erythematous rash on Day 7 (chest, extremities, chin) without mucosal involvement, though apparently one lesion was reported to have blistered. He had been receiving lamotrigine for 7 months. Both drugs were stopped, he received treatment, and the rash resolved on Day 12.

#### Thrombocytopenia

Three (3) patients experienced 4 events of thrombocytopenia.

1) A 2 year old girl was hospitalized for thrombocytopenia on Day 87 (dose of 0.5 mg/kg/d). She was taking concomitant valproate and phenytoin for 4 months prior to initiating clobazam. Her platelet count was abnormal at baseline: 118

GI/L (normal 252-582), and reached a nadir of 13 on Day 87. The following table presents some relevant laboratory values; clobazam and valproate were discontinued on Day 87:

Platelets (GI/L; normal 252-582)

Screening	118
Day 52	38
Day 81	26
Day 87	13
Day 89	26
Day 90	28
Day 91	20
Day 92	22
Day 96	125

Dr. Boehm points out that her valproate levels were documented to have been above therapeutic levels from Day 52 to at least Day 88.

2) A 6 year old boy on multiple medications including valproate (as well as many other AEDs) developed pneumonia and macrocytic anemia and thrombocytopenia (65; normal 150-450) on 20 mg of clobazam on Day 198. Platelets dropped to 57 on Day 199, and valproate was held for 3 doses. Clobazam was also stopped for one day, and re-started at 10 mg on Day 200, followed by 20 mg on Day 201. Thrombocytopenia resolved on Day 207 and the patient was discharged on clobazam and his original valproate dose. This patient was followed for an additional 2 years, with normal platelet counts subsequent to his discharge.

3) An 11 year old girl experienced multiple significant medical events over several years, some of which were accompanied by episodes of thrombocytopenia. Clobazam was never discontinued (the doses were sometimes increased), with resolution of the thrombocytopenia.

### Pancreatitis

There were 2 SAEs of pancreatitis.

- 1) A 7 year old boy experienced septic shock secondary to GI perforation on Day 620 of treatment. Clobazam was continued, and ultimately, the pancreatitis resolved.
- 2) An 11 year old boy was diagnosed with Guillian-Barre Syndrome on day 28 and with pancreatitis on Day 37. Clobazam was stopped (Day 28 and Day 30-50) and re-started. The clinical events resolved on Days 71-72.

### SAEs in Legacy Trials

In the Legacy Epilepsy Trial 301, 12/119 (10%) of clobazam and 37/116 (32%) of control patients (this study had several active controls but no placebo) had an SAE. Only convulsion (N=7) and self-injurious ideation (N=2) were reported in more than one patient. The other events are described by Dr. Boehm; most cannot reasonably be attributed to clobazam, and others are not well described.

In the Legacy Psychiatry trials, 5/1484 patients were reported to have had an SAE. Recall that events in these trials were not prospectively designated as SAEs, because they were conducted before there was a regulatory definition of SAEs. The sponsor designated these as SAEs based on a review of the records of patients who were hospitalized. The events could either not clearly be linked to clobazam (N=2 worsening of underlying psychiatric condition) or could reasonably be considered not related (alcoholic cirrhosis, appendicitis, reason unknown).

Discontinuations

During Phase 1 studies, 13/ 333 (3.7%) of subjects discontinued treatment due to an adverse event. Three (3) of these discontinued secondary to transaminase elevations.

- 1) A 43 year old man experienced ALT elevations on Day 14 (2 days of 40 mg/day) and AST elevations on Day 17. On Day 20, ALT was 203 U/L and AST was 121 U/L, and treatment was discontinued. There were no other abnormalities. These resolved about 2 weeks later.
- 2) A 45 year old woman experienced ALT and AST elevations on Day 14 (2 days of 40 mg/day). By Day 16, ALT was 212 U/L and AST was 198 U/L. Alk phos was also elevated at between 191-230 U/L. Drug was discontinued on Day 16, and labs returned to normal over about 10 days.
- 3) A 36 year old woman experienced ALT and AST elevations on day 3 (151 U/L and 180 U/L, respectively) on 30 mg/day. Drug was discontinued, and levels increased to a maximum of 278 U/L and 180 U/L, respectively, on Day 10, after which they returned to normal by Day 23.

The following chart presents the incidence of adverse events leading to discontinuations in the controlled trials; only those events leading to discontinuation in at least 2 patients/trial are presented:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59

Event						
Fatigue	0	0	0	0	0	2
Ataxia	0	0	0	0	0	4
Lethargy	0	0	1	1	1	3
Somnolence	0	1	0	0	2	3
Aggression	1	0	0	0	1	3
Insomnia	0	0	0	0	1	1

One case, not described in the table, was a patient who discontinued for rash.

A 2 year old boy experienced a mild rash on Day 11, and a severe rash on Day 13. The mild rash was associated with a palpable spleen, granulocytopenia, elevated ESR, anemia, liver enzyme elevations, and fever. On Day 16, AST and ALT were 365 U/L and 351 U/L, respectively, with HCT=29.5. Drug was stopped on Day 17. The mild rash resolved by Day 28 and the severe rash resolved by Day 66. This case has numerous features of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), though it is missing some common features (e.g., eosinophilia).

In the Legacy Epilepsy study, 13/119 (11%) of clobazam and 34/116 (29%) of control patients discontinued due to an adverse reaction. Most of the events occurred in only 1 patient, except for catastrophic personality disintegration (CPD; N=3; see below), abnormal behavior (N=3; different patients than those with CPD) drug ineffective (N=3), irritability (N=2), and weight increased (N=2). The other events are described by Dr. Boehm, page 35 of his review.

CPD consists of a constellation of symptoms that includes aggressive agitation, self-injurious behavior, insomnia, and incessant motor activity. The symptoms resolved with drug discontinuation.

The following table (taken from Dr. Boehm's table, page 36 of his review), presents those AE responsible for discontinuation in the Legacy Psychiatry studies that occurred in at least 2 clobazam patients and more frequently than in placebo patients:

#### US/Canada Studies

	Placebo	Clobazam	Diazepam
N	68	203	133
Event			

Somnolence	0	6 (3%)	4 (3%)
Confusional State	0	2 (1%)	1 (0.8%)
Depression	0	2 (1%)	2 (1.5%)

#### Non-CRF Studies (no exposure data)

N	364	615	453
Event			
Asthenia	1	4	0
Fatigue	1	3	1
Irritability	1	4	2
Somnolence	1	9	8
Syncope	0	2	2
Depression	2	4	2
Erectile Dysfunction	0	2	2
Urticaria	0	2	0

#### Significant Adverse Events

##### Seizures

In Study 1012, the incidence of a patient developing a new seizure type was 3.4% in the placebo group, and 1.7%, 3.2%, and 5%, for the LD, MD, and HD groups, respectively. These seizure types included petit mal, myoclonic, simple partial, and tonic seizures, and were similar among the groups (save for a single tonic convulsion in the HD group). Otherwise, there was no evidence that clobazam increased seizures or caused an increase in the incidence of status epilepticus.

##### Pneumonia

In Study 1012, the incidence of pneumonia was 1.7%, 3.4%, 3.2%, and 6.8% in the placebo, LD, MD, and HD groups, respectively. The cases were considered SAEs. In Study 1002, there were 2 non-serious cases of pneumonia in the HD group (5.5%). In open-label Study 1004, 46 patients reported at least one event of pneumonia.

The risk of pneumonia appeared to be constant for about 500 days after initiating

treatment. The sponsor performed extensive analyses to identify possible risk factors for pneumonia, and to see if there was an association between other AEs (e.g., somnolence, salivary hypersecretion, dose increases, etc.). No relationships were discovered, save for an apparent increased risk for pneumonia in younger patients and patients who were taking concomitant felbamate or opioids. Concomitant use of rufinamide (approved in this country for LGS) seemed to be associated with a decreased risk of pneumonia.

### Blood dyscrasias

The sponsor identified a total of 18 patients who experienced at least one event of a blood dyscrasia in the controlled trials: Study 1002, N=0; Study 1012, N=4; Study 1004, N=14. Of these 18 events, 16 were thrombocytopenia. One patient had a low RBC count, and one patient had leucopenia.

All of these patients were taking concomitant AEDs known to cause these events (valproate and/or carbamazepine). Three events were considered serious, and were previously discussed.

### Serious skin reactions

An extensive search of AE terms related to possible serious skin reactions yielded no cases, save for the one patient previously discussed, who had elements of DRESS.

### Liver injury

The following table presents the incidence of abnormal LFTs in Phase 1 studies:

	Pla/positive control	Clobazam
N	140	349
Aminotransferase >ULN	9.3%	12.6%
Aminotransferase >3XULN	1.4%	2.3%
Aminotransferase >5XULN	0	1%
ALP >1.5XULN	0	0.3%

In the controlled trials, the only finding of interest is described below:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59

Aminotransferase >ULN 15.6% 16.7% 12% 12% 10% 20%

In open-label Study 1004, 1.4% (N=4) patients had an AT > 3XULN and 0.7% (N=2) had an AT >5XULN. No patient had an AT>10XULN.

In open-label Study 1004, one patient had an SAE related to the liver:

A 5 year old girl developed a non-serious LFT elevation on Day 478, and a serious LFT elevation on Day 855. The first event occurred at a dose of 10 mg. The first event was associated with a peak ALT elevation of 9.88 X ULN that was still elevated on Day 660. She had AT elevations on Days 848, 869, and 898 (by the latter days, she was taking 15 mg/day of clobazam). An ultrasound showed cholelithiasis, but no liver abnormality. The dose was decreased to 5 mg by Day 898 (first reduced to 10 mg/day on Day 890), and the event resolved on Day 890. Drug was discontinued on Day 912, but LFTs remained elevated on Day 1024 (ALT 2.7XULN; AST 1.75XULN).

No other significant liver AEs were reported in other studies.

#### Somnolence-related AEs

The following chart displays the incidence of somnolence-related AEs in the controlled trials:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59
Any somnolence AE	28%	39%	22%	28%	32%	44%

A total of 13 clobazam-treated patients with a somnolence-related AE discontinued treatment.

The majority of somnolence-related AEs occurred within the first 25 days of initiation of treatment. In Study 1002, the median duration of a somnolence-related event was 20 days (range, 3-49). In Study 1012, the median duration was 26.5, 37.5, 15, and 5.5 days for LD, MD, HD, and placebo patients, respectively. The upper end of the ranges for these groups varied from about 90-100 days.

#### Common Adverse Events

The following chart, taken from Dr. Boehm's Table, pages 52-54, lists adverse events occurring in at least 5% of patients in any group, and at a greater incidence than in placebo:

Event	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59
<b>Somnolence-related</b>						
Events	13%	19%	22%	28%	32%	44%
Drooling	3%	0%	3%	0%	13%	14%
URI	9%	3%	10%	10%	13%	14%
Pyrexia	3%	6%	3%	17%	10%	12%
Aggression	6%	8%	5%	3%	8%	14%
Constipation	3%	8%	0%	2%	2%	10%
Ataxia	6%	3%	3%	3%	2%	10%
Vomiting	0%	6%	5%	9%	5%	7%
Nasopharyngitis	0%	11%	10%	9%	10%	7%
Decreased appetite	0%	3%	3%	3%	0%	7%
Cough	0%	0%	0%	3%	5%	7%
Insomnia	3%	6%	2%	2%	5%	7%
Irritability	6%	6%	5%	3%	11%	5%
Bronchitis	3%	0%	0%	2%	0%	5%
UTI	0%	0%	0%	2%	5%	5%
Increased appetite	0%	0%	0%	2%	3%	5%
Hyperactivity	3%	3%	3%	3%	3%	5%
Rash	0%	0%	3%	2%	3%	5%
Dysphagia	0%	0%	0%	0%	0%	5%
Fatigue	0%	0%	2%	5%	5%	3%
Viral infection	0%	11%	2%	0%	0%	3%
Otitis media	13%	0%	0%	0%	2%	2%
Pneumonia	0%	6%	2%	3%	3%	7%
Sinusitis	6%	6%	3%	0%	0%	2%
URI	6%	3%	0%	2%	2%	0%

Similar events were seen in the open-label Study 1004 and the Legacy trials.

#### Laboratory Measures

In Study 1012, hematology and chemistry evaluations were done at baseline, Week 3, Week 7, Week 11, and Week 15 (end of taper). In Study 1002, labs were collected at baseline, Week 3, Week 7, and Week 11 (end of taper).

## Hematology

In Phase 1 studies, 18/349 (5.2%) of patients had a potentially clinically significant (PCS) low hematocrit. The lowest value was 31%. In 11 patients, the value improved; in the remaining 7, the value was still PCS at the end of the study (varying from 31-37%).

In the controlled trials, the following incidence of PCS low hemoglobin and low hematocrit was seen:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59
Low hemoglobin	3%	16.7%	5.1%	1.7%	8.1%	16.9%
Low hematocrit	21.9%	22.2%	11.9%	13.8%	25.8%	27.1%

In most cases, the changes were small, and returned to normal with continued treatment.

There appeared to be no other important changes in hematology values.

## Chemistry

There were no important increases in PCS chemistry values in the controlled trials. The following chart displays shifts from normal or low baseline to high for the following parameters in the controlled trials:

	Study 1002		Pla	Study 1012		
	LD	HD		LD	MD	HD
N	32	36	59	58	62	59
AST High	12.5%	8.3%	3.4%	8.6%	6.5%	16.9%
BUN High	0%	2.8%	1.7%	0%	4.8%	10.2%
Sodium High	3.1%	5.6%	3.4%	5.2%	3.2%	10.2%

The following chart displays mean changes from baseline in the controlled trials for selected parameters of interest:

Study 1002	Study 1012		Pla	LD	MD	HD
	LD	HD				

N	32	36	59	58	62	59
ALP (U/L)	-1.9	8.3	-5.3	9.9	13.2	11.3
Triglycerides (mg/dL)	3.3	24.2	-6.9	8.5	18.1	9.4

#### Vital signs

There were no systematic drug-related changes in blood pressure or pulse in the controlled trials or Phase 1 studies.

#### EKG

The sponsor performed a thorough QT study in which daily doses of 40 mg and 160 mg were evaluated. The largest upper bound of the 90% confidence interval for the mean difference between either dose and placebo was less than 10 msec.

In Study 1012, there was a slight increase in the percent of patients who had a QTc increase of between 30-60 msec: 3.4%, 5.4%, 8.1%, and 9.1% for the placebo, LD, MD, and HD groups, respectively.

#### Post-Marketing Experience

As noted earlier, clobazam is marketed in 100 countries, first coming on the market in Australia in 1970. Lundbeck presumably has access to post-marketing data from 1976.

There are reports of rare significant medical events (pancytopenia, agranulocytosis, aplastic anemia, SJS, TEN, hepatic failure, jaundice, DRESS) for which the information is, in general, incomplete and/or the cases were confounded.

Some cases are of interest:

- 1) a 45 year old man with HIV, HCV, HBV, alcoholism and cirrhosis who developed a Hgb of 7.5 g/dL and a neutrophil count of 900/mm<sup>3</sup> on Day 2 of clobazam. Ten days later his Hgb dropped to 5.3g/dL and his neutrophil count dropped to 33/mm<sup>3</sup>. He had been on valproate and adacavir/lamivudine/zidovudine for 18 months. The latter combination was stopped on Day 12, and the valproate and clobazam were stopped 9 days later. A bone marrow biopsy showed global marrow hypoplasia without fibrosis. Six weeks after the onset of the event, his blood counts were normal, and the event resolved.
- 2) A patient developed erythema on carbamazepine and valproate. The drugs were discontinued, and the rash diminished. Clobazam was started when the other drugs were discontinued, and 1 ½ months later the rash

was worse (the original rash presumably had not entirely resolved). The patient experience fever and malaise, Over the next month, the patient became hospitalized, was treated with steroids, and the clobazam was discontinued. He was diagnosed with erythema multiforme exudativum. Presumably the rash resolved off clobazam.

## Non-clinical toxicology

As noted above, most of the non-clinical studies were done years ago by a previous sponsor. Dr. Fisher has reviewed these studies in detail.

In particular, he finds that the mouse and rat carcinogenicity studies and the reproductive and developmental toxicity studies were inadequate. The carcinogenicity studies were presented to the CAC, which found them to be inadequate. Deficiencies in the mouse carcinogenicity study included deaths in HD animals, inability to determine the number and type of organs examined microscopically in each animal, a reduced number of tissues were examined, and procedural deficiencies (e.g., identity tests on the drug not performed, no QA statement, protocol not available, etc.). Deficiencies in the rat carcinogenicity study were similar.

Deficiencies in the reproductive and developmental toxicity studies included (but were not limited to) dosing periods that did not cover the full period of organogenesis, inadequate doses, and inadequate assessment of various endpoints.

## Clinical Pharmacology

Clobazam is essentially 100% bioavailable compared to a solution. The T<sub>max</sub> varies from ½ to 4 hours. A high fat meal lowers the C<sub>max</sub> trivially, and the AUC not at all.

Clobazam is extensively metabolized; approximately 2% of the drug is uncovered in the urine unchanged. The primary enzyme responsible for clobazam metabolism is CYP3A4, with minor contributions from CYP2C19 and CYP2B6. The T<sub>1/2</sub> of clobazam is 36-42 hours.

N-desmethyclobazam (N-CLB) is the primary metabolite of clobazam. It is active, though presumably less so than clobazam, based on various in vitro binding studies and in vivo animal models of epilepsy. N-CLB is metabolized by CYP2C19. In poor metabolizers of CYP2C19, the circulating levels of N-CLB are 5 times greater than extensive metabolizers. The T<sub>1/2</sub> of N-CLB is 71-82 hours.

Evidence from patients with mild-moderate renal impairment suggests that there is no major difference in clobazam levels compared to healthy subjects. The sponsor did not provide information regarding the kinetics of clobazam in patients with severe or end-stage renal disease.

A small study in the literature suggested that the kinetics of clobazam in patients with liver impairment may not be significantly different from that of healthy subjects, though the t<sub>1/2</sub> of clobazam in patients with hepatic impairment is about twice that in normal subjects (52 and 22 hours, respectively), and the T<sub>max</sub> of the active metabolite, N-CLB in patients with hepatic impairment was also about twice that in normal subjects (88 and 48 hours, respectively). However, individual patient data were not available for a complete assessment, making any definitive conclusions about the effect of hepatic disease on the kinetics of clobazam impossible.

A study with ketoconazole (a strong 3A4 inhibitor) showed minimal changes in clobazam levels. Administration of omeprazole (a moderate C19 inhibitor) showed a 30-36% increase in clobazam and N-CLB AUC.

Clobazam appears to inhibit CYP2D6 and induce CYP3A4. Clobazam increased AUC and C<sub>max</sub> of dextromethorphan (a 2D6 substrate) by 90% and 59%, respectively. Clobazam decreased midazolam AUC and C<sub>max</sub> by 27% and 24%, respectively, and increased the AUC and C<sub>max</sub> of the metabolite 1'-hydroxymidazolam by 4- and 2-fold, respectively.

## CMC

There are no outstanding CMC deficiencies. The Office of Compliance has determined that the manufacturing and testing facility that has not been inspected need not be inspected prior to approval.

## CSS

Clobazam is a Schedule IV drug, and the CSS staff recommends that it be permanently placed in Schedule IV.

## DSI

DSI staff has inspected 3 domestic and one foreign site. They found regulatory violations for 2 investigators, but have concluded that the violations are not likely

to “critically impact primary efficacy and safety analyses;...”. The EIR has not been received from the field, though we have received verbal notification from Dr. El-Hage that there are no deficiencies that would preclude approval.

## COMMENTS

The sponsor has submitted the results of two randomized controlled trials that purport to establish the effectiveness of clobazam as adjunctive therapy for drop attacks in patients with LGS. The review team has concluded that these studies, taken together, provide substantial evidence of effectiveness for clobazam for the proposed indication.

I agree. The results clearly demonstrate the effectiveness of clobazam for this indication. Although study 1002 did not employ placebo, and only assessed the effect of treatment in a 4 week maintenance phase, there was a clear and convincing effect of the high dose in this study. In Study 1012, there was clear evidence of effectiveness at all doses, with a clear monotonic dose response.

One question related to effectiveness involves the question of which dose(s) to recommend in labeling.

Clearly, the HD is superior to the other two doses, but it is also associated with an increased incidence of adverse events. However, the LD and MD are both effective. For this reason, I believe all three doses can be recommended, though labeling should make clear that there is a dose response for seizure control. Achieving higher doses must be done by titration, and labeling can inform prescribers to dose to maximum tolerability, with provisions to consider treating with non-maximum doses if seizure control is adequate.

Of particular concern in this application was the possibility that patients would develop tolerance over time to the anti-seizure effects of clobazam, based on a widely held view that such tolerance can develop to the effects of benzodiazepines in general. To examine this question, several analyses were performed and described above. In particular, seizure frequencies were evaluated in the first, middle, and last 4 weeks of the maintenance phase of Study 1012 in both completers, and the intent-to-treat population. As the tables above demonstrate, a clear effect persists in all dose groups in all 3 epochs, though the drug-placebo difference is not always statistically significant for all doses (rarely for the MD, and more frequently for the LD). The lack of statistical significance for some of the epochs notwithstanding, I believe these analyses establish that significant tolerance did not develop, at least for the duration of this study.

Regarding safety, there are no safety issues that have been identified that would preclude approval. The common adverse events seen are largely consistent with the pharmacologic activity of benzodiazepines (in particular, somnolence and

sedation-related adverse events). The most common serious adverse event seen was pneumonia (14% of patients in the controlled trial and open-label extension). There were no other significant serious adverse events seen that could clearly be considered to have been related to clobazam, save for one patient who had an event that had some, but not all typical, elements of DRESS.

There were minimal dose-related changes seen in LFTs and hemoglobin and hematocrit. In most cases, these resolved with continued treatment.

Drs. Freed and Fisher note the inadequacies in the carcinogenicity and reproductive toxicity studies, though these studies have yielded some information (thyroid follicular cell adenomas in HD males, and increased fetal abnormalities). Although these studies are inadequate by current standards, I do believe that this should not preclude approval, though we should require that they be repeated post-marketing (as Post Marketing Requirements).

Unfortunately, we do not have entirely adequate information on the kinetics of clobazam and its active metabolite, N-CLB, in patients with severe renal or hepatic impairment. Nonetheless, I believe the application can be approved without this information, with dosing recommendations to titrate more slowly in these patients.

One final note.

Currently available benzodiazepines are labeled as Pregnancy Category D, meaning that there is adequate human data to establish that they are harmful to the developing fetus in humans. These labels are old, and reflect long-held views of the in utero effects of this class of drugs. However, during the review of this application, we have re-considered this question. Based on a review of the data in this application, the relevant literature, and previous reviews by Agency reviewers (Dr. Greg Dubitsky, Division of Psychiatry Products, in a review from 1996, and Dr. Ed Fisher, in a review from 1996), we have concluded that the human data are conflicting and not definitive (for example, early findings of cleft lip/palate have not been confirmed in later studies). For this reason, we have concluded that clobazam is more appropriately labeled Pregnancy Category C, meaning that animal data suggest that it is teratogenic, but that there is insufficient evidence in humans. We recognize that, should clobazam be approved (as we recommend), the risk of fetal harm with it will appear to be less than the risk with currently approved benzodiazepines. We recognize that this will appear to endorse the view that clobazam is different in this regard from the other members of the class when, in fact, at this time, we do not believe this is so.

(b) (4)



For the reasons given above, then, we recommend that this application be approved.

Russell Katz, M.D.

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RUSSELL G KATZ  
10/21/2011