CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210833Orig1s000

SUMMARY REVIEW

Summary Review

Date	October 25, 2018
From	Philip H. Sheridan, MD Eric Bastings, MD
Subject	Summary Review
NDA/BLA # and Supplement#	210833
Applicant	Aquestive Therapeutics (formerly MonoSol Rx, LLC)
Date of Submission	September 11, 2018
PDUFA Goal Date	November 11, 2018
Proprietary Name	Sympazan
Established or Proper Name	Clobazam Oral Film
Dosage Form(s)	Oral Film 5 mg, 10 mg, and 20 mg
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Applicant Proposed Dosing Regimen(s)	5 mg to 40 mg (doses greater than 5 mg daily to be divided BID). For patients ≤ 30 kg, initiate at 5 mg daily and titrate as tolerated up to 20 mg daily. For patients > 30 kg, initiate at 10 mg daily and titrate as tolerated up to 40 mg daily.
Recommendation on Regulatory Action	Approval of Class I Resubmission after previous Tentative Approval (pending expiration of the orphan exclusivity of the relied upon listed drug on Ocober 21, 2018)
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Recommended Dosing Regimen(s) (if applicable)	5 mg to 40 mg (doses greater than 5 mg daily to be divided BID). For patients ≤ 30 kg, initiate at 5 mg daily and titrate as tolerated up to 20 mg daily. For patients > 30 kg, initiate at 10 mg daily and titrate as tolerated up to 40 mg daily.

This Class I Resubmission after Tentative Approval of this 505(b)(2) application proposes a new dosage form of clobazam (clobazam oral film), and relies on a prior finding of safety and effectiveness for clobazam tablets (Onfi - NDA 202067), as the listed drug (LD). The applicant proposes the same indication (adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age or older), and the same dosing regimen as for Onfi (clobazam).

Clobazam Oral (b) (4) Film 10 mg and 20 mg were shown to be bioequivalent to the LD, Onfi (CLB) tablets, in the pivotal bioequivalence study (Study 162018) that was reviewed in the original 505(b)(2) application submitted on October 31, 2017.

The 505(b)(2) Clearance Meeting held on July 30, 2018, determined that this application could only be tentatively approved due to the unexpired orphan exclusivity of the relied upon listed drug Onfi (CLB) tablets.

A Tentative Approval letter was sent to the sponsor on August 31, 2018.

The sponsor has submitted a Class I Resubmission after Tentative Approval. There are no additional efficacy or safety data since the submission of the original 505(b)(2) application. The orphan exclusivity of the relied upon listed drug Onfi (CLB) tablets expired on October 21, 2018.

Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes.

Approval of Clobazam Oral Film is recommended.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
10/29/2018

ERIC P BASTINGS
10/30/2018
I concur and will issue an approval letter.

Summary Review

Date	August 29, 2018
From	Philip H. Sheridan, MD Eric Bastings, MD
Subject	Summary Review
NDA/BLA # and Supplement#	210833
Applicant	Aquestive Therapeutics (formerly MonoSol Rx, LLC)
Date of Submission	October 31, 2017
PDUFA Goal Date	August 31, 2018
Proprietary Name	Sympazan
Established or Proper Name	Clobazam Oral Film
Dosage Form(s)	Oral Film 5 mg, 10 mg, and 20 mg
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Applicant Proposed Dosing Regimen(s)	5 mg to 40 mg (doses greater than 5 mg daily to be divided BID). For patients ≤ 30 kg, initiate at 5 mg daily and titrate as tolerated up to 20 mg daily. For patients > 30 kg, initiate at 10 mg daily and titrate as tolerated up to 40 mg daily.
Recommendation on Regulatory Action	Tentative Approval (pending expiration of the orphan exclusivity of the relied upon listed drug)
Recommended Indication(s)/Population(s) (if applicable)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Recommended Dosing Regimen(s) (if applicable)	5 mg to 40 mg (doses greater than 5 mg daily to be divided BID). For patients ≤ 30 kg, initiate at 5 mg daily and titrate as tolerated up to 20 mg daily. For patients > 30 kg, initiate at 10 mg daily and titrate as tolerated up to 40 mg daily.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

This 505(b)(2) application proposes a new dosage form of clobabam (oral film), and relies upon a prior finding of safety and effectiveness for clobazam tablets (Onfi - NDA 202067). The applicant proposes the same indication (adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age or older), and the same dosing regimen as Onfi.

Lennox-Gastaut Syndrome (LGS) is a rare, severe, refractory epilepsy syndrome with onset in early childhood. LGS is categorized as a developmental and epileptic encephalopathy in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. LGS is characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. LGS is associated with higher rates of mortality than rates in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy patients (SUDEP). In addition to drugs approved for the general treatment of seizures, seven drugs are approved specifically for the treatment of seizures in patients with LGS: clobazam (tablets and oral suspension), rufinamide, topiramate, lamotrigine, felbamate, clonazepam, and cannabidiol.

The applicant provided an adequate pharmacokinetic bridge to clobazam tablets, and there are no new safety issues identified for this new dosage form of clobazam. Therefore, the risk-benefit profile established for Onfi is also applicable to this application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy which presents during childhood. LGS is a developmental and/or epileptic encephalopathy in which the seizures and the epileptic activity are thought to contribute to developmental delay and behavioral abnormalities. Onset of LGS typically occurs between ages 3 and 5 years. Some patients (20-60%) have evidence of delayed intellectual development at the time of diagnosis, and the severity of patients' cognitive and behavior impairments varies from minimally affected (rare) to profoundly impaired. Drop attacks are the most disabling of the seizure types (seen in >50% of LGS patients). A drop attack is a seizure that leads to a fall or would have caused a fall, thus frequently leading to injury. Non-convulsive status epilepticus (continuous seizure activity) is seen in 50-70% of patients. Seizure freedom is essentially never seen in patients with LGS, regardless of antiepileptic drugs (AEDs) or other epilepsy treatments. Children and adolescents with LGS	LGS is a severe epilepsy syndrome that is associated with refractory seizures, cognitive impairment, and increased risk of mortality related to seizures.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	have a higher mortality rate than the general epilepsy population. Commonly reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures.	
Current Treatment Options	Seven drugs are approved by FDA for reduction of seizures in patients with LGS: clobazam (tablet and oral suspension), rufinamide, topiramate, lamotrigine, felbamate, clonazepam, and cannabidiol. Many other anticonvulsant drugs are also used to treat seizures in patients with LGS, especially valproic acid (which is generally considered a first-line agent) and levetiracetam. There is the potential for severe adverse drug reactions with many of the approved and/or frequently used anticonvulsant drugs to treat seizures in LGS, such as hepatic failure (felbamate, lamotrigine, and valproic acid), serious skin reactions (lamotrigine, clobazam, rufinamide), and hematologic abnormalities (felbamate, lamotrigine, topiramate, rufinamide).	Seven drugs are approved by FDA for reduction of seizures in patients with LGS. Despite the availability of approved therapies, most patients continue to have poorly-controlled seizures. Additionally, some drugs are poorly tolerated or have the potential for serious adverse events. There remains a need for efficacious and safe therapies for the treatment of seizures in LGS.
Benefit	In the pivotal bioequivalence study (Study 162018), the applicant provided an adequate pharmacokinetic bridge to clobazam tablets. The study compared clobazam oral film (20 mg and 10 mg) with clobazam tablets (20 mg and 10 mg) in healthy volunteers under fasting conditions. Therefore, the prior finding of effectiveness of clobazam tablets for the proposed indication also applies to this new dosage form.	The prior finding of effectiveness of clobazam tablets applies to this new dosage form.
Risk and Risk Management	Similarly, the prior finding of safety of clobazam oral tablets applies to this new dosage form, as an adequate pharmacokinetic bridge to clobazam tablets was provided by the applicant.	The prior finding of safety of clobazam oral tablets applies to this new dosage form.

2. Background

This 505(b)(2) application proposes a new dosage form of clobabam (clobazam oral film - COF), and relies on a prior finding of safety and effectiveness for clobazam tablets (Onfi - NDA 202067), as the listed drug (LD). The applicant proposes the same indication (adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age or older), and the same dosing regimen as for Onfi. Clobazam (CLB) is also approved for the same indication as an oral suspension.

The precise mechanisms by which CLB exerts its anticonvulsant effect in humans is unknown. In addition to drugs approved for the general treatment of seizures, seven drugs are approved specifically for the treatment of seizures in patients with Lennox-Gastaut Syndrome (LGS): clobazam (tablets and oral suspension), rufinamide, topiramate, lamotrigine, felbamate, clonazepam, and cannabidiol.

LGS is a severe, refractory epilepsy syndrome with onset in early childhood. The syndrome is categorized as a developmental and epileptic encephalopathy in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndrome is characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. The syndrome is associated with higher rates of mortality than in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy (SUDEP).

LGS is characterized by a triad of findings: multiple seizure types, developmental delay, and an interictal electroencephalography (EEG) pattern of diffuse, slow spike-wave complexes. Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between 3 and 5 years of age. Etiologies can be identified in approximately 2/3 of patients with LGS and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex, brain malformations, and traumatic brain injuries. An initial diagnosis of infantile spasms may also be associated with a later diagnosis of LGS. A variety of genetic anomalies have been reported in patients with the diagnosis of LGS, including variants or mutations in the SCN1A, FOXG1, DNM1, and CHD2 genes.

This application provides a pharmacokinetic bridge to CLB tablets from the following two studies:

- Study 162018 Pivotal Bioequivalence Study
- Study 1895 Pilot Bioequivalence Study

3. Product Quality

The combined Quality Assessment review (Technical Lead: Dr. Wendy Wilson-Lee) from the Office of Pharmaceutical Quality (OPQ) found the application acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was necessary to support this 505(b)(2) application.

5. Clinical Pharmacology

The clinical pharmacology review was written by Dr. Dawei Li, and Dr. Angela Men was the OCP team leader.

Formulation:

COF is designed to rapidly disintegrate in saliva. Absorption is expected to occur primarily through the gastrointestinal tract after the dissolved film is swallowed. COF contains the active ingredient clobazam (b) (4) (b) (4). The COF product is a white rectangular film. The individual dosage strengths (5 mg, 10 mg, and 20 mg) are (b) (4). The proportionality of these doses is intended to provide consistent, proportional absorption of the active ingredient through the gastrointestinal tract following application to the lingual surface, subsequent dissolution in the oral cavity, and deglutition.

Pharmacokinetics:

Clobazam Oral (b) (4) Film 10 mg and 20 mg were shown to be bioequivalent to the LD, Onfi (CLB) tablets, in the pivotal bioequivalence study (Study 162018). The 90% confidence intervals of the ratios of geometric means for AUC and Cmax were within the range of 80% to 125% (see Table 1).

Table 1: Ratio and 90% confidence intervals of test (COF) versus reference (Onfi) in Study 162018

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

T = Test (COF) R = Reference (Onfi) CI = Confidence Interval

In addition, the 90% confidence intervals of the ratios of geometric means of AUC and Cmax for the active metabolite, N-desmethyl clobazam, were within the range of 80% to 125%.

In addition to the pivotal bioequivalence study (Study 162018), the sponsor had previously conducted a smaller pilot study (Study 1895), which did not establish bioequivalence, likely due to the small sample size and the relatively high inter-subject variability.

Food Effect:

A food effect study for COF was unnecessary, because of the largely gastrointestinal absorption of both COF and the LD (ONFI) , the insignificant food effect for the LD, and the previous approval of ONFI oral suspension without a food effect study.

Dosing:

COF (5 mg, 10 mg and 20 mg) is to be administered orally. The oral dissolving film is designed to be applied on top of the tongue where it adheres and dissolves (b) (4). The proposed doses are the same as those for the LD (see Table 2).

Table 2: Recommended Total Daily Dosing by Weight Group

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

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new efficacy studies were submitted. The application relies on a prior finding of effectivess for Onfi, through a pharmacokinetic bridge.

8. Safety

The clinical review was written by Dr. Natalie Getzoff.

The application relies on a prior finding of safety for Onfi (LD), through a pharmacokinetic bridge.

The safety findings in the pharmacokinetic studies conducted by the applicant were consistent with the safety profile of the LD.

9. Advisory Committee Meeting

No advisory committee meeting was necessary for this 505(b)(2) application that relies on a prior finding of safety and effectiveness for a previously approved drug (Onfi).

10. Pediatrics

PREA was triggered for this application, as the product is a new dosage form. As the referenced product (Onfi) is already approved for the proposed indication in patients 2 years of age and older, no additional studies are necessary in that age group. As studies are not practicable in pediatric patients under 2 years of age, a waiver will be granted for that age group.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff's clinical review.

Dr. Getzoff concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Office of Scientific Investigations (OSI) recommended accepting data without an on-site inspection because a recent inspection of the analytical site was completed and the site was classified as "No Action Required".

The 505(b)(2) Clearance Meeting held on July 30, 2018, determined that this application could only be tentatively approved due to the unexpired orphan exclusivity of the relied upon listed drug Onfi (CLB) tablets.

12. Labeling

Please refer to the final negotiated product label in the approval letter. Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
08/31/2018

ERIC P BASTINGS
08/31/2018
I concur.