Oral Soluble Film Products for Epilepsy: Clobazam (COSF) and Diazepam (DBSF)

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Aquestive
Conflict of Interest

- Dr. Rogawski serves as a paid consultant for Aquestive Therapeutics.
- Dr. Rogawski is currently or has previously served as consultant to other companies developing technology for similar applications, including Upsher-Smith Laboratories and Epalex Corporation.
How Does PharmFilm Work

• Polymers are used as film formers to hold API and excipients in place
• Patented techniques are used to ensure the API is uniformly distributed throughout the film
• pH modifiers and permeation enhancers cause transport across the buccal mucosa
• Begins to dissolve immediately on application to mucosa
• API released from buccal film is absorbed by the transmucosal route and is also swallowed
Clobazam Oral Soluble Film (COSF)

• An new alternative clobazam dosage form for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients aged 2 years and older (outside the United States for anxiety disorders and epilepsy)
• May be easier for some caregivers to administer than oral tablets or oral liquid suspension
• Demonstrates capability of film technology
Bioequivalence Study of COSF (162018)

- **Open-label, randomized, single-dose, 4-period, 4-arm, crossover, comparative bioavailability study**
- **Healthy, nonsmoking male and female volunteers (N=51)**
- **Treatments**
  - COSF 10 mg (N=47)
  - COSF 20 mg (N=45)
  - Onfi® (clobazam) Tablet 10 mg (N=47)
  - Onfi® (clobazam) Tablet 20 mg (N=47)
- **Washout:** 28 days between dosing
- **Blood sampling time points:**
  - 0.333, 0.667, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 28, 36, 48, 72, 96, 144, 240, 360, and 504 hours postdose in each period
- **Safety:** vital signs, physical exam, clinical labs, adverse events

Data on file, Aquestive Therapeutics.
Mean Plasma Concentration Profiles: COSF vs Onfi® (Study 162018)

Data on file, Aquestive Therapeutics.
## 20 mg Bioequivalence (Study 162018)

Bioequivalence of Clobazam Oral Soluble Film 20 mg vs Onfi® Tablets 20 mg – PK Population (N=45)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least-Squares Geometric Means</th>
<th>90% Geometric CI²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COSF 20 mg</td>
<td>Onfi 20 mg</td>
</tr>
<tr>
<td>AUC₀₋ₜ (ng·h/mL)</td>
<td>10531.45</td>
<td>10152.24</td>
</tr>
<tr>
<td>AUC₀₋ₐₙ (ng·h/mL)</td>
<td>10712.10</td>
<td>10344.68</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>386.59</td>
<td>376.84</td>
</tr>
</tbody>
</table>

¹Calculated using least-squares means according to formula e(Difference) X 100.
²90% geometric confidence interval using ln-transformed data.

Data on file, Aquestive Therapeutics.
### 10 mg Bioequivalence (Study 162018)

Bioequivalence of Clobazam Oral Soluble Film 10 mg vs Onfi® Tablets 10 mg – PK Population (N=47)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Least-Squares Geometric Means</th>
<th>90% Geometric CI (%)&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COSF 10 mg</td>
<td>Onfi 10 mg</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng·h/mL)</td>
<td>4554.83</td>
<td>4583.30</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/mL)</td>
<td>4714.55</td>
<td>4759.87</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>179.96</td>
<td>188.53</td>
</tr>
</tbody>
</table>

<sup>1</sup>Calculated using least-squares means according to formula $e^{\text{Difference}} \times 100$.

<sup>2</sup>90% geometric confidence interval using ln-transformed data.

Data on file, Aquestive Therapeutics.
Conclusions for COSF Bioequivalence Study (Study 162018)

• COSF 20 mg is bioequivalent to Onfi® 20 mg

• COSF 10 mg is bioequivalent to Onfi® 10 mg

• $T_{\text{max}}$ values for COSF were comparable to those for Onfi

• COSF is dose proportional over the 10-20 mg range

• COSF at doses of 10 and 20 mg was safe and well tolerated

Data on file, Aquestive Therapeutics.
Diazepam Buccal Soluble Film (DBSF)

• An alternative to Diastat® AcuDial™ (diazepam rectal gel) for the treatment of acute repetitive seizures (seizure clusters)
Fast track designation with option for rolling submission
Expected NDA filings via 505(b)(2) pathway in early 2018
DBSF: No ‘PK Non-Responders’

- Diastat in some subjects did not produce expected plasma concentrations of diazepam.
- In studies to date, DBSF has exhibited consistent plasma diazepam concentrations – including those subjects who did not obtain expected diazepam levels with Diastat.

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1Fasted conditions
Completed Human PK Studies with DBSF

- Bioavailability of DBSF 5 mg and Diastat® AcuDial™ 5 mg Rectal Gel (Study 1899)
- Bioavailability of DBSF 20 mg and Diastat® AcuDial™ 20 mg Rectal Gel (Study 1900)
- Dose Proportionality of DBSF 5, 10, 15 mg (Study 162013)
- Bioavailability of DBSF 15 mg vs Diastat® AcuDial™ 5, 12.5, and 20 mg Rectal Gel (Study 162921)
Geometric Mean Diazepam Plasma Concentrations (Linear Scale) (Study 162013)

Data on file, Aquestive Therapeutics.
Dose Proportionality ($C_{\text{max}}$) (Study 162013)

$C_{\text{max}}$ values were dose proportional.
DBSF: Diazepam 5, 10, 15 mg Buccal Soluble Film.

Data on file, Aquestive Therapeutics.
Dose Proportionality \((\text{AUC}_{0-t})\) (Study 162013)

\textbf{AUC}_{0-t} \text{ by Nominal Dose of Diazepam (Linear Scale)}

\text{AUC}_{0-t} \text{ values were dose proportional.}

DBSF: Diazepam 5, 10, 15 mg Buccal Soluble Film.

Data on file, Aquestive Therapeutics.
DBSF: Diazepam 15 mg Buccal Soluble Film.
Diastat AcuDial: Diazepam 5 mg (1 mL of 10 mg/2 mL), 12.5 mg (2.5 mL of 20 mg/4 mL), and 20 mg (4 mL of 20 mg/4 mL) rectal gel.

Data on file, Aquestive Therapeutics.
Relative Bioavailability (Study 162021)

• **DBSF**
  DBSF is known to be dose proportional for AUC

• **Diastat® AcuDial™**
  Diastat is dose proportional for AUC

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DBSF: Diazepam 15 mg Buccal Soluble Film.
Diastat AcuDial: Diazepam 5 mg (1 mL of 10 mg/2 mL), 12.5 mg (2.5 mL of 20 mg/4 mL), and 20 mg (4 mL of 20 mg/4 mL) rectal gel.

Data on file, Aquestive Therapeutics.
Proposed DBSF Dosing: Dose of DBSF in mg Equivalent to Dose of Diastat® AcuDial™ in mg

<table>
<thead>
<tr>
<th>Diastat Dose (mg)</th>
<th>Protocol-Specified DBSF Dose(^1) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
</tr>
<tr>
<td>12.5</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>17.5</td>
<td>12.5</td>
</tr>
<tr>
<td>20</td>
<td>12.5</td>
</tr>
</tbody>
</table>

\(^1\)Dose of DBSF expected to provide \(C_{\text{max}}\) equal to \(C_{\text{max}}\) for Diastat dose.

Data on file, Aquestive Therapeutics.
PK Features of DBSF vs Diastat® AcuDial™

- Dose-proportional kinetics
- Less intersubject variability
- No bioavailability failures

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>DBSF</th>
<th>Diastat® AcuDial™</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.81</td>
<td>0.50</td>
</tr>
<tr>
<td>10</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>12.5</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>1.9–1.27</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>1.5</td>
</tr>
</tbody>
</table>
DBSF Studies Ongoing

- Adult EMU Study
- Pediatric EMU Study
- Long-term Safety Study
The End