Sileo® (dexmedetomidine oromucosal gel) Introduction and Experience Program

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Noise Aversion: Encompasses the Various Terms Used to Describe Anxiety and Fear to Noise \(^1,^2\)

3) Based on online survey conducted by Harris Poll on behalf of Zoetis in November 2013 among 784 dog owners.

Reactivity
- Anxiety
  - Anticipated
  - Clear & Present Danger
  - Fear
  - Excessive Fear
  - Phobia

> 1/3 of Dogs Suffer from Noise Aversion\(^3\)
Canine Noise Aversion: A Welfare Concern

- Dogs are distressed and suffering
- Signs progress with time\(^1\)
  - Dogs can become sensitized to other noises
  - Increased intensity and number of signs
  - Duration of reaction increases
- Dogs can develop concurrent anxieties\(^2,3\)
- Social transmission has been reported\(^4\)
- Severe, uncontrolled signs can lead to surrender, abandonment or euthanasia\(^4\)

Dogs Do Not Outgrow Noise Aversion\(^1,5\)

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2) FR Market Research – Noise Aversion; February 2016; N=472 Dog Owners, N=454 General Practitioners.
Treatment: Multimodal Approach

Environment
- Avoid stimulus
- Provide safe haven
- Mask Noise
- Pheromones, Scents
- Wearables

Behavior Modification
- Counterconditioning
- Desensitization

Pharmacologic Agents
- Benzodiazepines
- Serotonergic Agents
- Alpha-2 agonist
- Nutraceuticals
- Homeopathic Therapy

Evidence is Lacking for Some
None Are FDA Approved for Treatment of Canine Noise Aversion

1) Sherman BL, Mills DS. 2008
3) Frank D, Beachamp G, Palestrinin c. JAVMA 2010
10) Cracknell, NR, Mills DS. The Vet J 2008
Pharmaceutical Agents: Recommended to Start As Soon As Possible for Best Outcomes¹

- Noise Aversion is a neurological disease: Effective treatment requires medications that can address the underlying cause
- Effective treatment may result in faster resolution:
  - Dogs have a shorter period of time to “learn” unwanted behaviors
  - Decreasing level of distress can improve learning of desired behaviors
- May prevent progression to more severe signs
- Less likelihood of surrender or euthanasia
- Improved quality of life for both pet owner and the dog

Sileo®
(dexmedetomidine oromucosal gel)
Sileo®: FDA Approved for the Treatment of Noise Aversion in Dogs

- 0.1 mg/mL of dexmedetomidine hydrochloride in a tasteless gel formulation
- Dosage: 125 mcg/m$^2$
- Administered between cheek and gum for oral transmucosal absorption
Important Safety Information

Do not use Sileo® in dogs with severe cardiovascular disease, respiratory, liver or kidney diseases, or in conditions of shock, severe debilitation, or stress due to extreme heat, cold or fatigue or in dogs hypersensitive to dexmedetomidine or to any of the excipients. Sileo should not be administered in the presence of preexisting hypotension, hypoxia, or bradycardia. Do not use in dogs sedated from previous dosing. SILEO has not been evaluated in dogs younger than 16 weeks of age or in dogs with dental or gingival disease that could have an effect on the absorption of SILEO. SILEO has not been evaluated for use in breeding, pregnant, or lactating dogs. Transient pale mucous membranes at the site of application may occur with SILEO use. Other uncommon adverse reactions included emesis, drowsiness or sedation. Handle gel-dosing syringes with caution to avoid direct exposure to skin, eyes or mouth. SILEO has not been evaluated for aversion behaviors to thunderstorms. See full Prescribing Information at ZoetisUS.com/SileoPI
Neurological Basis for Noise Aversion is Centered in the Locus Coeruleus\textsuperscript{1,2}

- Locus coeruleus mediates stress and anxiety
- Locus coeruleus neurons have a large number of alpha-2 receptors; main neurotransmitter is norepinephrine
- Exposure to stressors increase release of norepinephrine from the locus coeruleus
- The locus coeruleus projects to many other areas of the brain


Targeted Mode of Action Makes Sileo® the Logical Choice for Treatment of Noise Aversion$^1,2$

- Dexmedetomidine is a potent and selective alpha-2 adrenoceptor agonist
- Binds to alpha-2 receptors, inhibits release of norepinephrine
- Lower levels of norepinephrine lead to reduced anxiety and alleviation of behavioural signs

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Sileo® Pharmacokinetics: Implications on Clinical Effects
Sileo® Oral Transmucosally vs. Dexmedetomidine Intramuscularly; 125 mcg/m²

**Plasma Concentration Curve**

- **Sileo OTM 125 µg/m²**
- **Dexmedetomidine IM 125 µg/m²**

**Clinical Implication of Pharmacokinetics**

- Sileo Has 28% Bioavailability with Oral Transmucosal Administration
- Therefore only approximately 1/4 of administered dose is absorbed
- Results in minimal sedation and minimal effect on heart rate

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1) Orion data on file.
2) Sileo® (dexmedetomidine oromucosal gel) NADA 141-456. Prescribing Information.
What Happens When Sileo® Is Swallowed?

- Dexmedetomidine is absorbed from the gastric mucosa but...
- Undergoes extensive first pass metabolism\(^1\)
  - 98% of elimination is via hepatic biotransformation
- Results in negligible plasma concentration of dexmedetomidine after ingestion

Clinical Implication:
For optimal effect, SILEO must be administered oral transmucosally.
If swallowed, SILEO may not be effective\(^1\)

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1) Sileo® (dexmedetomidine oromucosal gel) NADA 141-456, Prescribing Information.
Sileo®
Clinical Field Safety and Efficacy Study
Clinical Study Conducted in the EU on New Year’s Eve

- Previous studies identified 125 mcg/m² as the lowest effective dose for Sileo® for the treatment of noise aversion

- Dogs with a previous history of having noise aversion to fireworks were enrolled in the study
  - Germany and Finland

- Randomized, double-blind, placebo-controlled

- Pet owners assessed the effect of SILEO
  - Efficacy: 2 different variables
  - Alertness
  - Adverse effects

- Allowed to administer up to 5 doses at 2 hour intervals, as needed
1st Variable: Owner Assessment of Treatment Effect (N=144)¹

- Pet owner assessed the treatment effect compared to the previous response to fireworks
- Sileo® had excellent or good treatment effect in 75% of dogs
- Placebo had excellent or good treatment effect in 33% of dogs
- Statistically significant difference at p< 0.0001 in favor of SILEO

¹ Sileo® (dexmedetomidine oromucosal gel) NADA 141-456, Prescribing Information.
2nd Variable: Owner Assessment of Signs and Extend of Signs (N=144)\(^1\)

- Pet owners were also asked to record observed behavioral signs and the extent of those signs before treatment administration and at 1 and 2 hours after administration.

- Mean sum of behavior scores over treatment period statistically significant (p=0.0069), in favor of Sileo.

- Trembling, panting, and trying to hide were lower in Sileo® dogs.

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1) Sileo® (dexmedetomidine oromucosal gel) NADA 141-456, Prescribing Information.
Sileo® Efficacy is Independent of Sedation¹,²

- Pet owners also assessed their dog’s alertness at 1 and 2 hours after dosing using this form.
- Any dog with signs of potential sedation in functional alertness (see green box on form) was excluded from the efficacy assessments in Slides 17 and 18.
- No signs of excessive sedation were observed in the Sileo treatment group.

Sedation did not explain the treatment effect of SILEO

2) Orion data on file.
## Clinical Field Study: Few Adverse Events Reported

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SILEO (N=89)</th>
<th>Placebo (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events n</td>
<td>Events n</td>
</tr>
<tr>
<td>Emesis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>1</td>
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</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

No Oral Mucosa Irritation Noted, Transient Pale Mucous Membranes Observed in Sileo® Treated Dogs

Sileo® (dexmedetomidine oromucosal gel) NADA 141-456, Prescribing Information
Sileo® Clinical Study Field: Summary of the Results

• Sileo was found effective in treating dogs with noise aversion
  – Anxiolytic effects of Sileo were:
    • Measurable
    • Clinically relevant
    • Statistically significant

• The Sileo treatment effect was found to be independent of sedation

• Treatment was safe
  – There were few adverse events reported during the study
Dosing Considerations
Sileo® is Designed For Easy at Home Administration: Dosing Chart

- Plunger of syringe marked with “dots”
- Each “dot” is equivalent to 0.25 mL of gel
- Dosing Chart:
  - Lists body weight ranges in pounds
  - Correlates body weight to number of “dots”
- Dose > 6 dots (1.5 mL) should be divided between both sides of the mouth

<table>
<thead>
<tr>
<th>Bodyweight (lb)</th>
<th>Number of dots</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4-12.1</td>
<td>1 ●</td>
</tr>
<tr>
<td>12.2-26.5</td>
<td>2 ●●</td>
</tr>
<tr>
<td>26.6-44.0</td>
<td>3 ●●●</td>
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<tr>
<td>44.1-63.9</td>
<td>4 ●●●●</td>
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<td>64.0-86.0</td>
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<td>86.1-110.2</td>
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<td>110.3-137.8</td>
<td>7 ●●●●●●●</td>
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<tr>
<td>137.9-166.4</td>
<td>8 ●●●●●●●●</td>
</tr>
<tr>
<td>166.5-196.2</td>
<td>9 ●●●●●●●●●</td>
</tr>
<tr>
<td>196.3-220.5</td>
<td>10 ●●●●●●●●●●</td>
</tr>
</tbody>
</table>

Dispose of syringe and any unused contents 2 weeks after first use, in accordance with regulations.
Sileo® Dosing is Tailored to the Situation

- The first dose administered:
  - Approximately 30–60 minutes before the fear and/or anxiety-eliciting noise stimulus
  - Or immediately after the dog shows first signs of anxiety or fear related to noise
  - Or when the owner detects a typical noise stimulus (e.g. fireworks) eliciting anxiety or fear in the dog

- If noise lasts longer than 2–3 hours and the dog’s signs of fear and/or anxiety reappear, another dose may need to be given
  - At least two hours interval between doses
  - Up to 5 doses can be given during one noise event

- Protect from light (replace in carton); use within 2 weeks after administering the first dose
How to Minimize Human Exposure And Accidental Overdose

- Instruct the pet owner to wear impermeable gloves when administering SILEO

- Review administration instructions with pet owner
  - Confirm correct dosage
  - Reinforce the need to set the locking ring in the “locked position” before administering
  - Administer between the cheek and gums

- Seek medical attention if you have concerns
  - Bring copy of package insert
What Happens in the Event of an Accidental Sileo® Overdose?

- Consideration for when SILEO is administered at a higher than label dose
  - Excess can flow out of the mouth or will be swallowed

- Worst Case: The entire syringe (3ml) is accidentally administered to a 2.5 kg dog
  - Assuming the entire dose is absorbed oral transmucosally
  - Exposure would be approximately equal to IV 450 mcg/m²; IV sedation dose is 375 mcg/m²
  - Outcome: The dog would be moderately sedated, in rare cases the dog may become more deeply sedated
  - Reversal with atipamezole, if there are concerns
## Sileo® Experience Program

### Inclusion and Exclusion Criteria

**Dogs Eligible for the Program:**
- Have a previous history of noise aversion
- Are 16 weeks of age or older
- Are healthy or have stable systemic disease

**Dogs Ineligible for Program:**
- Have conditions for which Sileo is contraindicated or has not been evaluated (see Important Safety Information on Slide 9)
- Have a history of hypersensitivity to alpha-2 adrenoceptor agonist
- Are concurrently receiving other psychoactive medications, homeopathic remedies, pheromones, nutraceuticals, special diet or thunder shirt (wraps) to control anxiety and fear
- Are currently receiving behavioral modification for noise aversion
Sileo® Experience Program Kit

1 Welcome Letter

2 Veterinary Staff Brochure
   - Program Overview
   - Product Review
   - Dosing Chart

3 Pet Owner Brochure
   - Introduction to SILEO
   - Behavior Checklist
   - What to expect from SILEO
   - Dosing & Administration Instructions
Please Review the Pet Owner Brochure with the Client

After Introducing SILEO on the First 2 Pages...

Check off which behaviors the dog has exhibited during noise aversion.

Set expectations for how Sileo® works: what the pet owner should expect to see and what to watch for.

Use an empty syringe as a ‘clinic sample’: wearing gloves, guide the pet owner through the dosing steps in the pictures below (also found in the Product Insert).
Please Complete the Survey on the Sileo® Experience Website

- www.experiencesileo.com
- Veterinarian Survey
  - Please fill this out for each dog owner/patient
  - You will receive a ‘Thank You’ email per completion
  - You will receive a ‘Reminder’ email to complete, in case you forget
- Dog Owner Survey
  - To be filled out within 48 hours of administering SILEO during a noise event
  - Dog Owner will receive a ‘Thank You’ email upon completion
- ASK: Please follow-up with your clients to hear about their experience and remind them to complete the survey

You will receive an email with a consolidation of feedback from all Dog Owners participating in this national SILEO Experience Program
Feedback from 2016 Early Experience Cases was positive and informative\(^1\)

**VETERINARIANS’ FEEDBACK**
- 95% planned to prescribe SILEO again
- 92% found prescribing discussion with clients straightforward
  - 14%, however, reported that explaining dosing and administration required additional discussion, e.g. dots as measurement, locking the ring on the syringe, wearing gloves, and timing of administration

**DOG OWNERS’ FEEDBACK**
- 90% ‘Satisfied’ to ‘Very Satisfied’ with their dog’s SILEO experience
- 91% ‘Satisfied’ to ‘Very Satisfied’ with ease of administration
- 88% ‘Satisfied’ to ‘Very Satisfied’ with their dog’s quality of life with SILEO treatment
- 91% ‘Satisfied’ to ‘Very Satisfied’ with their family’s quality of life with SILEO

We’re eager to hear your feedback
Sileo® Provides an Effective and Safe Treatment for Canine Noise Aversion that is Easy for Pet Owner to Administer

- Sileo fills an unmet need for noise aversion in dogs
- The only FDA approved drug for noise aversion in dogs
- Can be easily administered at home by the Pet Owner
- Provides veterinarians with a reliable, safe and effective solution
- By effectively treating noise aversion, Sileo can reduce the dog’s distress and suffering
- Resolution of clinical signs reduces likelihood of surrender or euthanasia; human animal bond is preserved

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Thank You!

Call into weekly office hours:
Dates: Wednesday March 22, 29, and April 5
Times: 12:30-1:30 PM or 7:00-8:00 PM, EDT
Call in number (855)-996-3947; Conference Code 232-539-0117

sharon.l.campbell@zoetis.com