Trazodone is a serotonin 2A antagonist and reuptake inhibitor that has been used in human medicine as a prescription therapy for depression, aggression, sleeplessness, and anxiety since 1981.\textsuperscript{1–3} It is available in 50-, 100-, 150-, and 300-mg tablets as well as 150- and 300-mg extended-release tablets.\textsuperscript{1} No products are labeled for veterinary use.

Trazodone selectively blocks serotonin reuptake, which enhances serotonin’s effects.\textsuperscript{4} It is an antagonist of 5-HT\textsubscript{2A}, H1-histaminic, and \(\alpha\textsubscript{1}\)-adrenergic receptors at low to moderate doses, resulting in various levels of sedation.\textsuperscript{3–6} It can have hypotensive effects.\textsuperscript{4} At higher doses, trazodone acts as a serotonin agonist, and serotonin syndrome can develop.\textsuperscript{3–6} Trazodone also has anxiolytic properties, but the exact mechanism of action is unknown.\textsuperscript{4}

USE IN VETERINARY MEDICINE
In 2008, Gruen and Sherman studied 56 dogs prescribed trazodone in combination with other primary behavior therapies and discovered that trazodone seemed to offer therapeutic benefit with relatively minimal adverse effects.\textsuperscript{7} Since then, studies have investigated the benefit of trazodone in postorthopedic surgery treatment plans involving confinement to enhance calm behavior and reduce anxiety in hospitalized dogs. Trazodone has generally been shown to be beneficial and relatively safe. Adverse events associated with trazodone can be divided into behavioral and systemic signs. Adverse
events previously reported in the literature include drugged or “spacy” behavior, drowsiness, panting, anxiety/restlessness/agitation, vomiting/gagging, behavioral change (counter surfing and trash raiding), excitation, sedation, increased hunger, colitis, and aggression (growling).\textsuperscript{5,7,8}

In veterinary medicine, trazodone is generally dosed at 1.7 to 19.5 mg/kg/d on a daily or as-needed basis with immediate action (not extended-release) tablets and can be given with food.\textsuperscript{1} When administered in combination with tricyclic antidepressants or selective serotonin reuptake inhibitors, it is recommended to begin dosing trazodone at 2 to 5 mg/kg and increase as needed to a maximum dose of 14 mg/kg/d.\textsuperscript{1} Trazodone should be administered about an hour before potential anxiety-inducing stimuli, as its onset of action is approximately 30 to 60 minutes.\textsuperscript{1,5} Gruen and colleagues reported owner-observed duration of effect lasting 4 hours or more.\textsuperscript{5} The parent compound has an elimination half-life of approximately 7 hours in immediate-release tablets.\textsuperscript{1} Trazodone undergoes extensive metabolism in the liver and is predominately excreted via the kidneys.\textsuperscript{1,4}

**EXPOSURE**

**Incidence and Clinical Signs**

The ASPCA Animal Poison Control Center reported 417 incidences involving single-agent trazodone exposures in 379 dogs from 2009 to 2013.\textsuperscript{1} In 104 dogs experiencing adverse effects, sedation and lethargy were reported in 43% of the dogs. Ataxia was reported in 16% and vomiting in 14%. Overall, lethargy, sedation, depression, somnolence, and subdued behavior are considered common signs of trazodone exposure.\textsuperscript{9} Additional information on signs reportedly exhibited by dogs exposed to trazodone alone from January 2003 to November 2016 and the lowest dose at which each sign was seen is provided in Table 1.

**Management**

Decontamination measures are an important component of exposure management. Induction of emesis within 1 hour of exposure is recommended in asymptomatic patients if no contraindications to emesis exist.\textsuperscript{9} Activated charcoal with sorbitol may be recommended in large exposures only.\textsuperscript{9}
Treatment of trazodone overdose generally consists of symptomatic and supportive care. Although adverse effects are often reported, relatively few cases have involved serious signs and no deaths are attributed to trazodone exposure to date. Special attention should be given to ensuring maintenance of cardiac output and being attentive to signs of hyperthermia or hypothermia and correcting as needed. IV fluid therapy may be needed to maintain blood pressure. Diazepam is the drug of choice for managing tremors or seizures, and atropine is suggested for treatment of bradycardia.

Being aware of signs associated with serotonin syndrome is important as this can be a serious and potentially life-threatening condition to manage. Serotonin syndrome develops as a result of an overabundance of serotonin in the central nervous system. It can be a risk in cases of exposure to high doses of trazodone. Clinical signs of serotonin syndrome in dogs, in order of most to least common, include vomiting, diarrhea, seizures, hyperthermia, hyperesthesia, depression, mydriasis, vocalization, death, blindness, hypersalivation, dyspnea, ataxia/paresis, disorientation, hyperreflexia, and coma. Cyproheptadine, a serotonin antagonist, helps combat serotonin syndrome signs. Phenothiazines should be used cautiously because of potential hypotensive effects.

**Interaction With Other Drugs**

Trazodone interacts with numerous drugs, and some of these interactions may have clinically significant effects. Of special interest are medications that may be strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) isoenzyme, which is involved in trazodone metabolism. Azole antifungals (e.g., ketoconazole, itraconazole, fluconazole) and macrolide antibiotics (e.g., erythromycin, telithromycin, clarithromycin) are CYP3A4 inhibitors and thus may enhance the effect of trazodone. Carbamazepine, phenobarbital, phenytoin, rifampicin, and modafinil, which are CYP3A4 inducers, may decrease the effect of trazodone.

Extreme caution should be used with concomitant trazodone and fluoxetine use and/or exposure as it is believed that fluoxetine may inhibit metabolism of trazodone. Additionally, fluoxetine and other serotonergic medications (e.g., paroxetine, sertraline, amitriptyline, clomipramine, amphetamines, dextromethorphan) as well as monoamine oxidase inhibitors (e.g., phenelzine, amitraz, selegiline), metoclopramide, and tramadol, could heighten the risk of serotonin syndrome when combined with trazodone.

Serotonin syndrome patients with severe cardiac disease or renal and/or hepatic function deficits should be monitored very closely and may merit additional treatment measures.

**Prognosis**

The prognosis for patients exposed to trazodone is generally good, especially when serotonin syndrome has not developed. Signs generally resolve in 12 to 24 hours.

**TABLE 1 Signs Associated With Trazodone Exposure in Dogs**

<table>
<thead>
<tr>
<th>SIGN</th>
<th>LOWEST DOSE (MG/KG) AT WHICH SIGN WAS SEEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>0.55</td>
</tr>
<tr>
<td>Depression/vomiting</td>
<td>1.35</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.82</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3.8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5.94</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>6.06</td>
</tr>
<tr>
<td>Vocalization</td>
<td>6.6</td>
</tr>
<tr>
<td>Tremors</td>
<td>8.17</td>
</tr>
<tr>
<td>Disorientation</td>
<td>8.28</td>
</tr>
<tr>
<td>Tachycardia/hypertension</td>
<td>8.83</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>11.8</td>
</tr>
<tr>
<td>Collapse</td>
<td>12.99</td>
</tr>
<tr>
<td>Mydriasis/bradycardia</td>
<td>16.23</td>
</tr>
<tr>
<td>Seizure</td>
<td>78.7</td>
</tr>
</tbody>
</table>
Toxicology Talk is written and reviewed by members of the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center (APCC). The mission of the APCC is to help animals exposed to potentially hazardous substances, which it does by providing 24-hour veterinary and diagnostic treatment recommendations from specially trained veterinary toxicologists.

It also protects and improves animal lives by providing clinical toxicology training to veterinary toxicology residents, consulting services, and case data review.

The ASPCA APCC includes a full staff of veterinarians, including board-certified toxicologists, certified veterinary technicians, and veterinary assistants, and its state-of-the-art emergency call center routinely fields requests for help from all over the world, including South America, Europe, Asia, and the Pacific Islands.

## References


### Toxicology Talk

**Description:**

**NexGard (afoxolaner) Chews** is a registered trademark of Merial. All rights reserved.

**Contact Information:**

©2015 Merial. All rights reserved.

**Description:**

Afoxolaner is available in four sizes of beef-flavored soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.1 mg/lb (2.5 mg/kg) body weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.1 mg/lb (2.5 mg/kg) body weight. Afoxolaner has the chemical composition, 1-Naphthalenecarboxamide, (4S)-1-[(2-(2,2-difluoroethyl)amino)ethyl].

**Indications:**

NexGard is a fast-acting adult flea and is indicated for the treatment and prevention of flea infestations (Ctenocephalides felis felis) and the treatment and control of B. longisporus tick (Boophilus microplus). NexGard is available as brown dog tick (Dermacentor variabilis), American Dog tick (Dermacentor variabilis), Lone Star tick (Amblyomma americanum), and Brown dog tick (Dermacentor variabilis) in infestations in dogs and puppies 6 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

**Dosage and Administration:**

NexGard is given orally once a month, at the minimum dosage of 1.1 mg/lb (2.5 mg/kg).

**Dosing Schedule:**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>NexGard Per Chewable (mg)</th>
<th>NexGard Administered (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 to 10 lbs.</td>
<td>1.5</td>
<td>15</td>
</tr>
<tr>
<td>11.1 to 20 lbs.</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>21.1 to 30 lbs.</td>
<td>3.0</td>
<td>30</td>
</tr>
<tr>
<td>31.1 to 60 lbs.</td>
<td>4.0</td>
<td>40</td>
</tr>
</tbody>
</table>

**Contraindications:**

There are no known contraindications for the use of NexGard.

**Warnings:**

Do not use in humans. Keep this and all other drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

**Precautions:**

The safe use of NexGard is breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures.

**Adverse Reactions:**

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 adult fowlers: 200 adult administered; 200 adult active control), no severe adverse reactions were observed with NexGard.

**Effectiveness:**

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a first seizure within one week after receiving the third dose. The dog was removed and evaluated. Use with caution in dogs with a history of seizures against adverse reactions in dogs with a history of seizures.

**To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Meravel at 1-888-457-4257 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVet/AnimalVetDrugs/SafetyHealth.**

**Mode of Action:**

Afoxolaner is a member of the oxamiphene class, found to be fatal at a dosing rate of 170 mg/kg and acute lethal per os 100 mg/kg. In particular, those that bind to the neurotransmitter gamma-aminobutyric acid (GABA), thereby delaying nerve transmission and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperactivity results in uncoordinated activity of the central nervous system and death of insects and arachnids. The selectivity of oxamiphene between insects and arachnids and mammals may be influenced by the differential sensitivity of the insects and arachnids’ GABA receptors versus mammalian GABA receptors.

**Effectiveness:**

In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated 99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fowlers 24 hours post-infection for 30 days, and was ≥ 93% effective at 12 hours post-infection through Day 21, and on Day 28, NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fowlers 24 hours post-infection for 30 days, and was ≥ 93% effective at 12 hours post-infection through Day 21, and on Day 28, NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28. In a separate well-controlled laboratory study, NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28, NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28.

**Precautions:**

NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28. NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28. NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28. NexGard was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 28.

**Animal Safety:**

In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (2.5 mg/kg) for three treatments every 28 days, followed by three treatments every 28 days for 30 days. In a total of 66 treatments, Dogs in the control group were sham-infested. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology parameters, clinical chemistries, coagulation studies, gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the sham-infested group that vomited four hours after treatment.

**Storage Information:**

Store at or below 30°C (86°F) with excipients permitted up to 40°C (104°F).

**New Supplies:**

NexGard is available in four sizes of beef-flavored soft chewables: 1.13, 2.83, 48, and 88 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3, or 6 beef-flavored chewables.

**References:**