# Comparison of Preference Demonstrated by Dogs When Offered Two Commercially Available Oral ectoparasiticide Products Containing Either Afoxolaner (NexGard®) or sarolaner (Simparica™)

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## ABSTRACT

### Background

Acceptability and palatability of oral formulations are critical issues in establishing and maintaining optimal owner compliance, especially for essential, regularly administered treatments such as monthly flea/tick control products. Such dosage forms are generally developed to be highly palatable if possible, to best ensure they are voluntarily and completely consumed by the pet. The present study aimed to compare the preference of dogs between two commercially available oral ectoparasiticide formulations of afoxolaner (NexGard®, Merial) and sarolaner (Simparica™ , Zoetis).

**Methods:** In two separate experiments, 204 individual dogs from two independent facilities (100 dogs at site 1 and 104 dogs at site 2), were simultaneously offered a choice of similarly-sized, commercially available afoxolaner and sarolaner chewable tablets. The 204 dogs were given an opportunity to smell both products, then both products were simultaneously offered to each dog by hand, allowing the dog to choose and consume one, or the other product, each day for 4 consecutive days. The products were offered from alternate hands on each day, to negate any handedness effect. Individual consumption and related behaviors were recorded. Each dog in the respective studies received offerings from the same individual (Investigator) throughout the studies. The total number of chewable tablets consumed

of each formulation was recorded, and the product preference of each dog was defined as the consumption of a given formulation on more days.

**Results:** A total of 622 (81.4%) afoxolaner chews and 142 (18.6%) sarolaner chews was consumed in both studies. The consumption ratio significantly ($p<0.0001$) favored NexGard over SIMPARICA at 4.4 to 1. Additionally, significantly ($p<0.0001$) more dogs consumed the NexGard Chewables than the SIMPARICA Chewables on each day.

In these two studies combined, for dogs showing a preference over the test period, 93.1 % ($p<0.0001$) of them preferred NexGard to SIMPARICA, where "preference" is defined as consuming the entire product on more days. The preference ratio of NexGard Chewables over SIMPARICA Chewables was 13.5 to 1.

**Conclusion:** This study demonstrated that when dogs were offered a choice between the two ectoparasiticide products, a significant preference was observed for the NexGard formulation.

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## INTRODUCTION

Medication adherence is a critical factor for maintaining effective preventive/control and treatment programs.[1] Adults typically understand the need for medications, and will take necessary medications in a timely manner (when they remember), even if the medication is not highly palatable. The challenge presented in veterinary medicine is more typical of human pediatric medicine. The parent (pet owner) is aware of the critical need for medication, but the child (or pet) does not understand and will not readily tolerate something that has no taste, doesn't taste good, or has an unpleasant after-taste, especially if a product is to be administered long-term. To address this challenge, flavorings have historically been added to medications in an effort to make consuming the medication more appealing or tolerable. As a result, many medications are now formulated as chewables, and oral solutions are promoted as acceptable in human and animal health. Unfortunately, simply adding a flavoring to a medication doesn't always make the product tolerable for the patient, especially when long term-administration is required.[2]

In general, long-term administration of medications has always been a challenge, even with flavor-added formulations. As a result, rather than relying on flavor-added formulations, there has been a trend to seek and develop more highly palatable formulations to carry medications. The consideration for this effort is to improve convenience, thereby maximizing compliance. For companion animals, highly palatable formulations of medications could be considered one means of facilitating the human-animal bond. Indeed, if the product is more desireable to a dog or cat, it would be considered a special treat by both the pet and the pet owner. There is no standard, widely accepted definition of palatability.

Recently, the Committee for Medicinal Products for Veterinary Use (CVMP) of European Medicines Agency ratified a guideline on the demonstration of palatability of veterinary medicinal products, in which palatability is defined as "the property of being acceptable to the mouth, "pleasant to the taste" or "acceptable to the taste". When applied to a Veterinary Medicine Product, this term suggests that the product is palatable enough to ensure voluntary uptake.[3]

Determining palatability in dogs and cats is complicated due to the subjective nature of the individual animal's response at any one time or over a period of time. A preference test is a two-option free choice testing format, designed to address the questions: "Does the animal prefer one option to another? Is the preference constant, over a period of time, rather than with a single offering? Since preference studies offer an alternative, allowing the animals to exercise a choice, such tests are more sensitive than

an acceptance test.[4]

Recently, several compounds from the isoxazoline class have been commercialized as orally administered ectoparasiticide treatment of dogs. The goal of the present study was to examine the preference exhibited by dogs when simultaneously offered the opportunity to choose between two of the oral formulations of molecules from the isoxazoline family: afoxolaner, formulated in a soft, braised beef-flavored chewable (NexGard®, Merial) and sarolaner, formulated as a liver-flavored chewable tablet (Simparica ™, Zoetis).

## MATERIALS AND METHODS

### Test Animals

Two separate experiments of similar design were conducted at two separate study sites. A total of 204 individual dogs, 100 dogs at site 1 (Summit Ridge Farms) and 104 dogs at site 2 (BerTek, Inc.), was included in the studies. At site 1, 49 females and 51 males were included. These dogs weighed between 6.85 kg and 18.65 kg (15.1-43 lbs), and were between the ages of 3.5 months and 14 years. At site 2, 57 males and 47 females were included. These dogs weighed between 9.9 kg and 16.8 kg (22.1 to 37.6 lbs) and were between the ages of 10 months and eight years.

### Animal Welfare and Management

These studies were conducted by experienced, independent contract research organizations. Animals at each site were managed similarly and with due regard for their well-being. Animals were handled in compliance with the Merial's Institutional Animal Care and Use Committee (IACUC) approvals, and the study protocols were reviewed and approved prior to study initiation by the Summit Ridge Farms' IACUC and the BerTek, Inc.'s IACUC. Both facilities meet USDA-APHIS animal welfare requirements, and the dogs were housed in cages of a size in accordance with the Animal Welfare Act. The dogs were allowed to acclimate to the test facility for at least 7 days. Willingness of the dogs to accept treats from an open hand was determined prior to study initiation. All dogs were fed a full, normal ration to satisfy their daily nutritional requirements each morning (at least 4 hours prior to testing), and fresh tap water was available by means of an automatic watering system. All dogs were evaluated twice daily, and cages and food bowls were cleaned and sanitized daily. Dogs were maintained with a 12-hours-of-light/12-hours-of-dark cycle with every attempt made to keep temperature ranges within targeted conditions (from 10°C to 30°C).

### Treatment

The two experiments were conducted on four consecutive days, but Day 0 was not the same day for both studies. Individual dogs were tested in the same manner by the same investigator on each day of the study. At each site, prior to study initiation, one product was chosen at random to be offered to each dog on the first day in the left hand, and the other product was offered to each dog on that day in the right hand. The hands holding the products were reversed each day (to ensure that any hand-preference of individual dogs was negated), for four consecutive days. Commercially available product was used in both assessments, with the dosage selected to minimize the potential total dose of medication administered to dogs during each four-day study, and to ensure the two products were close in size, so as not to create an unfair advantage for either product. NexGard Chewables, 2-4 kg (11.3 mg of afoxolaner), and SIMPARICA Chewables, 2.5-5 kg (10.0 mg of sarolaner), were offered to all dogs in both studies.

### Offering procedure

On Day 0, at site 1, NexGard was chosen at random to be offered in the left hand, and SIMPARICA was offered in the right hand. At site 2, SIMPARICA was randomly chosen to be offered in the left hand, and NexGard in the right. The hands holding product were reversed on each day of both studies to minimize any tendency for "handedness."

The same personnel conducted the offering and recording procedures for each

***Table 1.*** *Summary of dog preferences comparing NexGard and SIMPARICA*

| Day Offered | # Dogs | NexGard | SIMPARICA | None |
|---|---|---|---|---|
| Day 0 | 204 | 152* (82.2%) | 32 (17.8%) | 20 |
| Day 1 | 204 | 157* (83.1%) | 32 (16.9%) | 15 |
| Day 2 | 204 | 149* (76.4%) | 46 (23.6%) | 9 |
| Day 3 | 204 | 164* (84.1%) | 31 (15.9%) | 9 |
| Overall Preference | | 162* (93.1%) | 12 (6.9%) | 30 |

** Significantly different from 50% (p<0.0001)*

dog in this study, and offering began at least four hours after the regular morning feeding. At each offering, the products were held in the fingertips, positioned at the level of the dog's head, approximately one foot apart and equidistant from the dog, allowing the dog to sniff each product. Then the products were moved into the palms, and both hands were opened, allowing the dog the opportunity to take product from one hand or the other.

After the dog selected one of the products, the opposite hand was closed, and both hands were placed behind the Investigator's back. If the dog took neither of the products within one minute, "none" was noted in the raw data.

The dog was observed for consumption of the product it chose. If the product that the dog chose was then expelled from its mouth, the dog was allowed approximately 30 seconds to take the product back into its mouth and consume it. If, after this time period elapsed, the dog did not take the dropped product back into its mouth, the investigator picked up the product with the appropriate hand, and both products were offered again in the same fashion as the previous offering. If, after one minute, the dog chose neither product, "none" was recorded in the raw data for that dog, for that day. The identity of the product that was initially chosen by each dog (or "none"), as well as that of the product that was ultimately consumed by each dog (or "none"), were recorded in the original raw data.

The product consumed in its entirety was the preferred product on that day, and those data were recorded, so each dog's overall preference could be determined, as the dog is the experimental unit in this study.

**Statistical Methods**

All analyses and calculations were performed using SAS Version 9.4. Statistical significance was declared at a two-sided p-value of 0.05.

Consumption ratio was calculated based on the total numbers of tablets of each product consumed during the study. Proportion of tablets of each product consumed was compared using a chi squared test.

To determine the overall preference for NexGard, SIMPARICA, or neither, the number of times each product was entirely consumed was compared for each dog. If one product was consumed more frequently than the other, the dog was defined as preferring that product. Where the number of chewables consumed was tied (0/0, 1/1, 2/2), the dog's preference was defined as "none."

The proportion of dogs consuming NexGard on each day, and the proportion of dogs preferring NexGard over the four daily offerings, were compared to 50% (equal numbers of dogs preferring each product,) ignoring dogs that consumed neither product daily, and dogs that preferred neither product overall, using a chi squared test.

## RESULTS

A total number of 764 tablets was consumed by the 204 dogs during the 4 days of the studies including 622 (81.4%) afoxolaner chews and 142 (18.6%) sarolaner chews. Overall, there was a significant (p<0.0001) consumption ratio (4.4 to 1) in favor of NexGard over SIMPARICA. Significantly

($p<0.0001$) more dogs consumed the NexGard Chewables than the SIMPARICA Chewables on each day (Table 1).

In these two studies combined, for dogs demonstrating a preference over the test period, 93.1% ($p<0.0001$) of them preferred NexGard to SIMPARICA, where "preference" is defined as consuming the entire product on more days (Table 1). One hundred and sixty-two dogs preferred NexGard, whereas 12 dogs preferred SIMPARICA. The preference ratio of NexGard Chewables over SIMPARICA Chewables was 13.5 to 1.

## DISCUSSION

In these two studies combined, when offered a choice of both products, 13.5 times more dogs selected NexGard over SIMPARICA. Those results demonstrate a significant ($p<0.0001$) overall preference for the commercially available soft chew formulation of afoxolaner versus the commercially available formulation of sarolaner. A previous preference comparison of the commercially available oral formulations of afoxolaner (NexGard) and fluralaner (Bravecto®, Merck Animal Health) showed a preference ratio of 4.9 to 1, in favor of NexGard over BRAVECTO.[5]

Palatability of a product is influenced by the smell and taste of the product, and also by its more immediate physical characteristics (e.g. shape, size, texture, hardness, color) and cannot be claimed based solely on its composition (flavorings, sweeteners and/or masking agent) and formulation. The natural preference of dogs and cats is thought to trend toward meat-based flavors and complex mixtures of flavors[4], and no specific characteristic of the primary ingredients in each formulation can explain the difference in the desirability of the products. Therefore, in addition to the smell, taste, and physical characteristics, perhaps the manufacturing processes themselves impact palatability. One or all of these components may explain the difference observed in the present study.

In addition to palatability and acceptability, it is imperative to develop a formulation where the medication is consistently bioavailable, allowing for proper efficacy and safety. Since ectoparasites are the most common afflictions of dogs and cats[6] ensuring efficacy against these pests is critical. NexGard Chewables have been shown, in previous studies, to meet these criteria. The fast absorption of NexGard, as well as its long terminal half-life, allow for rapid elimination of fleas and ticks, as well as protection against such parasites for an entire month.[7]

Pet owners recognize the need to protect their companions from parasites, and they are willing to pay a premium price for ease of administration.[8] It has also been stated that one of the main reasons for pet owner-related parasite control failure is lack of compliance.[9] Thus, any means that would increase the convenience of administration should also favor compliance, increasing overall prevention against ectoparasites. So, in addition to efficacy and safety, which are the primary attributes of a pharmaceutical product, palatability is becoming a criterion for choosing an oral product, as it would positively affect convenience, and likely compliance.

This study demonstrated that, when dogs were offered a choice between the two commercially available formulations of isoxazoline compounds, afoxolaner formulated in a soft, braised beef-flavored chew (NexGard) and sarolaner, formulated as a chewable tablet (SIMPARICA), a significant ($p<0.0001$) preference was observed for the afoxolaner formulation.

**Disclaimers**

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