



# My Client Is Traveling to Asia & Africa. What Is the Risk for Rabies Exposure?

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Despite increasing detection of new *Lyssavirus* infections in bats and concerns about vampire bat-transmitted rabies in Latin America, most human rabies deaths worldwide result from cases of dog-transmitted rabies in Asia and Africa.

Canine rabies has been well controlled in many parts of the world, including North and South America and western Europe, but it remains endemic throughout Asia (including Eurasia) and Africa. Recent estimates indicate that, each year, approximately 15 million humans are exposed to rabies and 60 000 humans die from rabies as a result of being bitten by infected dogs.<sup>1</sup>

## Advising Clients Who Travel About Risks in Rabies-Endemic Areas

Although the term *urban rabies* has often been used to distinguish canine-maintained rabies cycles from wildlife or sylvatic rabies cycles, most cases of canine rabies occur in impoverished

communities in rural areas. This misnomer may contribute to canine rabies-control efforts, particularly in Asia, being focused on cities rather than rural areas.

In addition to a higher number of canine rabies cases, the rabies risk to humans in rural areas is increasing as a result of the unreliable availability of postexposure prophylaxis (PEP), which must be administered within 24 hours of a bite from an infected dog to ensure rabies prevention. Rabies immunoglobulin, a component of PEP critical for providing passive protection against the rabies virus, is almost nonexistent throughout much of Africa.

## The Real Risk

Potential exposure to rabies is not rare in Asia and Africa. In a study of backpackers traveling to Thailand, 4% of travelers experienced potential exposure from licks or bites of unknown dogs. Few of the travelers previously knew about the risk for transmission, and only 18% had received a pre-exposure vaccination before travel.<sup>2</sup>

For travelers to rabies-endemic areas, exposures often result from encounters with puppies. In these circumstances, a minor bite or lick may not seem unusual or alarming; however, these exposures

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represent a medical emergency and require immediate washing of the wound and administration of PEP within 24 hours. In a study of travelers who had sustained a high-risk bite injury in Africa or Asia, only 24% received both postexposure vaccination and immunoglobulin in the country visited.<sup>3</sup> Many travelers have to return home to complete or obtain the full course of PEP, which may place a burden on health services, even in rabies-free countries.

Fortunately, these exposures have rarely resulted in rabies deaths among travelers; however, treatment costs can be high, and travelers may spend months stressed about possible infection.

## RABIES CONTROL & PEP ADMINISTRATION: ONE HEALTH PERSPECTIVES

Rabies control is technically simple and well within reach. Key to rabies control is mass dog vaccination, which has been shown to be feasible and effective in all types of communities across Africa and Asia, even in areas where multiple dogs roam freely. Successful canine vaccination campaigns in Latin America, Asia, and Africa have shown that where dog rabies has been controlled, human rabies deaths have declined and can be eliminated.

Although availability of PEP needs to be improved, particularly in rural areas with the greatest risk for rabies infection, PEP must be administered judiciously to avoid spiralling costs. A One Health approach is critical, and good communication between clinicians and other veterinary team members is essential to assess the status of a biting animal and for incidents of rabies to be communicated by veterinarians to medical authorities.

PEP = postexposure prophylaxis

## Key Messages for Clients

- ▶ Consider vaccination before traveling.
- ▶ Rabies exposure *is possible*, especially in underdeveloped or rural areas.
- ▶ Be mindful of seemingly innocent or innocuous events that are risks, especially when in contact with puppies.

## References

1. Hampson K, Coudeville L, Lembo T, et al. Estimating the global burden of endemic canine rabies. *PLoS Negl Trop Dis*. 2015;9(4): e0003709.
2. Piyaphanee W, Shantavasinkul P, Phumratanaprapin W, et al. Rabies exposure risk among foreign backpackers in Southeast Asia. *Am J Trop Med Hyg*. 2010;82(6):1168-1171.
3. Gautret P, Shaw M, Gazin P, et al. Rabies postexposure prophylaxis in returned injured travelers from France, Australia, and New Zealand: a retrospective study. *J Travel Med*. 2008;15(1):25-30.



## TRIFEXIS® (spinosad + milbemycin oxime) Chewable Tablets

**Caution:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**Before using TRIFEXIS chewable tablets, please consult the product insert, a summary of which follows:**

### Indications:

TRIFEXIS is indicated for the prevention of heartworm disease (*Dirofilaria immitis*). TRIFEXIS kills fleas and is indicated for the prevention and treatment of flea infestations (*Ctenocephalides felis*), and the treatment and control of adult hookworm (*Ancylostoma caninum*), adult roundworm (*Toxocara canis* and *Toxascaris leonina*) and adult whipworm (*Trichuris vulpis*) infections in dogs and puppies 8 weeks of age or older and 5 pounds of body weight or greater.

### Dosage and Administration:

TRIFEXIS is given orally, once a month at the minimum dosage of 13.5 mg/lb (30 mg/kg) spinosad and 0.2 mg/lb (0.5 mg/kg) milbemycin oxime body weight. For heartworm prevention, give once monthly for at least 3 months after exposure to mosquitoes (see **EFFECTIVENESS**).

### Contraindications:

There are no known contraindications to the use of TRIFEXIS.

### Warnings:

Not for human use. Keep this and all drugs out of the reach of children. Serious adverse reactions have been reported following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS (see **ADVERSE REACTIONS**).

### Precautions:

Treatment with fewer than 3 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).

Prior to administration of TRIFEXIS, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. TRIFEXIS is not effective against adult *D. immitis*. While the number of circulating microfilariae may decrease following treatment, TRIFEXIS is not indicated for microfilariae clearance. Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Use with caution in breeding females. The safe use of TRIFEXIS in breeding males has not been evaluated.

Use with caution in dogs with pre-existing epilepsy (see **ADVERSE REACTIONS**). Puppies less than 14 weeks of age may experience a higher rate of vomiting.

### Adverse Reactions:

In a well-controlled US field study, which included a total of 352 dogs (176 treated with TRIFEXIS and 176 treated with an active control), no serious adverse reactions were attributed to administration of TRIFEXIS. All reactions were regarded as mild.

Over the 180-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence >1% (average monthly rate) within any of the 6 months of observation are presented in the following table. The most frequently reported adverse reaction in dogs in the TRIFEXIS group was vomiting.

### Average Monthly Rate (%) of Dogs With Adverse Reactions

Adverse Reaction	TRIFEXIS Chewable Tablets <sup>a</sup>	Active Control Tablets <sup>a</sup>
Vomiting	6.13	3.08
Pruritus	4.00	4.91
Lethargy	2.63	1.54
Diarrhea	2.25	1.54
Dermatitis	1.47	1.45
Skin Reddening	1.37	1.26
Decreased appetite	1.27	1.35
Pinna Reddening	1.18	0.87

<sup>a</sup>n=176 dogs

In the US field study, one dog administered TRIFEXIS experienced a single mild seizure 2 ½ hours after receiving the second monthly dose. The dog remained enrolled and received four additional monthly doses after the event and completed the study without further incident.

Following concomitant extra-label use of ivermectin with spinosad alone, a component of TRIFEXIS, some dogs have experienced the following clinical signs: *trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation*. Spinosad alone has been shown to be safe when administered concurrently with heartworm preventatives at label directions.

In US and European field studies, no dogs experienced seizures when dosed with spinosad alone at the therapeutic dose range of 13.5-27.3 mg/lb (30-60 mg/kg), including 4 dogs with pre-existing epilepsy. Four epileptic dogs that received higher than the maximum recommended dose of 27.3 mg/lb (60 mg/kg) experienced at least one seizure within the week following the second dose of spinosad, but no seizures following the first and third doses. The cause of the seizures observed in the field studies could not be determined.

For technical assistance or to report suspected adverse drug events, contact Elanco Animal Health at 1-888-545-5973. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>

### Post-Approval Experience (Mar 2012):

The following adverse reactions are based on post-approval adverse drug event reporting. The adverse reactions are listed in decreasing order of frequency: vomiting, depression/lethargy, pruritus, anorexia, diarrhea, trembling/shaking, ataxia, seizures, hypersalivation, and skin reddening.

### Effectiveness:

**Heartworm Prevention:** In a well-controlled laboratory study, TRIFEXIS was 100% effective against induced heartworm infections when administered for 3 consecutive monthly doses. Two consecutive monthly doses did not provide 100% effectiveness against heartworm infection. In another well-controlled laboratory study, a single dose of TRIFEXIS was 100% effective against induced heartworm infections. In a well-controlled six-month US field study conducted with TRIFEXIS, no dogs were positive for heartworm infection as determined by heartworm antigen testing performed at the end of the study and again three months later.

### Flea Treatment and Prevention:

In a well-controlled laboratory study, TRIFEXIS demonstrated 100% effectiveness on the first day following treatment and 100% effectiveness on Day 30.

In a well-controlled laboratory study, spinosad, a component of TRIFEXIS, began to kill fleas 30 minutes after administration and demonstrated 100% effectiveness within 4 hours. Spinosad, a component of TRIFEXIS, kills fleas before they can lay eggs. If a severe environmental infestation exists, fleas may persist for a period of time after dose administration due to the emergence of adult fleas from pupae already in the environment. In field studies conducted in households with existing flea infestations of varying severity, flea reductions of 98.0% to 99.8% were observed over the course of 3 monthly treatments with spinosad alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis and pruritus as a direct result of eliminating the fleas.

### Treatment and Control of Intestinal Nematode Infections:

In well-controlled laboratory studies, TRIFEXIS was ≥ 90% effective in removing naturally and experimentally induced adult roundworm, whipworm and hookworm infections.

### Palatability:

TRIFEXIS is a flavored chewable tablet. In a field study of client-owned dogs where 175 dogs were each offered TRIFEXIS once a month for 6 months, dogs voluntarily consumed 54% of the doses when offered plain as if a treat, and 33% of the doses when offered in or on food. The remaining 13% of doses were administered like other tablet medications.

NADA 141-321, Approved by the FDA. Manufactured for Elanco Animal Health, A Division of Eli Lilly & Company Indianapolis, IN 46285

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