Selamectin is an avermectin parasiticide with a variety of labeled uses in dogs and cats. It is unique in the avermectin class as it is applied topically and not administered orally. It was developed by Pfizer (now Zoetis) and approved by the U.S. Food and Drug Administration (FDA) in 1999 with the trade names Revolution and Stronghold. The trade name varies by geographic region.1

Recently, an abbreviated new animal drug application (ANADA) was approved by the FDA for a generic version of selamectin (Senergy).2 Senergy is currently distributed by Virbac and available in multiple color-coded tube formulations for dosing based on dog or cat body weight. Several other drug manufacturers have also submitted ANADAs for generic selamectin formulations.

In November 2018, the FDA approved Revolution Plus (selamectin and sarolaner topical solution; Zoetis, zoetis.com) for use in cats. Revolution Plus is now the most comprehensive feline antiparasitic product on the market with the addition of sarolaner to provide efficacy against 3 different tick species.3

MECHANISM OF ACTION
Selamectin belongs to the macrocyclic lactone family, which comprises 2 groups: avermectins and milbemycins. Members of the avermectin group—such as ivermectin, eprinomectin, and doramectin, as well as selamectin—are structurally related. Avermectins bind to glutamate-gated chloride channels, which causes increased permeability of chloride to neurons and leads to hyperpolarization and ultimately parasite death. Mammals do not have glutamate-gated chloride channels and are thus spared the life-threatening effects of avermectin binding.

However, avermectins, including selamectin, do bind GABA_A receptors present in the central nervous system of mammals. Normally, the intact blood–brain barrier with functional P-glycoprotein (P-gp) protects the GABA_A receptors. P-gp is a transmembrane efflux protein encoded by the ABCB1 (formerly MDR1) gene and it is responsible for actively transporting various
xenobiotics out of the central nervous system.\(^4\) However, some dogs have a genetic defect (\(ABCB1-1\Delta\)) that results in nonfunctional P-gp and increased risk for various adverse effects associated with excessive P-gp substrate drug concentrations in the central nervous system \((\text{BOX 1})\).\(^5\) The Washington State University Veterinary Clinical Pharmacology Laboratory genotypes dogs via a blood sample or cheek swab; samples can be submitted via veterinarian, or owners may send samples to the laboratory directly (\text{vcpl.vetmed.wsu.edu}). Dogs that are homozygous for the \(ABCB1-1\Delta\) mutation therefore cannot be treated with extra-label doses of ivermectin, as may be used for conditions such as demodectic mange. It is important to note that the labeled doses of FDA-approved heartworm prevention products are safe, even in homozygous mutant dogs.

Since selamectin is available only in a topical formulation, it is not as subject to significant oral overdose potential as may be seen with other avermectin products.\(^3\)

**Efficacy**

See \text{TABLE 1} for a summary of the labeled indications for selamectin in dogs and cats.

Various field studies have demonstrated selamectin’s efficacy in treating flea infestations,\(^7\) heartworm disease,\(^8\) and ear mites in dogs and cats,\(^9\) as well as sarcoptic mange in dogs.\(^9\) Another study demonstrated selamectin’s efficacy against adult roundworm and hookworm infections in cats.\(^10\) In dogs, Revolution (selamectin) has a label for controlling tick infestations due to \textit{Dermacentor variabilis}.\(^11\)

As nontraditional pets grow in popularity, veterinarians are faced with treatment decisions in species for which there are little to no pharmacologic data. While extra-label provisions allow veterinarians to select empiric treatments, the lack of data and overall understanding of adverse effect profiles of commonly used drugs can lead to treatment failures or even death. Veterinarians must follow all requirements for extra-label drug use as set forth by the FDA and rely on the limited studies available for the best-informed drug decision making. Several of these studies involving guinea pigs and rabbits are highlighted below.

**Guinea Pigs**

The most common ectoparasite infesting guinea pigs is the skin mite \textit{Trixacarus caviae},\(^12\) which causes intense pruritus. However, there is a dearth of feasible topical treatment options for these easily stressed animals. A clinical trial investigating a single topical dose of selamectin versus a one-time subcutaneous injection of ivermectin found that both treatments were successful at eliminating \textit{T caviae} mites. The authors concluded that the convenience of the single topical dose of

<table>
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<tr>
<th><strong>INDICATION</strong></th>
<th><strong>DOGS</strong></th>
<th><strong>CATS</strong></th>
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<tbody>
<tr>
<td>Prevention and control of flea infestations ((Ctenocephalides felis))</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevention of heartworm disease caused by \textit{Dirofilaria immitis}</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of ear mites ((Otodectes cynotis))</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of sarcoptic mange ((Sarcoptes scabiei))</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Control of tick infestations due to \textit{Dermacentor variabilis}</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Treatment and control of roundworm ((Toxocara cati))</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of hookworm ((Ancylostoma tubaeforme))</td>
<td>No</td>
<td>Yes</td>
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</table>
Selamectin made it the top treatment modality option. Based on the study protocol, a single dose of 15 mg/kg is recommended.

Rabbits

Cheyletiella mites, colloquially known as “walking dandruff,” usually cause pruritus, scaling, and subclinical disease in rabbits. These nonburrowing mites are zoonotic, which makes them especially relevant to rabbit owners. However, there are no FDA-approved products labeled for Cheyletiella in rabbits; veterinarians must extrapolate dosing of existing parasiticides based on available literature. Like guinea pigs, rabbits are easily stressed, making the ease of administration with selamectin’s topical formulation an important factor when formulating treatment protocols.

A team of researchers in South Korea treated 23 Cheyletiella-infested rabbits with a single dose of selamectin at 12 mg/kg and found all rabbits were mite-free at the end of 5 weeks. A retrospective study of cheyletiellosis treatments in pet rabbits examined medical records for various treatment protocols and divided the rabbits into 3 groups. Rabbits were treated with subcutaneous ivermectin alone, a combination of subcutaneous and oral ivermectin, or topical selamectin. The authors concluded that all 3 protocols were effective and safe for use, although the group receiving the combination of subcutaneous and oral ivermectin trended toward lower efficacy.

Textbooks and formularies may advocate particular products for flea control in rabbits; however, veterinarians must realize there is very little in the literature regarding actual pharmacokinetics and safety. A group of researchers at Kansas State University investigated the pharmacokinetics, efficacy, and adverse effects of 2 selamectin doses (10 mg/kg or 20 mg/kg) on flea-infested New Zealand white rabbits. Based on the flea populations in the rabbits, the study concluded that selamectin was rapidly absorbed transdermally and a dosage of 20 mg/kg applied every 7 days was recommended for treating flea-infested rabbits. While the study provides some evidence as to actual drug concentrations in that particular population of rabbits, there are no data on long-term safety of multiple selamectin applications in rabbits.

REVOLUTION PLUS

Revolution Plus, a selamectin and sarolaner topical solution, provides coverage against a variety of important parasites in cats. TABLE 2 summarizes how

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>REVOLUTION (SELAMECTIN)</th>
<th>REVOLUTION PLUS (SELAMECTIN AND SAROLANER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention and control of flea infestations (Ctenocephalides felis)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevention of heartworm disease caused by Dirofilaria immitis</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Treatment and control of ear mites (Otodectes cynotis)</td>
<td>Yes</td>
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<td>Treatment and control of sarcoptic mange (Sarcoptes scabiei)</td>
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</tr>
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<td>Control of tick infestations due to Dermacentor variabilis</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Treatment and control of roundworm (Toxocara cati)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of hookworm (Ancylostoma tubaeforme)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of infestation with Ixodes scapularis (black-legged tick)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of infestation with Amblyomma maculatum (Gulf Coast tick)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment and control of infestation with Dermacentor variabilis (American dog tick)</td>
<td>No</td>
<td>Yes</td>
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the addition of sarolaner changes the overall product profile. Sarolaner is a member of the isoxazoline class, which also includes fluralaner, aloxanlaner, and lotilaner.

Ticks in Cats
Many cat owners mistakenly assume that since their pets reside strictly indoors and groom fastidiously, they are not at risk of tick infestation. Cats are also notoriously difficult to medicate (whether via oral or topical route), and many owners may balk at the idea of a regularly scheduled medication administration date with their cat. Unfortunately, recent data suggest that cats are subject to tick infestations, including ticks that transmit zoonotic diseases, such as the black-legged tick (Ixodes scapularis can cause anaplasmosis and Lyme disease), the American dog tick (Dermacentor variabilis can cause tularemia and Rocky Mountain spotted fever, both potentially deadly to humans), and the Gulf Coast tick (Amblyomma maculatum can cause spotted fever).

In a series of studies funded by Zoetis, researchers experimentally infected cats with I scapularis, D variabilis, and A maculatum and divided the cats into 2 groups: placebo or selamectin plus sarolaner. In one of the studies with I scapularis and D variabilis, another cohort of cats was treated with selamectin alone. Based on the data from all of the studies, the sarolaner–selamectin combination product was effective against the current tick infestation and prevented reinfestation with all tick species for 4 weeks. Selamectin as a sole agent did not affect I scapularis and provided only some efficacy against D variabilis.

Heartworm Disease in Cats
Heartworm disease represents another treatment challenge for many cat owners. The obstacle does not lie with product availability, as there are many commercially available preventive options; rather, as with ticks, many owners assume that their indoor-only cat is not susceptible and simply opt out or forget to treat their cat.

Feline heartworm disease is more difficult to diagnose than canine heartworm disease, and clinical signs in cats may be mistaken for respiratory or gastrointestinal disease. While topical selamectin shields cats and dogs from heartworm disease caused by Dirofilaria immitis, there is mounting evidence that there are populations of D immitis resistant to conventional macrocyclic lactones in dogs. The role of macrocyclic lactone resistance and the relationship to D immitis are relatively unknown in cats. Using an experimentally formulated combination of topical selamectin and sarolaner, researchers employed by Zoetis assessed the efficacy of various dosing regimens against a macrocyclic lactone–resistant strain of D immitis. One dose of selamectin alone or selamectin plus sarolaner was incompletely efficacious at preventing the development of a macrocyclic lactone–resistant strain of D immitis in this population of cats; however, administering the selamectin and sarolaner combination product for 3 consecutive monthly doses was 100% efficacious. Ultimately, adding sarolaner to the already commercially available selamectin product did not impede selamectin’s ability to prevent heartworm disease in cats, and this study provides another perspective for veterinarians making drug recommendations for their feline patients.

CONCLUSION
While selamectin has been on the market for the past 20 years, its daily use has evolved thanks to new studies, popular pocket pets, and emerging infectious concerns. As always, veterinarians using drugs in an extra-label manner must adhere to the FDA requirements as set forth by the Animal Medicinal Drug Use Clarification Act and diligently assess the literature for pertinent updates. New product options represent exciting new tools in the crusade against parasites in companion animals.

References


18. Vatta AF, Young DR, King VL, Myers MR. Comparative efficacy of topical treatments with Revolution® Plus (selamectin and sarolaner) and Bravecto® for Cats (fluralaner) against Ixodes scapularis ticks on cats. Vet Parasitol. 2019;270(suppl 1):S58-S63.

