QUESTIONS TO ASK THE VETERINARIAN ABOUT MY ITCHY DOG

WHAT’S CAUSING MY DOG TO SCRATCH SO MUCH?
There are many reasons your dog may be itchy. Most commonly, dogs can be sensitive to seasonal pollens, outdoor and indoor molds, and dust mites (found in carpets, stuffed furniture, and bedding). Your dog may also be allergic to food, fleas, or even ingredients found in shampoos or laundry detergents. Only your veterinarian can determine the reason for your dog’s allergic itch and prescribe the necessary treatment. Don’t worry, your dog will get relief soon!

WHAT ARE THE SIGNS I SHOULD LOOK OUT FOR?
All dogs scratch, lick, and chew—but when you notice it becoming more frequent and excessive, it’s time to see the veterinarian. Here are some of the most common signs of allergic itch in dogs:

- Frequent licking, biting, or scratching
- Excessive rolling, rubbing, or scooting
- Recurrent ear problems (head shaking, ear discharge/odor, scratching at the ears)
- Hair loss
- Body odor
- Skin changes (rash, redness)

WHEN SHOULD I SCHEDULE THE APPOINTMENT?
Allergic itch in dogs is easier to treat early, when the first signs appear. Identifying the condition early and getting the right treatment can bring your dog faster relief and help prevent skin infections that can result from scratching. So, when you see the signs, call your veterinarian.

CAN’T I JUST TRY AN OVER-THE-COUNTER ANTIHISTAMINE TO RELIEVE MY DOG’S ALLERGIC ITCH?
Allergies in dogs are not the same as in humans. Medications we use to relieve our respiratory allergies may not be appropriate for our furry friends. Antihistamines are often not effective in treating allergic itch in dogs. In fact, they can put your dog at risk for progression of allergic itch and infection—because they don’t treat the underlying cause and the itch continues.

Allergic itch can also flare up during specific seasons (such as spring and fall, when seasonal allergens are at high levels). Antihistamines have been shown to offer little or no benefit in treating flare-ups in a majority of dogs with allergic itch.¹

ARE STEROIDS OK TO USE?
It’s important to talk with your veterinarian. Allergic itch in dogs is a lifelong condition that requires lifelong management. Some therapies may not be a good option if your dog requires long-term treatment.

In the short term, steroids can cause unwanted side effects such as excessive drinking, urinating, and appetite.²
ARE THERE TREATMENT OPTIONS OTHER THAN ANTIHISTAMINES OR STEROIDS?

Yes! Getting the right treatment early can help avoid unnecessary suffering and the costs associated with treatments that just don’t do the trick.

ASK YOUR VETERINARIAN ABOUT APOQUEL®.

APOQUEL is not a steroid or antihistamine. Unlike other medicines, APOQUEL blocks allergic itch at the source. So, it works on the underlying cause of allergic itch to provide fast relief.

WHAT SHOULD I KNOW ABOUT APOQUEL?

- In a short-term clinical study, the most common side effects of APOQUEL were vomiting and diarrhea.

APOQUEL works fast—
sstarts within 4 hours to relieve allergic itch—and controls it within 24 hours.

APOQUEL is the #1 prescribed medicine
for allergic dog itch and has been prescribed to over 7 million dogs.

INDICATIONS

Control of pruritus (itching) associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

IMPORTANT SAFETY INFORMATION

Do not use APOQUEL in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporine. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticides, antibiotics and vaccines.

For more information, please see the accompanying full Prescribing Information.
APOQUEL is not for use in dogs with serious infections.

APOQUEL is not for use in dogs less than 12 months of age (see Animal Safety).

Description: APOQUEL (oclacinib tablet) is a synthetic Janus Kinase (JAK) inhibitor. The chemical composition of APOQUEL is N-methyl[trans-4-(methyl-1H-pyrimidin-2(3H)-dipyrimidin-4-ylamino)cyclohexyl]methanesulfonamide (2Z)-2-butenedicarboxylic acid. The chemical structure of oclacinib tablet is:

![Chemical structure of oclacinib](image)

Indications: Control of pruritus associated with atopic dermatitis and control of atopic dermatitis in dogs at least 12 months of age.

Dosage and Administration: The dose of APOQUEL (oclacinib tablet) tablets is 0.4 to 0.6 mg oclacinib/kg body weight, administered orally, twice daily for up to 14 days, and then administered once daily for maintenance therapy. APOQUEL may be administered with or without food.

Dosing Chart

<table>
<thead>
<tr>
<th>Weight Range (in lb)</th>
<th>Weight Range (in Kg)</th>
<th>Number of Tablets to be Administered</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>3.6 mg Tablets</td>
</tr>
<tr>
<td>6.6</td>
<td>9.9</td>
<td>3.0 4.4 0.5</td>
</tr>
<tr>
<td>10.0</td>
<td>14.9</td>
<td>4.5 5.9 -</td>
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<tr>
<td>15.0</td>
<td>19.9</td>
<td>6.0 8.9 1 -</td>
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<tr>
<td>20.0</td>
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<td>30.0</td>
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<td>13.5 19.9 -</td>
</tr>
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<td>45.0</td>
<td>59.9</td>
<td>20.0 26.9 -</td>
</tr>
<tr>
<td>60.0</td>
<td>89.9</td>
<td>27.0 39.9 -</td>
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<tr>
<td>90.0</td>
<td>129.9</td>
<td>40.0 54.9 -</td>
</tr>
<tr>
<td>130.0</td>
<td>175.9</td>
<td>55.0 80.0 1.5</td>
</tr>
</tbody>
</table>

Warnings: APOQUEL is not for use in dogs less than 12 months of age (see Animal Safety). APOQUEL is not for use in dogs with serious infections. APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions (see Adverse Reactions and Animal Safety).

Human Warnings: This product is not for human use. Keep this and all other drugs out of reach of children. In case of accidental ingestion, seek medical attention immediately. In case of accidental ingestion, seek medical attention immediately.

Precautions: APOQUEL is not for use in breeding dogs, or pregnant or lactating bitches. The use of APOQUEL has not been evaluated in combination with glucocorticoids, cyclosporine, or other immunosuppressive agents. Dogs receiving APOQUEL should be monitored for the development of infections, including demodicosis, and neoplasia.

Adverse Reactions: Control of Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of oclacinib for the control of atopic dermatitis in dogs, 152 dogs treated with APOQUEL and 147 dogs treated with placebo (vehicle control) were evaluated as part of the Clinical Pharmacology Study. The dogs were treated with oclacinib (2.6 mg/kg) administered once daily for a total of 112 days. Mean time on this study was 372 days (range 1 to 610 days). Of these 299 dogs, one dog developed a Grade III mast cell tumor after 60 days of APOQUEL administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study. Additional dogs receiving APOQUEL were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

In the 283 dogs that received APOQUEL, the following additional clinical signs were reported after beginning APOQUEL (percentage of dogs with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specific dermal lumps (12.0%), otitis (9.8%), vomiting (9.2%), diarrhea (8.0%), histiocytosis (9.9%), cystitis (3.5%), anorexia (3.2%), lethargy (2.8%), yeast skin infections (5.5%), pododermatitis (2.5%), lipoma (2.1%), polydipsia (1.4%), lymphadenopathy (1.1%), nausea (1.1%), increased appetite (1.1%), aggression (1.1%), and weight loss (0.7).

Control of Pruritus Associated with Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of oclacinib for the control of pruritus associated with atopic dermatitis in dogs, 216 dogs treated with APOQUEL and 220 dogs treated with placebo (vehicle control) were evaluated for safety. During the 30-day study, there were no fatalities and no adverse reactions required hospital care. Adverse reactions reported (and percent of dogs affected) during Days 0-7 included diarrhea (2.3% APOQUEL, 0.9% placebo), vomiting (2.3%, APOQUEL, 1.8% placebo), lethargy (1.8% APOQUEL, 1.4% placebo), anorexia (1.4% APOQUEL, 0.0% placebo), and polydipsia (1.4% APOQUEL, 0.0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five APOQUEL group dogs were withdrawn from study because of: darkening of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystitis (1 dog); an infrequent footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on APOQUEL had decreased leukocytes (neutrophil, eosinophil, and monocyte counts) and serum globulin, and increased cholesterol and lipase compared to the placebo group but group means remained within the normal range. Mean lymphocyte counts were transiently increased at Day 14 in the APOQUEL group. Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received APOQUEL. Between the masked and unmasked study, 152 dogs received at least one dose of APOQUEL. Of these 152 dogs, two dogs were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatis and severe secondary pyoderma after 19 days of APOQUEL administration, and one dog that developed generalized demodicosis after 28 days of APOQUEL administration. Two other dogs on APOQUEL were withdrawn from study due to suspected or confirmed malignant neoplasia and subsequently euthanized, including one dog that developed signs associated with a heart base mass after 21 days of APOQUEL administration, and one dog that developed a Grade III mast cell tumor after 60 days of APOQUEL administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study. Additional dogs receiving APOQUEL were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

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/AnimalVeterinary/SafetyHealth.

Clinical Pharmacology: Mechanism of Action

Oclacinib inhibits the function of a variety of pruritogenic cytokines and pro-inflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity. It has little effect on cytokines involved in hematopoiesis that are dependent on JAK2. Oclacinib is not a corticosteroid or an antihistamine.

Pharmacokinetics

In dogs, oclacinib maleate is rapidly and well absorbed following oral administration, with mean time to peak plasma concentrations (tmax) of 0.8 to 1.0 hour. Following oral administration of 0.4-0.6 mg oclacinib/kg to 24 dogs, the mean (80% confidence limits [CL]) maximum concentration (Cmax) was 324 (281, 372) ng/mL and the mean area under the plasma concentration-time curve from 0 to extrapolated to infinity (AUC0-infinity) was 1890 (1680, 2110) ng/min/mL. The prandial state of dogs significantly affect the rate or extent of absorption. The absolute bioavailability of oclacinib maleate was 89%.

Oclacinib has low protein binding with 66.3-69.7% bound in fortified canine plasma at nominal concentrations ranging from 10-1000 ng/mL. The apparent mean (95% CL) volume of distribution at steady-state was 942 (870, 1014) mL/kg body weight.

Oclacinib is metabolized to the multiple metabolites and one major oxidative metabolite was identified in plasma and urine. Overall the major clearance route is metabolism with minor contributions from renal and biliary elimination. Inhibition of canine cytochrome P450 enzymes by oclacinib is minimal; the inhibitory concentrations (IC90) are 50 fold greater than the observed Cmax values at the use dose.

Mean (95% CL) total body oclacinib clearance from plasma was low – 316 (237, 396) mL/h/kg body weight (5.3 mL/min/kg body weight). Following IV and PO administration, the terminal t1/2 appeared similar with mean values of 3.9 (2.3, 4.7) and 4.1 (3.1, 5.2) hours, respectively.
A double-masked, 112-day, controlled study was conducted at 18 U.S. veterinary hospitals. The study enrolled 299 client-owned dogs with atopic dermatitis. Dogs were randomized to treatment with APOQUEL (152 dogs: tablets administered at a dose of 0.4-0.6 mg/kg per dose twice daily for 14 days and then once daily) or placebo (147 dogs: vehicle control, tablets administered on the same schedule). During the study, dogs could not be treated with other drugs that could affect the assessment of effectiveness, such as corticosteroids, anti-histamines, or cyclosporine. Treatment success for pruritus for each dog was defined as at least a 2 cm decrease from baseline on a 10 cm visual analog scale (VAS) in pruritus, assessed by the Owner, on Day 28. Treatment success for skin lesions was defined as a 50% decrease from the baseline Canine Atopic Dermatitis Extent and Severity Index (CADESI) score, assessed by the Veterinarian, on Day 28. The estimated proportion of dogs with Treatment Success in Owner-assessed pruritus VAS score and in Veterinarian-assessed CADESI score was greater and significantly different for the APOQUEL group compared to the placebo group.

Compared to the placebo group, mean Owner-assessed pruritus VAS scores (on Days 1, 2, 7, 14, and 28) and Veterinarian-assessed CADESI scores (on Days 14 and 28) were lower (improved) in dogs in the APOQUEL group. By Day 30, 86.4% (127/147) of the placebo group dogs and 15% (23/152) of the APOQUEL group dogs withdrew from the masked study because of worsening clinical signs, and had the option to enroll in an unmasked study and receive APOQUEL. For dogs that continued APOQUEL treatment beyond one month, the mean Owner-assessed pruritus VAS scores and Veterinarian-assessed CADESI scores continued to improve through study end at Day 112.

A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 299 client-owned dogs with atopic dermatitis. Dogs were randomized to treatment with APOQUEL (216 dogs: tablets administered at a dose of 0.4-0.6 mg/kg twice daily) or placebo (220 dogs: vehicle control, tablets administered twice daily). During the study, dogs could not be treated with other drugs that could affect the assessment of pruritus or dermal inflammation such as corticosteroids, anti-histamines, or cyclosporine. Treatment success for each dog was defined as at least a 2 cm decrease from baseline on a 10 cm visual analog scale (VAS) in pruritus, assessed by the Owner, on at least 5 of the 7 evaluation days. The estimated proportion of dogs with Treatment Success was greater and significantly different for the APOQUEL group compared to the placebo group.

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