ARE STEROIDS OK TO USE?
It’s important to talk with your vet. 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.

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 vet 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 vet. 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 vet.

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.

ARE STEROIDS OK TO USE?
It’s important to talk with your vet. 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.
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 VET ABOUT APOQUEL® (OCLACITINIB TABLET).**

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?**

- Apoquel works fast—
  - starts within **4 hours** to relieve allergic itch—and controls it within 24 hours.\(^3,4\)

- Apoquel is the #1 prescribed medicine
  - for allergic dog itch and has been prescribed to over **10 million** dogs.\(^5,6\)

- In a 5-year safety review, the most common individual side effects reported with Apoquel were vomiting, diarrhea, lethargy, anorexia, and bloodwork changes.\(^7\)

**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. Consider the risks and benefits of treatment in dogs with a history of recurrence of these conditions. New neoplastic conditions (benign and malignant) were observed in clinical studies and post-approval. Apoquel has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporines. 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.

**References:**

Apoptil (oclatinib tablet)

For oral use in dogs only

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

Description: Apoptil (oclatinib maleate) is a synthetic Janus Kinase (JAK) inhibitor. The chemical composition of Apoptil is N-methyl[trans-4-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino) cyclohexyl] methanesulfonamide (C22:2-butenenedioate). The chemical structure of oclacinib maleate is:

\[
\text{OCOOH} \quad \text{NHHMe}
\]

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

Dosage and Administration: The dose of Apoptil (oclatinib maleate) tablets is 0.18 to 0.27 mg oclacinib (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. Apoptil 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>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>Low High</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 0.1</td>
</tr>
<tr>
<td>15.0</td>
<td>19.9</td>
<td>6.0 8.9 1.0</td>
</tr>
<tr>
<td>20.0</td>
<td>29.9</td>
<td>9.0 13.4 1.0</td>
</tr>
<tr>
<td>30.0</td>
<td>44.9</td>
<td>13.5 19.9 0.1</td>
</tr>
<tr>
<td>45.0</td>
<td>59.9</td>
<td>20.0 26.9 2.0</td>
</tr>
<tr>
<td>60.0</td>
<td>89.9</td>
<td>27.0 39.9 1.0</td>
</tr>
<tr>
<td>90.0</td>
<td>129.9</td>
<td>40.0 54.9 1.5</td>
</tr>
<tr>
<td>130.0</td>
<td>175.9</td>
<td>55.0 80.0 2.0</td>
</tr>
</tbody>
</table>

Warnings: Apoptil is not for use in dogs less than 12 months of age (see Animal Safety). Apoptil modulates the immune system. Apoptil is not for use in dogs with serious infections. Apoptil may increase susceptibility to infection, including demodicosis, and exacerbation of neoplastic conditions (see Precautions, Adverse Reactions, Post-Approval Experience, and Animal Safety).

New neoplastic conditions (benign and malignant) were observed in dogs treated with Apoptil during clinical studies and have been reported in the post-approval period (see Adverse Reactions and Post-Approval Experience).

Consider the risks and benefits of treatment prior to initiating Apoptil in dogs with a history of recurrent serious infections or recurrent demodicosis or neoplasia (see Adverse Reactions, Post-Approval Experience, and Animal Safety).

Keep Apoptil in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Human Warnings: This product is not for human use. Keep this and all drugs out of reach of children. For use in dogs only. Wash hands immediately after handling the tablets. In case of accidental eye contact, flush immediately with water or saline for at least 15 minutes and then seek medical attention. In case of accidental ingestion, seek medical attention immediately.

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

Adverse Reactions: Control of Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of occlacinib for the control of atopic dermatitis in dogs, 152 dogs treated with Apoptil and 147 dogs treated with placebo (vehicle control) were evaluated for safety. The majority of dogs in the placebo group withdrew from the 112-day study by Day 16. Adverse reactions reported (and percent of dogs affected) during days 0-16 included diarrhea (4.6% Apoptil, 3.4% placebo), vomiting (3.9% Apoptil, 4.1% placebo), anorexia (2.6% Apoptil, 0% placebo), new cutaneous or subcutaneous lumps (2.6% Apoptil, 2.7% placebo), and lethargy (2.7% Apoptil, 4.1% placebo). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on Apoptil 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 Apoptil group.

Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received Apoptil. Between the masked and unmasked study, 283 dogs received at least one dose of Apoptil. Of these 283 dogs, two were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatitis and severe secondary pyodermia after 19 days of Apoptil administration, and another dog that developed generalized demodicosis after 28 days of Apoptil administration. Two other dogs on Apoptil 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 Apoptil administration, and one dog that developed a Grade III mast cell tumor after 60 days of Apoptil 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 Apoptil were hospitalized for diagnosis and treatment of pneumonia (one dog), transient bloody vomiting and stool (one dog), and cystitis with urethritis (one dog).

In the 283 dogs that received Apoptil, the following additional clinical signs were reported after beginning Apoptil (percentage of dogs with at least one report of the clinical sign as a non-pre-existing finding): pyodermia (12.0%), non-specific dermal lumps (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (6.0%), histiocytoma (3.9%), cystitis (3.5%), anorexia (3.2%), lethargy (2.8%), yeast skin infections (2.5%), 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 Allergic Dermatitis

In a masked field study to assess the effectiveness and safety of occlacinib for the control of pruritus associated with allergic dermatitis in dogs, 216 dogs treated with Apoptil and 220 dogs treated with placebo (vehicle control) were evaluated for safety. During the 30-day study, there were no hospitalizations and no adverse reactions requiring hospital care. Adverse reactions reported (and percent of dogs affected) during Days 0-7 included diarrhea (2.3% Apoptil, 0.9% placebo), vomiting (2.3% Apoptil, 1.8% placebo), lethargy (1.8% Apoptil, 1.4% placebo), anorexia (1.4% Apoptil, 0% placebo), and polydipsia (1.4% Apoptil, 0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five Apoptil group dogs were withdrawn from study because of: darkening areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystitis (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). Dogs in the Apoptil group had a slight decrease in mean white blood cell counts (neutrophil, eosinophil, and monocyte counts) that remained within the normal reference range. Mean lymphocyte count for dogs in the Apoptil group increased at Day 7, but returned to pretreatment levels by study end without a break in Apoptil administration. Serum cholesterol increased in 25% of Apoptil group dogs, but mean cholesterol remained within the reference range.

Continuation Field Study

After completing Apoptil field studies, 239 dogs enrolled in an unmasked (no placebo control), continuation therapy study receiving Apoptil for an unrestricted period of time. Mean time on this study was 372 days (range 1 to 610 days). Of these, one dog developed demodicosis following 273 days of Apoptil administration. One dog developed dermal pigmentated viral plaques following 266 days of Apoptil administration. One dog developed a moderate severe bronchopneumonia after 272 days of Apoptil administration; this infection resolved with antimicrobial treatment and temporary discontinuation of Apoptil. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of Apoptil administration. Six dogs were euthanized because of suspected malignant neoplasms: including thoracic metastatic, abdominal metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell carcinoma after 17, 120, 175, 49, 141, and 286 days of Apoptil administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 and 91 days of Apoptil administration. Two other dogs on Apoptil 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 Apoptil administration, and one dog that developed generalized demodicosis after 28 days of Apoptil administration. Two dogs each developed a Grade III mast cell tumor after 60 days of Apoptil administration.

Post-Approval Experience (2020)

The following adverse events are based on post-approval adverse drug experience reporting for Apoptil. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events reported in dogs are listed in decreasing order of reporting frequency.

- Vomiting, lethargy, anorexia, diarrhea, elevated liver enzymes, dermatitis (i.e. crusts, pododermatitis, pyoderma), seizures, polydipsia, and demodicosis.
- Benign, malignant, and unclassified neoplasms, dermal masses (including papillomas and histiocytomas), lymphoma and other cancers have been reported.
- Death (including euthanasia) has been reported.

Contact Information:

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Zoetis Inc. at 1-888-963-6471 or www.zoetis.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.
Clinical Pharmacology:

Mechanism of Action

Oclacitinib 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. Oclacitinib is not a corticosteroid or an antihistamine.

Pharmacokinetics

In dogs, oclacitinib maleate is rapidly and well absorbed following oral administration, with mean time to peak plasma concentrations (Tmax) of less than 1 hour. Following oral administration of 0.4-0.6 mg oclacitinib/kg to 24 dogs, the mean (90% confidence limits [CL]) maximum concentration (Cmax) was 324 (281, 372) ng/mL and the mean area under the plasma concentration-time curve from 0 and extrapolated to infinity (AUC0-inf) was 1890 (1690, 2110) ng/hr/mL. The prandial state of dogs does not significantly affect the rate or extent of absorption. The absolute bioavailability of oclacitinib maleate was 89%.

Oclacitinib has low protein binding with 66.3-69.7% bound in fortified canine plasma at nominal concentrations ranging from 10-100 ng/mL. The apparent mean (95% CL) volume of distribution at steady-state was 942 (870, 1014) mL/kg body weight.

Oclacitinib is metabolized in the dog to 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 oclacitinib is minimal; the inhibitory concentrations (IC50s) are 50 fold greater than the observed Cmax values at use doses.

Mean (95% CL) total body oclacitinib clearance from plasma was low – 316 (237, 396) mL/hr/kg body weight (3.4 mL/min/kg body weight). Following IV and PO administration, the terminal t1/2 appeared similar with mean values of 5.5 (2.2, 4.7) and 4.1 (3.1, 5.2) hours, respectively.

Effectiveness:

Control of Atopic Dermatitis

A double-masked, 112-day, controlled study was conducted at 18 U.S. veterinary hospitals. The study enrolled 199 client-owned dogs with 10 cm 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 at 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.

Estimated Proportion of Dogs with Treatment Success, Atopic Dermatitis

<table>
<thead>
<tr>
<th>Effectiveness Parameter</th>
<th>APOQUEL</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner-Assessed Pruritus VAS</td>
<td>0.66 (n = 131)</td>
<td>0.04 (n = 133)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Veteraninarian-Assessed CADESI</td>
<td>0.49 (n = 134)</td>
<td>0.04 (n = 134)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Compared to the placebo group, mean Owner-assessed pruritus VAS scores (on Days 1, 2, 7, 14, and 28) and Veteraninarian-assessed CADESI scores (on Days 14 and 28) were lower (improved) in dogs in the APOQUEL group. By Day 30, 86% (127/147) of the placebo group dogs had achieved a 2 cm reduction on the 10 cm Owner-assessed pruritus VAS 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.

Control of Pruritus Associated with Allergic Dermatitis

A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and other/unspecified allergic 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.

Estimated Proportion of Dogs with Treatment Success, Allergic Dermatitis

<table>
<thead>
<tr>
<th>Effectiveness Parameter</th>
<th>APOQUEL</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner-Assessed Pruritus VAS</td>
<td>0.67 (n = 203)</td>
<td>0.29 (n = 204)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Animal Safety:

Margin of Safety in 12 Month Old Dogs

Clinical safety was administered to healthy, one-year-old Beagle dogs twice daily for 6 weeks, followed by once daily for 20 weeks, at 0.6 mg/kg (1X maximum exposure dose, 8 dogs), 1.8 mg/kg (3X, 8 dogs), and 3.0 mg/kg (5X, 8 dogs) oclacitinib for 26 weeks. Eight dogs received placebo (empty gelatin capsule) at the same dosage schedule. Clinical observations that were considered likely to be related to oclacitinib maleate included papillomas and a dose-dependent increase in the number and frequency of interdigital furunculosis (cytosis) on one or more feet during the study. Additional clinical observations were primarily related to the interdigital furunculosis and included dermatitis (local alopecia, erythema, abrasions, scabbing/crusts, and edema of feet) and lymphadenopathy of peripheral nodes. Microscopic findings considered to be oclacitinib maleate-related included decreased cellularity (lymphoid) in Gut-Associated Lymphoid Tissue (GALT), spleen, thymus, cervical and mesenteric lymph node; and decreased cellularity of sternal and femoral bone marrow. Lymphoid hyperplasia and chronic active inflammation was seen in lymph nodes draining feet affected with interdigital furunculosis. Five oclacitinib maleate-treated dogs had microscopic evidence of mild interstitial pneumonia. Clinical pathology findings considered to be oclacitinib maleate-related included mild, dose-dependent reduction in hemoglobin, hematocrit, and reticulocyte counts during the twice daily dosing period with decreases in the leucocyte subsets of lymphocytes, eosinophils, and basophils. Total proteins were decreased over time primarily due to the albumin fraction.

Vaccine Response Study

An adequate immune response (serology) to killed rabies (RV), modified live canine distemper virus (CDV), and modified live canine parvovirus (CPV) vaccination was achieved in eight 16-week old vaccine naïve puppies that were administered oclacitinib maleate at 1.8 mg/kg oclacitinib (3X maximum exposure dose) twice daily for 64 days. For modified live canine parainfluenza virus (CPI), < 80% (6 of 8) of the dogs achieved adequate serologic response. Clinical observations that were considered likely to be related to oclacitinib maleate included enlarged lymph nodes, interdigital furunculosis, cysts, and pododermatitis. One oclacitinib maleate-treated dog (26-week-old) was euthanized on Day 74 after physical examination revealed the dog to be febrile, lethargic, with pale mucous membranes and frank blood in stool. Necropsy revealed pneumonia of short duration and evidence of chronic lymphadenitis of mesenteric lymph nodes. During the three month recovery phase to this study, one oclacitinib maleate-treated dog (32-weeks-old) was euthanized on Day 28 due to clinical signs which included enlarged prescapular lymph nodes, bilateral epiphora, lethargy, mild dyspnea, and fever. The dog showed an elevated white blood cell (WBC) count. Necropsy revealed lesions consistent with sepsis secondary to immunosuppression. Bone marrow hyperplasia was consistent with response to sepsis.

Margin of Safety in 6 Month Old Dogs

A margin of safety study in 6-month-old dogs was discontinued after four months due to the development of bacterial pneumonia and generalized demodex mange infections in dogs in the high dose (3X and 5X) treatment groups, dosed at 1.8 and 3.0 mg/kg oclacitinib twice daily, for the entire study.

Storage Conditions:

APOQUEL should be stored at controlled room temperature between 20° to 25°C (68° to 77°F) with excursions between 15° to 40°C (59° to 104°F).

How Supplied:

APOQUEL tablets contain 3.6 mg, 5.4 mg, or 16 mg of oclacitinib as oclacitinib maleate per tablet. Each strength tablets are packaged in 100 and 250 count bottles. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides.

Approved by FDA under NADA # 141-345