“Itching like a dog is bothering me!”

See How Apoquel Helps Dogs With Skin Allergies Get Fast Relief

Next to You, Apoquel Is a Dog’s Best Friend
If Your Dog’s Itching Like Crazy, Ask for Apoquel

All dogs itch sometimes, but when you notice it happening more and more, it could be a sign of a medical condition. Only your veterinarian can determine if your dog’s itch is due to an infection, parasites, or skin allergies.

When Is an Itch More Than Just an Itch?

It’s important to stop your dog’s itch and get to the underlying cause of itch early. This will help avoid additional skin problems and get your dog enjoying life again. So don’t wait—talk to your vet today.

Common Signs of Skin Allergies in Dogs

• Frequent scratching, licking, biting, or chewing
• Excessive rolling, rubbing, or scooting
• Recurrent ear problems: head shaking, ear discharge, or scratching at the ears
• Hair loss, body odor, or skin changes: rash, redness, greasy skin, or scabs

If your dog’s itching persists or if your dog exhibits any of the signs above, reach out to your vet today. Itching can be a medical problem that needs attention.

Even though common at-home treatments such as oatmeal baths, lotions, antihistamines or topical over-the-counter medications may temporarily relieve your dog’s itch, they may not be getting to the root of the problem.

Talk to Your Veterinarian Today

“Ask your vet for Apoquel.”
Apoquel Stops the Itch Right at the Source

Apoquel is a revolutionary medicine that works differently than other medicines. It’s a prescription tablet that goes right to the source—to stop the underlying cause of itch in dogs with skin allergies.

Fast
Apoquel Tablet starts relieving itch within 4 hours; both Apoquel Tablet and Apoquel Chewable control itch within 24 hours.

Effective
Works right at the source to stop itching and relieve inflammation from skin allergies (allergic dermatitis). Apoquel reduces the itch and also decreases inflammation, redness, or swelling of the skin—so your dog feels better as quickly as possible.

Safe
Can be used short-term or for long-term maintenance therapy in dogs 12 months of age and older.

Daily Tablet
Available as a tablet and a chewable to make daily dosing even easier, and can be given with or without food.

Apoquel is the #1 prescribed oral medication for allergic itch in dogs.

Apoquel May Be Used With Many Other Common Therapies, Including:

- Nonsteroidal anti-inflammatory drugs also called NSAIDs (e.g., carprofen)
- Vaccines (e.g., rabies)
- Allergy shots or drops (e.g., allergen-specific immunotherapy)
- Parasiticides
- Antibiotics and antifungals

The use of Apoquel has not been evaluated in combination with corticosteroids, cyclosporine, or other systemic immunosuppressive agents. Apoquel is not for use in dogs with serious infections or for use in breeding, pregnant, or lactating dogs.

Talk to Your Veterinarian Today

Next to You, Apoquel Is a Dog’s Best Friend
Apoquel Is Not a Steroid or an Antihistamine

Steroids

- May offer relief but may not be a good option if your dog requires long-term treatment
- 50% of dog owners report side effects with steroids
- Can cause side effects such as excessive drinking and urinating, increased appetite, and behavior changes (e.g., increased anxiety) even when used short term

Antihistamines

- Can relieve allergies in humans but are typically not effective at reducing the itch in dogs with skin allergies (allergic dermatitis)
- Can put your dog at risk for progression of skin allergies and secondary skin infections because they don’t treat the underlying cause of the itch so it continues
- Offer little or no benefit in treating flare-ups in a majority of dogs with skin allergies (allergic dermatitis)

Apoquel Side Effects: In a 5-year safety review, the most common individual side effects reported with Apoquel were vomiting, diarrhea, lethargy, anorexia, and blood work changes.

Indications

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

Apoquel and Apoquel Chewable Important Safety Information

Do not use Apoquel or Apoquel Chewable in dogs less than 12 months of age or those with serious infections. Apoquel and Apoquel Chewable 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 and Apoquel Chewable have 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 and Apoquel Chewable have been used safely with many common medications including parasiticides, antibiotics and vaccines.

See Accompanying Full Prescribing Information.

“Wow— rewards, too?!”
With each eligible Apoquel purchase, earn up to $80 in Rewards to pay for future vet care.

Sign up for Zoetis Petcare Rewards* and see full offer details at zoetispetcare.com/rewards

*Program Terms and Conditions apply.

To learn more about Apoquel, scan this code or visit apoqueldogs.com

Next to You, Apoquel Is a Dog’s Best Friend

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See Accompanying Full Prescribing Information.

References:
Adverse Reactions:
Control of Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of oclacitinib for the control of atopic dermatitis in dogs, 152 dogs treated with APOQUEL 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% APOQUEL, 3.4% placebo), vomiting (3.9% APOQUEL, 4.1% placebo), anorexia (2.6% APOQUEL, 0% placebo), new cutaneous or subcutaneous lump (2.6% APOQUEL, 2.7% placebo), and lethargy (1.4% APOQUEL, 4% placebo). 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.

Dosage and Administration: The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/0 (0.4 to 0.6 mg oclacitinib/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 (lb)</th>
<th>Weight Range (Kg)</th>
<th>Number of Tablets to be Administered</th>
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<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>3.6 mg Tablets</td>
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<tr>
<td></td>
<td></td>
<td>5.4 mg Tablets</td>
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<td></td>
<td></td>
<td>16 mg Tablets</td>
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<tr>
<td>6.6</td>
<td>9.9</td>
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<td>0.5</td>
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<td></td>
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<tr>
<td>10.0</td>
<td>14.9</td>
<td>4.5</td>
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<td>15.0</td>
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<td>45.0</td>
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<td>60.0</td>
<td>89.9</td>
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<td>90.0</td>
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<tr>
<td>130.0</td>
<td>175.9</td>
<td>55.0</td>
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<td>2</td>
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</tbody>
</table>

Warnings: APOQUEL is not for use in dogs less than 12 months of age (see Animal Safety). APOQUEL modulates the immune system. APOQUEL is not for use in dogs with serious infections. APOQUEL 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 APOQUEL 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 APOQUEL in dogs with a history of recurrent serious infections or recurrent demodicosis or neoplasia (see Adverse Reactions, Post-Approval Experience, and Animal Safety).

Keep APOQUEL 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 exposure using these data.

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.

Pharmacokinetics
In dogs, oclacitinib maleate is rapidly and well absorbed following oral administration, with mean time to peak plasma concentrations (T_{max}) 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 ([C]_{max}) was 324 (281, 372) ng/mL and the mean area under the plasma concentration-time curve from 0 and extrapolated to infinity (AUC_{0-inf}) was 1890 (1690, 2110) ng·h/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 10-1000 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 ([IC]_{50}) are 50 fold greater than the observed T_{max} values for use doses.

Mean (95% CL) total body oclacitinib 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 t_{1/2} appeared similar with mean values of 3.5 (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 299 client-owned dogs with cutaneous 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 Veterinarian, on Day 28. Treatment success for skin lesions was defined as a 50% decrease from the baseline ('apoquine' 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 (n = 203)</th>
<th>Placebo (n = 134)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner-Assessed Pruritus VAS</td>
<td>0.66 (n = 131)</td>
<td>0.44 (n = 133)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Veterinarian-Assessed CADESI</td>
<td>0.49 (n = 134)</td>
<td>0.44 (n = 134)</td>
<td>&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) andVeterinarian-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 and 15% (32/215) 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.

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 (n = 203)</th>
<th>Placebo (n = 204)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Proportion of Dogs with Treatment Success</td>
<td>0.67</td>
<td>0.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

After one week of treatment, 86.4% of APOQUEL group dogs compared with 42.5% of placebo group dogs had achieved a 2 cm reduction on the 10 cm Owner-assessed pruritus VAS. On each of the 7 days, mean Owner-assessed pruritus VAS scores were lower in dogs in the APOQUEL group (See Figure 1). Veterinarians used a 10 cm VAS scale to assess each dog’s dermatitis. After one week of treatment, the mean Veterinarian-assessed VAS dermatitis score for the dogs in the APOQUEL group was lower at 2.2 cm (improved from a baseline value of 6.2 cm) compared with the placebo group mean score of 4.9 cm (from a baseline value of 6.2 cm). For dogs that continued APOQUEL treatment beyond one week, the mean score continued to improve through study end at Day 30.

Animal Safety:
Margin of Safety in 12 Month Old Dogs
Clinical observations were considered likely to be related to oclacitinib maleate treatment included papillomas and a dose-dependent increase in the number and frequency of interdigital furunculosis (cysts) 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 lymphangitis 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 leukocyte 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 84 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 treatment included enlarged lymph nodes, interdigital furunculosis, cysts, and pododermatitis. One oclacitinib maleate-treated dog (26-weeks-old) was euthanized on Day 74 after physical examination revealed the dog to be febrile, lethargic, with pale mucous membranes and frank dyspnea. 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

Figure 1: Owner Assessed Pruritus VAS Scores by treatment for Days 0-7

<table>
<thead>
<tr>
<th>Day of Study</th>
<th>Mean VAS Score (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>6</td>
<td>Very Mild</td>
</tr>
</tbody>
</table>

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: December 2020 40033180A0P
Dosing Chart

Dosage and Administration:

Control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs, 152 dogs treated with oclacitinib FCT 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% oclacitinib FCT, 3.4% placebo), vomiting (3.9% oclacitinib FCT, 4.1% placebo), anorexia (2.5% oclacitinib FCT, 0% placebo), new cutaneous or subcutaneous lump (2.6% oclacitinib FCT, 2.7% placebo), and transient bloody vomiting and stool (0.5% oclacitinib FCT, 1.4% placebo). In most cases, diarrhea, vomiting, anorexia, and lethargy spontaneously resolved with continued dosing. Dogs on oclacitinib FCT 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 oclacitinib FCT group.

Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received oclacitinib FCT. Between the masked and unmasked study, 283 dogs received oclacitinib FCT, 150 dogs received a one dose of oclacitinib FCT. Of these 283 dogs, two dogs were withdrawn from study due to suspected treatment-related adverse reactions: one dog that had an intense flare-up of dermatitis and severe secondary pyoderma after 19 days of oclacitinib FCT administration, and one dog that developed generalized demodicosis after 28 days of oclacitinib FCT administration. Two other dogs on oclacitinib FCT 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 oclacitinib FCT administration, and one dog that developed a Grade III mast cell tumor after 60 days of oclacitinib FCT 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 oclacitinib FCT 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 oclacitinib FCT, the following additional clinical signs were reported after beginning oclacitinib FCT (percentage of dogs at which least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specified dermal lumps (12.0%), itch (9.8%), vomiting (5.2%), diarrhea (6.0%), hiccoughs (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 oclacitinib for the control of pruritus associated with allergic dermatitis in dogs, 216 dogs treated with oclacitinib FCT 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 requiring discontinuation of oclacitinib FCT. Adverse reactions reported (and percent of dogs affected) during Days 0-7 included diarrhea (2.3% oclacitinib FCT, 0.9% placebo), vomiting (2.3% oclacitinib FCT, 1.8% placebo), lethargy (1.1%), anorexia (1.4% oclacitinib FCT, 0.0% placebo), and polydipsia (1.4% oclacitinib FCT, 0.0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five oclacitinib FCT group dogs were withdrawn from study because of: darkening areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and anorexia (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea and vomiting (1 dog). One dog developed temporary discontinuation of oclacitinib FCT. One dog developed lethargy (1 dog). Dogs in the oclacitinib FCT 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 oclacitinib FCT Group increased at Day 7, but returned to pretreatment levels by study end without a break in oclacitinib FCT administration. Serum cholesterol increased in 25% of oclacitinib FCT group dogs, but mean cholesterol remained within the reference range.

Continuation Field Study

After completing oclacitinib FCT field studies, 239 dogs enrolled in an unmasked (no placebo control), continuation therapy study receiving oclacitinib FCT for an unrestricted period of time. Mean time on this study was 372 days (range 1 to 610 days). Of these 239 dogs, one dog developed demodicosis following 273 days of oclacitinib FCT administration. One dog developed dermal pigmentary viral plaques following 266 days of oclacitinib FCT administration. One dog developed a moderately severe bronchopneumonia after 272 days of oclacitinib FCT administration; this infection resolved with antimicrobial treatment and temporary discontinuation of oclacitinib FCT. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of oclacitinib FCT administration. Six dogs were euthanized because of suspected malignant neoplasms; including mammary metastasis, abdominal metastasis, splenic, frontal sinus, and intracranial neoplasms, and transitional cell carcinoma after 17, 120, 141, and 286 days of oclacitinib FCT administration, respectively. Two dogs each developed a Grade II mast cell tumor after 32 and 91 days of oclacitinib FCT administration, respectively. One dog developed low grade B-cell lymphoma after 392 days of oclacitinib FCT administration. Two dogs each developed an apocrine gland adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of oclacitinib FCT administration, respectively. One dog developed a low grade spindle cell sarcoma after 320 days of oclacitinib FCT administration.

Post-Approval Experience (2020)

The following adverse events are based on post-approval adverse drug experience reporting for oclacitinib FCT. Not all adverse events are reported to FDA/CVM. It is not always possible to definitively 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 demodiosis.

Benign, malignant, and unclassified neoplasms, dermal masses (including papillomas and neoplasms, and transitional cell carcinoma after 17, 120, 141, and 286 days of oclacitinib FCT administration, respectively. Two dogs each developed a Grade II mast cell tumor after 32 and 91 days of oclacitinib FCT administration, respectively. One dog developed a low grade B-cell lymphoma after 392 days of oclacitinib FCT administration. Two dogs each developed an apocrine gland adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of oclacitinib FCT administration, respectively. One dog developed a low grade spindle cell sarcoma after 320 days of oclacitinib FCT administration.

Post-Approval Experience (2020)

The following adverse events are based on post-approval adverse drug experience reporting for oclacitinib FCT. Not all adverse events are reported to FDA/CVM. It is not always possible to definitively 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 demodiosis.

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 1-888-963-8471 or www.zoetics.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 is a selective inhibitor of 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

A pharmacokinetic study was conducted to compare the bioavailability of APOQUEL CHEWABLE with oclacitinib FCT. Bioequivalence (BE) was demonstrated for the extent of exposure between APOQUEL CHEWABLE and oclacitinib FCT with the geometric mean ratio for the area under the curve from time zero to the last sampling time point 1.03 and the 90% confidence interval (CI) within the acceptable range of 0.80 to 1.25. However, BE was not demonstrated for the maximum concentration (Cmax), with the geometric mean ratio of 0.86 and 90% CI of 0.78 to 0.95, outside the acceptable range of 0.8 to 1.25. Based on simulations, in accordance with regulatory requirements, the differences in Cmax values between APOQUEL CHEWABLE and oclacitinib FCT after the first dose are likely to be minimal at steady-state.

In dogs, oclacitinib is rapidly and well absorbed following oral administration, with mean time values between APOQUEL CHEWABLE and oclacitinib FCT after the first dose are likely to be minimal at steady-state.

Oclacitinib has low protein binding with 66.3-69.7% bound in fortified canine plasma at nominal concentrations ranging from 10-100 ng/mL (ratio of dose to concentration was 1:20). The 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 (IC50) are 50 fold greater than the observed Cmax values at the use doses.

Effectiveness:
The effectiveness of APOQUEL CHEWABLE was established by pharmacokinetic data comparing oclacitinib FCT to APOQUEL CHEWABLE (see Clinical Pharmacology).

Center equivalence was not met for the lower 90% CI of the maximum concentration (Cmax), which may delay the speed of onset of effectiveness of APOQUEL CHEWABLE at the first dose or when transitioning from the oclacitinib FCT.

Control of Atopic Dermatitis

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 oclacitinib FCT (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 was defined as at least a 2 cm decrease from baseline on a 10 cm visual analog scale (VAS) in pruritus, assessed by the Veterinary, on Day 28. Treatment success for skin lesions was defined as a 50% decrease from the baseline Canine Atopic Dermatitis Extent and Severity Index (CADI) score, assessed by the Veterinary, on Day 28. The estimated proportion of dogs with Treatment Success in Owner-assessed pruritus VAS score and in Veteraninarian-assessed CADI score was greater and significantly different for the oclacitinib FCT group compared to the placebo group.

Estimated Proportion of Dogs with Treatment Success, Atopic Dermatitis

<table>
<thead>
<tr>
<th>Effectiveness Parameter</th>
<th>oclacitinib FCT</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>&lt;0.0001</td>
</tr>
<tr>
<td>Veteraninarian-Assessed CADI</td>
<td>0.49 (n = 134)</td>
<td>0.04 (n = 134)</td>
<td>&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 CADI scores (on Days 14 and 28) were lower (improved) in dogs in the oclacitinib FCT group. By Day 30, 86.4% (127/147) of the placebo group dogs and 15% (21/146) of the oclacitinib FCT group dogs withdrew from the masked study because of worsening clinical signs, and had the option to enroll in an unmasked study and receive oclacitinib FCT. After one week of treatment, the mean Owner-assessed pruritus VAS scores and Veteraninarian-assessed CADI scores continued to improve through study end at Day 112.

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 168 client-owned dogs with a history of allergic dermatitis, atopic dermatitis, food allergy, or other unspecified allergic dermatitis. Dogs were randomized to treatment with oclacitinib FCT (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 was measured by the fraction of dogs with a 2 cm reduction on the 10 cm Owner-assessed pruritus VAS. On each of the 7 days, mean Owner-assessed pruritus VAS scores were lower in dogs in the oclacitinib FCT group (see Figure 1). Veterinarians used a 10 cm VAS scale to assess each dog’s dermatism. After one week of treatment, the mean Veteraninarian-assessed dermatism score for the dogs in the oclacitinib FCT group was lower at 2.2 cm (improved from a baseline score of 6.2 cm) compared to the placebo group mean score of 4.8 cm (a baseline value of 6.2 cm). For dogs that continued oclacitinib FCT treatment beyond one week, the Veterinarian-assessed dermatism scores continued to improve through study end at Day 30.

Figure 1: Owner Assessed Pruritus VAS Scores by treatment for Days 0-7

Palatability

In a well-controlled U.S. field study, in which 1,662 doses of APOQUEL CHEWABLE were administered to 120 dogs, a total of 1,522 doses (91.6%) were accepted voluntarily within 5 minutes. Of the 140 doses unaccepted after 5 minutes, 134 (96%) were consumed with assisted (2X food treats by or piling), and 6 (4.4%) doses were refused.

Animal Safety

Margin of Safety in 12 Month Old Dogs

Oclacitinib maleate 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 parental and dose-dependent increase in the number and frequency of interdigital furunculosis (cysts) on one or more feet during the study. Additional clinical observations were primarily related to the interdigital furunculosis and included dermatisms (local alopecia, erythema, abrasions, scabbing/crusts, and excoriation 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 hematoglobin, 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 maleate maximum exposure dose) twice daily for 84 days. For modified live canine parvovirus vaccine (CPV), > 80% (6 of 8) of the dogs achieved adequate serologic response. Clinical observations that were considered likely to be related to oclacitinib maleate treatment included enlarged lymph nodes, interdigital furunculosis, cysts, and pododermatitis. One oclacitinib-maleate-treated dog (26-weeks old) was euthanized on Day 14 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 lymphohyalitis 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 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 CHEWABLE 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 CHEWABLE tablets contain 3.6 mg, 5.4 mg, or 16 mg of oclacitinib as oclacitinib maleate per tablet. Each strength chewable tablets are packaged in 100 and 250 count bottles. Each oclacitinib maleate tablet is pentagon shaped, scored, on both sides, and have a descriptive (S, S, M, M or L) debossed on one face across the score line. The S (small), M (medium) and L (large) markings correspond to the tablet strengths of 3.6 mg, 5.4 mg and 16 mg respectively.

Approved by FDA under NADA 141-555

Distributed by:

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