Apoquel® (oclacitinib tablet): Fast-Acting and Safe Itch Relief for Dogs

Your veterinarian has recommended Apoquel to help control your dog’s itch due to allergic skin disease. Apoquel provides fast, effective relief from itch and inflammation without many of the side effects associated with steroids.1,2

*Common side effects of steroids include polyuria, polydipsia and polyphagia. Side effects of Apoquel reported most often are vomiting, diarrhea, lethargy, anorexia and blood work changes.

WHAT IS ALLERGIC SKIN DISEASE?

Itching in dogs can be caused by fleas, food or environmental allergens such as pollens, molds or house-dust mites. The 4 most common allergies are:

- FLEA ALLERGY
- ENVIRONMENTAL INDOOR AND OUTDOOR ALLERGIES (pollen, dust mites, or mold)
- FOOD ALLERGY
- CONTACT ALLERGY (carpet, shampoo, environmental chemicals— insecticides, fertilizers)

WHAT IS APOQUEL USED FOR?

Apoquel is used for the control of itch associated with allergic skin disease and for control of atopic skin disease in dogs at least 12 months of age. Apoquel significantly reduces itching, and also decreases the associated inflammation, redness or swelling of the skin.

WHAT CAN I EXPECT WHEN MY DOG RECEIVES APOQUEL?

**Fast Relief**

- Apoquel starts to relieve itch within 4 hours, which is comparable to steroids.3
- Apoquel effectively controls itch within 24 hours.1

**Unique Treatment**

- Unlike other treatments, Apoquel targets a key itch signal in the nervous system and has minimal impact on the immune system. Apoquel also allows your veterinarian to continue to diagnose the underlying cause of itch while providing your dog with relief.1,4

**Safety**

Apoquel is safe to use in dogs 12 months of age and older. Additionally, Apoquel:

- Can be used long-term for maintenance therapy
- Can be used with many other drugs5:
  - Including NSAIDs, anti-infectives, parasiticides, antifungals, and allergen-specific immunotherapy
- The use of Apoquel has not been evaluated in combination with other systemic immunosuppressants, such as corticosteroids and cyclosporine

Apoquel is not for use in dogs with serious infections, or for use in breeding, pregnant, or lactating dogs.

**Apoquel is not a steroid.**

- 55% of dog owners report side effects with steroids5
- Common side effects of steroids include excessive urination, and increased thirst and appetite1,2,6

Apoquel works differently than steroids.7,8 Zoetis performed a comprehensive 5-year pharmacovigilance review of side-effects reported to them. In order of frequency, the most common adverse events were vomiting, diarrhea, lethargy, anorexia and blood work changes, and for each of these, the reported incidence rate was very rare, or less than 1 event per 10,000 treatments.9,10

Weighing the side effects and the need for itch relief can feel like you are on an emotional roller coaster. But, knowing the facts will help you and your dog’s veterinarian make the best choice for relief.

**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 accompanying full Prescribing Information.

**References:**

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Demodicosis, and neoplasia.

Precautions:
In case of accidental ingestion, seek medical attention immediately. This product is not for human use. Keep this and all drugs out of reach of children. For use accidental ingestion or overdose. Keep APOQUEL in a secure location out of reach of dogs, cats, and other animals to prevent

Animal Safety

Post-Approval Experience

of recurrent serious infections or recurrent demodicosis or neoplasia (see Precautions, Adverse Reactions, Post-Approval Experience and Adverse Reactions (one dermal, one anal sac) after approximately 210 and 320 days of APOQUEL administration, respectively. One dog developed low grade B-cell lymphoma after 392 days administration, two dogs each developed a Grade II mast cell tumor after 52 and 91 days of APOQUEL administration, were euthanized because of suspected malignant neoplasms: including thoracic metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell abdominal metastatic, splenic, frontal sinus, and intracranial neoplasms, and transitional cell neoplasms, 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 II 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 urethrosis (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-existing existing): pyoderma (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 oclacitinib for the control of pruritus associated with allergic 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 hospitalizations and no adverse reactions requiring 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, 0.4% placebo), and polydipsia (1.4% APOQUEL, 0% placebo). In most of these cases, signs spontaneously resolved with continued dosing. Five APOQUEL 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 lethargy (1 dog). Dogs in the APOQUEL 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 APOQUEL group increased at Day 7, but returned to pretreatment levels by study end without a break in APOQUEL administration. Serum cholesterol increased in 25% of APOQUEL group dogs, but mean cholesterol remained within the reference range.

Continuation Field Study

After completing APOQUEL field studies, 239 dogs enrolled in an unmasked (no placebo control) continuation therapy study receiving APOQUEL 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 APOQUEL administration, One dog developed dermal pigmented viral plaques following 266 days of APOQUEL administration. One dog developed a moderately severe bronchopneumonia after 272 days of APOQUEL administration; this infection resolved with antimicrobial treatment and temporary discontinuation of APOQUEL. One dog was euthanized after developing abdominal ascites and pleural effusion of unknown etiology after 450 days of APOQUEL 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 APOQUEL administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 and 91 days of APOQUEL administration, respectively. One dog developed low grade B-cell lymphoma after 392 days of APOQUEL administration. Two dogs each developed an apparent grade II adenocarcinoma (one dermal, one anal sac) after approximately 210 and 320 days of APOQUEL administration, respectively. One dog developed a low grade oral spindle cell sarcoma after 320 days of APOQUEL administration.

Post-Approval Experience (2020)

The following adverse events are based on post-approval adverse drug experience reporting for APOQUEL. 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 30 (19, 37) 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·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 baseline. 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 Tmax values for use doses.

Mean (95% CL) total body oclacitinib clearance from plasma was low – 316 (237, 396) mL/hr/kg body weight (3.3 mL/min/kg body weight). Following IV and PO administration, the terminal half-life 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 299 client-owned dogs with 10% or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, primary or secondary bacterial infection, yeast, or other/unspecified allergic 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 cytokine inhibitors. 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 score in 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 = 131)</th>
<th>Placebo (n = 133)</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>Veterinarian-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) 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% (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.

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 allergenic 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 dermatological findings, such as corticosteroids, anti-histamines, or cytokine inhibitors. 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>Owner-Assessed Pruritus VAS</td>
<td>0.67</td>
<td>0.29</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Animal Safety:

Margin of Safety in 12 Month Old Dogs
Clinically important adverse events considered likely to be related to oclacitinib maleate treatment included enlarged lymph nodes, interdigital furunculosis, cysts in subcutaneous tissues, and lameness, and were primarily related to the interdigital furunculosis (cysts) on one or more feet during the study.

Vaccine Response Study
An adequate immune response (serology) to killed rabies 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 parvovirus (CPV), < 80% (6 of 8) of the dogs achieved adequate serologic response. 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 (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 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 inflammatory/lymphoid hyperplasia of the GALT. Clinical pathology findings considered to be oclacitinib maleate-related included mild, dose-dependent reduction in hemoglobin, hematocrit, and red blood cell 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.

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>Score</th>
<th>Mean VAS Score (cm)</th>
</tr>
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<tbody>
<tr>
<td>Severe</td>
<td>8.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.0</td>
</tr>
<tr>
<td>Mild</td>
<td>2.0</td>
</tr>
<tr>
<td>Very Mild</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of Study</th>
<th>Mean VAS Score (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.0</td>
</tr>
<tr>
<td>1</td>
<td>6.0</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
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<tr>
<td>3</td>
<td>2.0</td>
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<tr>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
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<tr>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>0.0</td>
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Zoetis Inc.
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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 papillomas and a dose-dependent increase in the number and frequency of interdigital furunculosis (cysts) on one or more feet during the study.

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