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: APOQUEL (oclacitinib maleate) is a synthetic Janus Kinase (JAK) inhibitor. The chemical composition of APOQUEL is N-methyl-trans-4-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)loxycyclohexyl methanesulfonamide (Z)-2-butenamide.

The chemical structure of oclacitinib maleate is:

![chemical structure of oclacitinib maleate]

Dosing Chart

<table>
<thead>
<tr>
<th>Weight Range (in lb)</th>
<th>Number of Tablets to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.6</td>
<td>0.5</td>
</tr>
<tr>
<td>10.0</td>
<td>0.5</td>
</tr>
<tr>
<td>15.0</td>
<td>1</td>
</tr>
<tr>
<td>20.0</td>
<td>2</td>
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<tr>
<td>30.0</td>
<td>2</td>
</tr>
<tr>
<td>45.0</td>
<td>2</td>
</tr>
<tr>
<td>60.0</td>
<td>2</td>
</tr>
<tr>
<td>90.0</td>
<td>2</td>
</tr>
<tr>
<td>130.0</td>
<td>2</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 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: 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 systemic 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 oclacitinib for the control of atopic dermatitis in dogs, 102 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 (4.8% APOQUEL, 3.4% placebo), vomiting (3.9% APOQUEL, 4.1% placebo), anorexia (2.6% APOQUEL, 5.0% placebo), new cutaneous or subcutaneous lump (2.6% APOQUEL, 2.7% placebo), and lethargy (2.0% APOQUEL, 1.4% 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 mean values remained within the normal range. Mean lymphocyte counts were transiently increased at Day 17 in the APOQUEL group.

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 fatalities 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, 0.0% 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 areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystitis (1 dog); an inflammatory footpad and vomiting (1 dog); and diarrhea, vomiting, and lethargy (1 dog). In the placebo group, one dog developed an allergic reaction to a subcutaneous injection and was withdrawn from study.

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 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 melanoma (one dog), transient bloody vomiting and stool (one dog), and cystitis with urolithiasis (one dog).

Control of Pruritus Associated with Allergic Dermatitis

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 ulcers (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (8.0%), histiocytosis (9.9%), 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).

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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 (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-∞) was 1280 (1240, 1620) ng·h/mL. The prandial state of dogs did 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 to the dog 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 dose.

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 t½ appeared similar with mean values of 3.9 (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 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. The estimated proportion of dogs with Treatment Success was 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.

Estimated Proportion of Dogs with Treatment Success, Atopic Dermatitis

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

Effectiveness of Dogs with Treatment Success, Atopic Dermatitis

<table>
<thead>
<tr>
<th>Effectiveness Parameter</th>
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</tr>
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<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).

Vaccine Response Study

An adequate immune response (serology) to killed rabies (VR), modified live canine distemper virus (CDV), and modified live canine parvovirus (CPV) vaccination was achieved in eight 16-week old canine naive 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 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 blood in stool. 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

An adequate margin of safety was confirmed in 6-month-old dogs based on the following studies:

1. 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 polydipsia and a dose-dependent increase in the number and frequency of interdigital furunculosis (cysts) on one or more feet during the study.

2. Allergic dermatitis was assessed in 12 dogs each given 1X, 3X, or 5X maximum exposure dose of oclacitinib maleate. Clinical observations that were considered likely to be related to oclacitinib maleate included polydipsia 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 increased cellularity (lymphoid) in subcutaneous tissues (spleen, thymus, femoral and mesenteric lymph nodes, and skin), and decreased cellularity of sternal and femoral bone marrow. Lymphoid hyperplasia and chronic active inflammation were 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 subset of lymphocytes, eosinophils, and basophils. Total proteins were decreased over time primarily due to the albumin fraction.

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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 20 and 100 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.

NADA #141-345, Approved by FDA

Made in Italy

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

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