A FAST-ACTING AND SAFE TREATMENT FOR THE CONTROL OF ACUTE AND CHRONIC CANINE PRURITUS

APOQUEL® (oclacitinib tablet) Dosing Guide

• The dose of APOQUEL tablets is 0.18 to 0.27 mg/lb (0.4 to 0.6 mg/kg)
• APOQUEL should be given twice daily for up to 14 days of therapy and once daily thereafter for maintenance
• APOQUEL may be given with or without food
• APOQUEL may be used concomitantly with many other common therapies including vaccines, NSAIDs, antibiotics and allergen immunotherapy

Indications
Control of pruritus 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 infections or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and 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.


All trademarks are the property of Zoetis Inc., its affiliates and/or its licensors.
APQ-00025 ©2014 Zoetis Inc. All rights reserved. July 2014.
Oclacitinib 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)amino]cyclohexyl)methanesulfonamide (2Z)-2-butenioate.

The chemical structure of oclacitinib maleate is:

\[
\begin{align*}
\text{O} & \quad \text{SO} & \quad \text{NMe} \\
\text{C} & \quad \text{N} & \quad \text{H} \\
\text{C} & \quad \text{H} & \quad \text{C} \\
\text{C} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

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.

Adverse Reactions:
Oclacitinib is not for use in breeding dogs, or pregnant or lactating bitches. The use of oclacitinib has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.

Precautions:
APOQUEL is not for use in breeding dogs, or pregnant or lactating bitches. The use of oclacitinib has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.

Dosage and Administration:
The dose of APOQUEL (oclacitinib maleate) tablets is 0.18 mg/tablet (0.4 to 0.6 mg oclacitinib/kg body weight) administered orally. For oral use in dogs only.

Dogs receiving APOQUEL should be monitored for the development of infections, including demodicosis, and neoplasia.

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 study due to suspected or confirmed malignant neoplasia and subsequent euthanization, including one dog that developed associated signs with a heart base mass after 21 days of APOQUEL administration, and one dog that developed a Grade III mast cell tumor after 60 days of APOQUEL administration. One of the 147 dogs in the placebo group developed a Grade I mast cell tumor and was withdrawn from the masked study.

In the 283 dogs that received APOQUEL, the following additional clinical signs were reported after beginning APOQUEL administration: pruritus (5.5%), non-specific dermal lumps and swellings (3.0%), polydipsia (2.0%), lipoma (1.4%), polyuria (1.3%), 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 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), fever, 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 due to: darkening of areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy, and cystitis (1 dog); an inflated footpad and vomiting (1 dog); and diarrhea, vomiting, 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 thoricacic 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 III 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 apocrine gland adenocarcinoma (one demal, 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.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Zoetis Inc. at 1-888-963-8471 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 http://www.fda.gov/AnimalVets/safetyhealth.

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, 375) ng/mL and the mean area under the plasma concentration-time curve from 0 and extrapolated to infinity (AUClast) was 16900 (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.

**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)amino]cyclohexyl)methanesulfonamide (2Z)-2-butenioate.

**The chemical structure of célibataire n'a pas de...**

APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions (see **Adverse Reactions and Animal Safety**).
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 dose.

Mean (95% CI) 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 t1/2 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 239 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 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 was 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 evaluation 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 Veterinarian-assessed dermatitis scores continued to improve through study end at Day 30.

**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</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>

**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>

**Effectiveness Parameter**

Effectiveness Parameter | APOQUEL | Placebo | P-value |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></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>

**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 (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 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 ephemora, 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 20 and 100 count bottles. Each tablet is scored and marked with A0 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

**Animal Safety:**

**Margin of Safety in 6 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 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 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.

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

February 2013
428007800A&P