Control of Atopic Dermatitis

Immunomodulator

For oral use in dogs only

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

Description: APOQUEL CHEWABLE (oclacitinib chewable tablet) is a synthetic Janus Kinase (JAK) inhibitor. The chemical composition of oclacitinib maleate is N-methyl-1-(trans-4-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino) cyclohexyl)methanesulfonamide (2Z)-2-bromo-N-methylmaleimide.

The chemical structure of oclacitinib maleate is:

\[
\text{NHMe}
\]

\[\text{COH} \quad \text{COH} \quad \text{COH} \]

\[
\text{NHMe}
\]

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

Dosage and Administration: The dose of APOQUEL CHEWABLE (oclacitinib chewable tablet) is 0.18 to 0.32 mg oclacitinib/b (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.

Dosing Chart

<table>
<thead>
<tr>
<th>Weight Range (lb)</th>
<th>Weight Range (kg)</th>
<th>Number of Tablets to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>High</td>
<td>3.6 mg Tablets</td>
</tr>
<tr>
<td>6.6</td>
<td>9.9</td>
<td>3.0</td>
</tr>
<tr>
<td>10.0</td>
<td>14.9</td>
<td>4.5</td>
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<tr>
<td>15.0</td>
<td>19.9</td>
<td>6.0</td>
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<tr>
<td>20.0</td>
<td>29.9</td>
<td>9.0</td>
</tr>
<tr>
<td>30.0</td>
<td>44.9</td>
<td>13.5</td>
</tr>
<tr>
<td>45.0</td>
<td>59.9</td>
<td>20.0</td>
</tr>
<tr>
<td>60.0</td>
<td>89.9</td>
<td>27.0</td>
</tr>
<tr>
<td>90.0</td>
<td>129.0</td>
<td>40.0</td>
</tr>
<tr>
<td>130.0</td>
<td>175.9</td>
<td>55.0</td>
</tr>
</tbody>
</table>

Warnings: APOQUEL CHEWABLE is not for use in dogs less than 12 months of age (see Animal Safety).

APOQUEL CHEWABLE modulates the immune system.

APOQUEL CHEWABLE is not for use in dogs with serious infections.

APOQUEL CHEWABLE 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 oclacitinib film-coated tablets (FCT) 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 CHEWABLE 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 CHEWABLE in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

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

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

The use of APOQUEL CHEWABLE has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents.

APOQUEL CHEWABLE is not for use in breeding dogs, or pregnant or lactating bitches.

Adverse Reactions: The safety of APOQUEL CHEWABLE was established by pharmacokinetic data comparing oclacitinib film-coated tablets to APOQUEL CHEWABLE (see Clinical Pharmacology).

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 oclacitinib FCT and 147 dogs treated with placebo (vehicle control) were evaluated for treatment efficacy and safety. In this study, all dogs received oclacitinib FCT. Between the masked and unmasked study, 283 dogs received at least 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 non-compliant owners who confirmed malignant neoplasia and subsequent treatment, 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 with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), otitis (9.9%), vomiting (9.2%), diarrhea (6.0%), histiocytoma (3.9%), cystis (3.5%), anorexia (3.2%), lethargy (2.8%), yeast skin infections (2.5%), pododermatitis (2.5%), lipoma (2.0%), polydipsia (1.4%), lymphanedapathy (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 treatment efficacy and safety. In this 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% oclacitinib FCT, 0.9% placebo), vomiting (2.3% oclacitinib FCT, 1.8% placebo), lethargy (1.8% oclacitinib FCT, 1.4% placebo), 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 of areas of skin and fur (1 dog); diarrhea (1 dog); fever, lethargy and cystis (1 dog); an inflamed footpad and vomiting (1 dog); and diarrhea, vomiting, and 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 study was 272 days. During the 272 days of oclacitinib FCT administration, one dog developed demodicosis following 273 days of oclacitinib FCT administration. One dog developed dermal pigmented 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 without 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 non-neoplastic conditions: 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 oclacitinib FCT administration, respectively. Two dogs each developed a Grade II mast cell tumor after 52 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 oclacitinob FCT administration, respectively. One dog developed a low grade oral spindle cell carcinoma 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 APOQUEL CHEWABLE. All adverse events 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, pustulosis, papules), sealoils, polydipsia, and demodicosis.

Benign, malignant, and unclassified neoplasms, dermal masses (including papillomas and histiocytes), 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 Zoets Inc. at 1-888-963-8471 or www.zoets.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-4VETS or online at www.fda.gov/reportanimalads.

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 hepatic enzymes 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 last measurable concentration \( (\text{AUC}_\text{last}) \) of 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 \( (C_{\text{max}}) \), with the geometric mean ratio of 0.92 and 90% CI of 0.79 to 1.06. At steady state, the inhibitory concentrations \( (\text{IC}_{50}) \) for 50% enzyme inhibition for P-glycoprotein (P-gp) and oclacitinib is minimal; the inhibitory concentrations \( (\text{IC}_{50}) \) are 50 fold greater than the observed \( C_{\text{max}} \) values at the use dose.

Effectiveness:

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

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 control (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 Days 7, 14, and 28. Treatment success for pruritus 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 oclacitinib FCT group compared to the placebo group.

Effectiveness Parameter

<table>
<thead>
<tr>
<th></th>
<th>oclacitinib FCT</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Owner-Assessed Pruritus VAS</td>
<td>0.66 (n = 131)</td>
<td>0.04 (n = 133)</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Veterinarian-assessed CADESI</td>
<td>0.49 (n = 134)</td>
<td>0.04 (n = 134)</td>
</tr>
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Compared to the placebo group, mean Owner-assessed pruritus VAS scores (on Days 1, 2, 7, 14, and 28) and mean Veterinarian-assessed CADESI scores (on Days 14 and 28) were lower in the oclacitinib FCT 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 scores continued to improve through study end at Day 30.

Control of Pruritus Associated with Allergic Dermatitis
A double-masked, 50-day, controlled study was conducted at 25 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 oclacitinib FCT (218 dogs, tablets administered at a dose of 0.4-0.6 mg/kg per dose twice daily) or placebo control (218 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 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 owner, on at least 5 of the 7 evaluation days. The estimated proportion of dogs with Treatment Success was significantly different for the oclacitinib FCT group compared to the placebo group.

Owner-Assessed Pruritus VAS Treatment Success, Allergic Dermatitis

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<tr>
<td>Estimated Proportion of Dogs with Treatment Success</td>
<td>0.67 (n = 203)</td>
<td>0.29 (n = 204)</td>
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After one week of treatment, 86.5% of oclacitinib FCT 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 oclacitinib FCT 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 oclacitinib FCT 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 oclacitinib FCT treatment beyond one week, the Veteranin-assessed dermatitis scores continued to improve through study end at Day 30.

Urban U.S. Field Study

Effectiveness

Compared to the placebo group, mean Owner-assessed pruritus VAS scores (on Days 1, 2, 7, 14, and 28) and mean Veterinarian-assessed CADESI scores (on Days 14 and 28) were lower in the oclacitinib FCT 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 scores continued to improve through study end at Day 30.

Control of Pruritus Associated with Allergic 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 control (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 pruritus or dermal inflammation 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 Days 7, 14, and 28. Treatment success for pruritus 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 oclacitinib FCT group compared to the placebo group.

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