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clinician's forum™

Expert views from a roundtable for veterinarians on Apoquel® (oclacitinib tablet) and Apoquel® Chewable (oclacitinib chewable tablet)

A *Clinician's Brief* Supplement

Incorporating Apoquel® Chewable Tablets into Practice

Apoquel tablet provides fast relief of clinical signs associated with allergic skin disease, with >15 million dogs having benefited from its antipruritic and anti-inflammatory effects since its launch in 2013.[1] However, delivery of oral medications can be challenging for some pet owners. Apoquel Chewable tablets provide the same benefits in a formulation that is readily accepted by dogs with allergic and atopic dermatitis,[2] making it a clear first-choice treatment for many itchy allergic dogs.

HOW APOQUEL IS BEING USED IN PRACTICE

Dr. Aiken: How do you use Apoquel tablets in your practice today? How has that evolved in the last 10 years as your level of comfort and experience with it has grown?

Dr. Stokking: I use Apoquel in most of my allergic patients. I also recommend it for patients that come in with flea allergy, especially those that are not going to tolerate steroids well. I love using Apoquel tablets during diet trials. Apoquel is also very helpful while dogs are undergoing immunotherapy for allergy treatment. For my patients on Cytopoint®, I make sure they have Apoquel at home just in case they can't return for their next injection at the prescribed interval and their itch comes back before they can get back to the clinic.

Dr. Scotton: In my general practice, probably 95% of the pruritic dogs I see just need itch relief and respond well to Apoquel or steroids. Since we've had Apoquel, I'm using fewer antihistamines, fatty acids, shampoos, and other modalities because we've got a medication that is effective 80% to 90% of the time in my hands, with fewer side effects. Apoquel has made it so much easier to treat canine allergic dermatitis in general practice.

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Even the most effective drug will not work if it is not given, if doses are skipped, or if doses are administered but not consumed.

—Dr. Stokking

INCORPORATING APOQUEL CHEWABLE TABLETS INTO PRACTICE

Dr. Aiken: Dr. Hillier, tell us about the chewable formulation. Are there differences between Apoquel tablet and Apoquel Chewable, other than the fact that it's chewable?

Dr. Hillier: Apoquel Chewable tablets are a flavored formulation of the original Apoquel tablet formulation. The original Apoquel tablets and Apoquel Chewable tablets have the same indications, and the dosing instructions and tablet strengths are the same. No additional safety studies were required for the approval of Apoquel Chewable tablets in the US. Both provide rapid relief and start controlling allergic itch in 4 hours.[3,4a] No clinically relevant difference in efficacy is expected to be detectible between the formulations after the first dose, once a veterinarian has made the decision to treat with Apoquel, we anticipate that most clinicians will default to Apoquel Chewable tablets. The formulation for the chewable tablet has pork liver powder added to increase palatability and voluntary acceptance by dogs. I can think of 2 exceptions when I'd choose the Apoquel film-coated tablet: the first is a food trial, when we would prefer to avoid anything that's flavored, which could complicate assessment of response to a food trial, and the second is for a food-allergic dog that you know has a hypersensitivity to pork. These 2 circumstances would account for a minority[5,6] of dogs being treated, so essentially, Apoquel Chewable tablets are going to be the treatment for most dogs.

Dr. Aiken: Dr. Stokking, you took part in the clinical trial with Apoquel Chewable tablets.[2] Would you share some of your experiences?

Dr. Stokking: First, even the most effective drug will not work if it is not given, if doses are skipped, or if doses are administered but not consumed. If a couple doses of Apoquel are missed with once-daily dosing, you're well beyond the range where you're going to have much of an effect. Then the owner is going to say, "Well, Apoquel doesn't work anymore," but Apoquel probably would be working if the dog actually got it. So, how can we help? I was an investigator in a 2-week trial to determine whether the chewable Apoquel would be readily accepted by dogs (see ***Clinical Trial of the Oral Acceptance of Apoquel Chewable Tablets***, page 4).[2] We had quite a range of patients, which was important because all dogs are different. All the patients had to have been on routine flea management and had to have been diagnosed with allergic or atopic dermatitis. Some of the patients did have a component of food allergy. The inclusion criteria for this study were that Apoquel was required for management and that Apoquel could be safely administered twice daily for 2 weeks. We didn't have a single refusal to consume the Apoquel Chewable among the patients at my clinic. Most accepted the medication without assistance every time, meaning the owner didn't have to hide it in food or try multiple times; the dog ate it out of their hand or from a bowl with only the tablet in it. None of my patients developed an aversion after 1 or 2 weeks of dosing. The chewable tablets are also scored in half, just like the original tablet, so we could safely and accurately dose to a half tablet. These dogs had been well-controlled already taking Apoquel and required dosing twice daily to manage their clinical signs. They had to have been withdrawn from Apoquel for 7 days prior to being enrolled in the study. All owners liked the ease of administration and were pleased with the results. In my study population, the chewable was readily accepted by 100% of my patients, and none of my clients reported any noticeable difference in efficacy.

Dr. Aiken: Now that Apoquel Chewable tablets are available, what choice will you make when prescribing for new patients or patients already on Apoquel, knowing that the cost of each formulation is the same?

Dr. Scotton: For my patients, my default setting is to go for whatever is easier for the client and better accepted by the dog, so I'd suggest trying the chewable unless the

[a]Data for Apoquel Chewable is based on a model study for canine flea allergic dermatitis

patient is already on the tablets and that is working well. I think it also helps open up that conversation with the client if you have an option to offer.

Dr. Stokking: If it becomes available for me to prescribe in my specialty dermatology practice, I would most likely reach for the chewable formulation first, as long as I wasn't concerned about a patient having a pork allergy and if I wasn't actively conducting an elimination diet trial. If I wanted to transition a patient from the tablet to the chewable, I would ask the client to monitor for any GI signs or a flareup. But I didn't see any of that during the trial.

Dr. Wright: Do you think owners might perceive it as a more pleasurable experience than the original?

Dr. Stokking: Yes, my clients in the study[2] thought the experience was more positive than when administering other medications. You can watch the dog chew, enjoy, and swallow it, so you can be comfortable that the medication was actually taken.

Dr. Hillier: I don't see why one wouldn't go with the chewable tablet if they understand the potential upsides we've talked about today. There's some powerful new research from Human Animal Bond Research Institute and Zoetis showing that, among >16,000 pet owners globally, 89% of people described their dog as like a child, family member, or companion.[7] The research showed a clear correlation across cultures between the strength of the bond and better veterinary care for pets, and we know that chewables ease caregiver burden, increase compliance, and place less stress on that bond.

Dr. Aiken: How do you feel about giving Apoquel Chewable to dogs with allergies to foods other than pork?

Dr. Stokking: In my study group, I was fine doing it, as long as we monitored and made sure there were no adverse reactions.

Prof. Mueller: With food-allergic animals, starting the chewable is like a re-challenge. If the dog gets itchier after a few days, then we switch back to the non-flavored tablet. If it's not getting itchy over the next 2 weeks, then no worries. To put this into perspective, consider that food allergy occurs in about 20% of allergic dogs,[6] but only 2% of food-allergic dogs are allergic to pork.[5] That means that <1% (about 1 in 200) of all allergic dogs will not tolerate pork.[b] More than 99% of all allergic dogs will not react to pork, either in the diet or in flavored medications.

CAREGIVER BURDEN & COMPLIANCE

Dr. Aiken: What is the benefit to you personally in practice by being able to prescribe Apoquel Chewable?

Dr. Scotton: When clients are stressed, they pass that along to the veterinarian and staff, and everyone is unhappy. If I can prescribe something that makes their life easier, it's a win–win. I have seen it work with other chewables (eg, worming).

Dr. Wright: There's been such a focus in recent years on mental health and wellness. How do you see this helping veterinarians and pet owners if we can reduce the burden of care for dog owners?

Dr. Spitznagel: We found in our work that a burdened owner is calling or emailing at about twice the rate as compared with a nonburdened owner. So, if Apoquel Chewable tablets reduce the level of burden that an owner is experiencing, that's potentially fewer phone calls, right? Think of it this way: for the owner, it's an act of self-care to be giving your dog a treat rather than a medication.

Dr. Aiken: Dr. Wright, what have you found in your studies that illustrated some of the difficulties owners have in administering medications to their dogs?

Dr. Wright: Apoquel and Cytopoint are great, innovative therapies, but they can be more expensive for pet owners than steroids, so they may not be used in all cases. We've found that's especially likely in cases of acute pruritus because veterinarians and pet owners may be more concerned about long-term tolerability of steroids yet are open to using them for short periods. A study evaluated 1590 pet owners' willingness to pay for therapies for canine pruritus,[8] with the goal of identifying key drivers in dog owner preference when considering flavored chewable therapies such as Apoquel Chewable tablets versus conventional tablet/capsule-based therapies. From the responses, we are seeing a willingness to pay for the chewable that holds up across cultures and countries. It's been interesting to see the challenges and mitigation strategies pet owners use to administer pills to their dogs, like hiding or disguising the tablets in food ranging from cream cheese to ham and cheese. Pet owners may put the Apoquel in a treat and then find the Apoquel on the floor hours later when they notice their dog is itching. We also found that it makes it difficult for owners of these chronic dogs to go on vacation when they worry about the pet sitter not being able to administer the medication to them. We asked owners what was most important to them and found that the ability to bond with their pet and enjoy life with them was rated quite high, as well as wanting to be a good pet parent. They want to be successful in completing the full course of therapy, and they worry they're not getting the positive effect

[b]Calculation: 0.2 × 0.02 = 0.004 × 100 = 0.4%

You can watch the dog chew, enjoy, and swallow it, so you can be comfortable that the medication was actually taken.

—Dr. Stokking

of the treatment when missing doses. Our interviews with veterinarians have confirmed these findings from pet owners. Pilling difficulties are often discussed with veterinarians, particularly if owners are anxious from a previous experience or have a dog that is difficult to pill. A pet owner made this closing remark: "I would have paid whatever to get a tablet that was chewable." Dog owners are really hoping for a way to make this process easier.

CLINICAL TRIAL OF THE ORAL ACCEPTANCE OF APOQUEL CHEWABLE TABLETS[2]

- **Subjects:** 121 client-owned dogs treated at 10 general practice veterinary clinics
  - Dogs were 1 to 14 years of age, weighed 8.1 lb to 133.8 lb (3.7-60.7 kg), and required twice-daily treatment with Apoquel for allergic or atopic dermatitis.
- **Dosage:** Apoquel Chewable tablets were administered twice daily for a minimum of 7 days at the label dose (0.4-0.6 mg/kg) based on the dosing table.
- **Results:** 1,673 total dose administrations were successfully completed in 121 dogs.
  - 91.6% of doses were accepted voluntarily within 5 minutes.
  - 8% were consumed with assistance outside of the 5-minute offering time.
  - 0.4% of doses were not consumed.
  - The per-dose percent acceptance rate for the 14 offered doses showed minimal variation, ranging from 89.9% to 93.3%.
- **Conclusion:** Dogs found the chewable tablets to be very palatable, and no aversion occurred with repeated dosing.

Dr. Hillier: Maybe veterinarians need to change their mindset from one of an expectation that most owners can do this to a more realistic mindset that most cannot or will have difficulty. That will make a difference for everybody for whom pilling is a challenge. We can certainly provide a better solution for many.

Dr. Aiken: Dr. Maddison, in your work on compliance, you cite 2 canine studies in which only 27% of owners gave the prescribed number of doses at the correct time each day during short-term antibiotic treatment.[9] How does the caregiver burden impact compliance?

Prof. Maddison: As veterinarians, we've been guilty of saying, "Give these tablets 3 times a day" without really considering whether this is going to be feasible for this client. There's some evidence that there are clients who won't tell the veterinarian about these issues but might tell a veterinary nurse or a technician. We need to use a shared decision-making model—what we call the "negotiated agreement," which involves discussing what is feasible for them, whether it's being able to administer a medication or afford diagnostics or treatment—rather than the traditional paternalistic model where we just tell clients what to do.

Dr. Aiken: Why do you think veterinarians would *not* ask owners if they're having difficulty pilling?

Dr. Scotton: Veterinarians in general practice generally don't have the time to ask all those questions in a 10-minute consultation.

Prof. Maddison: I also think veterinarians are focused on the solution. We also may assume that, because we can do it, the pet owner can do it. When I first began lecturing about compliance, I found that veterinarians don't think it's an issue for their clients. The evidence, however, shows quite clearly that veterinarians cannot predict which clients are going to be compliant.

Dr. Aiken: The need for palatable medications in veterinary medicine has been cited,[10] but most medications are still not palatable or chewable. What are the benefits of palatable medications?

Dr. Stokking: Certainly compliance and a better human–animal bond, because you're not trying to force the animal to do something.

Dr. Spitznagel: I would add reduced caregiver burden; the owner is giving a treat, instead of trying to figure out how to give a pill.

Dr. Scotton: If the pet enjoys taking

something, it's positive reinforcement for the owner to remember to give the medication. It's so easy to forget things that are inconvenient or you don't really enjoy doing.

Dr. Aiken: Prof. Maddison, how do you tie palatability, acceptance, and routes of administration into your work with compliance?

Prof. Maddison: Studies in pediatric medicine have shown that 1 factor that contributes to poor compliance with parents giving their children medication is the child's reaction to the medication.[11] It's the same thing with pet owners; they don't want to stress their pet, and they feel really bad if they have to give them something the pet really doesn't like. Medications developed with palatability and ease of administration in mind tend to be more readily accepted and more widely used.

Ms. Shaw: We have more dermatology tools than ever before, but atopic dermatitis is a long-term condition for these patients. Having a palatable, chewable medication that you can use on a daily basis could become a daily ritual between the owner and pet. I can see this as a game changer in the same way the original Apoquel was.

PET OWNER COMPLIANCE & PREFERENCES WITH ORAL MEDICATIONS

- Sixty-five percent of pet owners reported challenges with giving their dog tablet-based treatments.[12]
- Seventy percent of pet owners preferred the chewable tablet over the film-coated tablet.[12c]
- Thirty percent of pet owners must build extra time into their day or interrupt their daily routine to administer a conventional tablet.[12]
- Twenty-five percent of pet owners felt stressed or unhappy about the difficulties experienced with administering a tablet.[12]

[c]Responses based on owner review of Apoquel tablet and Apoquel Chewable product profiles in a survey.

KEY TAKEAWAYS

- Apoquel tablets and Apoquel Chewable provide fast relief of allergic itch beginning in 4 hours[3,4d] and effectively control allergic itch within 24 hours.[13,14] Apoquel tablet has been prescribed to >15 million dogs over the last 10+ years.[1]
- Apoquel controls itch and inflammation caused by allergic dermatitis.[3,15,16] These effects have been shown to be equal to steroids in terms of speed of onset and efficacy.[3]
- Pet ownership is changing; as a profession working with today's pet owners, veterinarians need to understand and evolve their prescribing habits, when possible, to meet the needs of owners.
- Many owners have trouble pilling their dog; more palatable, chewable formulations may help increase compliance and reduce caregiver burden and can help create a positive dosing experience for the pet and the owner.
- Apoquel, a medication for fast and effective relief of allergic itch, is now available in a chewable formulation. In a clinical field trial, which was conducted to assess overall palatability, >91% of doses were voluntarily accepted by client-owned dogs.[2]
- Apoquel chewable tablets provide the benefits of Apoquel tablets but in a formulation that is readily accepted by dogs, making it a clear first-choice treatment for many itchy allergic dogs and their caregivers.

[d]Data for Apoquel Chewable is based on a model study of canine flea-allergic dermatitis.

Apoquel® and Apoquel® Chewable 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 for Apoquel® and Apoquel® Chewable
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 the full Prescribing Information at **Apoqueltabletandchewablepi.com**.

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apoquel®
(oclacitinib tablet)

3.6 mg 5.4 mg 16 mg

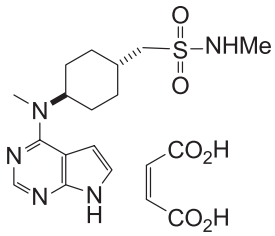
Immunomodulator

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-ylamino) cyclohexyl]methanesulfonamide (2Z)-2-butenedioate.

The chemical structure of oclacitinib maleate is:



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 (oclacitinib maleate) tablets is 0.18 to 0.27 mg oclacitinib/lb (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

Weight Range (in lb)		Weight Range (in Kg)		Number of Tablets to be Administered		
Low	High	Low	High	3.6 mg Tablets	5.4 mg Tablets	16 mg Tablets
6.6	9.9	3.0	4.4	**0.5**	-	-
10.0	14.9	4.5	5.9	-	**0.5**	-
15.0	19.9	6.0	8.9	**1**	-	-
20.0	29.9	9.0	13.4	-	**1**	-
30.0	44.9	13.5	19.9	-	-	**0.5**
45.0	59.9	20.0	26.9	-	**2**	-
60.0	89.9	27.0	39.9	-	-	**1**
90.0	129.9	40.0	54.9	-	-	**1.5**
130.0	175.9	55.0	80.0	-	-	**2**

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

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

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

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 (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 group means remained within the normal range. Mean lymphocyte counts were transiently increased at Day 14 in the APOQUEL group.

Dogs that withdrew from the masked field study could enter an unmasked study where all dogs received APOQUEL. Between the masked and unmasked study, 283 dogs received at least one dose of APOQUEL. 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 APOQUEL administration, and one dog that developed generalized demodicosis after 28 days of APOQUEL administration. Two other dogs on APOQUEL 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 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. Additional dogs receiving APOQUEL 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 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-specified 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 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% 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 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 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 apocrine gland 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 1-888-963-8471 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 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 (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 ($AUC_{0\text{-}inf}$) 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 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_{50s}) are 50 fold greater than the observed C_{max} 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 $t_{1/2}$ 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 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.

Estimated Proportion of Dogs with Treatment Success, Atopic Dermatitis

Effectiveness Parameter	APOQUEL	Placebo	P-value
Owner-Assessed Pruritus VAS	0.66 (n = 131)	0.04 (n = 133)	$p<0.0001$
Veterinarian-Assessed CADESI	0.49 (n = 134)	0.04 (n = 134)	$p<0.0001$

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.

Control of Pruritus Associated with Allergic Dermatitis

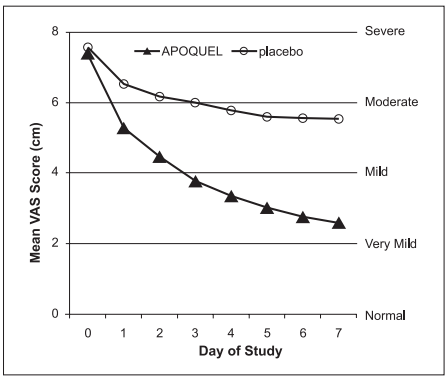
A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and other/unspecified 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.

Owner-Assessed Pruritus VAS Treatment Success, Allergic Dermatitis

Effectiveness Parameter	APOQUEL (n = 203)	Placebo (n = 204)	P-value
Estimated Proportion of Dogs with Treatment Success	0.67	0.29	$p<0.0001$

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 Veterinarian-assessed dermatitis scores continued to improve through study end at Day 30.

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



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 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.

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 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 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

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: December 2020

40033180A&P

apoquel® chewable
(oclacitinib chewable tablet)

3.6 mg 5.4 mg 16 mg

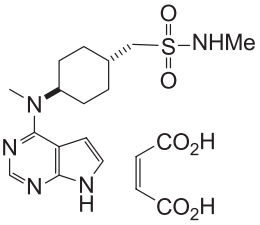
Immunomodulator

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-butenedioate.

The chemical structure of oclacitinib maleate is:



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 0.27 mg oclacitinib/lb (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

Weight Range (in lb)		Weight Range (in Kg)		Number of Tablets to be Administered		
Low	High	Low	High	3.6 mg Tablets	5.4 mg Tablets	16 mg Tablets
6.6	9.9	3.0	4.4	**0.5**	-	-
10.0	14.9	4.5	5.9	-	**0.5**	-
15.0	19.9	6.0	8.9	**1**	-	-
20.0	29.9	9.0	13.4	-	**1**	-
30.0	44.9	13.5	19.9	-	-	**0.5**
45.0	59.9	20.0	26.9	-	**2**	-
60.0	89.9	27.0	39.9	-	-	**1**
90.0	129.9	40.0	54.9	-	-	**1.5**
130.0	175.9	55.0	80.0	-	-	**2**

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 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 (2.6% oclacitinib FCT, 0% placebo), new cutaneous or subcutaneous lump (2.6% oclacitinib FCT, 2.7% placebo), and lethargy (2.0% 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 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 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 with at least one report of the clinical sign as a non-pre-existing finding): pyoderma (12.0%), non-specified 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 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 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% placebo), and polydipsia (1.4% oclacitinib FCT, 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 cystitis (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 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 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 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 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 oclacitinib FCT administration, respectively. One dog developed a low grade oral 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 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 1-888-963-8471 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 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
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 zero to the last sampling time point [$AUC_{0\text{-}t(last)}$] 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_{max}), 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 the dosage regimen, the small differences in C_{max} 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 to peak plasma concentrations (T_{max}) of less than 2 hours. Following oral administration of a single 5.4 mg APOQUEL CHEWABLE to 42 dogs, the mean C_{max} was 292 ng/mL and the mean area under the plasma concentration-time curve from 0 and extrapolated to infinity ($AUC_{0\text{-}inf}$) was 2570 ng·hr/mL.

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.

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 intravenous and oral administration, the terminal half-life appeared similar with mean values of 3.5 (2.2, 4.7) and 4.1 (3.1, 5.2) hours, respectively.

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_{50s}) are 50 fold greater than the observed C_{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**).

Bioequivalence was not met for the lower 90% CI of the maximum concentration (C_{max}), 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 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 oclacitinib FCT group compared to the placebo group.

Estimated Proportion of Dogs with Treatment Success, Atopic Dermatitis

Effectiveness Parameter	oclacitinib FCT	Placebo	P-value
Owner-Assessed Pruritus VAS	0.66 (n = 131)	0.04 (n = 133)	$p<0.0001$
Veterinarian-Assessed CADESI	0.49 (n = 134)	0.04 (n = 134)	$p<0.0001$

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 oclacitinib FCT group. By Day 30, 86% (127/147) of the placebo group dogs and 15% (23/152) 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. For dogs that continued oclacitinib FCT 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.

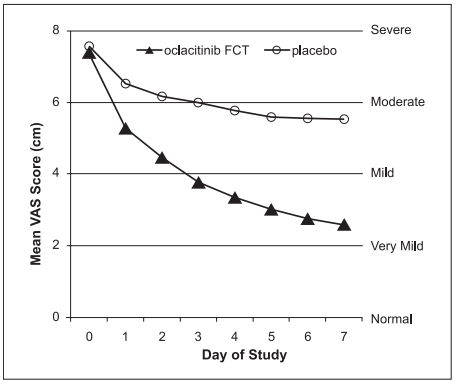
Control of Pruritus Associated with Allergic Dermatitis
A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and other/unspecified allergic dermatitis. Dogs were randomized to treatment with 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 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 oclacitinib FCT group compared to the placebo group.

Owner-Assessed Pruritus VAS Treatment Success, Allergic Dermatitis

Effectiveness Parameter	oclacitinib FCT (n = 203)	Placebo (n = 204)	P-value
Estimated Proportion of Dogs with Treatment Success	0.67	0.29	$p<0.0001$

After one week of treatment, 86.4% 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 Veterinarian-assessed dermatitis 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 unconsumed after 5 minutes, 134 (8%) were consumed with assistance (with food treats or by pilling), and 6 (0.4%) 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 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.

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 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 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 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 chewable tablet is pentagon shaped, scored on both sides and have a dose descriptor (S S, M M or L 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.

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