Apoquel® (oclacitinib tablet) is the most prescribed treatment for canine allergic itch[1] for a reason

apoquel® (oclacitinib tablet)
FIRST CHOICE FOR FAST RELIEF

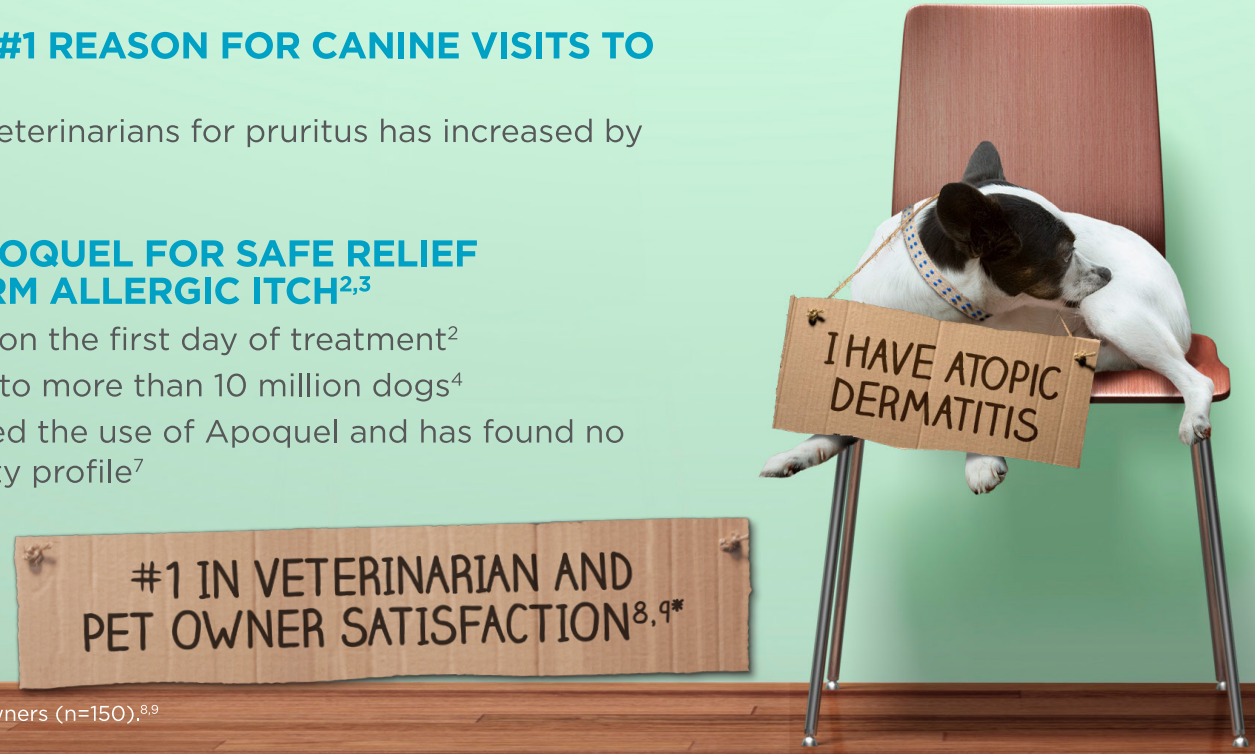
SINCE 2014, APOQUEL HAS DEMONSTRATED SAFETY AND EFFICACY IN THE TREATMENT OF ALLERGIC ITCH.[2,3] IT HAS BEEN PRESCRIBED TO OVER 10 MILLION DOGS.[4]

SKIN ALLERGIES ARE THE #1 REASON FOR CANINE VISITS TO VETERINARY PRACTICES[5]

- The number of dogs visiting veterinarians for pruritus has increased by over 40% since 2016[6]

START AND STAY WITH APOQUEL FOR SAFE RELIEF OF SHORT- AND LONG-TERM ALLERGIC ITCH[2,3]

- Apoquel controls allergic itch on the first day of treatment[2]
- Apoquel has been prescribed to more than 10 million dogs[4]
- Zoetis has rigorously monitored the use of Apoquel and has found no significant change to the safety profile[7]



*Based on survey data from veterinarians (n=250) and pet owners (n=150).[8,9]

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 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 accompanying full Prescribing Information.

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The safety profile of Apoquel® (oclacitinib tablet) is supported by pharmacovigilance data over 5 years[7]

apoquel® (oclacitinib tablet)
FIRST CHOICE FOR FAST RELIEF

ZOETIS HAS A COMPREHENSIVE POST-APPROVAL SURVEILLANCE PROGRAM FOR REPORTING PHARMACOVIGILANCE DATA TO REGULATORY AGENCIES[7]

During a pharmacovigilance 5-year safety review, adverse reactions were rare[7,10]*

- The most commonly reported individual adverse reactions (in decreasing order: vomiting, diarrhea, lethargy, anorexia and blood-work changes) associated with the use of Apoquel were very rare[7,10]*
- Results are consistent with pre-approval pivotal efficacy and safety studies. Apoquel is performing as expected under field conditions[7]

*Rare is defined as more than 1 but less than 10 dogs reacting per 10,000 dogs treated; very rare is defined as less than 1 dog reacting per 10,000 dogs treated. Reported incidence rate (calculated) is an estimated rate. Includes all adverse reactions regardless of whether the product was administered per label directions, concomitantly or if a potential causal relationship existed.[10]

The benefits of Apoquel treatment extend to pet owners and their quality of life[3,11]

- In a recent study, owners of dogs taking Apoquel had their quality of life improved by 84% by Day 60[11]
- 91% of dog owners were confident that treatment with Apoquel was effective[3]

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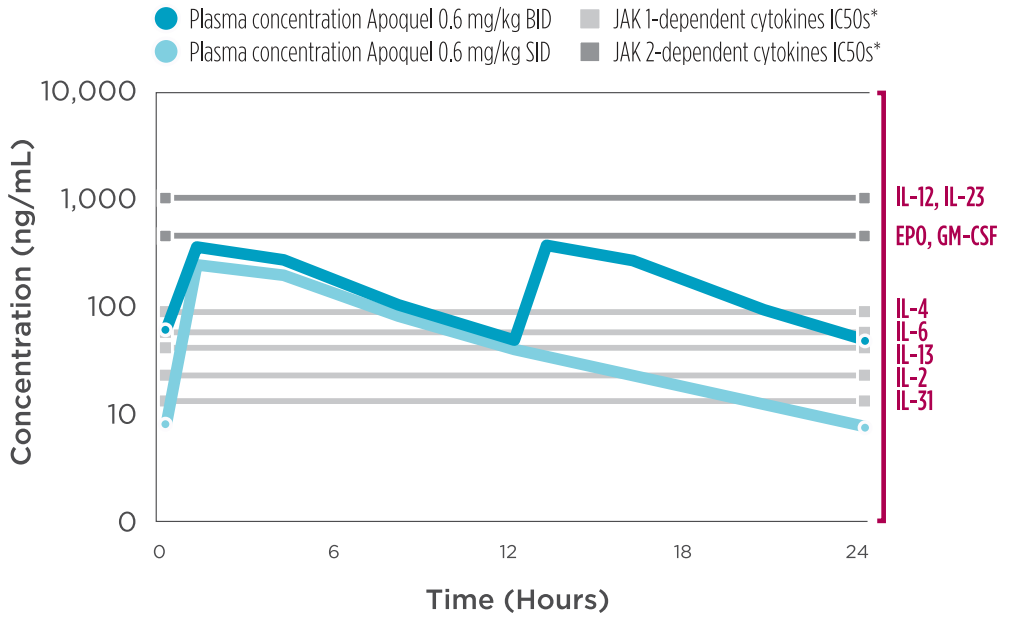
Apoquel® (oclacitinib tablet) is designed to control allergic itch and inflammation due to allergic dermatitis with minimal impact on the immune system

apoquel® (oclacitinib tablet)
FIRST CHOICE FOR FAST RELIEF

Nonsteroidal Apoquel inhibits the function of pruritogenic and proinflammatory cytokines, specifically the JAK1- and JAK3-dependent cytokines involved in canine allergies[12]

- At label doses, Apoquel has only a **minimal effect on JAK2-dependent cytokines** involved in hematopoiesis and innate immunity[12]
- **Once-daily dosing** was selected to **balance efficacy and safety for long-term use**, allowing cytokines involved in the immune response to recover their function before the next dose
- A vaccine response study in young dogs supports that **B- and T-cell responses were maintained** even at exaggerated doses of Apoquel, and provides evidence against broad immunosuppression[13]

MEAN APOQUEL PLASMA CONCENTRATION[14]



*IC50s: Concentration of oclacitinib that inhibits activity by 50% in cell model systems.

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

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Apoquel® (oclacitinib tablet) was shown to be safe for short- and long-term use in several studies

apoquel® (oclacitinib tablet)
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Side effects of Apoquel were similar to placebo[2]

- In short-term clinical trials, the most commonly reported adverse events were vomiting and diarrhea[2]
  - These AEs were observed in less than 5% of dogs and were similar to placebo
  - In most cases, AEs resolved on their own or with supportive care with continued dosing and were self-limiting

Adverse Reactions that Began During the Allergic Dermatitis Study (Days 0-7)[2]

Adverse Reactions	Number (%) of Dogs Placebo Group (n=220)	Number (%) of Dogs Apoquel (n=216)
Diarrhea	2 (0.9)	5 (2.3)
Vomiting	4 (1.8)	5 (2.3)
Lethargy	3 (1.4)	4 (1.8)
Anorexia	0 (0.0)	3 (1.4)
Polydipsia	0 (0.0)	3 (1.4)

Long-term safety data

- In an open-label continuation therapy study, Apoquel was shown to be safe, well-tolerated and suitable for use for an extended duration[3]
  - The most common side effects included urinary tract infection, vomiting, otitis, pyoderma and diarrhea
- A margin of safety study in 12-month-old dogs using elevated dosing (up to 5x the label) for 26 weeks supports no limit to the duration of therapy on the label[15]
  - Papillomas and pododermatitis were observed
  - Apoquel was well-tolerated. Side effects were mild and nonprogressive

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

IMPORTANT SAFETY INFORMATION
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No evidence of higher risk for new neoplasms with Apoquel® (oclacitinib tablet) treatment[16]

apoquel® (oclacitinib tablet)

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- In a long-term continuation study, the rate of neoplasia was not greater than what would be expected in the general population of dogs[3,17]
- In the 5-year post-approval safety review, the 2 most commonly reported neoplasias were papillomas and histiocytomas, each with very rare incidence rates (less than 1 dog reacting per 10,000 dogs treated)[7,10]
- The results of a study of over 300 dogs with allergic dermatitis treated with Apoquel for a mean of 36 months, compared with an age- and breed-matched control group on other allergy treatments, supported that allergic dogs on Apoquel long term were not more likely to develop malignant or benign neoplasia than dogs on other treatments[16]

INDICATIONS

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

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For more information, please see the accompanying full Prescribing Information.

References: 1. Vetstreet Pruritus Projection Trend Report, July 2021 Monthly Report-Market Share of Unique Pruritus Patients. **2.** Cosgrove SB, Wren JA, Cleaver DM, et al. Efficacy and safety of oclacitinib for the control of pruritus and associated skin lesions in dogs with canine allergic dermatitis. *Vet Dermatol*. 2013;24(5):479-e114. doi:10.1111/vde.12047. **3.** Cosgrove SB, Cleaver DM, King VL, et al. Long-term compassionate use of oclacitinib in dogs with atopic and allergic skin disease: safety, efficacy and quality of life. *Vet Dermatol*. 2015;26(3):171-e35. doi:10.1111/vde.12194. **4.** Data on file, Unique Patient Count from Launch, 2021, Zoetis, Inc. **5.** Nationwide Mutual Insurance. Skin allergies, ear infections among the most common conditions that prompt veterinary visits. https://news.nationwide.com/common-pet-conditions-that-prompt-veterinary-visits/. Published March 28, 2022. Accessed April 6, 2022. **6.** Vetstreet/Covetrus Pruritus Projection Trend Report: December, 2021. **7.** Data on file, A Five-Year Post-Approval Safety Review for Apoquel® in the US (May 2013 to August 2018), Zoetis Inc. **8.** Data on file, Apoquel®/Cytopoint® Pet Tracker, Wave 6, 2019, Zoetis Inc. **9.** Data on file, Apoquel®/Cytopoint® Vet Tracker, Wave 11, 2018, Zoetis Inc. **10.** Volume 6C Summary of the Product Characteristics: SPC European Commission, Brussels. 1 Vol. 6C. July 10, 2006, 1-11. **11.** Data on File, Study No. 20SORDER-01-01, 2021, Zoetis Inc. **12.** Gonzales AJ, Bowman JW, Fici GJ, et al. Oclacitinib (Apoquel®) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *J Vet Pharmacol Ther*. 2014;37(4):317-324. doi:10.1111/jvp.12101. **13.** Data on file, Study No. 1462N-60-09-927, Zoetis Inc. **14.** Collard WT, Hummel BD, Fielder AF, et al. The pharmacokinetics of oclacitinib maleate, a Janus kinase inhibitor, in the dog. *J Vet Pharmacol Ther*. 2014;37(3):279-285. doi:10.1111/jvp.12087. **15.** Data on file, Study No. 1462N-60-10-A29, Zoetis Inc. **16.** Lancellotti BA, Angus JC, Edginton HD, et al. Age- and breed-matched retrospective cohort study of malignancies and benign skin masses in 660 dogs with allergic dermatitis treated long-term with versus without oclacitinib. *J Am Vet Med Assoc*. 2020;257(5):507-516. doi:10.2460/javma.257.5.507. **17.** Schiffman JD, Breen M. Comparative oncology: what dogs and other species can teach us about humans with cancer. *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1663):20140231. doi:10.1098/rstb.2014.0231.

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apoquel®
(oclacitinib tablet)

3.6 mg 5.4 mg 16 mg

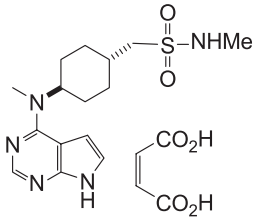
Immunomodulator

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-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

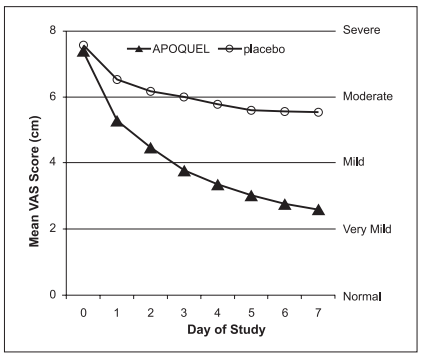
A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and other/unspecified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

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