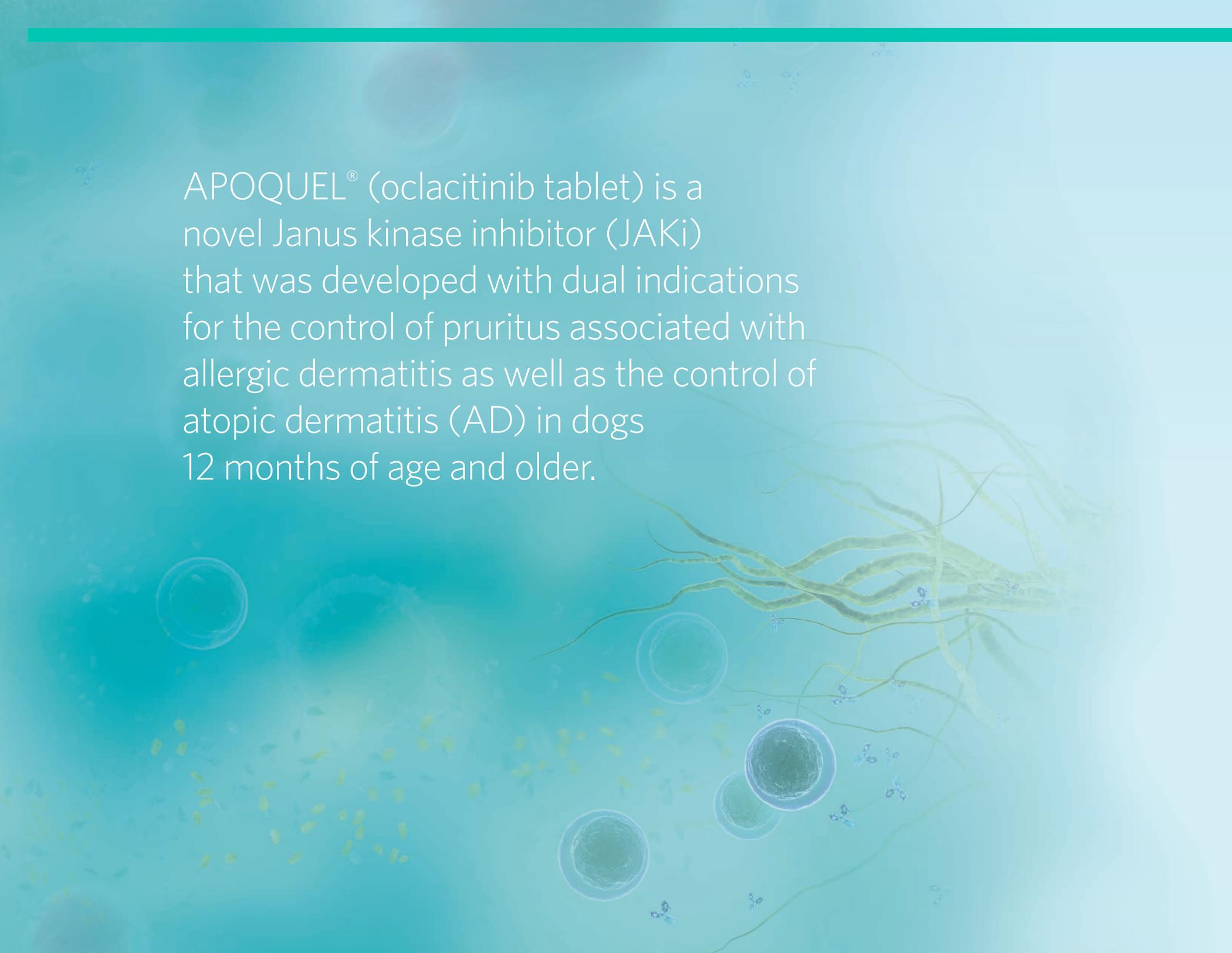




**apoquel**<sup>®</sup>  
(oclacitinib tablet)

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US Technical Monograph

The background of the slide is a light teal color with a microscopic theme. It features several large, semi-transparent circular structures that resemble cells or vesicles. Interspersed among these are thin, green, fibrous or filamentous structures that appear to be part of a biological network. Small, blue, Y-shaped or cross-shaped particles are scattered throughout the scene, some appearing to interact with the larger structures. The overall aesthetic is clean and scientific.

APOQUEL<sup>®</sup> (oclacitinib tablet) is a novel Janus kinase inhibitor (JAKi) that was developed with dual indications for the control of pruritus associated with allergic dermatitis as well as the control of atopic dermatitis (AD) in dogs 12 months of age and older.

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The background of the slide is a light blue, ethereal scene filled with various microscopic elements. There are several large, spherical cells with textured, almost crystalline surfaces. Some of these cells have a dark red or purple center. Scattered throughout the field are numerous smaller, teardrop-shaped particles in shades of yellow and light blue. The overall effect is that of a complex biological or chemical environment.

### **IMPORTANT SAFETY INFORMATION**

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*For more information please see full Prescribing Information on pages 76-77*

# 1 Introduction

**ALLERGIC SKIN DISEASE is one of the most common reasons dogs are presented to their veterinarians.<sup>1</sup> Pruritus, or itching, is the hallmark presentation in dogs with allergic disease. The scratching, licking, rubbing, and other behaviors that are associated with allergic and atopic disease are a significant driver for owners to seek treatment for their allergic dog.**

Since itch is a prime concern for dog owners, stopping the itch while working to identify the underlying cause is a prime therapeutic objective for veterinarians treating allergic dogs. There are many reasons for this, medical as well as practical.

#### **Scratching in response to itch can result in:**

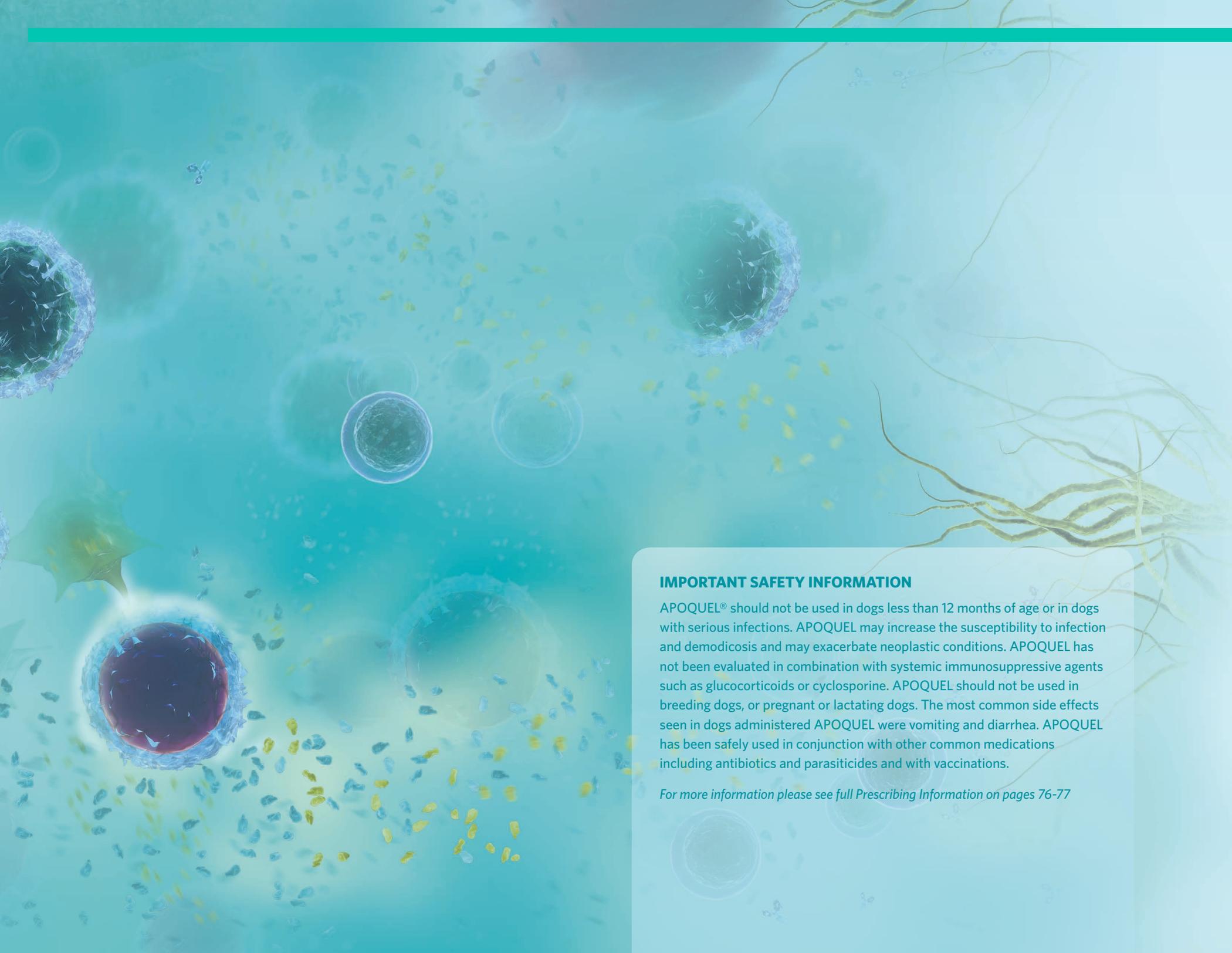
- Additional skin irritation and damage with the potential for secondary infection
- Diminished barrier function of the skin which allows additional exposure to allergens and on-going stimulation of the immune response to the allergen
- A dramatic decrease in quality of life of the dog and its family. This can include: disruption of sleep for the dog and the owner, a decrease in normal interactions between the pet and family members, and decreased interest in play on the part of the dog

Current therapeutic options available to veterinarians for treating pruritus

in dogs due to allergic and atopic skin disease are not ideal; many have poor efficacy and others have significant clinical disadvantages and can cause additional negative impact on the quality of life of the dog and its family. New research detailing the pathophysiology of allergic skin disease has paved the way for a new, more targeted treatment that provides rapid efficacy without many of the multiple systemic impacts of glucocorticoids. These new therapies have the potential to transform the acute and long-term management of allergic skin conditions in dogs by:

- Facilitating proper diagnosis from initial presentation
- Improving owner acceptance of treatment recommendations and willingness to treat
- Eliminating the negative impact of treatment on the quality of life of the dog and the pet owner

Zoetis scientists pioneered research on the neuroimmunology of allergic disease in the dog. This innovative science led to the discovery of APOQUEL® (oclacitinib tablet), a targeted new therapy for the treatment of allergic and atopic skin disease in dogs over 12 months of age that provides rapid relief of itch, controls inflammation without many of the side effects of glucocorticoids, and can be used long-term. ●

The background of the entire page is a light blue, semi-transparent image showing various biological structures. There are several large, spherical cells with textured, spiky surfaces. Some of these cells have a dark red or purple center, while others are clear or light blue. Scattered throughout the field are numerous smaller, yellow and blue particles, possibly representing bacteria or other microorganisms. On the right side, there are thin, branching, yellowish structures that resemble roots or delicate fibers. The overall aesthetic is clean and scientific, typical of a pharmaceutical or medical document.

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*For more information please see full Prescribing Information on pages 76-77*

# 2 Science of Itch & Allergic Skin Disease

## IN THIS CHAPTER

Pruritus in the Dog

Neuroimmunology: A New Perspective on Itch

Understanding Itch Stimulation at the Molecular Level:  
The Role of Janus Kinase (JAK) Enzymes

Clinical Ramifications of Chronic Itch

## PRURITUS IN THE DOG

Itch is one of the most common complaints of owners who bring their dog to a veterinary clinic, and veterinarians feel quite familiar with the treatment of itch. However, recently detailed science provides a basis for a radical change in the way pets suffering from itch are treated.

Pruritus is defined as an “unpleasant sensation that triggers a desire to scratch.”<sup>2</sup> Itch, like pain, is one of the body’s basic defense mechanisms. A fundamental biologic function of itch is to alert an animal to the presence of potentially harmful toxins or other hazards such as disease-carrying insects and to stimulate a reflex aimed at getting rid of these hazards. Itch can

manifest acutely, like the reflex to remove fleas and other parasites. However, chronic itch, like pain, can become self-perpetuating and pathologic in itself. Chronic itch necessitates more than symptomatic treatment, requiring a thorough diagnostic work-up to identify the underlying cause, and multimodal therapy to manage the insidious effects.

## NEUROIMMUNOLOGY: A NEW PERSPECTIVE ON ITCH

Today, itch is understood to be the result of a complex interface between the nervous system and the immune system, and pruritus is seen as a physiologic perception based in pathways within this network of sensory neurons.



*Itch is now understood to result from a complex interaction between the nervous system and the immune system. Understanding the biochemistry of this interaction creates an opportunity to develop new therapies, targeted at the source of the itch and without the multi-systemic effects of glucocorticoids.*

Understanding the biochemistry of this interplay creates new therapeutic opportunities to create targeted, anti-pruritic treatments.

The current understanding of the pathobiology of the itch and inflammation process starts with transepidermal exposure and absorption of allergens through an epidermis of a patient that may have a defective barrier (Figure 1).

Pruritus or itch results from stimulation of nonmyelinated nerve fibers located in the skin at the junction of the dermis and the peridermis, and within the epidermis. A variety of different molecules released by cells in the skin are among the most important biochemical factors that cause itch by stimulation of these nerve fibers. We also know that specific nerve pathways in the periphery and in the spinal cord exclusively transmit pruritic sensations have been identified (Figure 2).<sup>3</sup>

Historically, histamine has been considered to be the primary biochemical mediator of itch and inflammation. Histamine is one of the most easily recognized and widely researched mediators of pruritus. Pre-formed histamine is present in large amounts in most mast cell granules, and following cell activation, it is released into the surrounding tissue where it induces pruritus via H1 receptors on nerve fibers.<sup>4</sup> Experimentally, histamine can induce intense pruritus; however, its role in most clinical presentations of

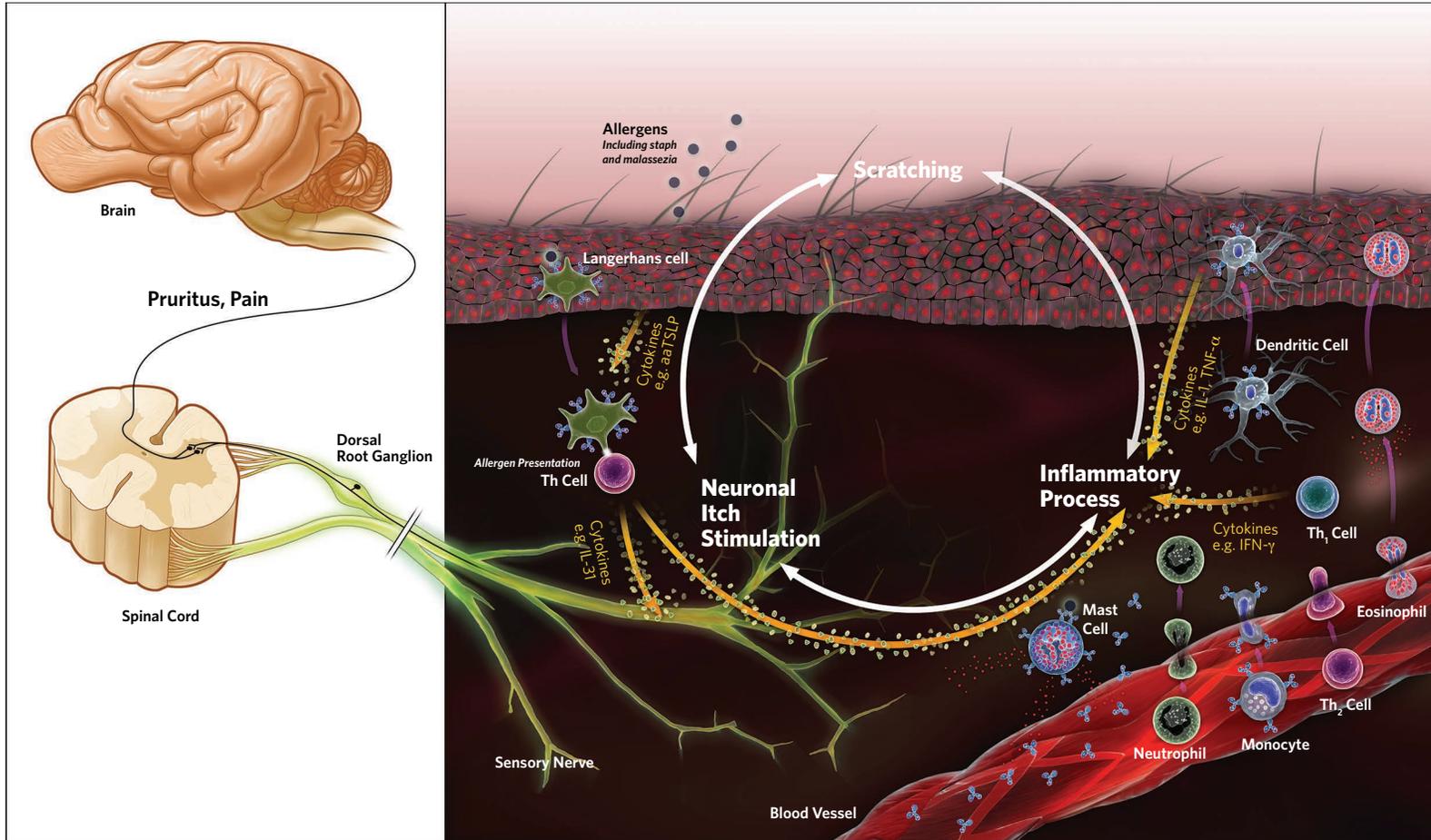


**Figure 1 | Allergens crossing the epidermis – Schematic diagram of an allergen penetrating the cell layers of the epidermis.**

allergic skin disease is not as impactful. While anti-histamines are useful in decreasing pruritus in urticarial conditions, pure histamine-induced itching in allergy is rare in clinical practice.

More recently other mediators such as cytokines have been shown to play a key role in this process.<sup>5</sup> Cytokines are protein signaling molecules that cells such as lymphocytes and keratinocytes produce and use for inter-cellular communication. Cytokines convey their information by binding to specific receptors on the cell membrane to induce a biologic response. After a cytokine binds to its cell membrane receptor it triggers specific intracellular

*The role of histamine in most cases of allergic skin disease is relatively non-impactful. More recently, other mediators such as cytokines have been shown to play a key role in this process.*



**Figure 2 | Components of Itch** - A schematic diagram of the cellular and molecular components of the itch process. Inflammation leads to the release of itch mediators such as cytokines, chemokines, and neuropeptides. Itch mediators stimulate receptors on itch-specific sensory neurons, which relay signals through the spinal cord to brain regions involved in itching.

*IL-31 has been identified as one of the key mediators of canine itch.*

dogs. Other interleukins thought to be involved in mediating pruritus are IL-2 and IL-6.<sup>6,7</sup>

### THE PATHOBIOLOGY OF ITCH STIMULATION

But just how is itch stimulated at a cellular and molecular level?

Canine atopic dermatitis (AD) can serve as a model of this.

The process has 3 basic steps:

1. **SENSITIZATION** to an allergen and priming of the immune system
2. **HYPERSENSITIVITY** following re-exposure to the allergen and a biological response that results in pruritus and inflammation
3. **PROGRESSION** due to chronic stimulation

#### STEP 1: SENSITIZATION

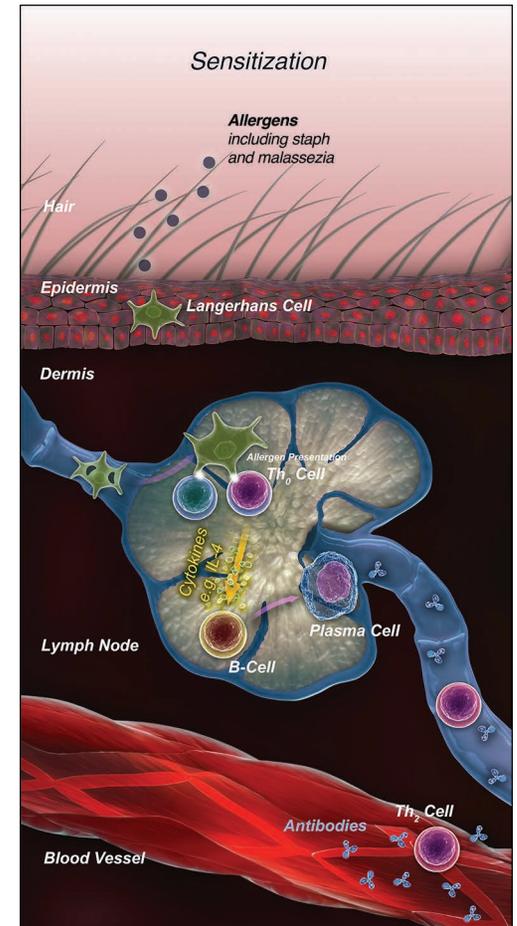
Sensitization is the initial step in allergic disease (Figure 3).<sup>3</sup> Dogs with AD may have a compromised skin barrier. This defective barrier enables allergens from the environment to cross. The body recognizes allergens as foreign and presents them to the immune system in a complex, but well-understood process.

*Sensitization, the first step in allergic dermatitis, occurs when allergens cross through the epidermis and are presented to the naïve immune system in the lymph node.*

pathways, one of which is the JAK pathway. In the skin, cytokines regulate acute and chronic processes such as neuronal itch stimulation and inflammation. Interleukin (IL)-31 has been identified as one of the cytokines responsible for itch in

The components in the process of sensitization are as follows:

- After the allergen crosses the skin, the Langerhans cell, a naïve dendritic cell in the skin, captures, phagocytizes, and antigenically packages the allergen on its surface
- The dendritic cell then migrates to the locally draining lymph node and presents the allergen to a naïve, helper T lymphocyte (Th0). The dendritic cells activate T-helper cells and polarize them toward a T helper 2 (Th2) phenotype resulting in the production of cytokines such as IL-4 and IL-13
- These cytokines act as protein messengers that stimulate nearby cells to action
- IL-4 and IL-13 stimulate B lymphocytes within the lymph node to become plasma cells. Plasma cells secrete allergen-specific immunoglobulin E (IgE) antibodies



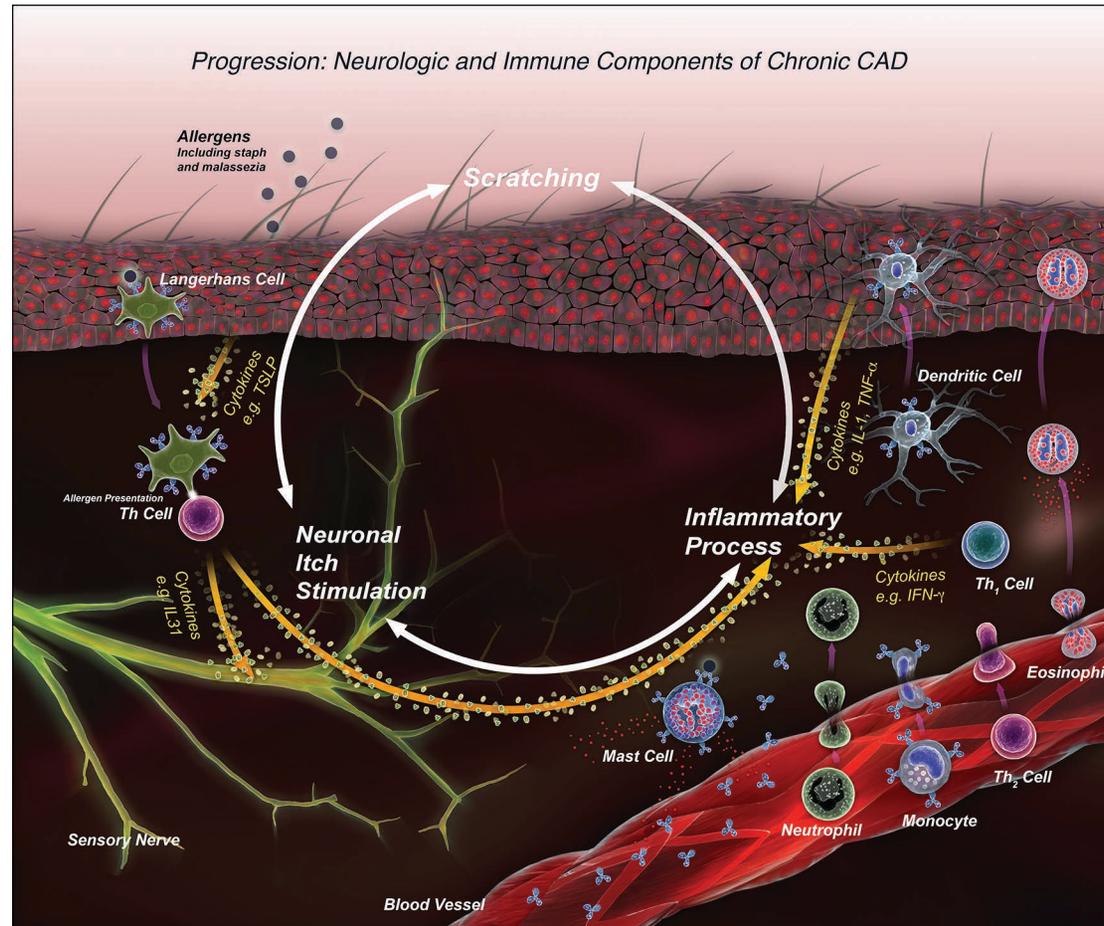
**Figure 3 | Sensitization to the Allergen - Diagram of the itch-initiating process of sensitization. See text for detailed description.**

- Activated Th2 lymphocytes enter the circulation and travel to the skin with the help of chemokines
- Allergen-specific IgE antibodies enter the circulation, travel to other tissues, and bind to the surface of mast cells and basophils in the skin as well as the Langerhans cell

The dog is now “sensitized” to the allergen, and its immune system is now “primed” and poised to mount an allergic reaction the next time it encounters the allergen.

**STEP 2: RE-EXPOSURE TO THE ANTIGEN RESULTS IN HYPERSENSITIVITY CAUSING INFLAMMATION AND ITCH**

Upon re-exposure the allergen binds to allergen-specific IgEs on the Langerhans cell and is presented to the Th2 cells in the dermis. The Th2 cells are then activated to produce more cytokines, such as IL-31, IL-4 and IL-13, locally in the dermis. IL-31 binds to receptors on specialized sensory neurons in the skin called “itch-selective neurons,” stimulating the transmission of a nerve impulse to the brain via the dorsal root ganglion in the spinal cord. The dog responds with scratching and other pruritic behaviors. The allergen also binds to allergen-specific IgEs on the surface of cutaneous mast cells. The mast cells degranulate and release other inflammatory mediators including histamine, serotonin, and



**Figure 4 | Progression of Allergic Disease - Diagram of itch progression. See text for detailed description.**

*During a hypersensitivity reaction, pruritogenic cytokines such as IL-31 are produced and bind to receptors on specialized neurons in the skin. This sends a signal to the brain that tells the dog to scratch.*

*This interface between the immune system and the nervous system provides the basis for our new understanding of the neuroimmunology of itch.*

Substance P, as well as other cytokines. Inflammation associated with acute allergy occurs causing the skin to become reddened, tender, swollen and warm.

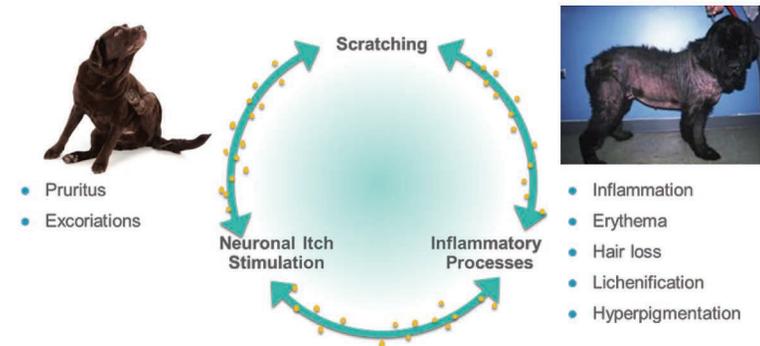
### STEP 3: DISEASE PROGRESSION FUELS THE CYCLE OF ITCH RESULTING IN CHRONIC CHANGES IN THE SKIN

Scratching, rubbing, licking and other pruritic behaviors cause further damage to the skin. Bacteria, yeast, and allergens produce more inflammation, and additional cells enter the skin (Figure 4). The skin thickens, and the skin barrier deteriorates. This results in an unrelenting itch-scratch-itch cycle (Figure 5).

Once this cycle begins, it can be difficult to break, and dogs can represent over and over for treatment of their allergic condition along with secondary effects such as bacterial skin infections.

## UNDERSTANDING ITCH STIMULATION AT THE MOLECULAR LEVEL: THE ROLE OF JAK ENZYMES

There are 4 types of JAK enzymes: JAK1, JAK2, JAK3 and TYK2 (Figure 6). JAK enzymes are attached to the intracellular region of cytokine receptors in various tissues in the body, including the skin and peripheral and central



**Figure 5 | Clinical Impact of cytokine dysregulation - Clinical signs associated with cytokine dysregulation.**

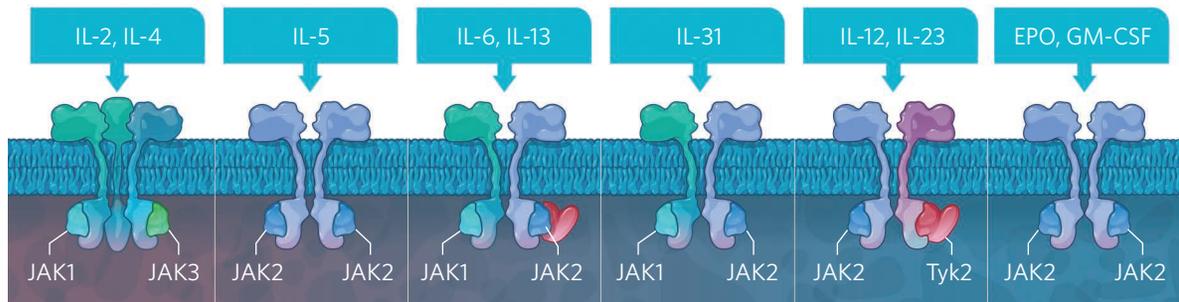
nervous systems. JAK1 is the isoenzyme form most closely associated with pro-allergic, pruritogenic and pro-inflammatory processes mediated by IL-2, IL-4, IL-13 and IL-31.

Cytokine receptors on various cells occur in pairs, each corresponding to one of the 4 types of JAK receptors inside the cell.

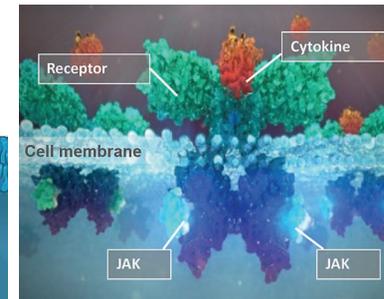
If IL-31 is a key to itch signaling in the dog, what role do JAK enzymes play in this process? The JAK enzymes are pivotal players in the biochemical cascade that takes place within a cell and generates the itch signal.

The following two diagrams describe how cytokines bind on the surface of a cell and activate the intracellular JAK- Signal Transducer and Activator of Transcription (STAT) pathway to cause the pruritus and inflammation that are hallmark signs of allergic disease (Figures 7 and 8). Here is how it happens.

In an allergic dog, when IL-31 binds to cell surface receptors on sensory neurons in the skin, this triggers intracellular pathways within the nerve cells that are mediated by JAK enzymes. Activated JAK enzymes activate STAT



**Figure 6 | JAK Pairing and Cytokine Stimulation** - Schematic diagram showing the pairing of cytokine receptors with JAK enzymes. (EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor.)



**Figure 7 | Cytokine Binding** - Molecular model of the extracellular cytokine receptor-JAK enzyme complex.<sup>7</sup>

proteins to induce gene transcription in the cell's nucleus, which stimulates biologic responses such as an itch signal.

Activation of the JAK-STAT pathway also results in several other ancillary biologic activities that contribute to the inflammation and pruritic processes that contribute to acute allergy in dogs but can also exacerbate clinical signs and contribute to chronic allergy. These activities include the following:

- IgE production
- Lymphocyte proliferation
- Production of additional cytokines that continue to stimulate the itch
- Enhanced expression of cytokine receptors on cells
- Production of chemokines that attract additional cells into the skin, causing dermal thickening

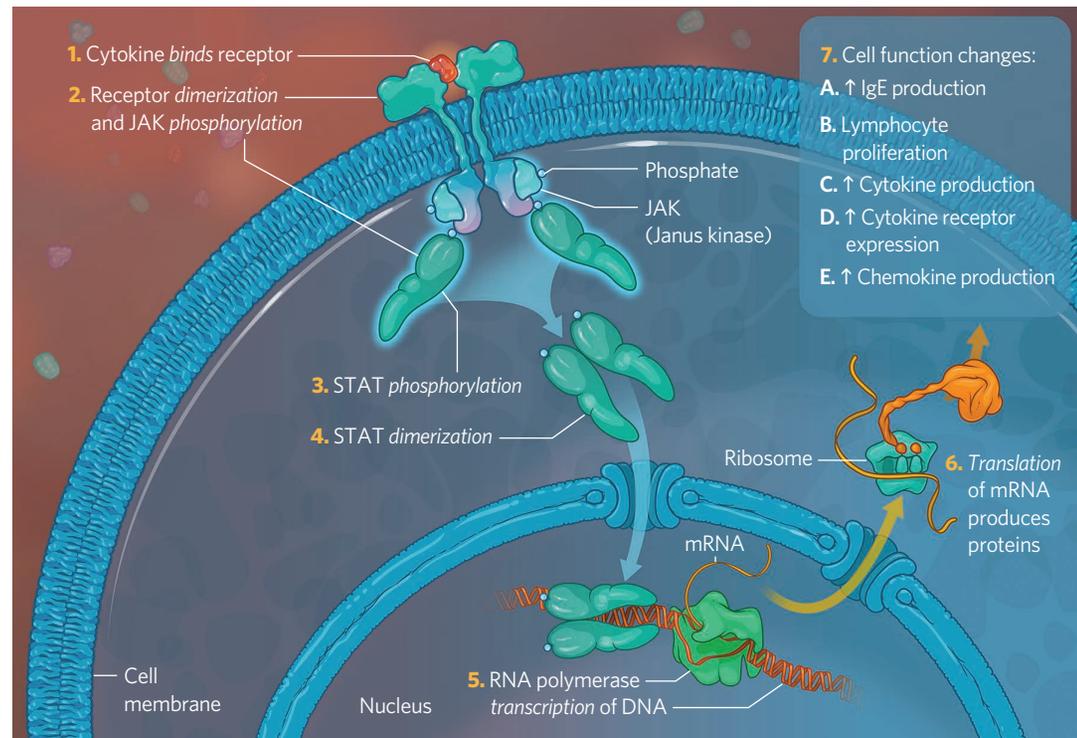


## CLINICAL RAMIFICATIONS OF CHRONIC ITCH

A mechanistic description of chronic itch would include the following elements. Chronic itch results when peripheral and central nerves are over-stimulated, which leads to activation and proliferation of pruritus-mediating nerve fibers. Sensitized nerve fibers have been shown to more readily stimulate pruritus. In addition to this direct effect, as outlined above, cytokines can produce long-term changes in the skin that can perpetuate the disease. Researchers have shown that some patients with AD have significantly elevated levels of nerve growth factor and Substance P which contributes to an increase in intradermal

*When itch becomes chronic, further changes can occur that exacerbate pruritus and produce long-term alterations in the skin that perpetuate the disease. Central sensitization can lead to proliferation of cells and activation of pruritus-inducing nerve fibers. The end result is a continuous cycle of pruritus, scratching and skin damage.*

itch fibers in the skin and leads to more intense pruritus over time.<sup>2</sup> Nerve growth factor also inhibits apoptosis and induces cell proliferation, leading to an increase in mast cells and upregulation of other pruritogenic substances that worsen the itch or cause it to persist. ●



**Figure 8 | Intracellular signaling by JAK enzymes** – Summary of the basic biology of the JAK signaling pathway.<sup>6,7,8</sup> Specific receptors on the surface of a cell recognize specific cytokines. When a cytokine binds to its receptor like a key in a lock, the message is carried into the cell by the activation of the JAK that's bound to the intracellular portion of the receptor. The JAK activates an intracellular STAT protein which relays the message to the cell nucleus to produce the activity (biological responses) associated with that cytokine. Cytokine signaling is terminated by a negative feedback mechanism. De-phosphorylation of the receptor complex by tyrosine phosphatases is one mechanism. Cytokine signaling can also be terminated by negative feedback involving specific inhibitors induced by cytokine activation. For example, suppressor of cytokine signaling (SOCS) proteins, induced by STAT activation, inhibit signals in JAK pathways.



The background of the entire page is a microscopic view of a cell culture. It features several large, spherical cells with a textured, blueish-purple surface. Some of these cells have a darker, reddish-purple center. The surrounding medium is filled with numerous smaller, blue and yellow particles, likely representing various cellular components or debris. The overall color palette is a mix of light blue, teal, and white, with a soft, ethereal glow.

### **IMPORTANT SAFETY INFORMATION**

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*For more information please see full Prescribing Information on pages 76-77*

# 3 | A New Approach to Itch Therapy

## IN THIS CHAPTER

### Traditional Approach to the Treatment of Allergic Skin Conditions in the Dog and Canine Atopic Dermatitis

#### Cytokines as Therapeutic Targets for Acute and Chronic Itch

Every practicing veterinarian, whether a specialist or generalist, knows what chronic itch looks like and can readily bring to mind the name of a patient



Inflammation and secondary infection in an atopic dog

that clinically fits this picture. Chronically allergic dogs frequently present suffering from thickened skin, (lichenification), hyperpigmentation, alopecia, odor, and infections. Their owners are frustrated, often tired from being up all night listening to their dog scratching, and at their wits' end. The stockpile of treatments these owners have at home from multiple rounds of treatment over the year can rival what's found on a veterinarian's pharmacy shelves.

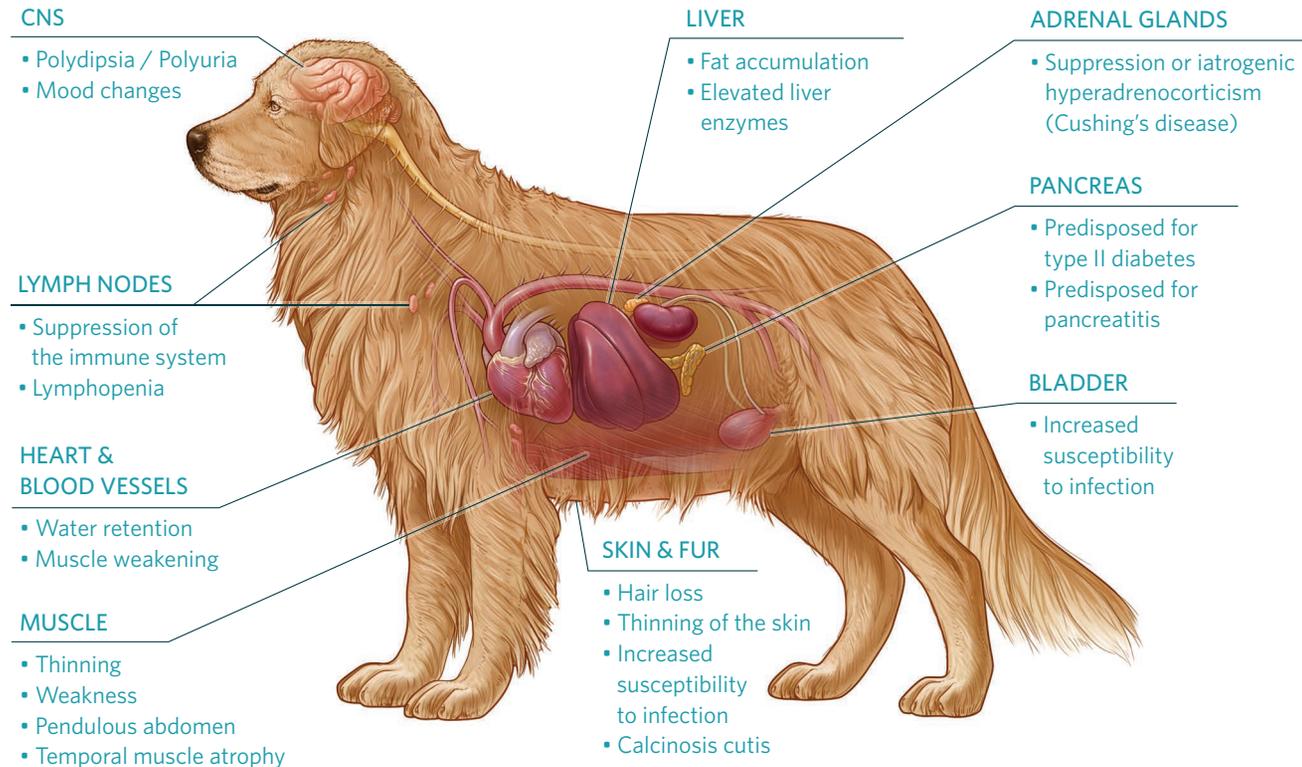
## TRADITIONAL APPROACH TO THE TREATMENT OF ALLERGIC SKIN CONDITIONS IN THE DOG AND CANINE ATOPIC DERMATITIS

Current guidelines for treating pruritic skin conditions require identification of the underlying cause of the pruritus, management of the secondary infections (eg, *Staphylococcus*, *Malassezia*, etc.), and treatment regimens tailored to the level of severity of symptoms. Therapy commonly requires a multimodal approach aimed at:

- Treating the underlying cause
- Addressing the itch
- Minimizing self-trauma to prevent additional damage to the skin barrier function
- Taking steps to eliminate triggers of acute flares

Most typically, current treatment of itch in dogs involves the use of some type of glucocorticoid. Corticosteroids are very effective in addressing the pruritus and inflammation associated with various allergic conditions. However, they are associated with well-known, multi-systemic side effects and are medically appropriate only for short-term or intermittent use (Figure 9). Additionally, patients must be gradually weaned off therapy, making dosing regimens complicated. And pet owners frequently complain about unacceptable side effects such as polyuria and polydipsia. This has led to a search for alternatives to steroid therapy.

Antihistamines are commonly tried alternatives to treat allergic dogs; however, they can make patients lethargic and drowsy, and there is little evidence to demonstrate that they are efficacious. Cyclosporine A (cyclosporin) has been shown to have a significant clinical effect, but there is



**Figure 9 | Drawbacks of corticosteroid therapy – Overview of the multi-systemic side effects of corticosteroid therapy in dogs.<sup>9</sup>**

typically a delay in onset of action of several weeks that makes it inappropriate as solo therapy. In addition, many dogs experience significant GI upset.

In recent years, pruritus has become increasingly viewed as more than a bothersome component of allergic disease in both human and veterinary dermatology. Many experts now consider pruritus a clinical sign that should be

*Current options for the treatment of allergic dermatitis in dogs have many downsides, including: lack of efficacy, delayed onset of action and multi-systemic effects. In addition, bothersome side effects such as polyuria/polydipsia/polyphagia, etc. can be seen even with the use of low doses of steroids. Many of these side effects can seriously impact the patients' and pet owners' quality of life.*

For many patients management requires a combination of systemic and topical therapies which frequently add up to a bag of treatments for the owner to implement

immediately addressed. This is in part due to the recognition of the pathologic effects of chronic itch; as well as understanding the significant impact of itch on the patient's quality of life.

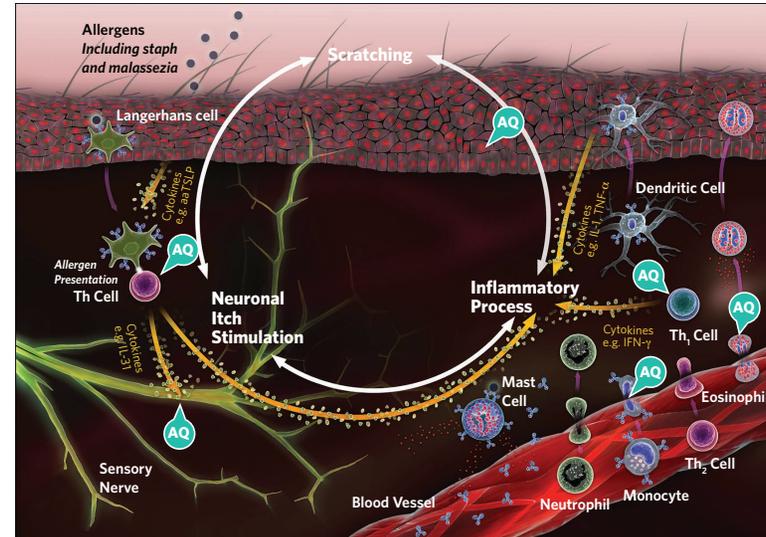


## CYTOKINES AS THERAPEUTIC TARGETS FOR ACUTE AND CHRONIC ITCH

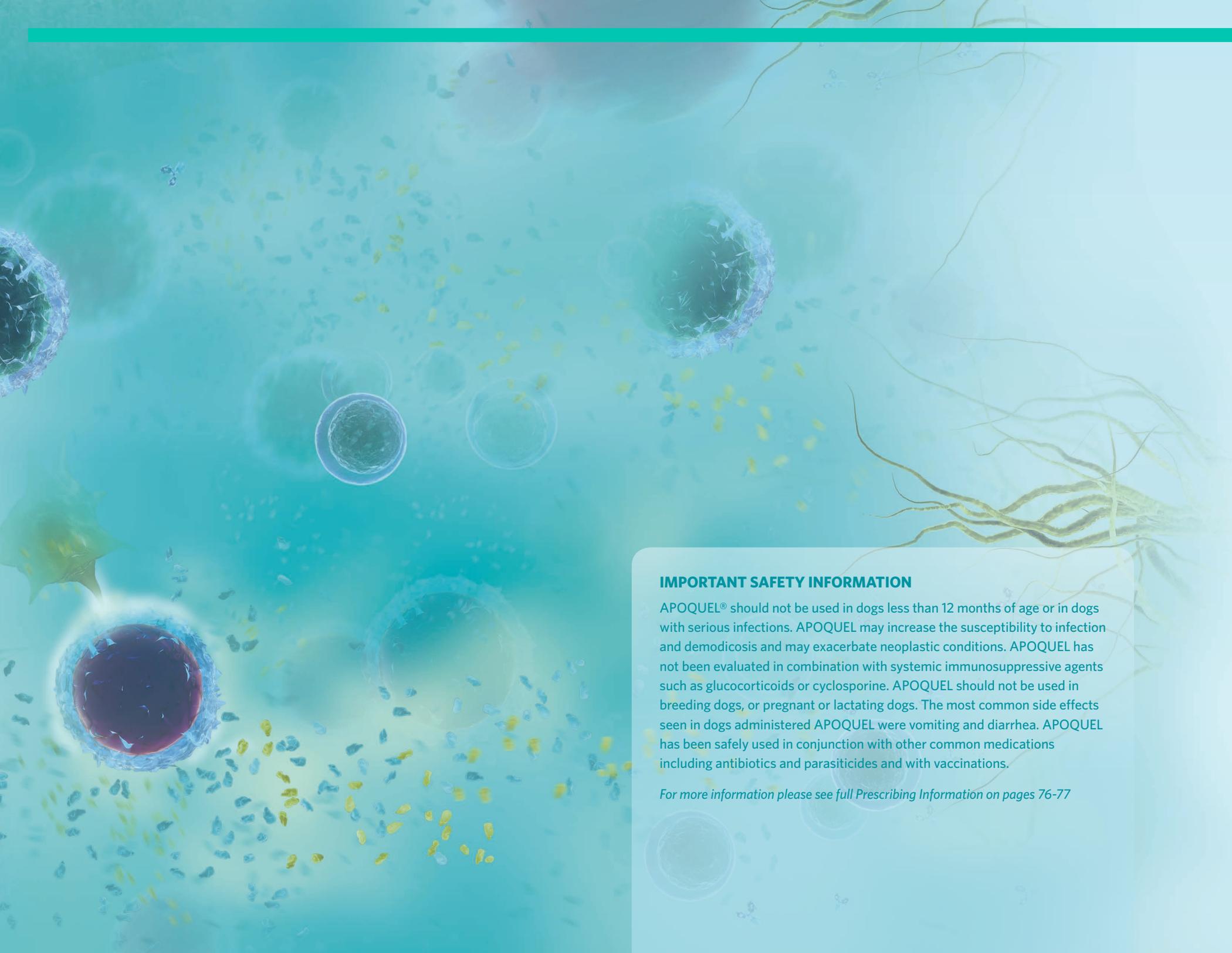
Cytokines play key roles in skin inflammation and neurologic signals that trigger itch. Suppression of the transmission of these signals through inhibition of cytokines is the backbone of a new therapeutic approach to controlling the itch and inflammation in allergic and atopic patients. Scientists now believe that targeted therapies hold the potential for better treatment options:

products without multi-systemic effects that can be used safely for short and long-term treatment. This is based both on the increasing understanding that cytokines are involved at multiple points in the biochemical cascade, as part of both acute and chronic itch, and about the contributions cytokines make to the physical changes in the skin of allergic patients.

**APOQUEL® (oclocitinib tablet) targets JAK1 enzymes and inhibits the activity of IL-31 and other pruritogenic, pro-inflammatory and pro-allergic cytokines (Figure 10).** ●



**Figure 10 | APOQUEL® targets cytokines at multiple sites in the cycle of itch - APOQUEL® inhibits the action of pruritogenic, pro-allergic and pro-inflammatory cytokines such as IL-4, IL-13, and IL-31, through the inhibition of JAK1 enzyme activity at multiple cellular locations.**  
(AQ, APOQUEL; Th, T helper cell)

The background of the slide is a complex, artistic representation of a microscopic or cellular environment. It features various spherical structures, some with textured, crystalline surfaces, and others that are more translucent. There are also elongated, fibrous structures resembling roots or neural pathways. The color palette is dominated by shades of teal, light blue, and pale yellow, creating a clean, scientific aesthetic. The overall composition is dense and layered, suggesting a complex biological system.

### **IMPORTANT SAFETY INFORMATION**

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*For more information please see full Prescribing Information on pages 76-77*

# 4 APOQUEL<sup>®</sup> (oclacitinib tablet) – At a Glance

## IN THIS CHAPTER

Product Summary

Dosing and Presentation

## PRODUCT SUMMARY

APOQUEL<sup>®</sup> (oclacitinib tablet) is a synthetic Janus kinase inhibitor. Oclacitinib has anti-pruritic and anti-inflammatory properties in dogs and has application in controlling allergic and atopic dogs 12 months of age and older (Table 1).

Table 1 | Overview of APOQUEL<sup>®</sup>

APOQUEL	DESCRIPTION <sup>10</sup>
<b>Active / Drug class</b>	Oclacitinib is a novel, targeted JAK inhibitor that is selectively targeted to inhibit JAK1 enzymes
<b>Indications</b>	Control of pruritus associated with allergic dermatitis in dogs at least 12 months of age
	Control of atopic dermatitis in dogs at least 12 months of age
<b>Dosing and administration</b>	0.18 to 0.27 mg/lb (0.4-0.6 mg/kg) administered orally twice daily for up to 14 days followed by 0.18 to 0.27 mg/lb (0.4-0.6 mg/kg) once daily for maintenance therapy
	Can be given with or without food
<b>Presentation</b>	Film-coated tablet scored in half
	3 tablet strengths: 3.6 mg, 5.4mg, and 16 mg for convenient dosing of dogs ranging from 3-80 kg (6.6-130 lbs)
	Available in bottles of 20 or 100 tablets

*Continued on next page*

Table 1 (Continued) | Overview of APOQUEL®

APOQUEL	DESCRIPTION <sup>10</sup>
<b>Efficacy<sup>32</sup></b>	APOQUEL® delivers onset of activity within 4 hours, comparable to steroids
	APOQUEL® effectively controlled itch within 24 hours in clinical trials
	Faster onset than prednisolone and dexamethasone in laboratory model studies
	Sustained anti-pruritic and anti-inflammatory efficacy throughout dosing period
	Similar efficacy to prednisolone in clinical study in dogs with allergic dermatitis
	Improvement in both pruritus and skin lesions in dogs with atopic dermatitis
	Faster onset of relief compared to Atopica (cyclosporine A) in a clinical study in dogs with atopic dermatitis
<b>Safety</b>	Efficacy maintained with continued dosing
	Safe for short- and long-term therapy; no label limitation to duration of therapy
	Most commonly reported side effects are vomiting and diarrhea
<b>Other</b>	Lack of many of the bothersome side effects associated with corticosteroids (polyuria, polyphagia, panting) <sup>12</sup>
	Can use while conducting intradermal or serum allergy testing
	No restrictions on concurrent use of vaccines during treatment
	High margin of safety regarding potential for metabolic drug-drug interactions due to minimal inhibition of cytochrome P450

## DOSING AND PRESENTATION

The dose of APOQUEL® (oclacitinib) is 0.18 to 0.27 mg/lb (0.4-0.6 mg/kg) administered orally twice daily for up to 14 days followed by 0.18 to 0.27 mg/lb (0.4-0.6 mg/kg) once daily for maintenance therapy (Table 2).

APOQUEL® can be administered with or without food. ●



Table 2 | APOQUEL® dosing chart

DOG BODY WEIGHT (lb)	NUMBER OF TABLETS TO BE ADMINISTERED <sup>11</sup>		
	3.6 MG TABLETS	5.4 MG TABLETS	16 MG TABLETS
6.6-9.9	0.5	-	-
10.0-14.9	-	0.5	-
15.0-19.9	1.0	-	-
20.0-29.9	-	1.0	-
30.0-44.9	-	-	0.5
45.0-53.9	0.5	-	0.5
54.0-59.9	-	0.5	0.5
60.0-89.9	-	-	1.0
90.0-129.9	-	-	1.5
130.0-175.9	-	-	2.0

NOTE: The dosing chart on the current label recommends administering two (2) of the 5.4 mg tablets to achieve the proper dose for dogs weighing between 45 to 59.9 pounds. An alternative means of achieving the targeted label dose for dogs weighing between 45.0-53.9 lbs is to administer one-half (1/2) of a 3.6 mg tablet plus one-half (1/2) of a 16 mg tablet. An alternative means of achieving the targeted label dose for dogs weighing between 54.0-59.9 lbs is to administer one-half (1/2) of a 5.4 mg tablet plus one-half (1/2) of a 16 mg tablet. This allows a dog up to 90 pounds to be treated with one-half (1/2) or one (1) total tablet daily.

A microscopic view of various cells and particles. In the foreground, there are several large, spherical cells with textured, blue, spiky outer membranes. One of these cells has a dark red, solid interior. Surrounding these are numerous smaller, more uniform spherical cells, some with clear centers and some with darker centers. The background is a light blue, hazy environment filled with many tiny, dark blue and yellowish particles, possibly representing a cellular or tissue environment.

### **IMPORTANT SAFETY INFORMATION**

APOQUEL® should not be used in dogs less than 12 months of age or in dogs with serious infections. APOQUEL may increase the susceptibility to infection and demodicosis and may exacerbate neoplastic conditions. APOQUEL has not been evaluated in combination with systemic immunosuppressive agents such as glucocorticoids or cyclosporine. APOQUEL should not be used in breeding dogs, or pregnant or lactating dogs. The most common side effects seen in dogs administered APOQUEL were vomiting and diarrhea. APOQUEL has been safely used in conjunction with other common medications including antibiotics and parasiticides and with vaccinations.

*For more information please see full Prescribing Information on pages 76-77*

# 5 APOQUEL<sup>®</sup> (oclacitinib tablet) Pharmacology

## IN THIS CHAPTER

Mode of Action of APOQUEL<sup>®</sup> (oclacitinib tablet)

Laboratory Studies Assessing In Vivo Pharmacologic Effects of APOQUEL<sup>®</sup> (oclacitinib tablet) in Dogs

Lack of Interference with Diagnostic Testing

## PHARMACOLOGY SUMMARY

- **APOQUEL selectively targets inhibition of JAK1-dependent cytokines involved in itch and allergy**
  - By selectively targeting the pro-allergic and pro-inflammatory cytokines, APOQUEL stops itch at its source, without the multi-systemic side effects of glucocorticoids
- **APOQUEL has both anti-pruritic and anti-inflammatory effects**
- **APOQUEL has a rapid onset of effect**
  - In laboratory model studies, APOQUEL<sup>®</sup> decreased pruritus within 4 hours of dosing; faster than prednisolone or dexamethasone worked in that model
  - APOQUEL decreased pruritus significantly in 24 hours in clinical cases of allergic dermatitis
  - Unlike cyclosporine, there is no delay before patients experience the benefit of the anti-pruritic and anti-inflammatory effects of APOQUEL
- **There is no limit to the duration of administration on the APOQUEL label**
  - The dose regimen developed for clinical use of APOQUEL was selected

to maximize efficacy and minimize the potential for side effects with chronic administration

- **APOQUEL is rapidly and well absorbed following oral administration**
  - The average time to maximum plasma concentration ( $T_{max}$ ) in dogs is less than 1 hour. APOQUEL is 89% bioavailable following oral dosing
- **APOQUEL can be administered with or without food**
- **APOQUEL has low protein binding in dogs (66.3% - 69.7%)**
- **The major clearance mechanism for APOQUEL in dogs is metabolism**
  - APOQUEL is metabolized to one major metabolite, an oxygenation product, and several smaller metabolites
- **No accumulation was observed when dogs were dosed with APOQUEL for 6 months**
- **APOQUEL minimally inhibits cytochrome P450 isoenzymes therefore minimizing the potential for any clinically-relevant drug-drug interactions**
  - The inhibitory concentrations ( $IC_{50s}$ ) of oclacitinib for cytochrome P450 isoenzymes are 50-fold greater than the observed maximum plasma concentration ( $C_{max}$ ) values at the use dose. Thus, only in an acute overdose situation would these concentrations be reached
  - Unlike cyclosporine, there is no label statement cautioning against concurrent use with drugs that are metabolized by cytochrome P450
- **Unlike glucocorticoids, APOQUEL does not interfere with results of intradermal or serum allergy testing** and diagnostic testing can be completed while a dog is being treated with APOQUEL

### MODE OF ACTION OF APOQUEL® (oclacitinib tablet)

APOQUEL® is a selective JAKi that, at the label dose, primarily inhibits JAK1, the form of the enzyme involved in the action of cytokines associated with pruritus

**Table 3 | APOQUEL® and JAK inhibition – APOQUEL® inhibition of JAK enzymes and biological processes** <sup>14,15,16,17</sup>

CELL-BASED ASSAY	JAK PAIR IMPACTED	IC <sub>50</sub> , nM (± SE)*
Canine IL-2 function in beagles whole blood	JAK1 / JAK3	63 ± 3 (n=24)
Canine IL-2 function in mixed breed whole blood	JAK1 / JAK3	189 ± 39 (n=23)
Human IL-4 function in cells	JAK1 / JAK3	249 ± 19 (n=11)
Human IL-6 function in cells	JAK1 / JAK2	159 ± 58 (n=5)
Human IL-13 function in cells	JAK1 / TYK2	115 ± 7 (n=2)
Canine IL-31 function in cells	JAK1 / JAK2	36 ± 6 (n=5)
Canine (beagle) EPO function in cells	JAK2	1020 ± 189 (n=9)
Human GM-CSF function in cells	JAK2	1090 ± 110 (n=10)
Human IL-12 function in cells	JAK2 / TYK2	>3000
Human IL-23 function in cells	JAK2 / TYK2	>3000

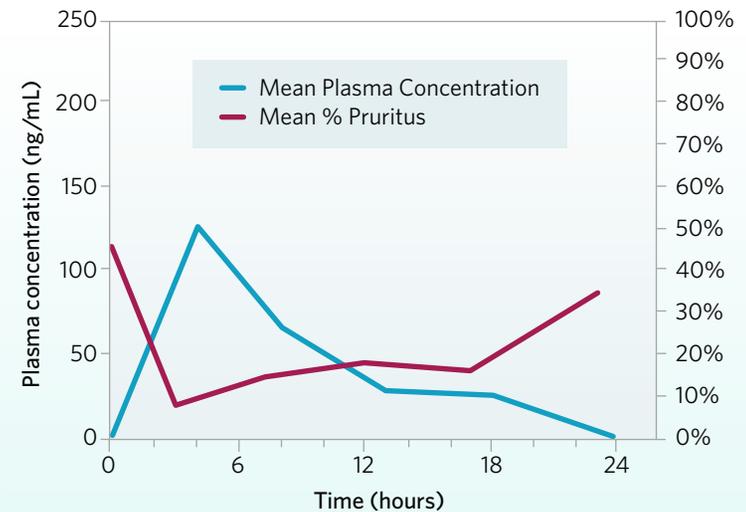
\* IC<sub>50</sub>, half maximal inhibitory concentration; a quantitative measure indicating the concentration of a particular drug that is needed to inhibit a given biological process (or component of a process, e.g., an enzyme) by half. The IC<sub>50</sub> provides a measure of the effectiveness of a compound in inhibiting a biological or biochemical function.

and inflammation, with minimal impact on JAK2, the form of the enzyme associated with cytokines involved in hematopoiesis and innate immune function (Table 3).

There is a direct relationship between plasma levels of oclacitinib and the reduction in pruritus when measured in laboratory dogs in which pruritus was induced by injection of IL-31 (Figure 11).

The label dose and label dosing regimen for APOQUEL® was specifically chosen in order to maximize the effect on JAK1-dependent cytokines

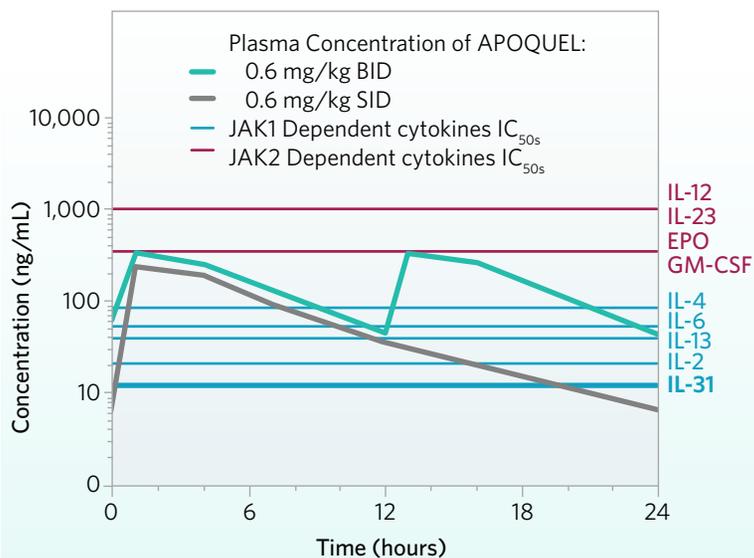
**Figure 11 | Relationship of APOQUEL® to level of pruritus – Dog model: plasma concentration of oclacitinib and magnitude (%) of IL-31-induced pruritus after a 0.4 mg/kg dose of oclacitinib.**



**APOQUEL® (oclacitinib tablet) has an ideal pharmacokinetic profile for oral administration:**

- **Rapid absorption**
- **High oral bioavailability**
- **Can be administered with or without food**

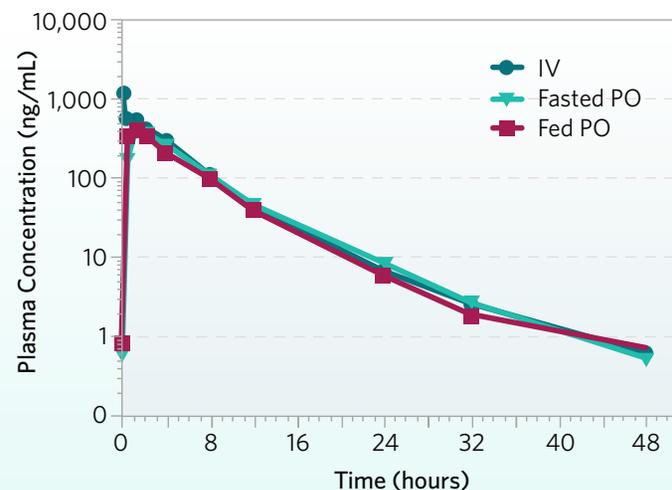
**Figure 12 | APOQUEL® dose relationship to degree of cytokine inhibition**  
 - Relationship between plasma concentration of APOQUEL® and IC<sub>50</sub> of various JAK1 dependent and JAK2 dependent cytokines.<sup>15,16,17,18</sup>



associated with allergy and atopic conditions in dogs and minimize the effect on JAK2-dependent cytokines associated with innate immune function and hematopoiesis, reducing the potential for side effects associated with this inhibition (Figure 12). The regimen also provides ‘downtime’ or a period of time between doses during which cytokine function recovers and suppression is not complete, thereby allowing normal, homeostatic functions of cytokines to resume in order to deliver the widest safety margin with chronic dosing.

APOQUEL® pharmacokinetics are ideal for oral administration. It is rapidly and well-absorbed with a T<sub>max</sub> of less than 1 hour. The oral bioavailability of

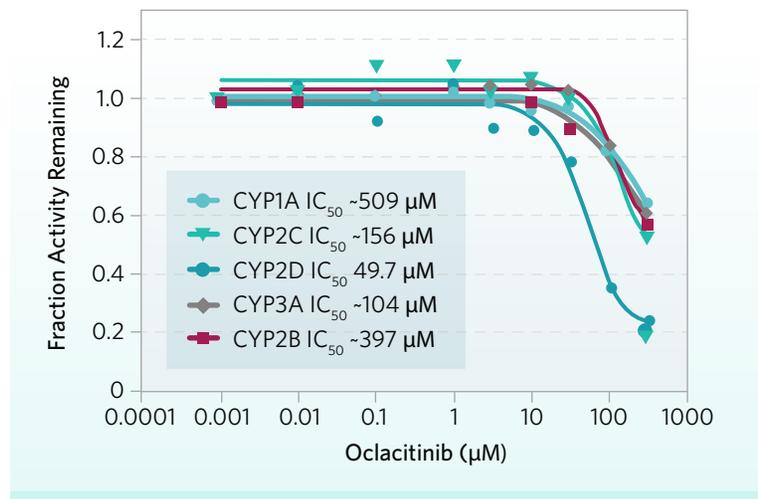
**Figure 13 | APOQUEL® dosing with and without food** - Mean oclacitinib plasma concentration - time profiles after intravenous and oral APOQUEL® administration in dogs under fed and fasted conditions.<sup>10,19</sup>



oclacitinib is 89% in dogs. It has been shown that the prandial state does not significantly impact the absorption of APOQUEL, and it can be administered to dogs with or without food (Figure 13).

The in vitro inhibition of canine liver cytochrome P450 enzymes by oclacitinib was minimal (Figure 14). The  $IC_{50s}$  of oclacitinib for cytochrome P450 isoenzymes are 50- fold greater than the observed  $C_{max}$  values at the use dose. Based on this pharmacologic data, clinically relevant drug-drug interactions would not be predicted to occur with oclacitinib; and in the clinical trial none were observed. Unlike the Atopica® (cyclosporine) label, there is no label statement that drug-drug interactions or resultant toxicity are possible if APOQUEL is administered with other drugs. APOQUEL® has very low protein binding in dogs (66.3% - 69.7%).

**Figure 14 | Inhibition of cytochrome P450 - The in vitro inhibition of canine liver cytochrome P450 enzymes by oclacitinib.<sup>10,20</sup>**



The major clearance mechanism for oclacitinib in dogs is metabolism. APOQUEL is metabolized to one major metabolite, an oxygenation product, and several smaller metabolites.

Additional pharmacologic parameters for oclacitinib are presented in Table 4.

### LABORATORY STUDIES ASSESSING IN VIVO PHARMACOLOGIC EFFECTS OF APOQUEL® (oclacitinib tablet) IN DOGS

When initially investigating APOQUEL®, Zoetis scientists utilized several laboratory models of canine pruritus and allergic diseases, including an IL-31 model and a flea-allergic dermatitis (FAD) model. Early in the development

**Table 4 | Summary of APOQUEL® pharmacologic parameters as listed in the US label.<sup>10</sup>**

Mean CL (mL/h/kg)	316
Mean CL (mL/min/kg)	5.3
Vd <sub>ss</sub> (mL/kg)	942
AUC <sub>0-∞</sub> (ng•h/mL)	1890
C <sub>max</sub> (ng/mL)	324
T <sub>max</sub> (hours)	< 1
t <sub>1/2</sub> (hours) IV	3.5
t <sub>1/2</sub> (hours) PO	4.1

CL, clearance; Vd<sub>ss</sub>, volume of distribution at steady state; AUC<sub>0-∞</sub>, area under the plasma concentration-time curve from 0 to infinity; h, hour; t<sub>1/2</sub>, terminal half-life; IV, intravenous; PO, oral.

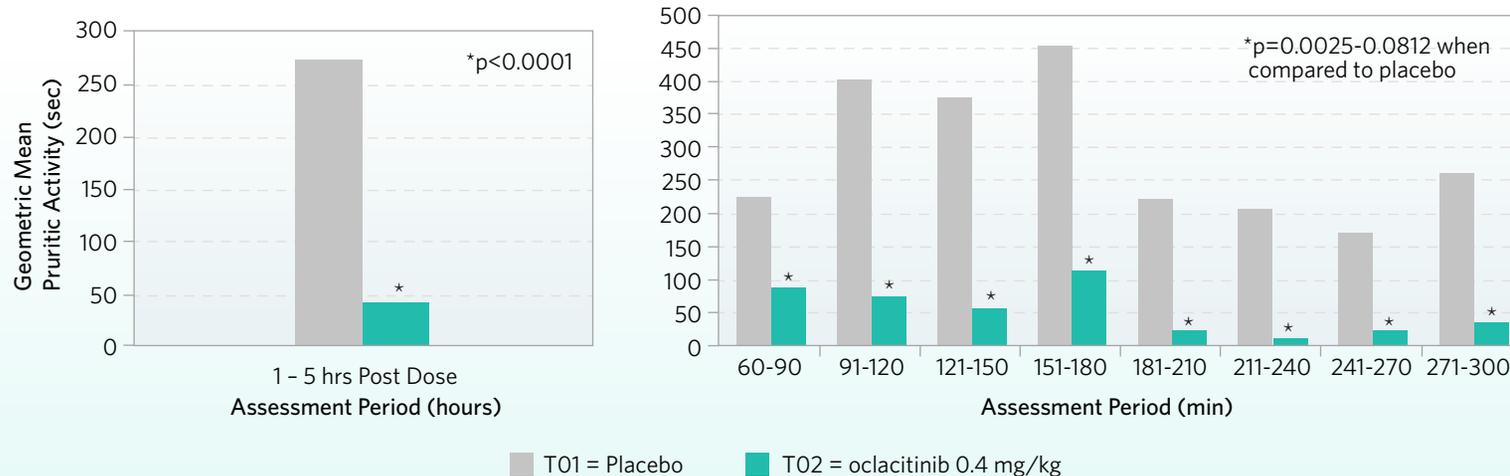
process, these models were used to confirm the in vivo efficacy of oclacitinib relative to the molecule's two key pharmacologic effects - anti-pruritic and anti-inflammatory. The models were also used to benchmark APOQUEL against products currently used therapeutically in allergic and atopic disease to ensure that oclacitinib delivered on Zoetis' objective to identify a molecule that provided clinical advantages over currently available therapies, including:

- Rapid onset of effect - as fast or faster than glucocorticoids
- Robust anti-pruritic efficacy - similar, if not superior, to current treatments in its ability to decrease pruritus and heal skin lesions
- Fewer multi-systemic effects - particularly desirable was the potential for less polyuria and polydipsia than glucocorticoids

*Oclacitinib significantly decreased pruritus within 1 hour of administration to flea-allergic dogs in a laboratory study.*

The first study evaluated the onset of the anti-pruritic action of oclacitinib in flea-allergic, mixed breed dogs.<sup>15,21,22</sup> A single dose of 0.4 mg/kg oclacitinib (n=8) was compared to placebo (n=8). The pruritic behaviors assessed including scratching, licking and rubbing were measured from 1-5 hours following dosing of test drug (oclacitinib or placebo). Starting at 1 hour and throughout the 5 hour observation period oclacitinib significantly reduced

**Figure 15 | Effect of oclacitinib on canine pruritus** - In a laboratory model, oclacitinib (citrate salt) significantly reduced pruritus in dogs with flea-allergic dermatitis (FAD) over a 4 hour observation period beginning 1 hour post-dose.



*Oclacitinib significantly reduced (p=0.0013) pruritus induced in laboratory dogs by injecting IL-31 within 1-3 hours after administration but no significant decrease was seen with prednisolone.*

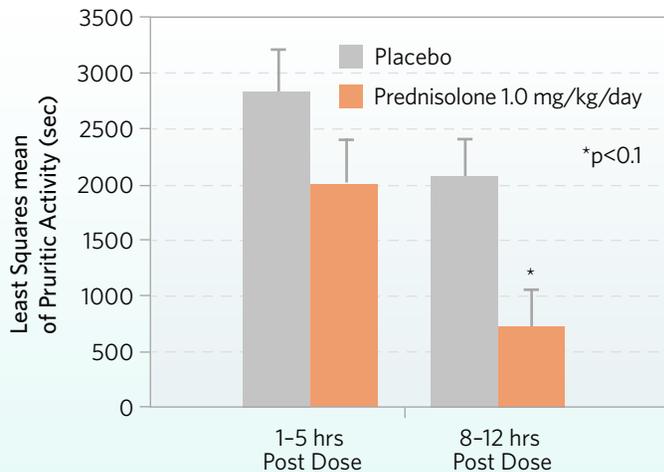
pruritus compared to negative control at as early as the first time interval and at each time interval measured (Figure 15).

In a separate study using the same model, the onset of action of oral prednisolone dosed at 1 mg/kg bodyweight was tested (Figure 16).<sup>15,23</sup>

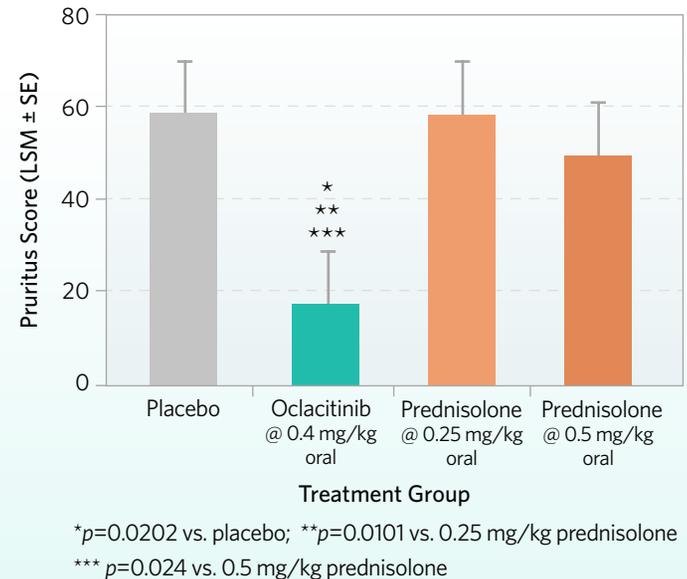
Statistically significant differences ( $p < 0.1$ ) from placebo were observed 8-12 hours after the administration of prednisolone, but no significant decrease in pruritus was observed in the 1-5 hour timeframe.

The comparative anti-pruritic efficacy of oclacitinib was also tested in a laboratory model of pruritus induced by IL-31, a known pruritogen in dogs associated with canine allergic dermatitis (Figure 17).<sup>22,24</sup> Laboratory dogs (8 per group) received a single oral dose of the following: oclacitinib at label dose (0.4 mg/kg), prednisolone (0.25 mg/kg) or prednisolone (0.50 mg/kg). Mean pruritic scores were measured 1-3 hours following dosing.

**Figure 16 | Validation of the FAD pruritus model using current treatments - Inhibition of pruritus after prednisolone administration in flea allergic dogs. Data are LS-mean ±SE.**



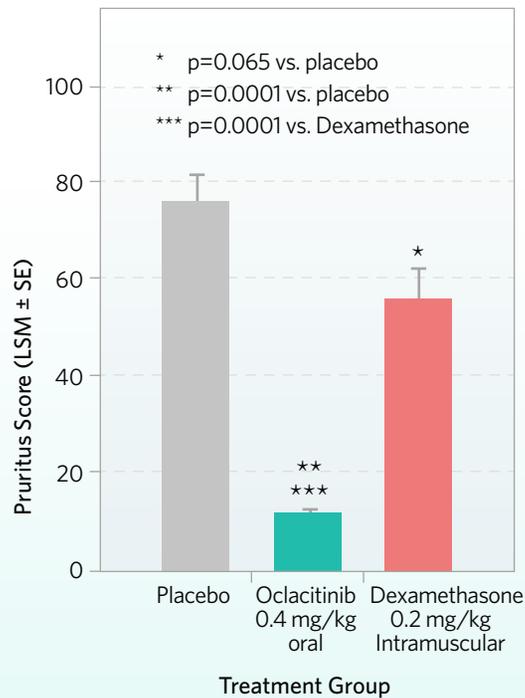
**Figure 17 | Relative inhibition of IL-31-induced pruritus by oclacitinib and prednisolone in a canine model - Inhibition of IL-31-induced pruritus by a single dose of oclacitinib or prednisolone in flea allergic dogs.**



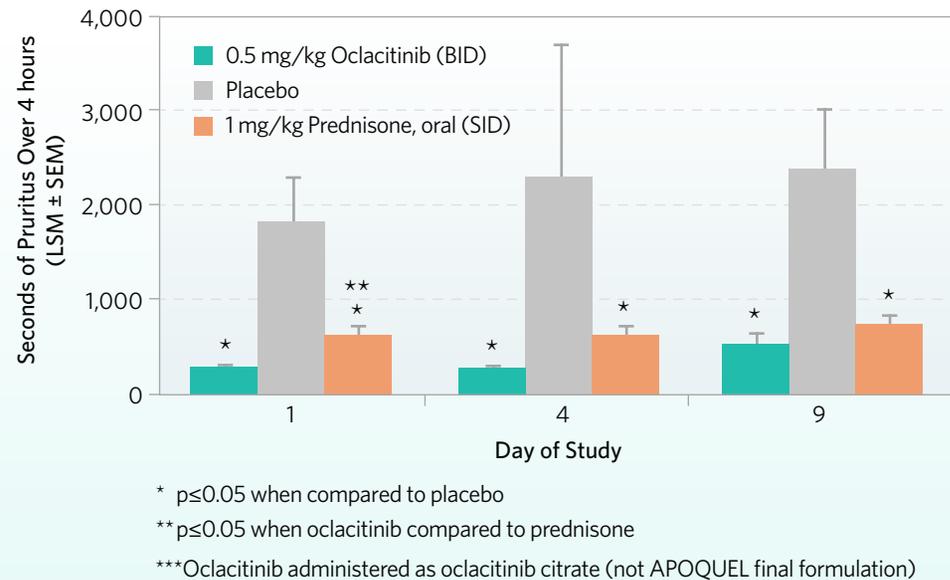
It was also of interest at this initial pre-clinical stage to characterize oclacitinib with respect to its onset of anti-pruritic activity compared to injectable products. This was tested in a laboratory investigation using the same

laboratory model of IL-31 induced pruritus.<sup>25,26</sup> The study compared a single, oral dose of oclacitinib at label dose (0.4 mg/kg per os) with a single dose of dexamethasone (0.2 mg/kg injected intramuscularly). At 1-3 hours post dosing, mean pruritus scores assessed by a blinded investigator were significantly lower ( $p=0.0001$ ) in the oclacitinib-treated dogs ( $n=8$ ) than in the dogs ( $n=8$ ) receiving the dexamethasone injection (Figure 18).

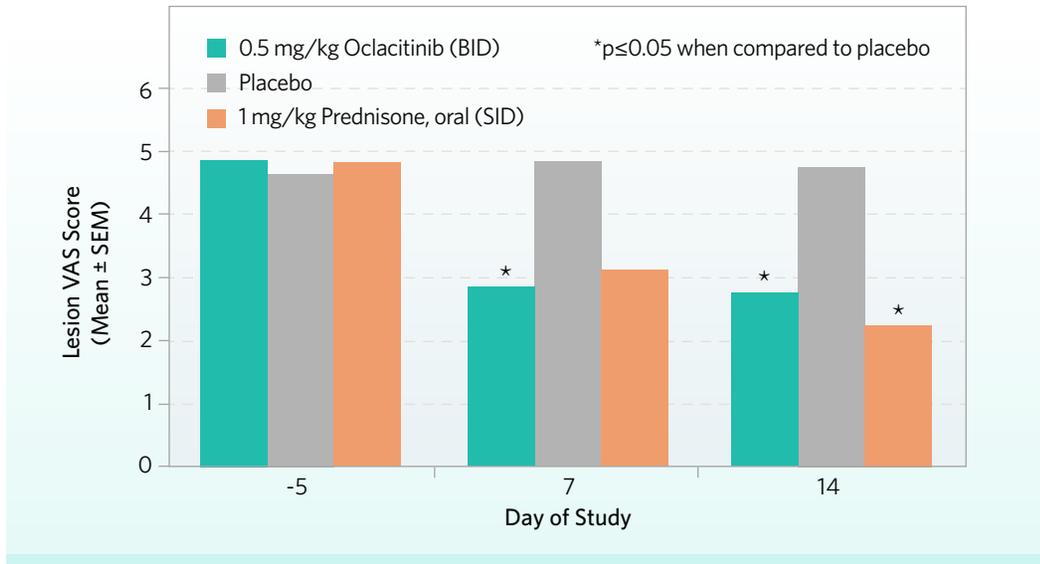
**Figure 18 | Relative inhibition of IL-31-induced pruritus by oclacitinib and dexamethasone in a canine model - Effects of placebo, oclacitinib, and dexamethasone on IL-31-induced pruritus in laboratory Beagles.**



**Figure 19 | Relative anti-pruritic effects of oclacitinib and prednisone using a canine model - Effects of placebo, oclacitinib (citrate salt), and prednisone on mean durations of pruritus (seconds) in flea allergic mongrel dogs, recorded during 4-hour sampling intervals on various study days.\*\*\***



**Figure 20 | Relative effect of oclacitinib and prednisone on skin lesions using a canine model – Effects of placebo, oclacitinib (citrate salt), and prednisone on lesion scores in flea allergic mongrel dogs on various study days. Oclacitinib administered as oclacitinib citrate (not APOQUEL final formulation)**



**Table 5 | Impact of oclacitinib and prednisolone on results of intradermal tests (IDT) – Number of dogs (%) by the observed change in sensitivity to IDT.**

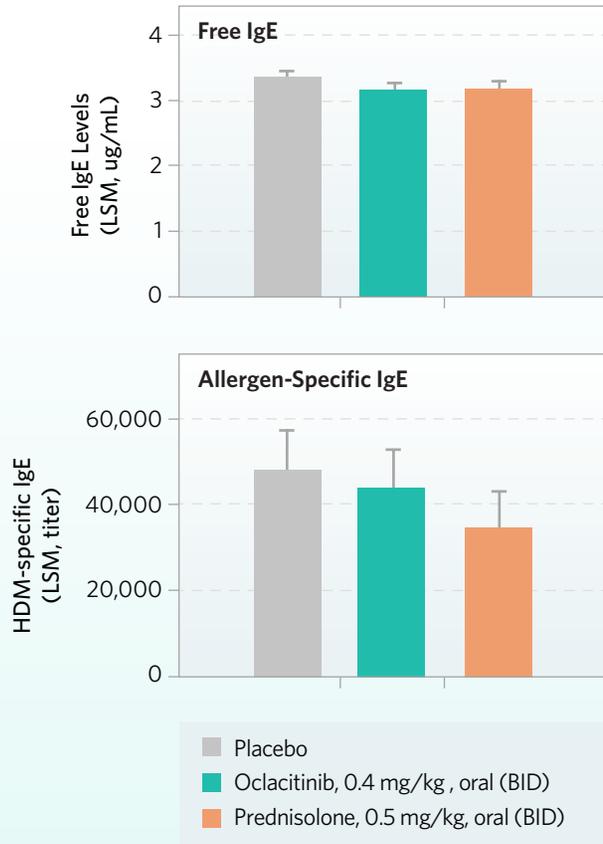
TREATMENT GROUP	INCREASE	NO CHANGE	DECREASE	LOSS
Placebo (n=8)	0	5 (62.5%)	3 (37.5%)	0
Oclacitinib (n=8)	1 (12.5%)	2 (25%)	5 (62.5%)	0
Prednisolone (n=8)	0	0	4 (50%)	4 (50%)

The final laboratory investigation explored the effects of oclacitinib on pruritus and skin lesions in dogs with FAD. Dogs were infested with fleas for 1 month prior to treatment and treated for 21 days (Figures 19 and 20).<sup>27</sup> The results reported show the durations of pruritus and lesion scores in dogs treated orally with either placebo, or with oclacitinib 0.5 mg/kg twice daily for 14 days or prednisone 1 mg/kg SID for 14 days. Dogs in the study continued on study and received treatment through Day 21, but results are not reported here as only on-label dosing is represented (twice daily dosing through Day 14). Oclacitinib and prednisone were associated with significant reductions in pruritus after 1 day of treatment that persisted throughout the treatment period (Figure 19). An investigator blinded to the treatment groups assessed skin lesions in the dogs using a visual analog scale (VAS) score. After 7 days of treatment, only oclacitinib-treated dogs had a statistically significant decrease in VAS lesion scores compared to placebo (Figure 20).

### LACK OF INTERFERENCE WITH DIAGNOSTIC TESTING

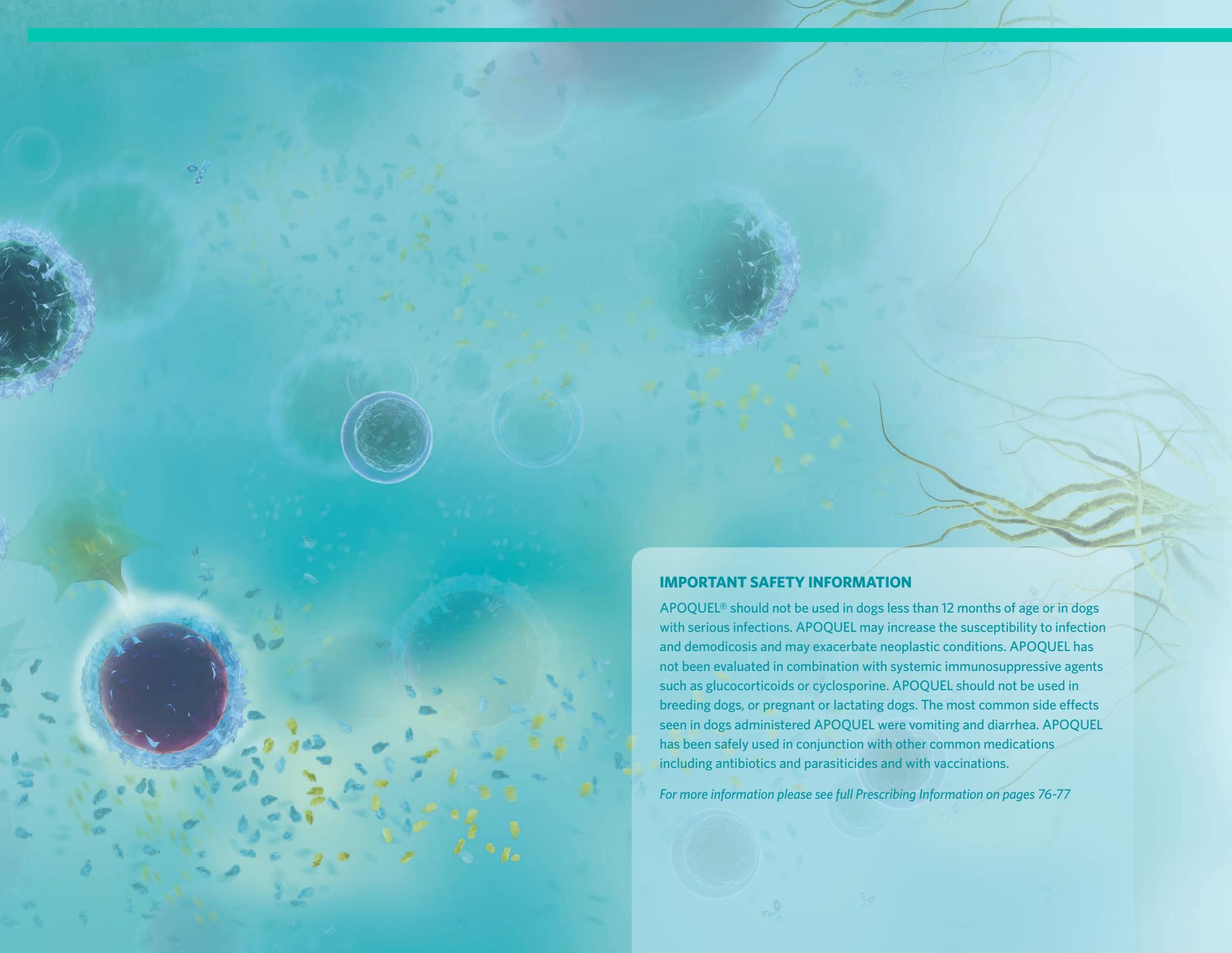
A laboratory study was conducted to assess the impact of the label dose of oclacitinib on the results of intradermal tests (IDT).<sup>28</sup> Laboratory dogs (8 per group) sensitized to house dust mite underwent baseline IDT for sensitivity to house dust mite antigen prior to being randomized and

**Figure 21 | Impact of oclacitinib and prednisolone on results of serology testing - Effects of placebo, oclacitinib, and prednisolone on serology testing.**



treated for 14 days with placebo, oclacitinib at 0.4 mg/kg BID, or prednisolone at 0.5 mg/kg BID. After 14 days of treatment, each dog underwent a second IDT and results were recorded as an increase, no change, a decrease, or complete loss of sensitivity. Following treatment, all prednisolone-treated dogs demonstrated a decrease or total loss of sensitivity while oclacitinib-treated dogs demonstrated one of the following: an increase, no change, or decrease in IDT sensitivity (Table 5).

In addition, data is available showing that oclacitinib did not interfere with IgE serology testing (Figure 21).<sup>28,29</sup> ●

The background of the entire page is a light blue, semi-transparent image of a microscopic environment. It features various biological structures: several large, spherical cells with textured, spiky surfaces; smaller, clear spherical vesicles; and a network of thin, yellowish, fibrous structures resembling roots or neural pathways on the right side. The overall aesthetic is clean and scientific.

### **IMPORTANT SAFETY INFORMATION**

APOQUEL® should not be used in dogs less than 12 months of age or in dogs with serious infections. APOQUEL may increase the susceptibility to infection and demodicosis and may exacerbate neoplastic conditions. APOQUEL has not been evaluated in combination with systemic immunosuppressive agents such as glucocorticoids or cyclosporine. APOQUEL should not be used in breeding dogs, or pregnant or lactating dogs. The most common side effects seen in dogs administered APOQUEL were vomiting and diarrhea. APOQUEL has been safely used in conjunction with other common medications including antibiotics and parasiticides and with vaccinations.

*For more information please see full Prescribing Information on pages 76-77*

# 6 APOQUEL<sup>®</sup> (oclacitinib tablet) Efficacy

## IN THIS CHAPTER

Treatment of Pruritus Associated with Allergic Dermatitis in Dogs

Treatment of Canine Atopic Dermatitis

## EFFICACY SUMMARY

- **APOQUEL provides rapid relief of pruritus to dogs with allergic dermatitis and AD. Dogs in clinical field trials showed a significant decrease in pruritus within 24 hours of treatment initiation**
  - Unlike Atopica, APOQUEL does not need to be administered for several weeks before there is a clinical response
- **APOQUEL has been shown to be effective for treating pruritus associated with allergic dermatitis due to a variety of underlying causes:**
  - Flea allergy dermatitis
  - Food allergy
  - Contact allergy
  - AD
- **APOQUEL demonstrated similar efficacy to prednisolone in decreasing pruritus in dogs with allergic dermatitis**
- **APOQUEL has been shown to be effective in the control of canine AD, including improvements in:**
  - Pruritus
  - Erythema
  - Lichenification
  - Skin excoriations or lesions
- **APOQUEL demonstrated a sustained decrease in pruritus and improved skin condition over the full course of treatment in dogs with AD**
- **APOQUEL has been shown to be effective and safe when used short-term and long-term. There is no label limit to the duration of treatment with APOQUEL**
- **APOQUEL has been administered to more than 1200 canine patients enrolled in clinical field studies around the world**

The efficacy and safety of APOQUEL® has been studied extensively in over 1200 client-owned dogs in more than 8 countries around the world. Several of the studies are fully detailed here, and a full listing of peer-reviewed publications on APOQUEL (at the time of publication of this volume) is included in the Bibliography. The studies in this section support the use of APOQUEL for the control of allergic and atopic conditions in dogs over 12 months of age at a dose of 0.4-0.6 mg/kg (0.18-0.27 mg/lb) BID for up to 14 days, followed by 0.4-0.6 mg/kg (0.18-0.27 mg/lb) SID for maintenance therapy.

APOQUEL® (ocloclatinib tablet) has been shown to be effective in decreasing pruritus and improving skin lesions associated with allergic dermatitis and in controlling signs of AD in dogs over 12 months of age. In post-approval clinical trials, APOQUEL was as effective as prednisolone for the control of allergic dermatitis in dogs and as effective as Atopica® at controlling AD. APOQUEL efficacy was observed without many of the side effects typically associated with corticosteroids such as polyuria and polyphagia, and without the delay in onset of activity expected with cyclosporine.

**Table 6 | Summary of APOQUEL® clinical trials in allergic dogs – Overview of APOQUEL® global clinical study program in allergic dermatitis.**

REGION / COUNTRY	COMPARATOR / NUMBER OF DOGS ENROLLED	NUMBER OF CLINICS IN STUDY
United States	APOQUEL: 216 dogs Negative control (placebo): 220 dogs	26
Australia	APOQUEL: 61 dogs Delta Cortef® (prednisolone): 62 dogs	12
Japan	APOQUEL: 19 dogs Negative control (placebo): 15 dogs	10

## CONTROL OF PRURITUS ASSOCIATED WITH ALLERGIC DERMATITIS IN DOGS

APOQUEL® has been studied as a control for pruritus associated with allergic dermatitis due to a variety of underlying causes including, but not limited to, flea allergy dermatitis, AD, contact dermatitis, and food allergy. The multi-centered studies reported here were of similar design and conducted in all global regions, as listed in Table 6.

## CLINICAL FIELD EFFICACY AND SAFETY OF APOQUEL® (ocloclatinib tablet; US)<sup>30</sup>

Four hundred thirty-six (436) pure and mixed breed dogs were enrolled in this blinded, well-controlled trial in 26 veterinary practices across the United States. Investigators were general veterinary practitioners. The dogs ranged in age from 0.5 to 18 years old and weighed between 6.6 and 135.7 pounds. Male and female dogs were equally represented. To be included in the study, dogs had to be otherwise healthy excluding their pruritic condition and had to demonstrate a moderate level of pruritus as assessed by their owner using a 10-cm VAS. The underlying cause of the pruritus in these dogs was attributed by the veterinary investigator to one or more of the presumptive diagnoses summarized in Table 7.

*A quantified assessment by the owner was considered the most meaningful measure of a dog's level of pruritus during treatment.*

Dogs were randomized to treatment with either placebo BID (n=220) or APOQUEL® at 0.4-0.6 mg/kg orally BID (n=216). On each day of the study phase (Days 0-7) the owner assessed the dog's level of pruritus using a

pruritus VAS. Prior to treatment and after 7 days of treatment, the veterinary investigator assessed the dog's level of dermatitis. At the end of the study (Day 7) the dog completed the study and the veterinarian could elect to enter the dog into the continuation phase of the study lasting from Day 8 to Day 28.

Since pruritus can be evidenced at various points in a day, and a dog spends more time with the owner at home than at the clinic during an examination, a quantified assessment by the owner was considered the most meaningful measure of the dog's level of pruritus during treatment. The primary efficacy variable was the proportion of dogs treated that achieved at least a 2-cm reduction (one description or category on the scale – see Appendix 1) from

**Table 7 | Presumptive Diagnosis of Allergic Patients (US Trial) – Pruritic dermatoses presumptive diagnoses in APOQUEL-treated dogs. Each dog may have had more than one presumptive diagnosis for their pruritus and allergic dermatitis.**

PRESUMPTIVE DIAGNOSIS BY VETERINARY INVESTIGATOR	NUMBER (%) OF DOGS
Atopic dermatitis*	175 (81%)
Atopic dermatitis alone	90 (41.5%)
Flea allergy dermatitis	72 (33.3%)
Contact dermatitis	24 (11.1%)
Food hypersensitivity	48 (22.2 %)
Sarcoptic mange	2 (0.9 %)
Other allergic dermatitis	12 (5.6%)

\* In 41.5% of dogs, AD was identified as sole presumptive diagnosis, although investigators were allowed to identify 1 or more presumptive causes of the dog's allergic dermatitis.

*In a clinical trial evaluating dogs with allergic dermatitis due to flea allergy, contact dermatitis, food hypersensitivity, AD, and other underlying causes, APOQUEL® (oclacitinib tablet) significantly decreased pruritus within 24 hours compared to control; the improvement continued throughout the 1-week treatment period.*

baseline (Day 0) on a 10-cm owner-assessed pruritus VAS score on at least 5 of 7 treatment days (70%) from Days 1 to 7. Secondary variables included: the VAS dermatitis score assessed by the veterinary investigator prior to treatment (Day 0) and after 7 days of treatment on the final study day (Day 7); and the numerical value for the VAS pruritus score, assessed by the owner on each day of treatment.

Based on the primary efficacy variable (Table 8) in this study, APOQUEL®-

**Table 8 | Evaluation of primary efficacy variable (US trial) – Primary efficacy outcome; treatment success (Days 1-7) on owner pruritus VAS.**

TREATMENT GROUP (NUMBER OF CASES EVALUABLE FOR EFFICACY)	TREATMENT SUCCESS* LS MEAN (95% CI)	P VALUE
APOQUEL® (n=203)	0.67 (0.59, 0.73)	p<0.0001
Placebo (n=204)	0.29 (0.23, 0.36)	

LS, least squares.

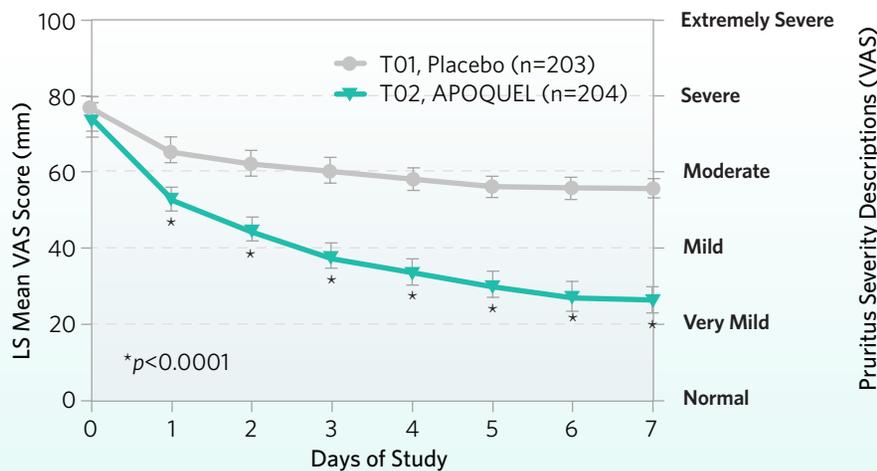
\* Treatment success = 2 cm reduction (from baseline) in owner-assessed pruritus scores on at least 70% of the study days assessed; back-transformed from logit scale to original scale.

treated dogs were more than twice as likely to achieve treatment success as dogs treated with negative control.

In this study, APOQUEL® rapidly and significantly decreased pruritus in dogs diagnosed with a variety of underlying allergic conditions and continued to control pruritus throughout the treatment period (Figure 22).

- After a single day of treatment, the mean owner-assessed VAS pruritus score in APOQUEL-treated dogs was significantly ( $p < 0.0001$ ) reduced compared to negative control dogs
- On each of the 7 treatment days, the mean owner-assessed pruritus was significantly ( $p < 0.0001$ ) lower than the negative control dogs

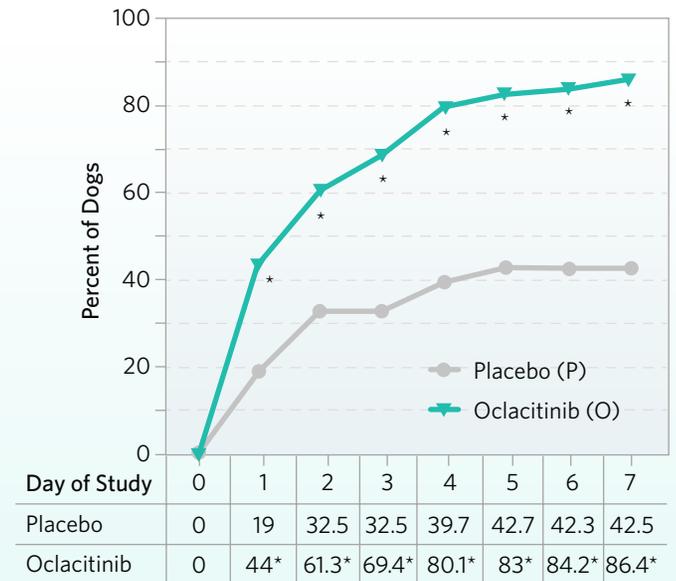
**Figure 22 | Anti-pruritic efficacy of APOQUEL® (US trial) - Owner-assessed pruritus VAS scores (LS means) on each day of treatment. (LS, Least squares)**



APOQUEL® was reliably efficacious in controlling itch across the various patients that presented with allergic dermatitis due to a variety of underlying causes (Figure 23).

- On each of the 7 treatment days, the percentage of APOQUEL-treated dogs that achieved a 2 cm decrease in pruritus from baseline level was significantly greater than the percentage of dogs treated with control that

**Figure 23 | Impact of APOQUEL® on pruritus (US trial) - Percentage of dogs achieving a 2-cm reduction in owner pruritus VAS scores in an efficacy and field safety study of APOQUEL® for the control of pruritus associated with allergic dermatitis in dogs.**



\*Oclacitinib is significantly different from Placebo ( $p < 0.0001$ )

achieved this level of decrease in pruritus

- After 1 week of treatment, almost 9 out of 10 (86.4%) APOQUEL-treated dogs achieved a 2-cm reduction on the owner-assessed pruritus VAS compared to only 42.5% of dogs in the placebo group ( $p < 0.0001$ )

In addition to decreasing pruritus, APOQUEL<sup>®</sup> improved skin lesions in allergic dogs as measured by the veterinarian-assessed dermatitis VAS score (Figure 24).

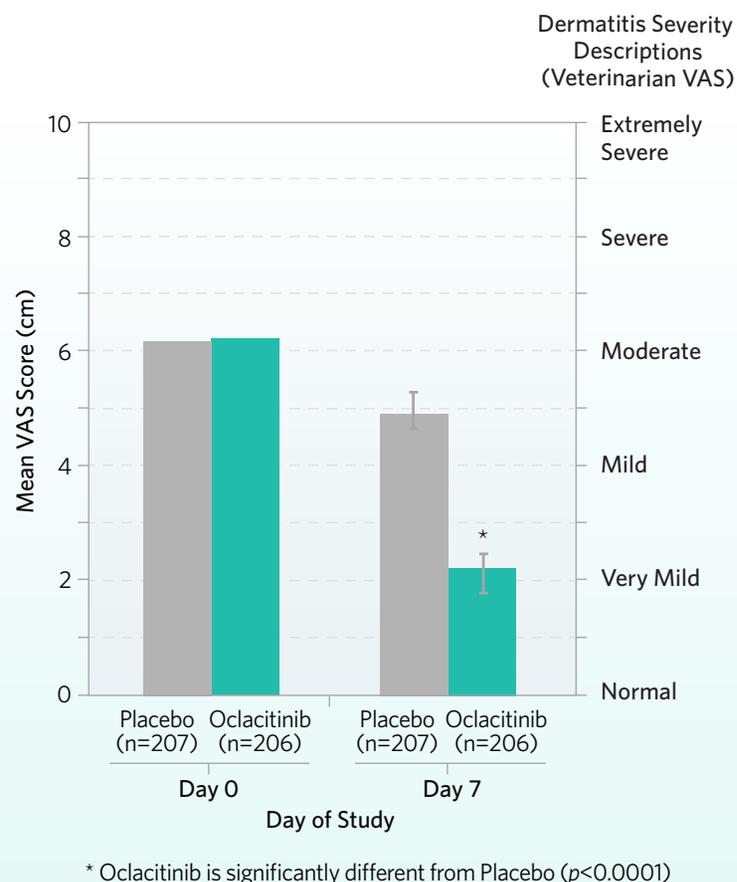
- After 7 days of treatment there was a decrease in the mean dermatitis score in APOQUEL-treated dogs from moderate to very mild. This was a significantly greater decrease in dermatitis level compared to that observed in control dogs ( $p < 0.0001$ )

#### EFFICACY OF APOQUEL<sup>®</sup> (oclacitinib tablet) COMPARED TO PREDNISOLONE FOR CONTROL OF PRURITUS ASSOCIATED WITH ALLERGIC DERMATITIS<sup>31</sup>

This study was conducted in 12 veterinary clinics by general practitioners across Australia. The objective was to compare APOQUEL (n=61) at label dose (0.4-0.6 mg/kg BID for 14 days followed by 0.4-0.6 mg/kg SID) to Delta-Cortef<sup>®</sup> (prednisolone; n=62) at label dose (0.5-1.0 mg/kg SID for 6 (±1) days followed by 0.5-1.0 mg/kg every other day for the duration of treatment) for the control of pruritus and clinical signs of allergic dermatitis in client-owned dogs. Dogs were dosed for up to 28 (±2) days. The primary

*Based on the primary efficacy parameter, the response to treatment with APOQUEL<sup>®</sup> (oclacitinib tablet) was significantly better than with prednisolone. At all other timepoints assessed, pruritus level as measured by the owner using VAS was similar between the treatment groups.*

**Figure 24 | Veterinary assessment of APOQUEL<sup>®</sup> efficacy (US trial) -** Veterinarian-assessed dermatitis VAS scores in an efficacy and field safety study of APOQUEL<sup>®</sup> for the control of pruritus associated with allergic dermatitis in dogs.



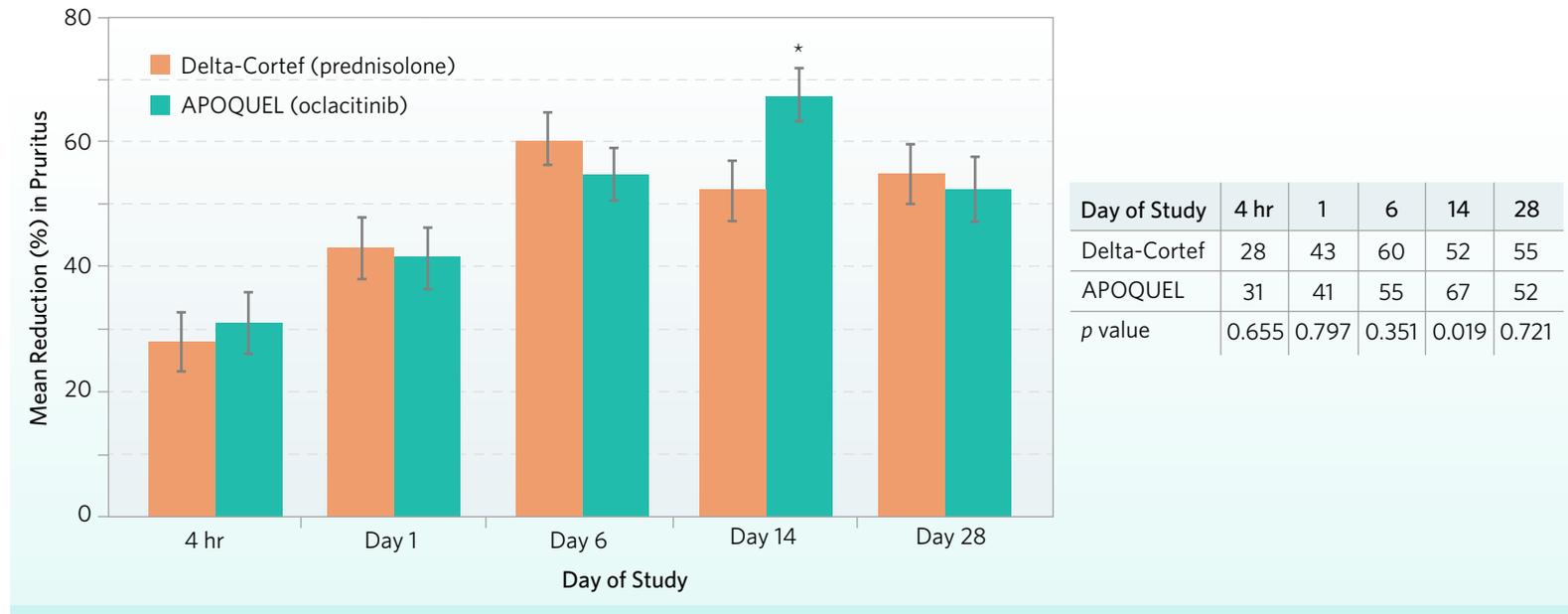
efficacy variable was the mean percentage reduction in pruritus from baseline (pre-treatment) as measured by the owner after 14 (±2) days of treatment using a 10-cm VAS (see Appendix 1).

Secondary efficacy variables included the following: (1) owner VAS score for pruritus measured at each owner assessment, (2) the percentage change from baseline in owner-assessed pruritus at each assessment, (3) VAS assessment of allergic dermatitis by the veterinary investigator, (4) the percentage reduction from baseline in allergic dermatitis as assessed by the veterinary investigator, (5) VAS assessment of response to treatment by the

**Table 9 | Presumptive diagnosis of allergic patients (Australian trial) -** Diagnoses of dogs enrolled in the study.

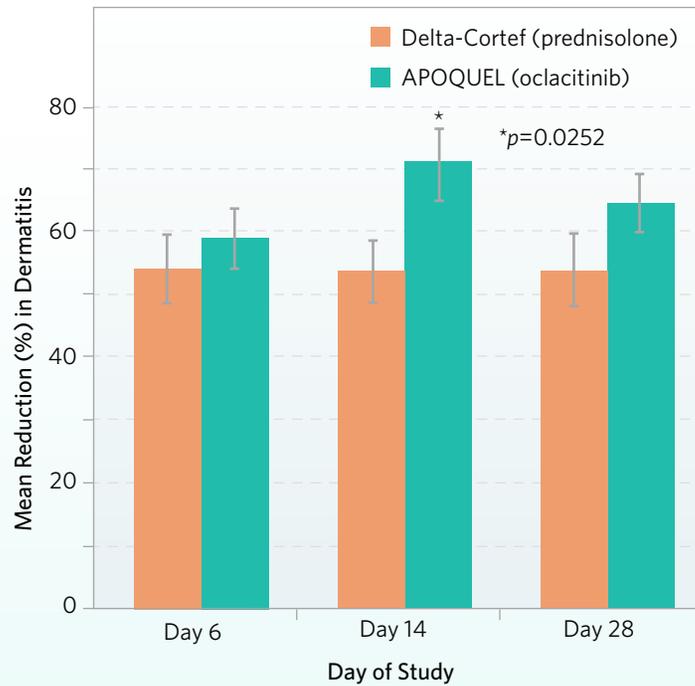
PRESUMPTIVE DIAGNOSIS BY VETERINARY INVESTIGATOR	PERCENT (%) OF APOQUEL DOGS WITH DIAGNOSIS	PERCENT (%) OF DELTA-CORTEF DOGS WITH DIAGNOSIS
Atopic dermatitis	96.7%	98.4%
Flea allergy dermatitis	32.8%	40.3%
Contact dermatitis	47.5%	41.9%
Food hypersensitivity	23.0%	19.4%

**Figure 25 | Reduction of pruritus by APOQUEL (Australian trial) -** Percent reduction from baseline of owner assessment of pruritus VAS scores (least squares mean ± SE). Percent reduction from baseline at Day 14 was the primary efficacy variable.



Day of Study	4 hr	1	6	14	28
Delta-Cortef	28	43	60	52	55
APOQUEL	31	41	55	67	52
p value	0.655	0.797	0.351	0.019	0.721

**Figure 26 | Reduction in dermatitis with APOQUEL (Australian trial) –** Percent reduction from baseline of veterinary assessment of dermatitis VAS scores (least squares mean ± SE).



Day of Study	6	14	28
Delta-Cortef	54	54	54
APOQUEL	59	71	64
p value	0.487	0.025	0.164

veterinary investigator on Day 28, and (6) VAS assessment of response to treatment by the owner on Day 28.

The allergic dermatitis in the enrolled dogs could be attributed to one or more underlying conditions (Table 9).

Response in both treatment groups was rapid with a decrease in the mean owner-assessed VAS score by 4 hours post-treatment. The mean owner-assessed pruritus VAS score in allergic dogs treated with APOQUEL® was statistically lower than in prednisolone-treated dogs at 14 days of treatment (p=0.0087). At other evaluation timepoints in this study, the responses to APOQUEL and prednisolone were statistically similar between groups.

Likewise, the percent reduction in owner-assessed VAS score was statistically greater in the APOQUEL®-treated group than in the prednisolone-treated group (p=0.0193) at Day 14 (Figure 25). The response to treatment (RTT) assessed by the veterinary investigators on the final study day was statistically greater (p=0.0109) in the APOQUEL group than in the prednisolone group. The overall RTT assessed by the pet owners was not significantly different (p=0.1665) in the APOQUEL-treated group versus the prednisolone-treated group.

The percentage reduction in veterinarian-assessed allergic dermatitis VAS scores from baseline values was significantly greater (p=0.0252) in the oclacitinib group than in the prednisolone-treated group



**Alopecia and hyperpigmentation in a chronically atopic dog**

at the Day 14 assessment (Figure 26). Also, least squares mean values for the veterinary-assessed VAS score were significantly lower in the APOQUEL-treated group at the Day 14 assessment ( $p=0.0022$ ).

### CONTROL OF CANINE ATOPIC DERMATITIS

APOQUEL has been studied for the control of AD. These studies support the use of APOQUEL at 0.4-0.6 mg/kg BID for 14 days followed by 0.4-0.6 mg/kg SID for maintenance in dogs with AD. Many of these dogs have been safely treated for extended periods, including some that have been tracked for almost 2 years as part of a continued-use study. The multi-centered studies were of similar design and conducted in multiple global regions as listed in Table 10.

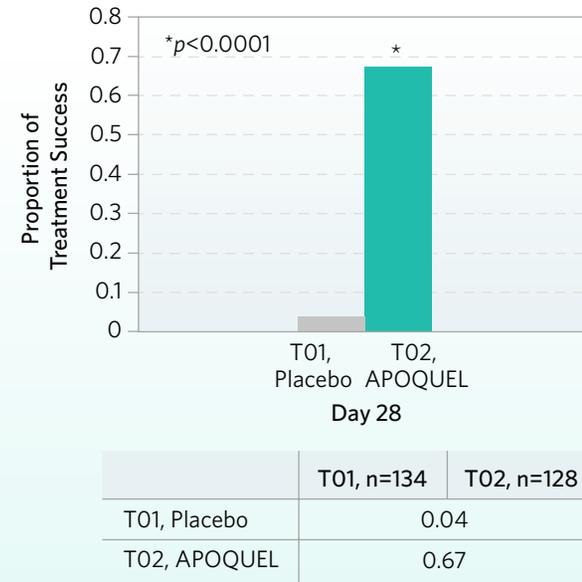
**Table 10 | Summary of APOQUEL® clinical trials in atopic dogs - Overview of APOQUEL global clinical study program in AD.**

REGION / COUNTRY	COMPARATOR / NUMBER OF DOGS ENROLLED	NUMBER OF CLINICS IN STUDY
United States	APOQUEL: 152 Negative control (placebo): 147	19 (18 had enrolled cases)
Australia	APOQUEL: 114 Atopica® (cyclosporine): 112	8
Japan	APOQUEL: 24 Atopica® (cyclosporine): 22	8

### CLINICAL FIELD EFFICACY AND SAFETY FOR CANINE ATOPIC DERMATITIS (US)<sup>32</sup>

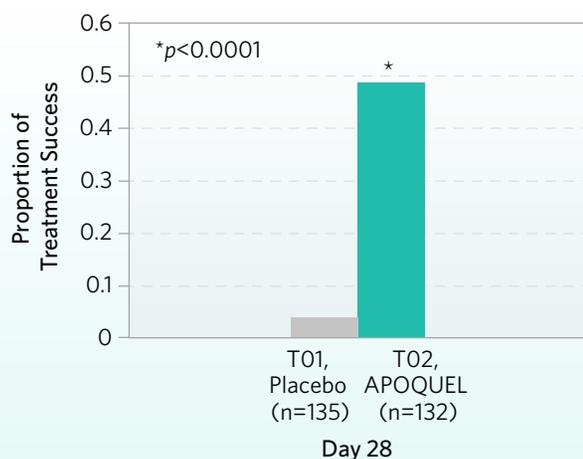
A multi-centered, placebo-controlled clinical field trial was conducted at 19 dermatology referral practices across the United States. Only 18 of the 19

**Figure 27 | Evaluation of owner-assessed pruritus (US trial) - Primary efficacy parameter; owner-assessed pruritus VAS. The proportion of dogs by treatment group that were treatment successes.**



clinics enrolled cases to the study. All of the study investigators were board-certified veterinary dermatology specialists. The dogs treated were male and female, both neutered and intact, pure and mixed breeds, ranging in age from 1 to 13 years at the start of therapy. Dogs were randomized to treatment with either placebo or APOQUEL. APOQUEL-treated dogs were dosed at 0.4-0.6 mg/kg twice daily for 14 days followed by once daily for the duration of treatment up to Day 112. Two-hundred ninety nine (299) dogs were enrolled, received at least one treatment, and were evaluated for safety.

**Figure 28 | Impact of APOQUEL® on veterinary- assessed CADESI-02 (US trial) – Primary efficacy parameter; investigator-assessed CADESI-02 scale at Day 28. The proportion of dogs by treatment group that were treatment successes.**



The primary efficacy parameters were the number of dogs achieving treatment success for owner-assessed pruritus and veterinary-assessed skin lesions after 28 ( $\pm 2$ ) days of treatment. Owners assessed pruritus using a 10-cm VAS. Secondary assessment variables included the following: (1) treatment success for Days 56, 84 and 112; (2) lesion scores (measured by CADESI-02 score) assessed by the veterinary investigator at each clinic visit; (3) overall pruritus score measure on VAS at each owner assessment; (4) overall assessment of dermatologic condition by the veterinarian based on VAS; and (5) assessment of response to treatment by the owner and veterinarian based on VAS. Safety was assessed in all dogs based on reported adverse events, body weight, complete blood count (CBC), and clinical chemistry and urinalysis results.

For the primary efficacy parameters, owner-assessed pruritus and veterinary-assessed skin lesions, the proportion of APOQUEL-treated dogs that were treatment successes was statistically greater ( $p < 0.0001$ ) than the proportion of dogs in the placebo-treated group that were considered a treatment success (Figures 27 and 28).

In the APOQUEL-treated dogs that continued on the study beyond 1 month (Day 28  $\pm 2$ ), the mean owner-assessed pruritus score (measured by VAS) continued to improve through the final assessment on Day 112 (Figure 29). As might be expected, by the Day 28 assessment, 86% of placebo-treated dogs had been withdrawn from the study based on worsening clinical signs; and these dogs were allowed to enroll in an open label trial in which they were treated with APOQUEL.

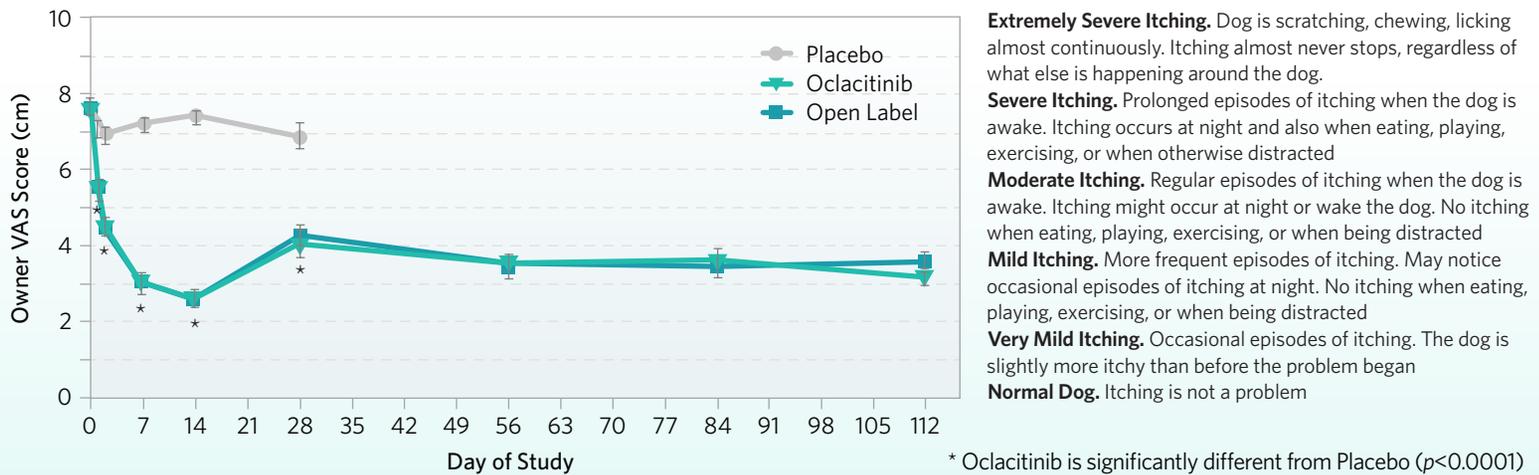
CADESI-02 scores assessed by the veterinary dermatologists for APOQUEL-treated dogs were significantly better than those for placebo-treated dogs at each timepoint assessed ( $p < 0.0001$ ). For the APOQUEL-treated dogs that continued on the study beyond 1 month, the mean CADESI-02 scores remained improved through the final study evaluation at Day 112 (Figure 30).

### **APOQUEL® (occlacitinib) EFFICACY COMPARED TO ATOPICA<sup>13</sup>**

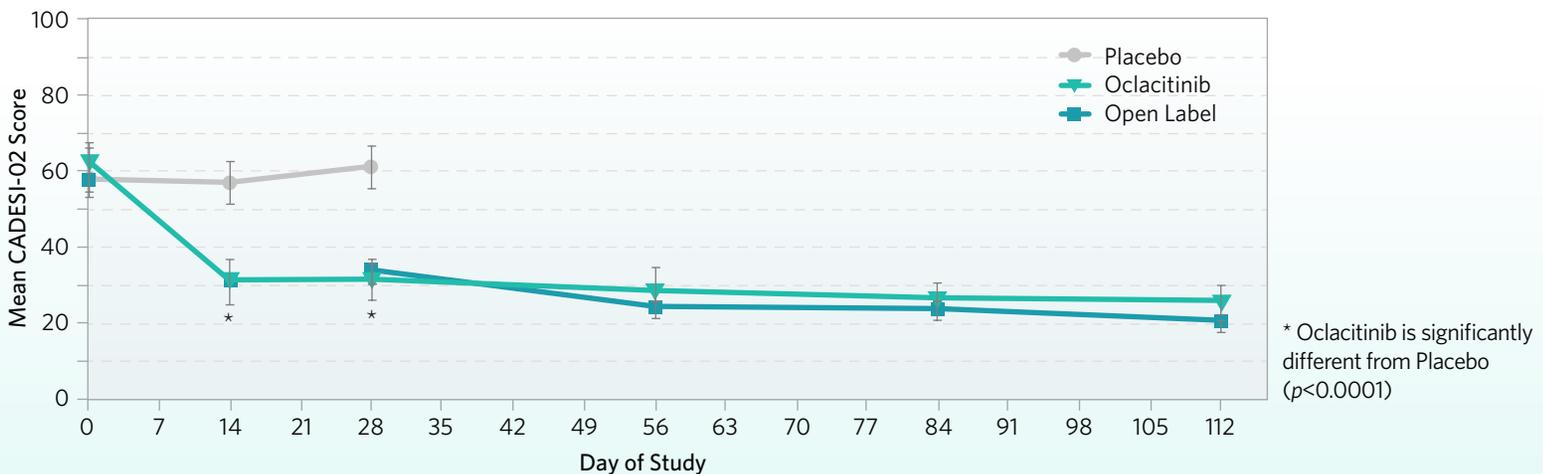
The study was conducted in 226 dogs enrolled by veterinary dermatology specialists at study sites across Australia. The objective was to compare APOQUEL® (n=114) at label dose (0.4-0.6 mg/kg BID for 14 days followed by 0.4-0.6 mg/kg SID) to Atopica® (cyclosporine; n=112) dosed at label dose (3.1-6.7 mg/kg SID) for the control of AD in client-owned dogs. Dogs were dosed for up to 84 ( $\pm 2$ ) days.

The primary efficacy variables measured were: (1) the percentage reduction from baseline for owner-assessed pruritus using a 10-cm VAS scale (Appendix 1), and (2) percentage reduction from baseline in veterinary-assessed CADESI-02 (Appendix 3). Each primary variable assessment incorporated a non-inferiority statistical test at Day 28.

**Figure 29 | Evaluation of owner-assessed pruritus with ongoing treatment (US trial) – Owner assessment of pruritus VAS scores (mean).**



**Figure 30 | Impact of APOQUEL® on veterinary-assessed CADESI-02 (US trial) – Investigator-assessed skin lesion (CADESI-02) least squares mean scores.**



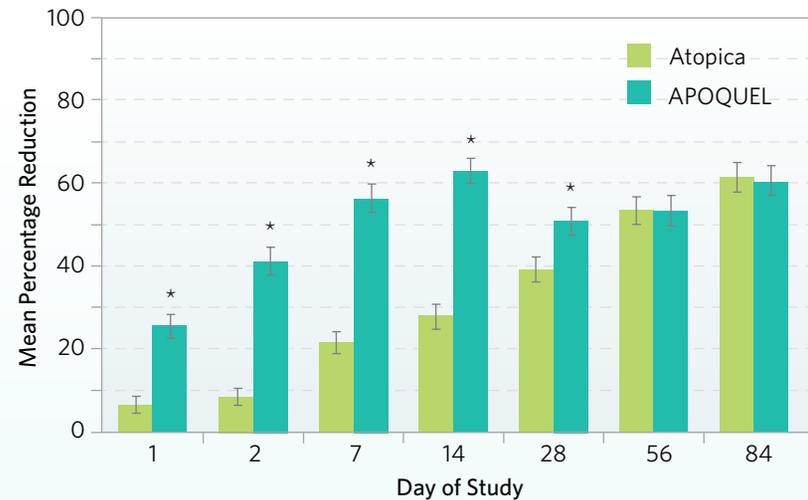
*In this study of 226 dogs in Australia with AD, APOQUEL® was as efficacious as, and at several timepoints superior to, Atopica in controlling AD in dogs.*

- *Owners reported a significant decrease in pruritus in the APOQUEL-treated dogs compared to the Atopica-treated dogs at each assessment during the first 28 days of treatment. When assessed at Days 56 and 84, the decrease in pruritus in the APOQUEL-treated dogs was similar to the Atopica-treated dogs*
- *The reduction from baseline in CADESI-02 scores assigned by veterinary dermatologists was significantly lower in APOQUEL-treated dogs at Day 14. At all other assessments, the reduction from baseline in CADESI-02 scores was similar in the APOQUEL-treated dogs and Atopica-treated dogs*

Secondary efficacy variables included: (1) owner-assessed VAS score for pruritus and the proportion of dogs with  $\geq 50\%$  reduction from baseline score at each owner assessment timepoint, (2) CADESI-02 scores assessed by the veterinary dermatologist and the proportion of animals with  $\geq 50\%$  reduction from baseline score at each investigator assessment timepoint, (3) VAS dermatitis scores assessed by the veterinary dermatologist and the percentage reduction from baseline in VAS dermatitis score at each investigator assessment timepoint, (4) RTT assessed by the owner using VAS on the final study day, and (5) RTT assessed by the investigator using VAS on the final study day.

Veterinary investigators were masked to the treatment allocation of the patients, but Atopica was dispensed in its original foil packaging so owners

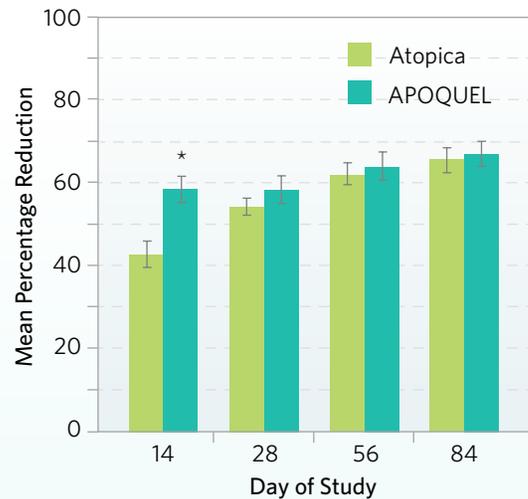
**Figure 31 | Impact of APOQUEL® on owner-assessed pruritus (Australian study) - Percentage reduction from baseline in owner-assessed pruritus VAS (mean  $\pm$ SE) (full study results have been submitted for publication).**



\* Treatment difference is significant at 0.05

Day of Study		1	2	7	14	28	56	84
LS Mean (N)	Atopica	6.51 (104)	8.59 (88)	21.69 (103)	27.92 (92)	39.20 (101)	53.57 (85)	61.49 (87)
	APOQUEL	25.60 (110)	41.35 (100)	56.63 (107)	63.17 (109)	50.93 (103)	53.47 (92)	60.95 (83)
p-value		<0.0001	<0.0001	<0.0001	<0.0001	0.0057	0.9813	0.9047

**Figure 32 | Impact of APOQUEL® on veterinary-assessed CADESI-02 scores (Australian study) – Percentage reduction from baseline in veterinary-assessed CADESI-02 scores (mean ±SE) (full study results have been submitted for publication).**



\* Treatment difference is significant at 0.05

Day of Study		14	28**	56	84
LS Mean (N)	Atopica	42.99 (93)	54.38 (101)	61.83 (85)	65.37 (87)
	APOQUEL	58.65 (109)	58.33 (102)	63.84 (92)	66.88 (83)
p-value		<0.0001	0.2799	0.6011	0.7065

\*\* Apoquel is non-inferior to Atopica at Day 28, based on a non-inferiority margin of 15% and significance of 0.05

*Vomiting and diarrhea were reported in over 3 times more Atopica-treated dogs than APOQUEL-treated dogs in the study.*

were not masked in this study. To be enrolled, dogs had to have a history compatible with a diagnosis of chronic, non-seasonal AD, be at least 12 months of age, and weigh between 3.0 and 80 kg. Enrolled dogs had to exhibit at least a moderate degree of itching or pruritus as assessed by their owner prior to treatment, and had to be assigned a minimum baseline score of 25 on CADESI-02.

The percentage decrease from baseline in owner-assessed pruritus was significantly better in the APOQUEL-treated dogs compared to the Atopica-treated dogs on Days 1, 2, 7, 14 and 28, and was similar between the two treatment groups on Days 56 and 84 (Figure 31).

The percentage reduction from baseline in veterinary-assessed CADESI-02 scores for APOQUEL-treated dogs was significantly better on Day 14 ( $p < 0.0001$ ) than the Atopica-treated group; and thereafter the percent reduction in CADESI-02 scores were similar for the two treatments (Figure 32).

More than 70% of the APOQUEL®-treated dogs experienced a reduction of 50% or greater decrease from baseline levels in CADESI-02 after 2 weeks of treatment compared to 42% ( $p < 0.0001$ ) of Atopica-treated dogs.

Veterinary-assessed dermatitis VAS scores for APOQUEL-treated dogs were significantly lower than those reported for Atopica-treated dogs at Day 14, and were similar between the two groups for the remaining duration of the treatment period. APOQUEL-treated dogs achieved a significantly higher percentage VAS reduction from baseline in veterinary-assessed dermatitis than Atopica-treated dogs after 14 days of treatment. There were no significant differences between the treatment groups in percent reduction

**Table 11 | Summary of adverse events** – Most frequently reported adverse events in each randomized treatment group (full study results have been submitted for publication).

CLINICAL SIGN	ALL ADVERSE EVENTS		RELATIONSHIP TO TEST ARTICLE (Excluding Pre-Existing Conditions) AS ASSESSED BY VETERINARY INVESTIGATOR			
			LIKELY		POSSIBLE	
	ATOPICA n (%)	APOQUEL n (%)	ATOPICA n (%)	APOQUEL n (%)	ATOPICA n (%)	APOQUEL n (%)
Any adverse event	94 (83.9)	71 (62.3)	22 (19.6)	10 (8.8)	62 (55.4)	44 (38.6)
Vomiting	49 (43.8)	16 (14.0)	19 (17.0)	4 (3.5)	32 (28.6)	12 (10.5)
Diarrhea	18 (16.1)	4 (3.5)	9 (8.0)	1 (0.9)	6 (5.4)	2 (1.8)

from baseline in veterinary-assessed dermatitis at the other assessments (Days 28, 56, and 84).

In this study, abnormal clinical signs were reported over the full duration of the study (84 ± 2 days); and occurred in both APOQUEL-treated and Atopica-treated groups (Table 11). Excluding those related to pre-existing conditions, abnormal signs were assessed by the veterinary investigator as being ‘likely-related’ to therapy with the test article occurred in 22 of 112 (19.6%) Atopica-treated dogs and 10 of 114 (8.8%) APOQUEL-treated dogs. Of these, gastrointestinal signs were the most frequently reported signs. Vomiting was reported in >43% of the Atopica-treated dogs and in 14% of the APOQUEL-treated dogs. Diarrhea was reported in >16% of the Atopica-treated dogs and in 3.5% of the APOQUEL-treated dogs. This is consistent with the product labeling for both products. Another 62 of 112 (55.4%) events were considered ‘possibly-related’ to Atopica treatment and another 44 of 114 (38.6%) events were considered ‘possibly-related’ to APOQUEL treatment. Other signs were

observed with less frequency or were considered unrelated/unclassifiable as to causality by the investigator.

### LONG-TERM CONTINUATION THERAPY<sup>33</sup>

All client-owned dogs completing any of the US field safety and efficacy studies that also met enrollment criteria were afforded the opportunity to be treated with APOQUEL (oclacitinib) by enrolling in a long-term, open-label, continuation therapy study. Beginning in 2009 and continuing through 2013,

*Two hundred thirty-nine (239) dogs previously enrolled in clinical trials elected to be treated with APOQUEL® (oclacitinib tablet) in an open-label continuation trial. Some dogs in this trial have been treated for almost 2 years with APOQUEL®.*

when the product was approved, enrolled dogs were assessed periodically for efficacy by the owner and veterinarian, and reported adverse events were documented. Assessments were performed at approximately 90-day intervals.

This study provides the opportunity to report the on-going efficacy and safety of APOQUEL when used in a field setting over several years. As of October 31, 2012, the first time the observations of this study were formally summarized for the US label summary:

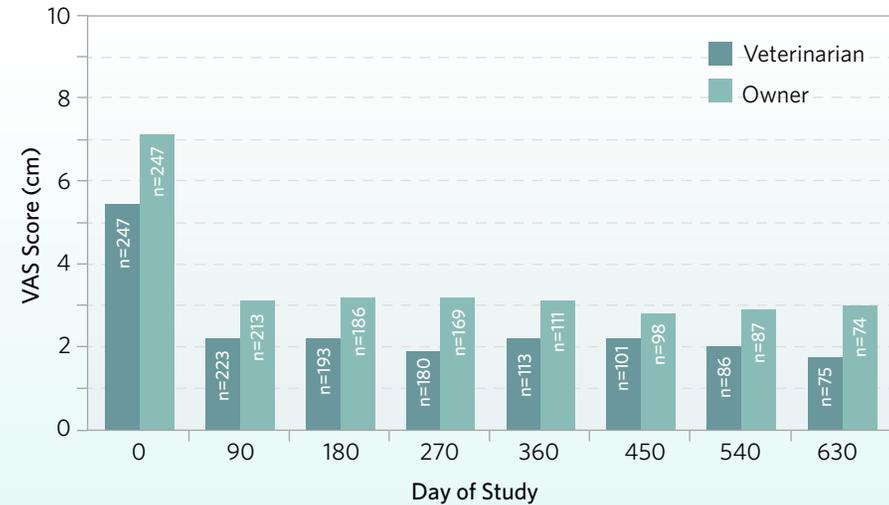
- Two hundred thirty-nine (239) dogs were treated with APOQUEL
- The mean time of enrollment in the study was 372 days (range: 1-610 days)

By May 1, 2013, 50% of the dogs enrolled had been on study for 1-2 years.

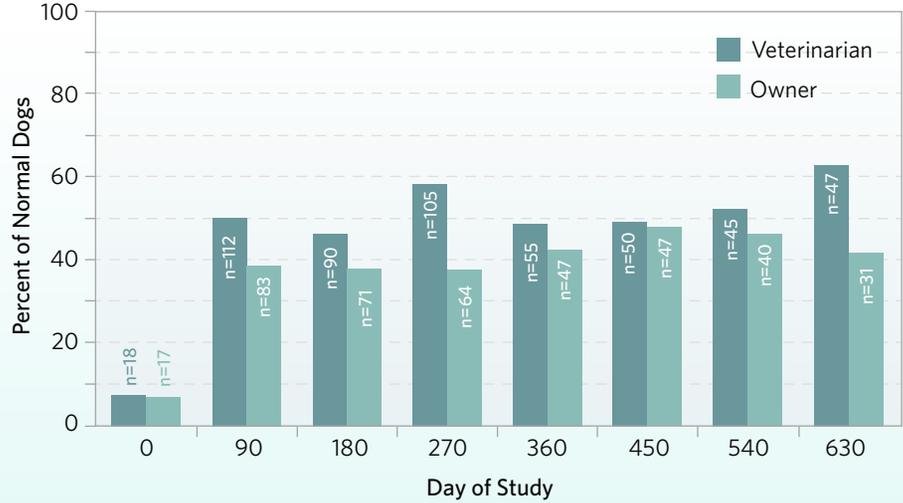
Over time, scores assigned by dog owners for pruritus and by veterinary investigators for dermatitis, both using a VAS, reflected the on-going benefit of APOQUEL treatment in controlling pruritus (Figure 33).

APOQUEL treatment enabled a large percent of dogs treated to maintain a 'normal' level of itching where normal is defined as a VAS score of less than 2.0 on a 10-cm VAS (Figure 34).<sup>34</sup> ●

**Figure 33 | Anti-pruritic efficacy of APOQUEL® with ongoing therapy (US trial) - Veterinarian dermatitis and owner pruritus assessments during long-term continuation therapy with APOQUEL.**



**Figure 34** | Dogs returned to a normal level (VAS score < 2 cm) of pruritus with ongoing APOQUEL® therapy (US trial) – Veterinarian dermatitis and owner pruritus assessments during long-term continuation therapy with APOQUEL.



A microscopic view of various cells and particles. There are several large, spherical cells with textured surfaces, some containing internal structures. Smaller, more uniform spherical cells are also visible. The background is a light blue-green color with numerous small, dark blue and yellowish particles scattered throughout. The overall appearance is that of a biological or medical illustration.

### **IMPORTANT SAFETY INFORMATION**

APOQUEL® should not be used in dogs less than 12 months of age or in dogs with serious infections. APOQUEL may increase the susceptibility to infection and demodicosis and may exacerbate neoplastic conditions. APOQUEL has not been evaluated in combination with systemic immunosuppressive agents such as glucocorticoids or cyclosporine. APOQUEL should not be used in breeding dogs, or pregnant or lactating dogs. The most common side effects seen in dogs administered APOQUEL were vomiting and diarrhea. APOQUEL has been safely used in conjunction with other common medications including antibiotics and parasiticides and with vaccinations.

*For more information please see full Prescribing Information on pages 76-77*

# 7 APOQUEL<sup>®</sup> (oclacitinib tablet) Safety

## IN THIS CHAPTER

Safety in Clinical Field Studies

Laboratory Safety Studies

Vaccination and APOQUEL<sup>®</sup>

## SAFETY SUMMARY

- **Studies in over 1200 client-owned dogs with allergic or atopic dermatitis document the safety of APOQUEL at the label dose under field conditions**
- **APOQUEL safety studies using elevated dosing over prolonged durations support no limit to the duration of therapy on the label**
- **Effects observed in laboratory safety studies with APOQUEL are characterized as:**
  - Related to the pharmacologic effect of APOQUEL
  - Reversible
  - Related to dose
  - Related to the age and intrinsic immune status of the dog
- **The most commonly reported adverse events in clinical field trials conducted to support global registrations were gastrointestinal signs (vomiting and diarrhea) and dermatitis. These adverse events were observed in less than 5% of APOQUEL-treated dogs**
- **In an open-label continuation therapy study, some dogs have been treated with APOQUEL for almost 2 years**
  - Two hundred thirty-nine (239) dogs have been treated with APOQUEL in this open-label study
  - The US label references data from October 2012, at which point the mean time of enrollment in the continuation study was 372 days (range: 1-610 days)
- **APOQUEL was safe when used concomitantly with many types of commonly prescribed medications, including the following:**
  - Multiple classes of anti-infectives
    - Antifungal medications
    - Shampoos and emollients
  - Vaccines
  - Parasiticides
  - NSAIDs and anti-inflammatory drugs
- **Unlike Atopica, there is no label restriction for concurrent use of APOQUEL with vaccines or a cautionary statement regarding use with drugs that affect the cytochrome P450 system.**
- **APOQUEL is for use in dogs over 3.3 kg bodyweight and at least 12 months of age**
- **The use of APOQUEL has not been tested in pregnant or lactating bitches or in dogs intended for breeding**
- **The use of APOQUEL has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents**
- **APOQUEL should not be used in dogs with serious infections, and dogs taking APOQUEL should be monitored for the development of infections, including demodicosis, and for development of neoplasia**

The safety of APOQUEL® has been documented in studies involving over 1200 dogs in both laboratory studies as well as clinical field trials. The results of these studies confirm that APOQUEL, administered at the label dose to dogs 12 months of age or older, is safe and well tolerated in dogs. The studies also supported labeling with an unlimited duration of treatment, an important aspect of treatment for chronic conditions such as AD. At label dose in clinical field trials, the most commonly reported adverse events observed with APOQUEL treatment were gastrointestinal signs (vomiting and diarrhea) and dermatitis. The adverse clinical signs reported in clinical trials were typically self-resolving without discontinuation of APOQUEL treatment.

**Table 12 | Summary of most frequently reported adverse events in allergic dogs (US trial) - Summary of the most frequent adverse clinical signs during the study phase occurring in > 1 animal (not pre-existing).**

CLINICAL SIGN STUDY PHASE (DAYS 0-7)	PLACEBO n=220*	APOQUEL n=216*
	n (%)	n (%)
Vomiting	4 (1.8)	5 (2.3)
Diarrhea	2 (0.9)	5 (2.3)
Dermatitis	2 (0.9)	3 (1.4)
Lethargy	2 (0.9)	3 (1.4)
Anorexia	0 (0.0)	3 (1.4)
Polydipsia	0 (0.0)	3 (1.4)

\*Average days at risk: placebo group=7.6, APOQUEL group=7.8.

## SAFETY IN CLINICAL FIELD STUDIES

Globally, more than 1200 clinical patients with allergic and atopic skin disease have been enrolled in pre-approval studies evaluating the efficacy and safety of APOQUEL. These patients include client-owned dogs that have been safely treated with the label dose of APOQUEL for more than 2 years under a continuation therapy protocol open to dogs that were enrolled in any clinical trial.

Clinical field safety and efficacy studies, in which dogs with naturally occurring disease are treated, help predict the side effect profile of a drug. These studies enroll dogs of many breeds and ages meant to mirror the target population in which the drug will be used once approved and marketed.

### ALLERGIC DERMATITIS<sup>30</sup>

Dogs were enrolled at 26 general veterinary practices in this placebo-controlled study to demonstrate the efficacy and safety of APOQUEL for the treatment of pruritus associated with allergic dermatitis. The dogs were treated twice daily with oclacitinib at 0.4-0.6 mg/kg (n=216) or placebo (n=220) for up to 7 (+ 2) days during the study period.

The dogs treated in the study with APOQUEL ranged in age from 6 months to 18 years and weighed between 3 and 56 kg. The dogs studied were male (48.6%) and female (51.4%), neutered (~95%) and intact (~5%), and purebred (68.5%) and mixed breeds (31.5%). The most frequently represented pure breeds enrolled were Golden Retrievers, Labrador Retrievers, Shih Tzus, and Jack Russell Terriers.

During the study period, the most commonly reported adverse events were gastrointestinal signs (vomiting and diarrhea; Table 12).

**Table 13 | Summary of changes in laboratory tests in allergic dogs (US trial)**

– Summary of the most frequent hematology/clinical chemistry abnormalities during the study phase occurring in > 1 animal (not pre-existing).

HEMATOLOGY / CLINICAL CHEMISTRY ABNORMALITY STUDY PHASE (DAYS 0-7)	PLACEBO n=220*	APOQUEL n=216*
	n (%)	n (%)
Elevated hepatic enzyme activity**	6 (2.7)	8 (3.7)
Anemia (not otherwise specified)	1 (0.5)	3 (1.4)

\* Average days at risk: placebo group=7.6, APOQUEL group=7.8.

\*\* Could be attributed to elevated activity of alkaline phosphatase (ALP), hepatic transaminase (ALT, AST), or gamma-glutamyl transferase (GGT), all coded to the Veterinary Dictionary for Drug Related Affairs (VEDDRA) code hepatopathy.

During the 7-day study phase, the most commonly reported changes in clinical chemistry and hematology were a decrease in red cell number and mass and an elevation of liver enzymes (Table 13). These changes were not associated with clinical signs in a large percent of the dogs. All dogs with anemia (categorized as not otherwise specified), except one dog treated with APOQUEL, had red blood cell counts below the reference range before starting study treatment. None of the reports of anemia in the APOQUEL group were considered likely related to APOQUEL treatment.

### ATOPIC DERMATITIS<sup>32</sup>

Dogs were enrolled at 18 dermatology specialty veterinary practices in this placebo-controlled study to demonstrate the efficacy and safety of APOQUEL® for the control of clinical manifestations of AD. The dogs were treated twice daily with oclacitinib (n=152) at 0.4-0.6 mg/kg for 14 days followed by 0.4-0.6 mg/kg once daily, or with placebo (n=147) using the

**Table 14 | Summary of most frequently reported adverse events in atopic dogs (US trial)**

– Summary of reports from Day 0-14 (±2) and listed in decreasing order of frequency for the APOQUEL® treatment group, as documented on the US label.<sup>10</sup>

CLINICAL SIGN	PLACEBO (n=147)*	APOQUEL (n=152)*
Diarrhea	3.4%	4.6%
Vomiting	4.1%	3.9%
Anorexia	0	2.6%
New cutaneous or subcutaneous lump	2.7%	2.6%
Lethargy	1.4%	2.0%

\* Abnormal clinical signs were tabulated per animal.

same dose regimen. Treatment was administered for up to 112 days during the study period.

The dogs treated in the study with APOQUEL ranged in age from 1 to 13 years and weighed between 3.4 and 77.2 kg. Male and female dogs were equally represented and the majority (>90%) were neutered.

The most commonly reported side effects from Days 0-14 (±2) in the APOQUEL-treated dogs were diarrhea, vomiting, and anorexia (Table 14).

In the global clinical trials for allergic and atopic dogs, APOQUEL-treated dogs were treated with a wide variety of concurrent drugs, including: anti-infectives, anesthetics, NSAIDs, and ectoparasiticides (see Appendix 4).

### CONTINUATION THERAPY

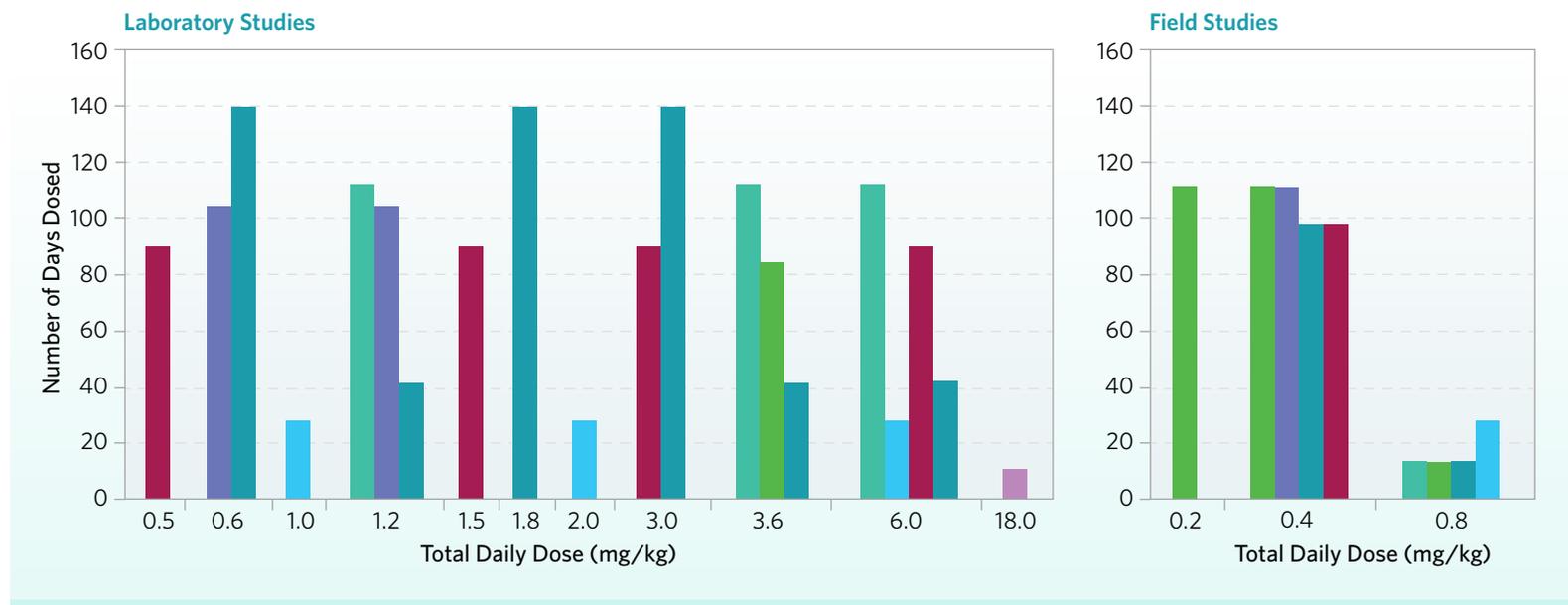
The most common adverse events (reported in 5% or more of the dogs as a non-pre-existing finding as summarized through December 31, 2012) reported in the 239 dogs enrolled in the Long-term Continuation Study and treated with APOQUEL were: urinary tract infection/cystitis (10.9%), vomiting (10.1%), otitis (9.3%), pyoderma (9.3%), and diarrhea (6.1%). In most cases, these abnormal health events did not require discontinuation of dosing, therapy continued, and the abnormal clinical signs spontaneously resolved or responded to appropriate supportive care. No dogs were

withdrawn from the study as a result of these reports of abnormal clinical signs. Because the continuation therapy study was open-label, a comparison to a control group in incidence was not possible.

### LABORATORY SAFETY STUDIES

The overall objective of laboratory studies conducted to support global registration is to describe effects of drug exposure at exaggerated doses or durations in order to identify target and non-target effects of the molecule.

**Figure 35 | Summary of APOQUEL® dosing in laboratory and field safety studies** – Summary of APOQUEL dosing in dogs for various laboratory safety studies (left panel) and field safety studies (right panel). Individual studies are color-coded. Each bar shows the maximum duration of treatment at a single dose level.



These effects are then further scrutinized in clinical field trials in which client-owned animals with naturally occurring disease are treated with the anticipated label dose (Figure 35).

The laboratory animal safety studies conducted with APOQUEL found, in general, the side effects observed in dogs exposed to exaggerated dose levels for an extended duration were:

- Related to the pharmacologic effects of the drug
- Reversible
- Dose-related
- Related to the age and intrinsic immune status of the dogs treated

### LABORATORY SAFETY IN DOGS OVER 12 MONTHS OF AGE<sup>18</sup>

The principal laboratory safety study supporting the registration of APOQUEL® in dogs was a rigorous test of the molecule’s potential for toxicity. In this study, dogs approximately 12 months old at initiation of the study were dosed with oclacitinib maleate at 0, 0.6, 1.8 or 3.0 mg/kg orally twice daily for 6 weeks, and then once daily for an additional 20 weeks. Typically doses in this type of study represent 1x, 3x and 5x the label dose. However, because the APOQUEL label dose is twice daily for 14 days and then once daily for maintenance therapy, the drug exposures in this study were higher than the 1x, 3x and 5x doses of a typical margin of safety study. The clinical signs observed were related to the pharmacologic action of APOQUEL which works by moderating the enhanced immune response in dogs with allergic and atopic conditions (Table 15). The effects observed in APOQUEL-treated dogs in this study were generally mild and non-progressive.

The most commonly noted clinical observations in this study were dermatitis (which included pododermatitis, interdigital cysts, moist dermatitis, swelling between toes, ulcerated footpads) and papillomas. Typical findings at 1x the label dose included interdigital cysts (furunculosis) and associated lymphadenopathy and occasional papillomas on gross pathology. Minimal

changes in histopathology were seen in dogs dosed at 1x; the changes were typically mild and reversible with cessation of treatment. At multiples of the label dose, additional histopathologic findings included decreased cellularity in lymphoid organs and decreased cellularity in bone marrow. These histopathologic findings were generally not clinically relevant in dogs 12 months of age or older at the initiation of treatment and were seen with

**Table 15 | Summary of clinical observations in laboratory safety studies in adult dogs - 12 months of age and older.**

VARIABLE	RESULTS
Body weight	No effects
Feed consumption	No effects
Ophthalmologic exam	No effects
Clinical observations (masked)	Foot and skin observations (dermatitis*, papules, edema, erythema, local alopecia) with enlarged lymph nodes peripherally; cutaneous papillomas; minimal gastrointestinal effects
Gross lesions (masked)	Interdigital furunculosis, enlarged lymph nodes associated with affected feet; dose-related number and severity
Microscopic lesions	Decreased cellularity of lymphoid tissues and of bone marrow with no clear changes in myeloid:erythroid ratio, lymphoid hyperplasia and chronic active inflammation in nodes draining feet; groups generally increasing in severity with dose
Clinical pathology	Mild hematological effects and mild decrease in proteins; no clinically significant chemistry changes

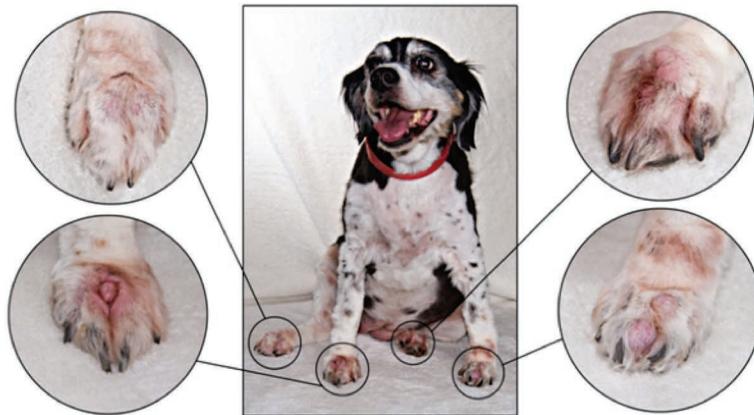
\* Dermatitis term includes pododermatitis, interdigital cysts (IDC), moist dermatitis, swelling between toes, and ulcers on pads.

*APOQUEL® (oclacitinib tablet) is for use in dogs 12 months of age and older.*

chronic dosing at doses that approached or exceeded 5x the label dose.

Some of the most commonly reported changes in APOQUEL®-treated dogs included decreases in RBC mass, a decrease in reticulocytes, and a decrease in lymphocytes. These changes were typically dose related. In laboratory safety studies, changes in clinical pathology and hematology in dogs treated with 1x the label dose for durations of up to 6 months were not biologically significant, and the variations observed were typically not outside normal ranges.

When younger dogs (6 months of age at initiation of treatment) were



**Allergic pododermatitis**

exposed to elevated doses of oclacitinib for extended durations, the changes in histopathology were similar in nature to those of older dogs, but were likely to be more severe and more likely to be associated with clinical signs such as systemic bacterial infections and demodicosis. Along with the fact that AD is a diagnosis of exclusion rarely made in young dogs, these findings in younger dogs contributed to the limitation of the label to treatment in dogs 1 year of age or older.

### VACCINATION AND APOQUEL®

**RESPONSE TO VACCINATION:** With any chronically administered therapy, particularly one that acts pharmacologically by modulating the immune response, the ability to concurrently administer the product with commonly administered vaccines is an important asset. A study was undertaken to demonstrate that APOQUEL®-treated dogs could mount a

*In laboratory safety studies, dogs 1 year of age and older have been safely dosed at elevated doses up to 10x the label dose, and for prolonged durations of up to 26 weeks.*

*Taken together, the laboratory safety studies demonstrated that side effects related to APOQUEL® (oclacitinib tablet) treatment are:*

- *Related to the pharmacologic effects of the drug*
- *Reversible*
- *Dose-related*
- *Related to the age and intrinsic immune status of the dogs treated*

serological response when vaccinated with multivalent modified live vaccine containing canine distemper virus (CDV), canine parvovirus (CPV), canine parainfluenza (CPI) virus (Duramune® Max-5) and with killed rabies virus (RV) vaccine (IMRAB®).

Sixteen week old dogs were treated with 1.8 mg/kg (3x the high end of the label dose) APOQUEL® twice daily for 12 weeks; control dogs were administered placebo. On Days 28 and 56 of treatment, dogs were administered Duramune® Max-5. On Day 56, they received a single dose of IMRAB®. Adequate

*There is no label contraindication against vaccinating dogs treated with APOQUEL® (oclacitinib tablet).*

serological responses were met for RV, CDV, and CPV in all dogs. Adequate serological response was met for CPI in 6 of 8 dogs (Table 16).

It is noteworthy that despite the young age of the dogs and the elevated dose levels administered for prolonged durations, no dogs developed demodicosis. ●

**Table 16 | Summary of antibody titers in dogs vaccinated while being treated with APOQUEL®** - Summary of virus antibody titers measured on Day 84, one month after primary vaccinations, in dogs treated with placebo or APOQUEL®.

VIRUS ANTIBODY TITER CRITERIA			
VIRUS	"STANDARD" TITER CRITERION	PLACEBO (BID)	APOQUEL (1.8 mg/kg BID)
		Titer Criteria Met: Either 4-fold Dilution or "Standard" Titer Met	Titer Criteria Met: Either 4-fold Dilution or "Standard" Titer Met
Distemper	1:32	8 of 8	8 of 8
Parvovirus	1:80	8 of 8	8 of 8
Parainfluenza	1:16	8 of 8	6 of 8
Rabies	1:50 0.5 IU/mL	8 of 8	8 of 8

A microscopic view of various cells and particles. In the foreground, there are several large, spherical cells with textured, blue, spiky outer layers. One of these cells has a dark red, solid interior. Surrounding these are numerous smaller, more uniform spherical cells, some appearing translucent. The background is a light blue, hazy environment filled with many tiny, dark blue and yellowish particles, possibly representing a cellular or molecular environment.

### **IMPORTANT SAFETY INFORMATION**

APOQUEL® should not be used in dogs less than 12 months of age or in dogs with serious infections. APOQUEL may increase the susceptibility to infection and demodicosis and may exacerbate neoplastic conditions. APOQUEL has not been evaluated in combination with systemic immunosuppressive agents such as glucocorticoids or cyclosporine. APOQUEL should not be used in breeding dogs, or pregnant or lactating dogs. The most common side effects seen in dogs administered APOQUEL were vomiting and diarrhea. APOQUEL has been safely used in conjunction with other common medications including antibiotics and parasiticides and with vaccinations.

*For more information please see full Prescribing Information on pages 76-77*

# 8 The APOQUEL® (oclacitinib tablet) Difference

## IMPACT OF ALLERGIC AND ATOPIC DISEASE

### KEAURA'S LEGACY

Allergic and atopic skin diseases take their toll on the dogs who suffer from them, as well as the families who love them. The itch and scratching, and the dermatitis associated with canine AD, disrupts lives - as do many of the therapies used to treat the disease such as corticosteroids, shampooing and messy topical treatments.

The continuation therapy program described previously in this monograph was initiated because of a police dog named Keaura and his devoted partner on the force and in life, Officer John Lamantia. Keaura was diagnosed with AD approximately 7 years prior to the initiation of the clinical trials with APOQUEL®. Over those years, Keaura underwent diagnostic testing and, like many atopic patients, was treated at various points with many different therapies: specialized diets, medicated shampoos, corticosteroids, antihistamines, immunotherapy, cyclosporine, antifungals, and antibacterials for his secondary pyoderma. But none of these treatments effectively relieved his pruritus without causing side effects that kept him off the job...until he was treated with APOQUEL®.

Dr. Tiffany Tapp, the veterinary dermatologist treating Keaura, wrote to Zoetis

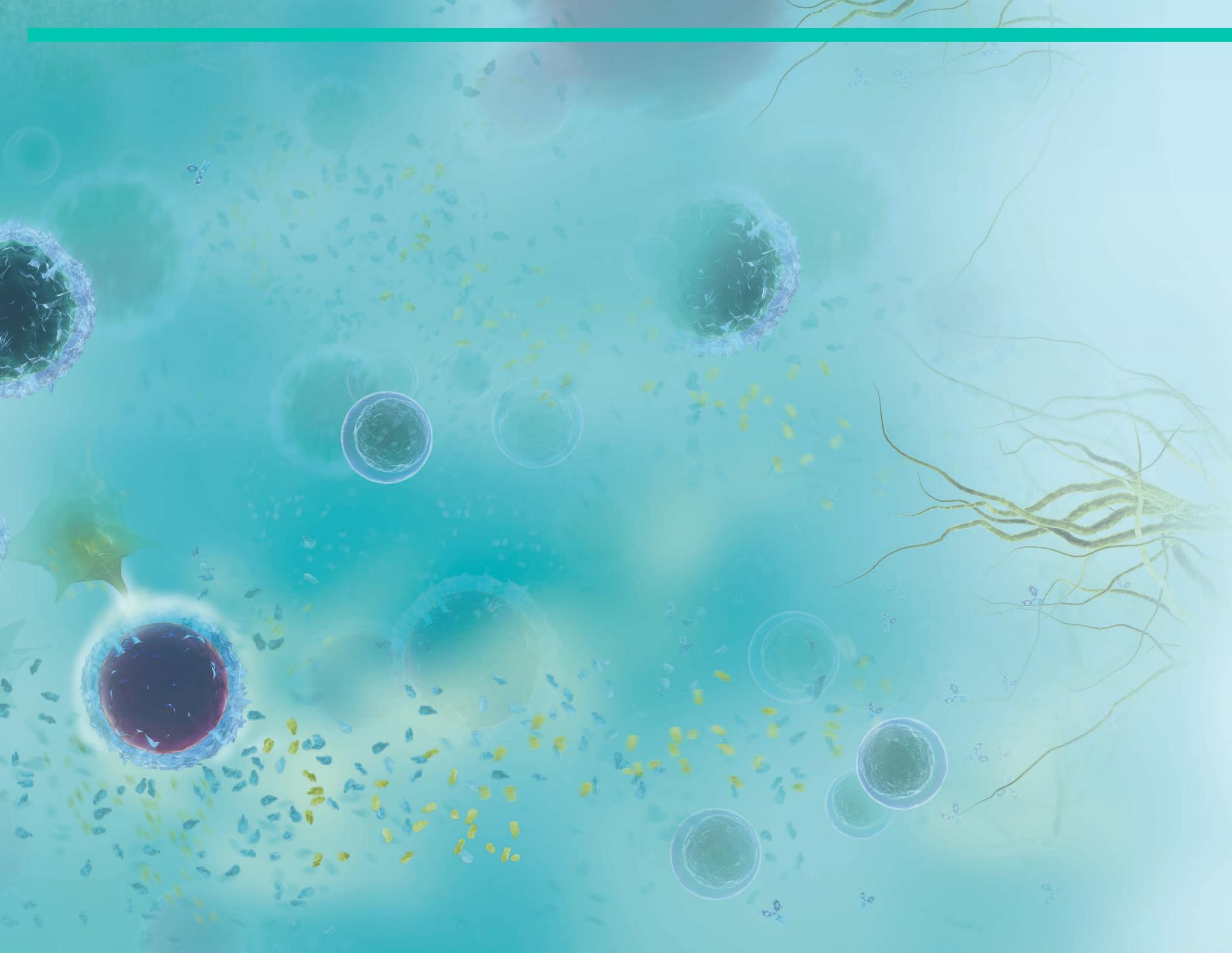
explaining that no other therapy had controlled Keaura's atopic disease as well as APOQUEL® while still allowing him to continue to work as a police dog. She asked if there was any way for Keaura to continue to be treated with oclacitinib until it became commercially available.



Keaura was able to continue therapy for several years after he first enrolled in the clinical study. And he pioneered a program that benefited more than 200 other atopic dogs. Most of

those dogs were not working dogs, their only job was to provide love and companionship for their human family. But for many pet owners, returning a family member to full time service is just as important as the police work Keaura was able to continue.

Don't we all know an atopic dog like Keaura who doesn't need to suffer from an unmanageable disease for 7 years and would like to get back to work, even if that work is just to contribute to the happiness in the family? ●



# 9 Appendices

## IN THIS CHAPTER

Appendix 1: Pet Owner Visual Analog Scale (VAS)

Appendix 2: Veterinarian Visual Analog Scale (VAS)

Appendix 3: Canine Atopic Dermatitis Extent and Severity Index-02 (CADESI-02)

Appendix 4: List of Concurrently Used Therapies from Clinical Studies

Appendix 5: Summary of APOQUEL® Clinical Efficacy Studies

Appendix 6: Summary of APOQUEL® Laboratory Safety Studies

Appendix 7: Label

## APPENDIX 1: PET OWNER VISUAL ANALOG SCALE (VAS) USED TO MEASURE SEVERITY OF PRURITUS

Using this tool, a 'score' for the degree of pruritus a dog is experiencing is obtained by marking lines based on corresponding clinical descriptions. The location on the 10-cm line is measured from the bottom to the hatch mark and a score from 0-10 is assigned. The lines to the left of each text column indicate 10-cm rulers with text descriptors aligned at 2-cm intervals. These allow measurements of affected areas.

### INSTRUCTIONS TO OWNER

This is designed to record the severity of the dog's itchiness (pruritic activity) during the past 24 hours. Itching can include scratching, biting, licking, clawing, nibbling, and/or rubbing. Read all the descriptions below starting from the bottom. Then use a marker pen (not pencil) to place a single horizontal cross-mark anywhere on the vertical line that runs down the left-hand side to indicate the point at which you think your dog's level of itchiness lies.

### OWNER

**Extremely Severe Itching.** Dog is scratching, chewing, licking almost continuously. Itching almost never stops, regardless of what else is happening around the dog.

**Severe Itching.** Prolonged episodes of itching when the dog is awake. Itching occurs at night and also when eating, playing, exercising, or when otherwise distracted

**Moderate Itching.** Regular episodes of itching when the dog is awake. Itching might occur at night or wake the dog. No itching when eating, playing, exercising, or when being distracted

**Mild Itching.** More frequent episodes of itching. May notice occasional episodes of itching at night. No itching when eating, playing, exercising, or when being distracted

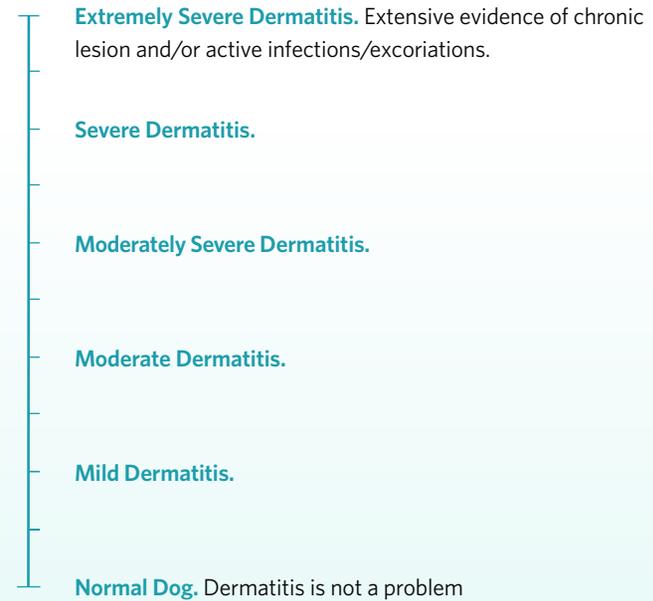
**Very Mild Itching.** Occasional episodes of itching. The dog is slightly more itchy than before the problem began

**Normal Dog.** Itching is not a problem

*10 cm lines with text descriptors at 2 cm intervals*

**APPENDIX 2:  
VETERINARIAN VISUAL ANALOG SCALE (VAS) USED  
TO MEASURE AMOUNT OF DERMATITIS**

**VETERINARIAN**



*10 cm lines with text descriptors at 2 cm intervals*

### APPENDIX 3: CANINE ATOPIC DERMATITIS EXTENT AND SEVERITY INDEX-02 (CADESI-02)

VALIDATED MEASURE  
USED BY VETERINARY  
DERMATOLOGISTS  
(INVESTIGATORS)  
TO ASSESS SKIN LESIONS

- Assesses 3 factors for each anatomic site assessed: erythema (E), lichenification (L), and excoriations (E)
- Each of 120 observations scored on a scale from 0-3:
  - 0 = normal or absent
  - 1 = mild
  - 2 = moderate
  - 3 = severe
- Maximum total score of 360 is possible

SITE	E	L	X	SITE	E	L	X	SITE	E	L	X
FACE				ABDOMEN				FOOT, LEFT HIND, DORSAL			
PINNA LEFT, CONVEX				THORAX, DORSAL				UMB, RIGHT FRONT, MEDIAL			
PINNA LEFT, CONCAVE				THORAX, LATERAL LEFT				UMB, RIGHT FRONT, LATERAL			
PINNA RIGHT, CONVEX				THORAX, LATERAL RIGHT				FOOT, RIGHT FRONT, PALMAR			
PINNA RIGHT, CONCAVE				LUMBAR, DORSAL				FOOT, RIGHT FRONT, DORSAL			
NECK, DORSAL				FLANK, LEFT				UMB, RIGHT HIND, MEDIAL			
NECK, VENTRAL				FLANK, RIGHT				UMB, RIGHT HIND, LATERAL			
NECK, LATERAL LEFT				UMB, LEFT FRONT, MEDIAL				FOOT, RIGHT HIND, PLANTAR			
NECK, LATERAL RIGHT				UMB, LEFT FRONT, LATERAL				FOOT, RIGHT HIND, DORSAL			
AXILLA, LEFT				FOOT, LEFT FRONT, PALMAR				PERINEUM			
AXILLA, RIGHT				FOOT, LEFT FRONT, DORSAL				TAIL, DORSAL			
STERNUM				UMB, LEFT HIND, MEDIAL				TAIL VENTRAL			
INGUINAL, LEFT				UMB, LEFT HIND, LATERAL				COMMENTS:			
INGUINAL, RIGHT				FOOT, LEFT HIND, PLANTAR							
SUBTOTALS				SUBTOTALS				SUBTOTALS			
TOTAL CADESI SCORE											

## APPENDIX 4: LIST OF CONCURRENTLY USED THERAPIES FROM CLINICAL STUDIES<sup>35</sup>

APOQUEL® (oclacitinib tablet)-treated dogs received various concomitant medications in pivotal field studies in the US and EU, some of which are listed in this Appendix.

Some of the categories of concurrent therapies received by APOQUEL-treated dogs included the following:

- Anti-infectives
- Anti-inflammatories (including NSAIDs)
- Antiparasitics
- Anesthetics/sedatives
- Vaccines
- Cyclosporine

### Number of APOQUEL-treated dogs that received select ANTI-INFECTIVES

APOQUEL FIELD TRIALS	
ANTI-INFECTIVE	Total (n=1416)
Cefalexin	140
Cefovecin	19
Cefpodoxime	95
Enrofloxacin	16
Enrofloxacin, combination	59
Ketoconazole	126
Marbofloxacin	9

### Number of APOQUEL-treated dogs that received select ANTI-INFLAMMATORIES

APOQUEL FIELD TRIALS	
ANTI-INFLAMMATORY	Total (n=1416)
Acetylsalicylic acid	4
Carprofen	23
Coxibs	3
Firocoxib	1

**Number of APOQUEL-treated dogs  
that received select ANTIPARASITICS**

APOQUEL FIELD TRIALS	
ANTIPARASITIC	Total (n=1416)
Amitraz, combinations	13
Fipronil	272
Fipronel, combinations	247
Imidacloprid	185
Ivermectin	265
Ivermectin, combinations	103
Milbemycin	127
Milbemycin, combinations	79
Moxidectin, combinations	66
Nitenpyram	17
Selamectin	318
Spinosad	113

**Number of APOQUEL-treated dogs  
that received select ANESTHETICS / SEDATIVES**

APOQUEL FIELD TRIALS	
ANESTHETIC / SEDATIVE	Total (n=1416)
Alprazolam	4
Isoflurane	8
Phenobarbital	6

**Number of APOQUEL-treated dogs that received select VACCINES**

APOQUEL FIELD TRIALS	
VACCINE	Total (n=1416)
Bordetella vaccine	27
Borrelia vaccine	1
Rabies virus vaccine	30
Live Canine distemper virus + live Canine adenovirus + live Canine parainfluenza virus + live Canine parvovirus + inactivated Leptospira virus	12
Live Canine distemper virus + live Canine adenovirus + live Canine parainfluenza virus + live Canine parvovirus + inactivated Canine coronavirus + inactivated Leptospira virus	5

**Number of APOQUEL-treated dogs that received select VACCINES  
(continued)**

APOQUEL FIELD TRIALS	
VACCINE	Total (n=1416)
Canine distemper virus + Canine adenovirus + Canine parainfluenza virus + Canine parvovirus	13
Canine distemper virus + Canine adenovirus + Canine parainfluenza virus	2
Canine parainfluenza virus	4
Canine adenovirus	2
Canine parvovirus	1
Inactivated Leptospira	9
Inactivated Canine coronavirus	1

**Number of APOQUEL-treated dogs  
that received CYCLOSPORINE and select OTHER AGENTS**

APOQUEL FIELD TRIALS	
AGENT	Total (n=1416)
Immunotherapy	259
Cyclosporine	4
I.V. solutions	3
Levothyroxine sodium	47
Sodium chloride	1

## APPENDIX 5: SUMMARY OF APOQUEL® CLINICAL EFFICACY STUDIES

STUDY NAME	STUDY NUMBER	ITCH or AD
Efficacy and field safety of APOQUEL® for the control of pruritus associated with allergic dermatitis in the dog	1962C-60-09-930	Itch
Field safety and efficacy of APOQUEL® compared to placebo for the control of atopic dermatitis in client-owned dogs	1962C-60-10-A02	AD
Replacement therapy protocol for dogs removed from 1962C-60-10-A02	1962C-60-10-A08	AD
Dose confirmation: field safety and efficacy of APOQUEL® compared to placebo for the control of atopic dermatitis in client-owned dogs	1962C-60-10-A16	AD
Dose confirmation: replacement therapy for dogs removed from 1962C-60-10-A16	1962C-60-10-A17	AD

## APPENDIX 6: SUMMARY OF APOQUEL® LABORATORY SAFETY STUDIES

STUDY NUMBER AND TITLE	PURPOSE
<b>Study 1462N-60-10-A29:</b> <b>Margin of safety (MOS) study of APOQUEL® administered for 26 weeks to adult dogs</b>	Determine the MOS of APOQUEL® administered orally to 12-month-old Beagle dogs at 1x, 3x, and 5x the maximum exposure dose of 0.6 mg/kg for a total of 26 weeks
<b>Study 1462N-60-08-905:</b> <b>MOS study of APOQUEL® administered for 26 weeks to adult dogs with recovery period</b>	Determine the MOS of APOQUEL® administered orally to 6-month-old Beagle dogs at 1x, 3x, and 5x BID the maximum exposure dose for a planned duration of 26 weeks
<b>Study 1462N-60-09-927:</b> <b>The effect of oral APOQUEL® on the response to primary vaccination in dogs</b>	Demonstrate the safety of APOQUEL® in 4-month-old vaccine-naïve Beagle puppies, prior to and following primary vaccination at 3x the maximum exposure dose for 3 months

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## APOQUEL® (oclacitinib tablet)

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# apoquel<sup>®</sup>

(oclacitinib tablet)

3.6 mg

5.4 mg

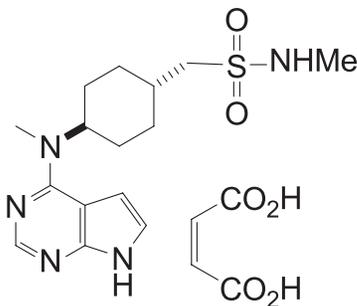
16 mg

## 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 is not for use in dogs with serious infections. APOQUEL may increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions (see **Adverse Reactions** and **Animal Safety**).

## Human Warnings:

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

## Precautions:

APOQUEL is not for use in breeding dogs, or pregnant or lactating bitches. The use of APOQUEL has not been evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents. Dogs receiving APOQUEL should be monitored for the development of infections, including demodicosis, and neoplasia.

## Adverse Reactions:

### Control of Atopic Dermatitis

In a masked field study to assess the effectiveness and safety of oclacitinib for the control of atopic dermatitis in dogs, 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.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Zoetis Inc. at 1-888-963-8471 or [www.zoetis.com](http://www.zoetis.com).

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

## Clinical Pharmacology:

### Mechanism of Action

Oclacitinib inhibits the function of a variety of pruritogenic cytokines and pro-inflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity. It has little effect on cytokines involved in hematopoiesis that are dependent on JAK2. Oclacitinib is not a corticosteroid or an antihistamine.

### Pharmacokinetics

In dogs, oclacitinib maleate is rapidly and well absorbed following oral administration, with mean time to peak plasma concentrations ( $T_{max}$ ) 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 ( $AUC_{0-\infty}$ ) 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<sub>50</sub>) are 50 fold greater than the observed C<sub>max</sub> 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<sub>1/2</sub> 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

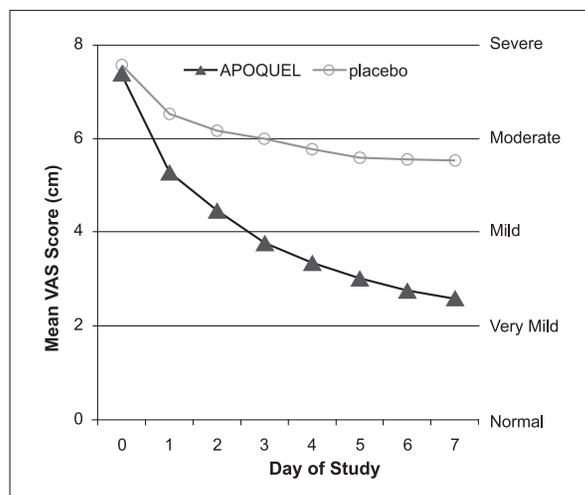
A double-masked, 30-day, controlled study was conducted at 26 U.S. veterinary hospitals. The study enrolled 436 client-owned dogs with a history of allergic dermatitis attributed to one or more of the following conditions: atopic dermatitis, flea allergy, food allergy, contact allergy, and other/unspecified 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 20 and 100 count bottles. Each tablet is scored and marked with AQ and either an S, M, or L that correspond to the different tablet strengths on both sides.

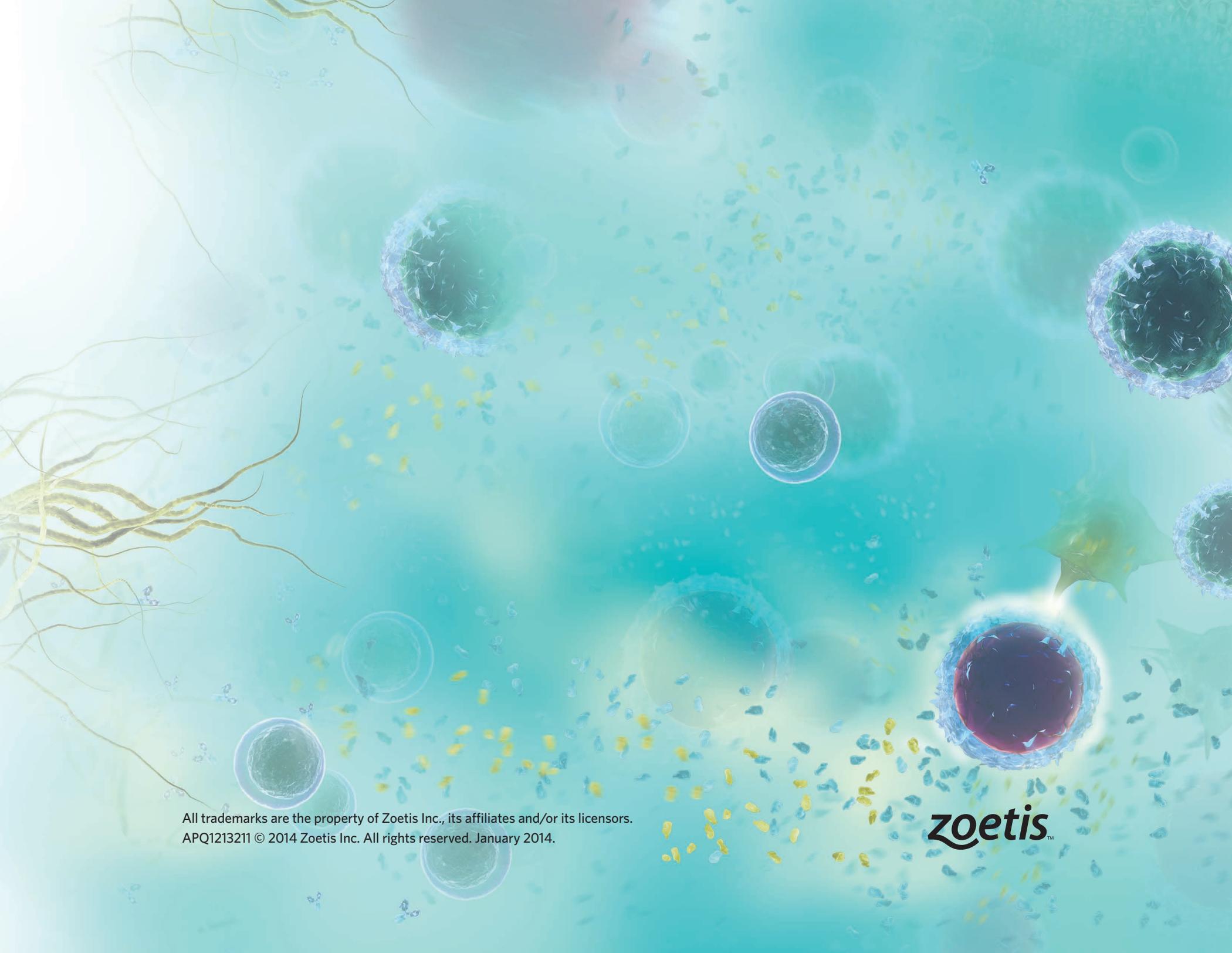
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