apoquel®
oclacitinib

European Technical Monograph

APOQUEL® (oclacitinib) is a novel Janus kinase inhibitor (JAKi) therapy that was developed with dual indications for the treatment of pruritus associated with allergic dermatitis as well as the treatment of clinical manifestations of atopic dermatitis (AD) in dogs.

zoetis

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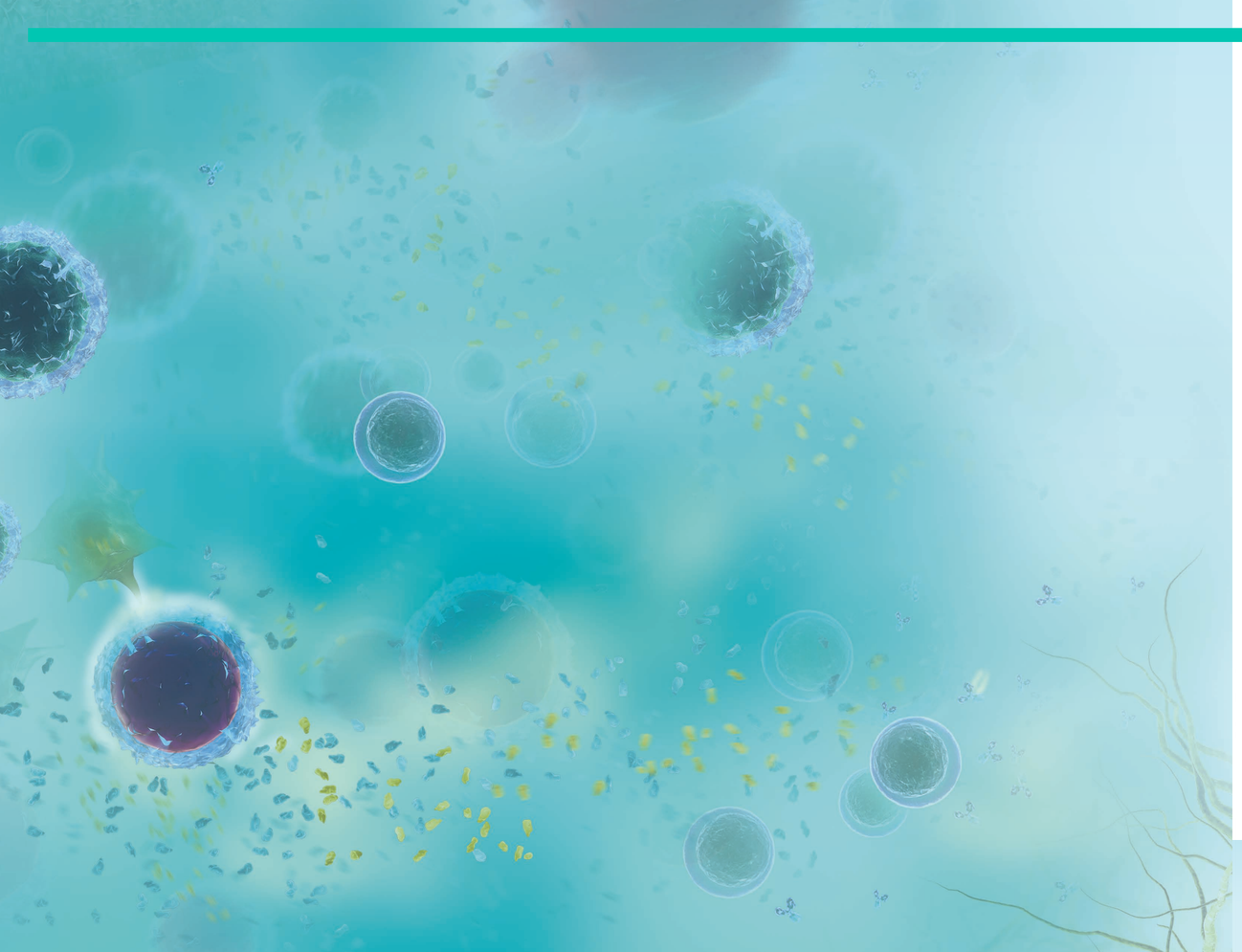


1 Introduction

ALLERGIC SKIN DISEASE is one of the most common reasons dogs are presented to their veterinarians.[1] 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 new, more targeted treatments that provide 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), a targeted new therapy for the treatment of allergic and atopic skin disease in dogs that provides rapid relief of itch, controls inflammation without many of the side effects of glucocorticoids, and can be used long-term.

2 Science of Itch & Allergic Skin Disease

IN THIS CHAPTER

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."[2] 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 be 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).[3]

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.[4] Experimentally, histamine can induce intense pruritus; however, its role in most clinical presentations of

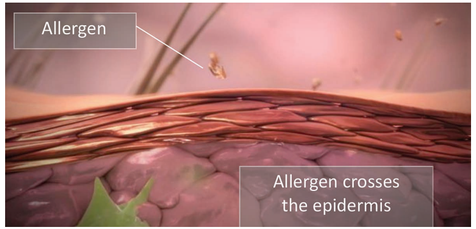


Figure 1 | Allergens crossing the epidermis – Schematic diagram of an allergen penetrating the cell layers of the epidermis.

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.[5] 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 medtiators such as cytokines have been shown to play a key role in this process.

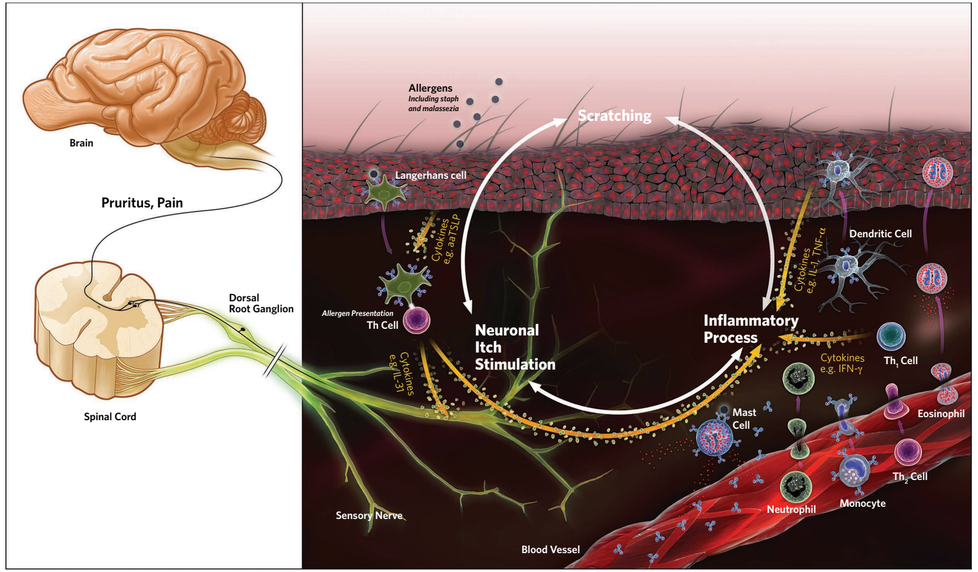


Figure 2 | Components of Itch – A schematic diagram of the cellular and molecular components of the itch process. Inflammation leads to the release of itch mediators such as cytokines, chemokines, and neuropeptides. Itch mediators stimulate receptors on itch-specific sensory neurons, which relay signals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

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

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 dogs. Other interleukins thought to be involved in mediating pruritus are IL-2 and IL-6.[6,7]

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).[3] 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.

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

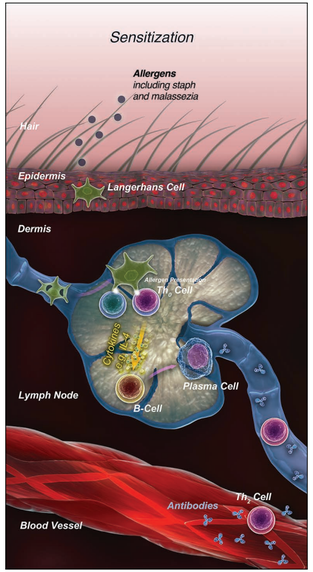


Figure 3 | Sensitization to the Allergen – Diagram of the itch-initiating process of sensitization. See text for detailed description.

- 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

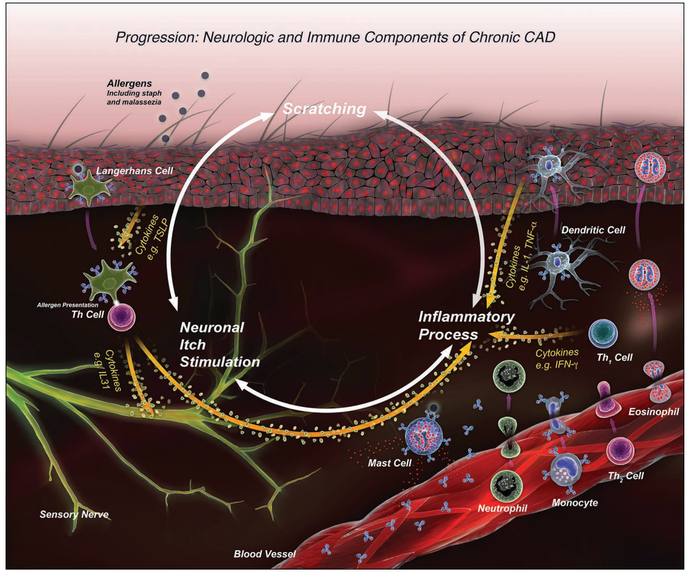


Figure 4 | Progression of Allergic Disease – Diagram of itch progression. See text for detailed description.

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

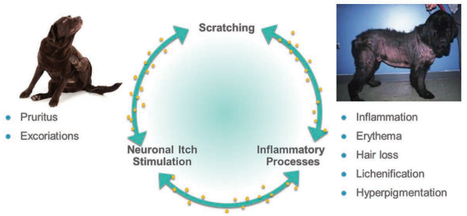


Figure 5 | Clinical Impact of cytokine dysregulation - Clinical signs associated with cytokine dysregulation.

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 atopic 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

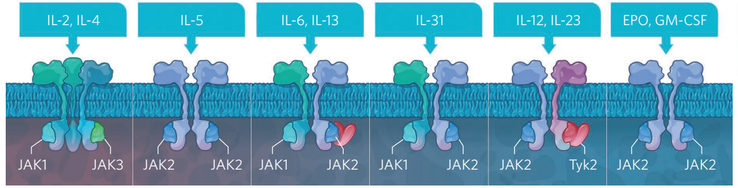


Figure 6 | JAK Pairing and Cytokine Stimulation - Schematic diagram showing the pairing of cytokine receptors with JAK enzymes. (*EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor.*)

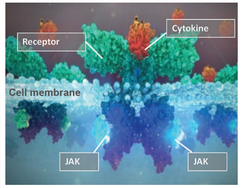


Figure 7 | Cytokine Binding - Molecular model of the extracellular cytokine receptor-JAK enzyme complex.[7]

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.[2] 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. ●

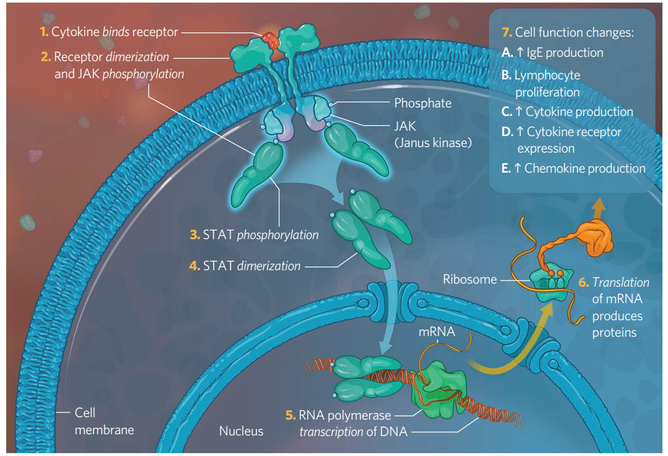
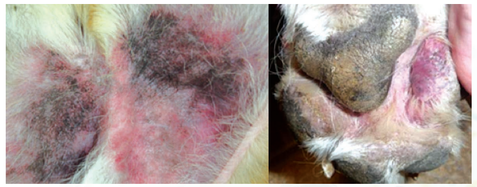


Figure 8 | Intracellular signaling by JAK enzymes – Summary of the basic biology of the JAK signaling pathway.[6,7,8] Specific receptors on the surface of a cell recognize specific cytokines. When a cytokine binds to its receptor like a key in a lock, the message is carried into the cell by the activation 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.

3 A New Approach to Itch Therapy

IN THIS CHAPTER

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 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.



Inflammation and secondary infection in an atopic dog

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.

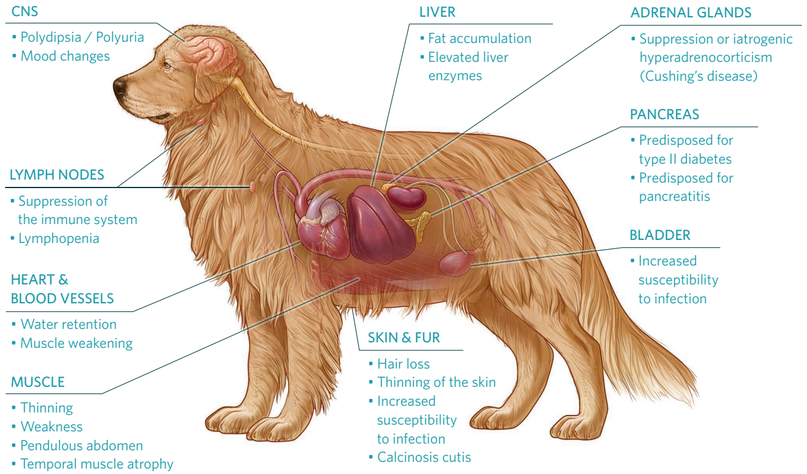


Figure 9 | Drawbacks of corticosteroid therapy – Overview of the multi-systemic side effects of corticosteroid therapy in dogs.[9]

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 (ciclosporin) has been shown to have a significant clinical effect, but there is typically a delay in onset of action of several weeks that makes it inappropriate as solo therapy.

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 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.

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

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

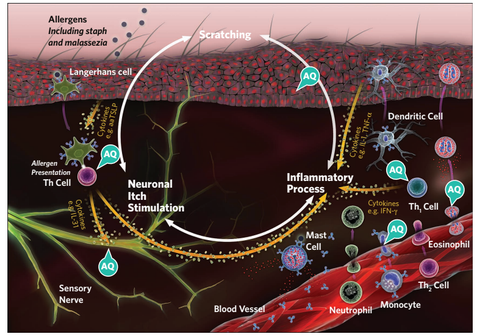
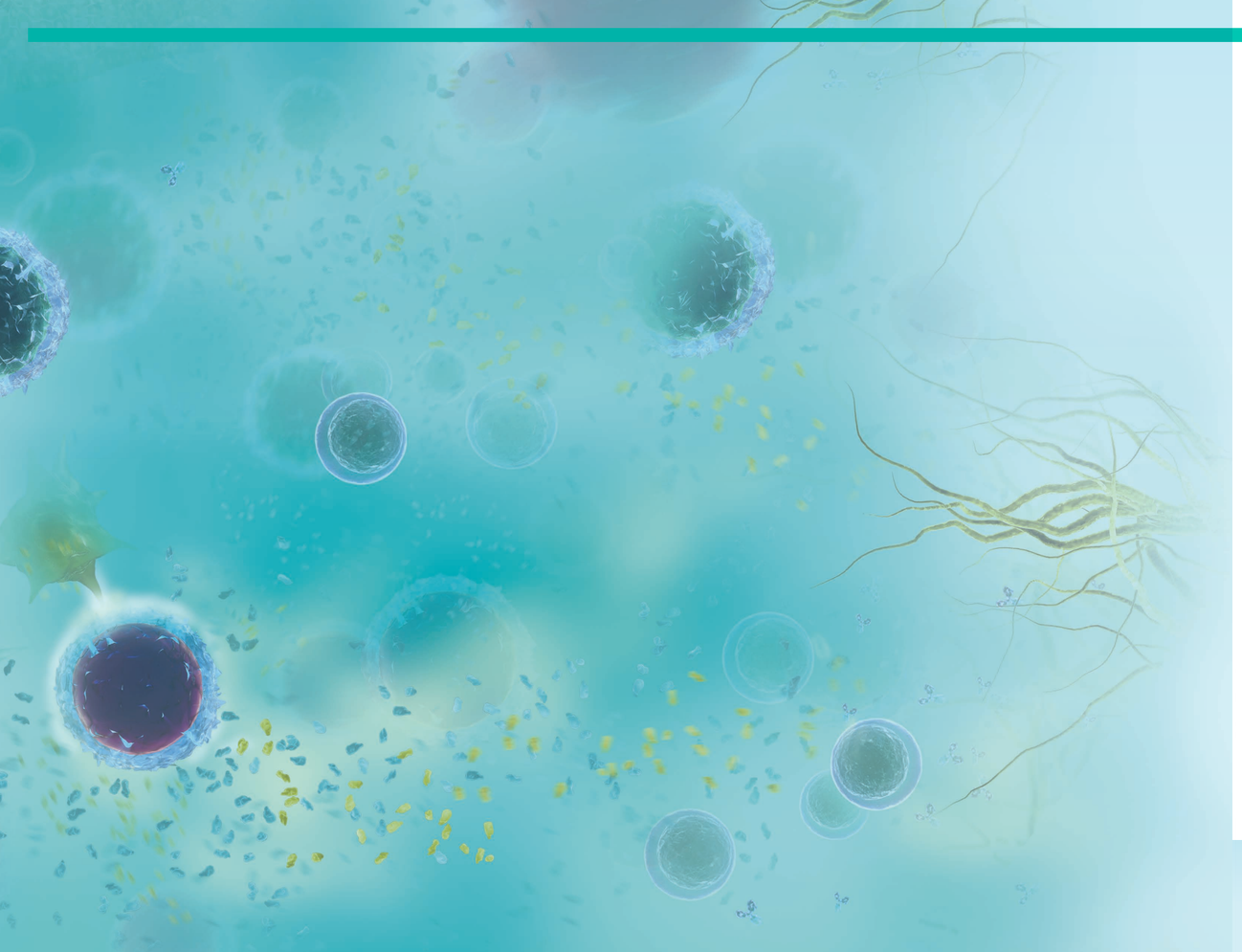


Figure 10 | APOQUEL® targets cytokines at multiple sites in the cycle of itch - APOQUEL® inhibits the action of pruritogenic, pro-allergic and pro-inflammatory cytokines such as IL-4, IL-13, and IL-31, through the inhibition of JAK1 enzyme activity at multiple cellular locations.
(AQ, APOQUEL; Th, T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



4 APOQUEL® (oclacitinib) – At a Glance

IN THIS CHAPTER

PRODUCT SUMMARY

APOQUEL® (oclacitinib) is a Janus kinase (JAK) inhibitor that inhibits the activity of a variety of cytokines dependent on JAK enzyme activity. The cytokines targeted by oclacitinib are proinflammatory and pruritogenic, and play a role in allergic responses and itch stimulation. However, oclacitinib may also exert effects on other cytokines (for example those involved in host defense and haematopoiesis) with the potential for unwanted effects (Table 1).

Table 1 | Overview of APOQUEL®

APOQUEL	DESCRIPTION [1]
Active / Drug class	Oclacitinib is a novel, targeted JAK inhibitor that is selectively targeted to inhibit JAK1 enzymes
	Treatment of pruritus associated with allergic dermatitis in dogs
	Treatment of clinical manifestations of atopic dermatitis in dogs
Dosing and administration	0.4-0.6 mg/kg administered orally twice daily for up to 14 days followed by 0.4-0.6 mg/kg once daily for maintenance therapy
	Can be given with or without food
Presentation	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
	All tablet strengths packaged in aluminium/PVC/Aclar blisters (each strip containing 10 film-coated tablets)
	Pack sizes of 20 or 100 tablets

Continued on next page

Table 1 *(Continued)* | **Overview of APOQUEL®**

APOQUEL	DESCRIPTION[11]
Efficacy	Rapid decrease in itch within 4 hours of administration in laboratory model studies – no lag in treatment effect
	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
	Similar efficacy to Atopica (cyclosporine A) in a clinical study in dogs with atopic dermatitis
	Efficacy maintained with continued dosing
Safety	Safe for short- and long-term therapy; no label limitation to duration of therapy
	Most commonly reported side effects are vomiting and diarrhea
	Lack of many of the bothersome side effects associated with corticosteroids (polyuria, polyphagia, panting)[12]
Other	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

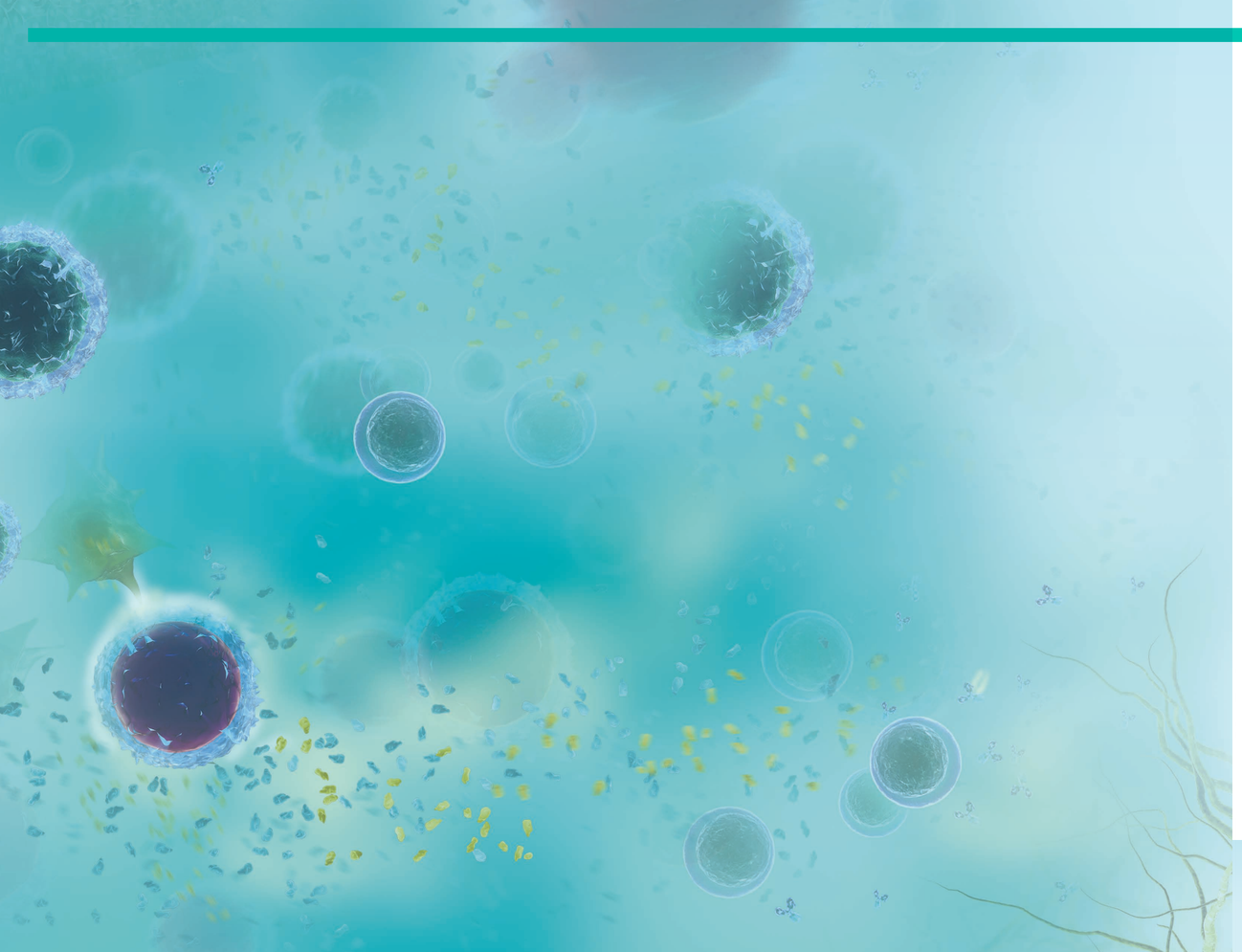
DOSING AND PRESENTATION

The dose of APOQUEL® (oclacitinib) is 0.4-0.6 mg/kg administered orally twice daily for up to 14 days followed by 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, kg	STRENGTH AND NUMBER OF APOQUEL® TABLETS TO BE ADMINISTERED		
	3.6 MG TABLETS	5.4 MG TABLETS	16 MG TABLETS
3.0-4.4	½	–	–
4.5-5.9	–	½	–
6.0-8.9	1	–	–
9.0-13.4	–	1	–
13.5-19.9	–	–	½
20.0-26.9	–	2	–
27.0-39.9	–	–	1
40.0-54.9	–	–	1 ½
55.0-80.0	–	–	2



5 APOQUEL®(oclacitinib) Pharmacology

IN THIS CHAPTER

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® 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_{60s}) 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 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)

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 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 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.

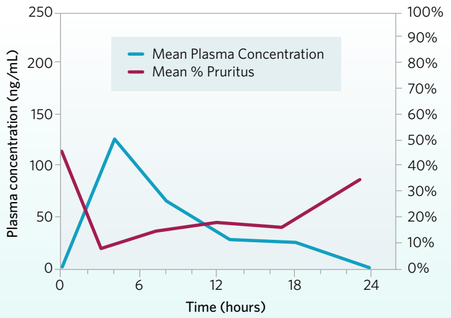
APOQUEL® pharmacokinetics are ideal for oral administration. It is rapidly and well-absorbed with a T_{max} of less than 1 hour. The oral bioavailability of

Table 3 | APOQUEL®and JAK inhibition – APOQUEL® inhibition of JAK enzymes and biological processes [14,15,16,17]

CELL-BASED ASSAY	JAK PAIR IMPACTED	IC_{50}, 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_{50}, 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_{50} provides a measure of the effectiveness of a compound in inhibiting a biological or biochemical function.

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) 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_{50} of various JAK1 dependent and JAK2 dependent cytokines.[15,16,17,18]

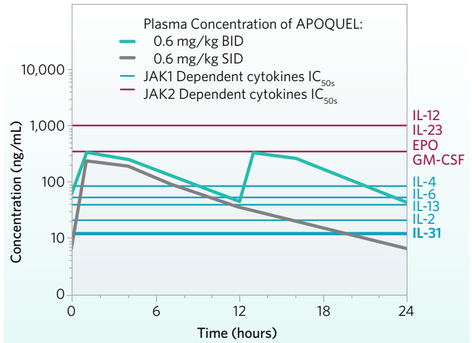
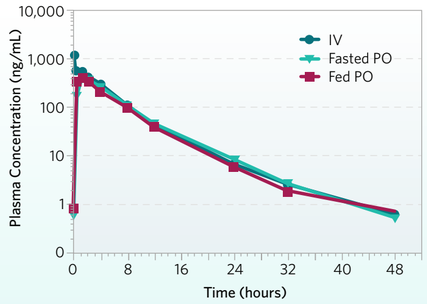


Figure 13 | APOQUEL® dosing with and without food – Mean oclacitinib plasma concentration – time profiles after intravenous and oral APOQUEL® administration in dogs under fed and fasted conditions.[10,19]

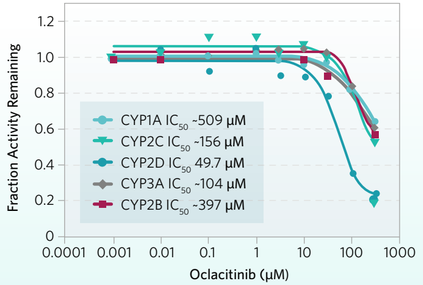


oclacitinib is 89% in dogs. It has been shown that the prandial state does not significantly affect the rate or extent of the absorption of APOQUEL, and it can be administered to dogs with or without food (Figure 13).

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. APOQUEL® has very low protein binding in dogs (66.3% - 69.7%).

The major clearance mechanism for oclacitinib in dogs is metabolism.

Figure 14 | Inhibition of cytochrome P450 – The in vitro inhibition of canine liver cytochrome P450 enzymes by oclacitinib.[10,20]



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) 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 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

Table 4 | Summary of APOQUEL® pharmacologic parameters as listed in EU summary of product characteristics.[11]

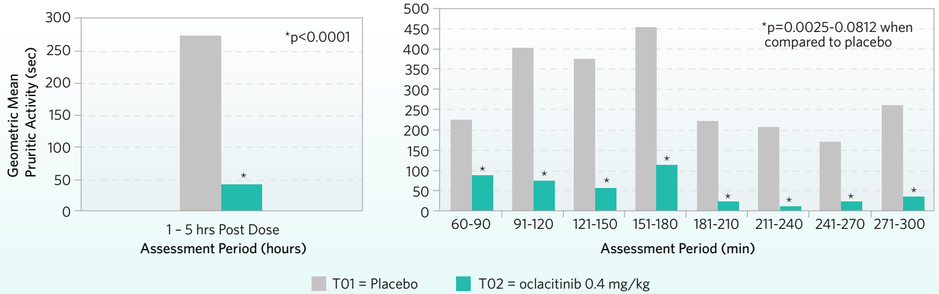
Mean CL (mL/h/kg)	316
Mean CL (mL/min/kg)	5.3
Vd_{ss} (mL/kg)	942
C_{max} (ng/mL)	333
T_{max} (hours)	< 1
$t_{½}$ (hours) IV	3.5
$t_{½}$ (hours) PO	4.1

CL, clearance; Vd_{ss}, volume of distribution at steady state; h, hour; $t_{½}$, terminal half-life; IV, intravenous; PO, oral.

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.[15,21,22] 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.

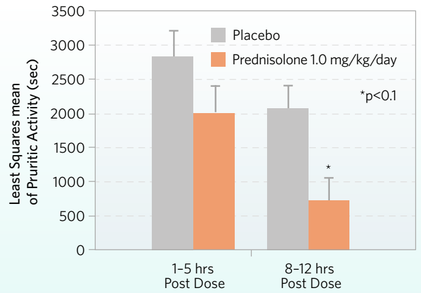


Oclacitinib significantly reduced (p=0.0013) pruritus induced in laboratory dogs by injecting IL-31 within 1-3 hours after administration but no significant decrease was seen with prednisolone.

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).[15,23]

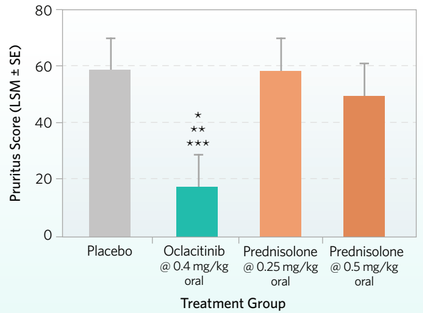
Figure 16 | Validation of the FAD pruritus model using current treatments – Inhibition of pruritus after prednisolone administration in flea allergic dogs. Data are LS-mean ±SE.



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).[22,24] 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 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.



*p=0.0202 vs. placebo; **p=0.0101 vs. 0.25 mg/kg prednisolone
*** p=0.024 vs. 0.5 mg/kg prednisolone

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.[25,26] 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.

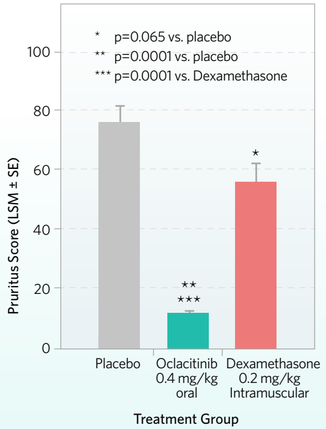
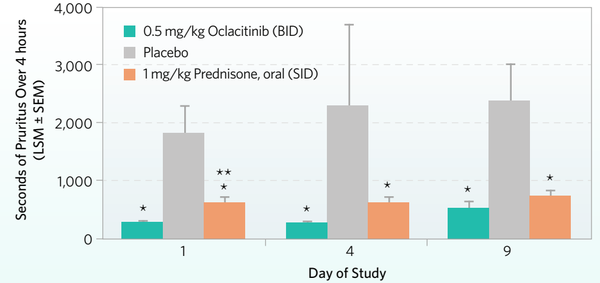


Figure 19 | Relative anti-pruritic effects of oclacitinib and prednisone using a canine model – Effects of placebo, oclacitinib (citrate salt), and prednisone on mean durations of pruritus (seconds) in flea allergic mongrel dogs, recorded during 4-hour sampling intervals on various study days.***



* p≤0.05 when compared to placebo
** p≤0.05 when oclacitinib compared to prednisone
***Oclacitinib administered as oclacitinib citrate (not APOQUEL final formulation)

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)*

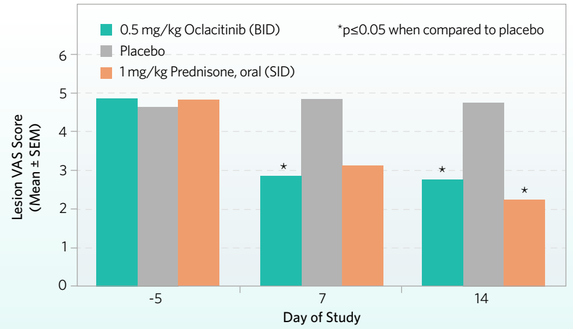


Table 5 | Impact of oclacitinib and prednisolone on results of intradermal tests (IDT) – Number of dogs (%) by the observed change in sensitivity to IDT.

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%)

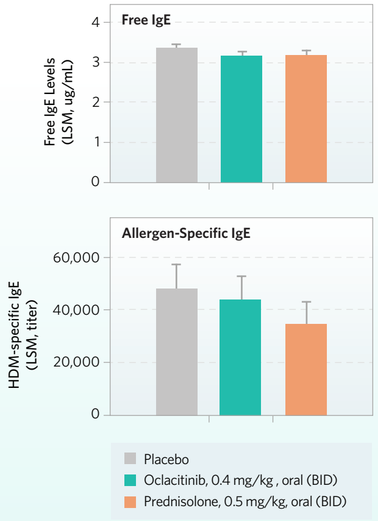
The final laboratory investigation explored the effects of oclacitinib on pruritus and skin lesions in dogs with FAD. Dogs were infested with fleas for 1 month prior to treatment and treated for 21 days (Figures 19 and 20).[27] The results reported show the durations of pruritus and lesion scores in 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).

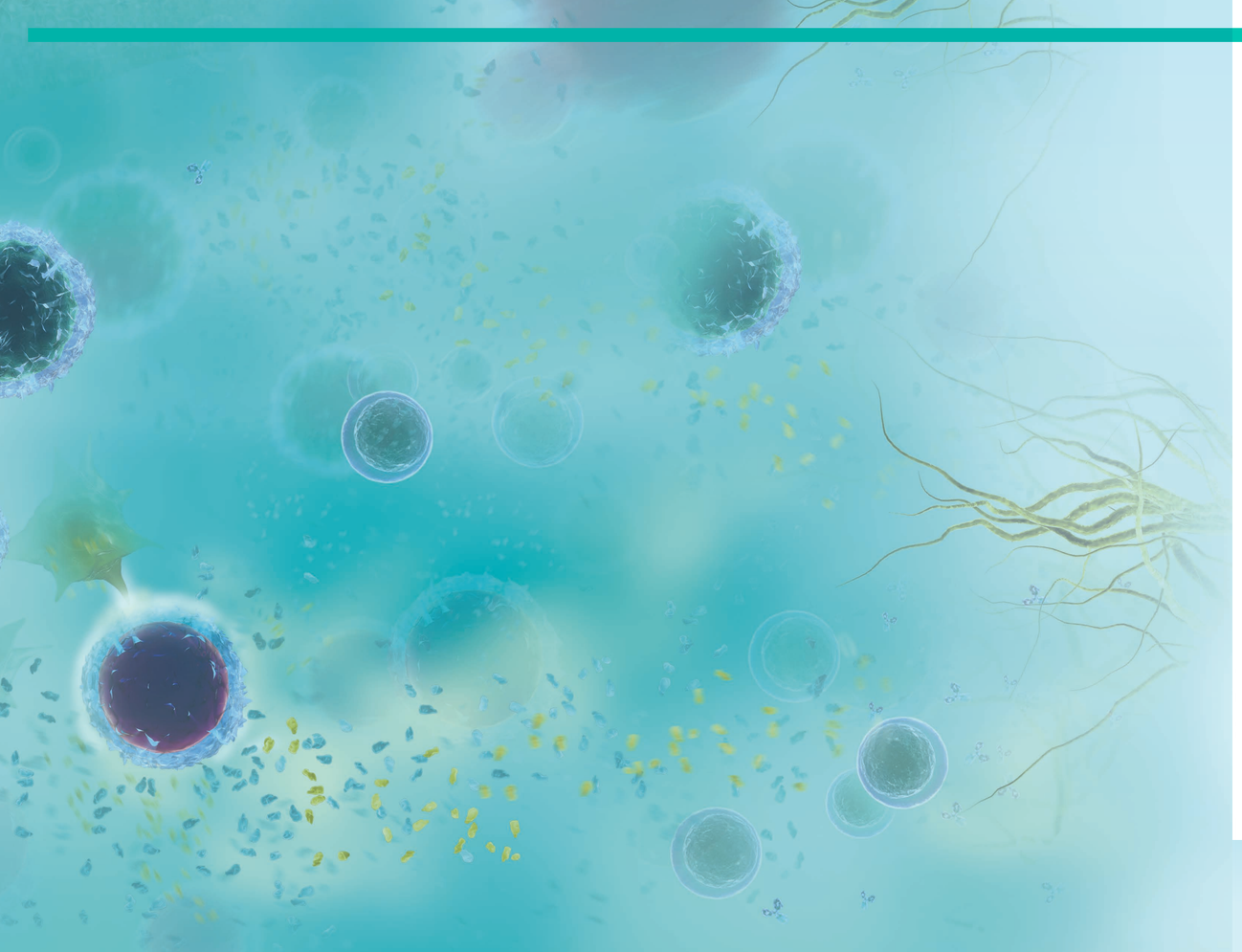
LACK OF INTERFERENCE WITH DIAGNOSTIC TESTING

A laboratory study was conducted to assess the impact of the label dose of oclacitinib on the results of intradermal tests (IDT).[28] 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 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).[28,29] ●

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





6 APOQUEL®(oclacitinib) Efficacy

IN THIS CHAPTER

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 has been shown to be effective in the treatment of clinical manifestations of AD in dogs**
- **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 treatment 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 14 days, followed by 0.4-0.6 mg/kg (0.18-0.27 mg/lb) SID for maintenance therapy.

APOQUEL® (oclacitinib) 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 treatment 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

PRURITUS ASSOCIATED WITH ALLERGIC DERMATITIS IN DOGS

APOQUEL® has been studied as a treatment 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® (oclacitinib; US)[30]

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) 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)	

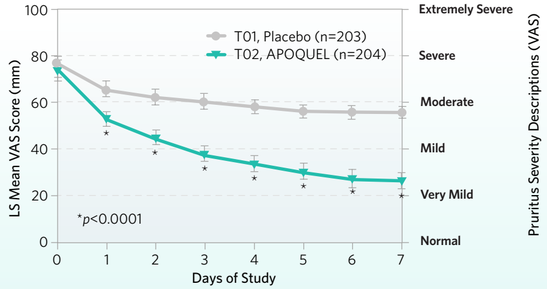
LS, least squares.
* Treatment success = 2 cm reduction (from baseline) in owner-assessed pruritus scores on at least 70% of the study days assessed; back-transformed from logit scale to original scale.

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

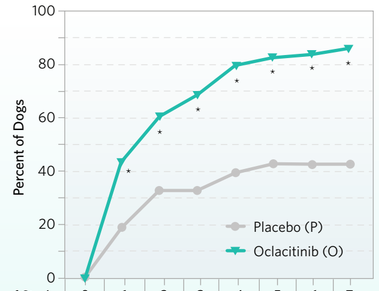
Figure 22 | Anti-pruritic efficacy of APOQUEL® (US trial) – Owner-assessed pruritus VAS scores (LS means) on each day of treatment. (LS, Least squares)



APOQUEL® was reliably efficacious in treating 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 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 ($p < 0.0001$)

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.



Day of Study	0	1	2	3	4	5	6	7
Placebo	0	19	32.5	32.5	39.7	42.7	42.3	42.5
Oclacitinib	0	44*	61.3*	69.4*	80.1*	83*	84.2*	86.4*

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

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

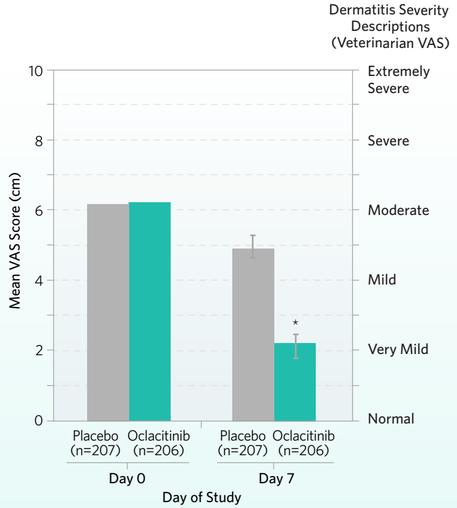
- After 7 days of treatment there was a decrease in the mean dermatitis score in APOQUEL-treated dogs from moderate to very mild. This was a significantly greater decrease in dermatitis level compared to that observed in control dogs ($p < 0.0001$)

EFFICACY OF APOQUEL® (oclacitinib) COMPARED TO PREDNISOLONE FOR CONTROL OF PRURITUS ASSOCIATED WITH ALLERGIC DERMATITIS[31]

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® (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® (oclacitinib) 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® efficacy (US trial) – Veterinarian-assessed dermatitis 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 ($p < 0.0001$)

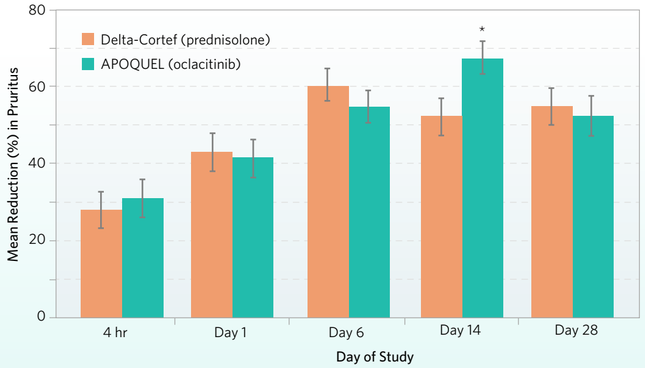
efficacy variable was the mean percentage reduction in pruritus from baseline (pre-treatment) as measured by the owner after 14 (±2) days of treatment using a 10-cm VAS (see Appendix 1).

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

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

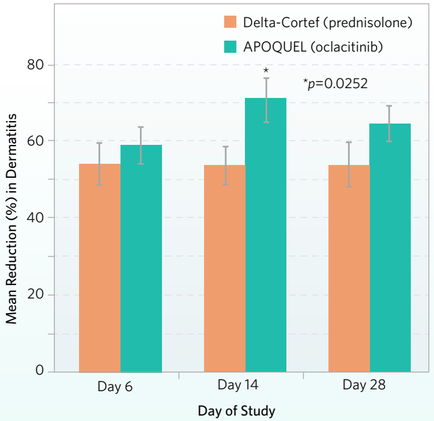
PRESUMPTIVE DIAGNOSIS BY VETERINARY INVESTIGATOR	PERCENT (%) OF APOQUEL DOGS WITH DIAGNOSIS	PERCENT (%) OF DELTA-CORTEF DOGS WITH DIAGNOSIS
Atopic dermatitis	96.7%	98.4%
Flea allergy dermatitis	32.8%	40.3%
Contact dermatitis	47.5%	41.9%
Food hypersensitivity	23.0%	19.4%

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).



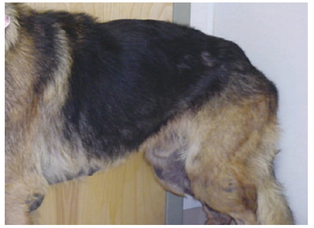
Day of Study	6	14	28
Delta-Cortef	54	54	54
APOQUEL	59	71	64
p value	0.487	0.025	0.164

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).

CANINE ATOPIC DERMATITIS

APOQUEL has been studied for the treatment of clinical manifestations of atopic dermatitis in dogs. 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.

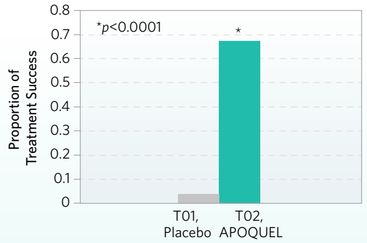
Table 10 | Summary of APOQUEL® clinical trials in atopic dogs – Overview of APOQUEL global clinical study program in AD.

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)[32]

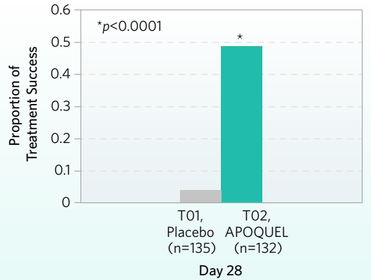
A multi-centered, placebo-controlled clinical field trial was conducted at 19 dermatology referral practices across the United States. Only 18 of the 19 clinics enrolled cases to the study. All of the study investigators were board-certified veterinary dermatology specialists. The dogs treated were male 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 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.



	T01, n=134	T02, n=128
T01, Placebo	0.04	
T02, APOQUEL	0.67	

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 (±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 ±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.

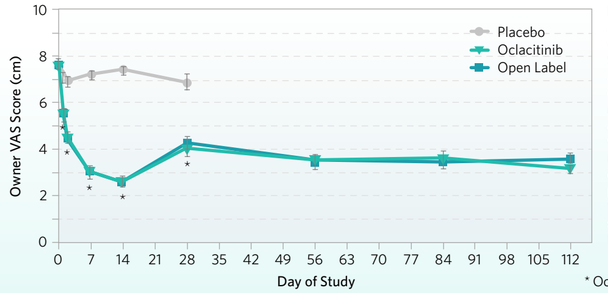
CADESI-02 scores assessed by the veterinary dermatologists for APOQUEL-treated dogs were significantly better than those for placebo-treated dogs at each timepoint assessed (p <0.0001). For the APOQUEL-treated dogs that continued on the study beyond 1 month, the mean CADESI-02 scores remained improved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

APOQUEL® (oclacitinib) EFFICACY COMPARED TO ATOPICA[13]

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 treatment of clinical manifestations of AD in client-owned dogs. Dogs were dosed for up to 84 (±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.

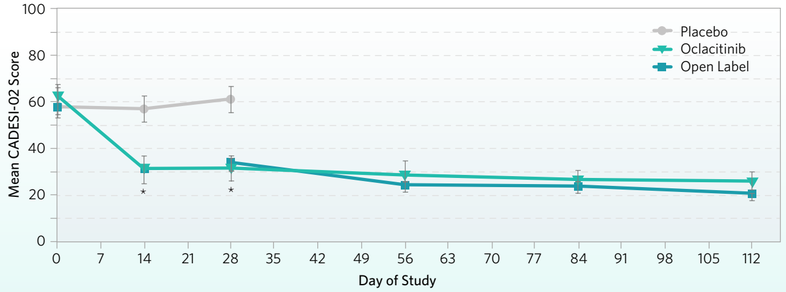
Figure 29 | Evaluation of owner-assessed pruritus with ongoing treatment (US trial) – Owner assessment of pruritus VAS scores (mean).



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

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

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



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

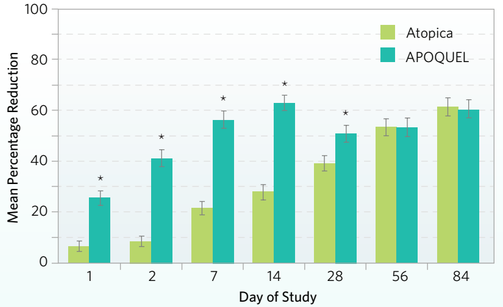
In this study of 226 dogs in Australia with AD, APOQUEL® was as efficacious as, and at several timepoints superior to, Atopica in controlling AD in dogs.

- *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 after 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 ≥ 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 ≥ 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 sore 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

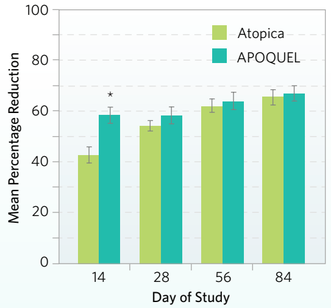
Figure 31 | Impact of APOQUEL® on owner-assessed pruritus (Australian study) – Percentage reduction from baseline in owner-assessed pruritus VAS (mean ±SE) (full study results have been submitted for publication).



* 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 CASESI-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 CASESI-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[33]

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) 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 on 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).[34]

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.

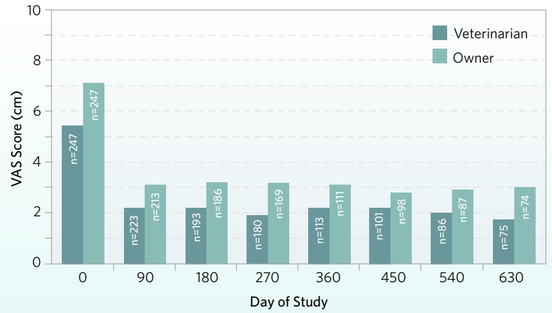
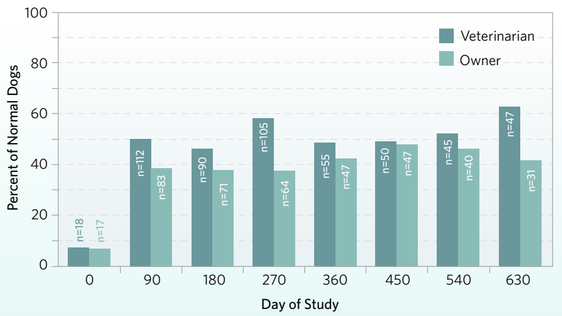
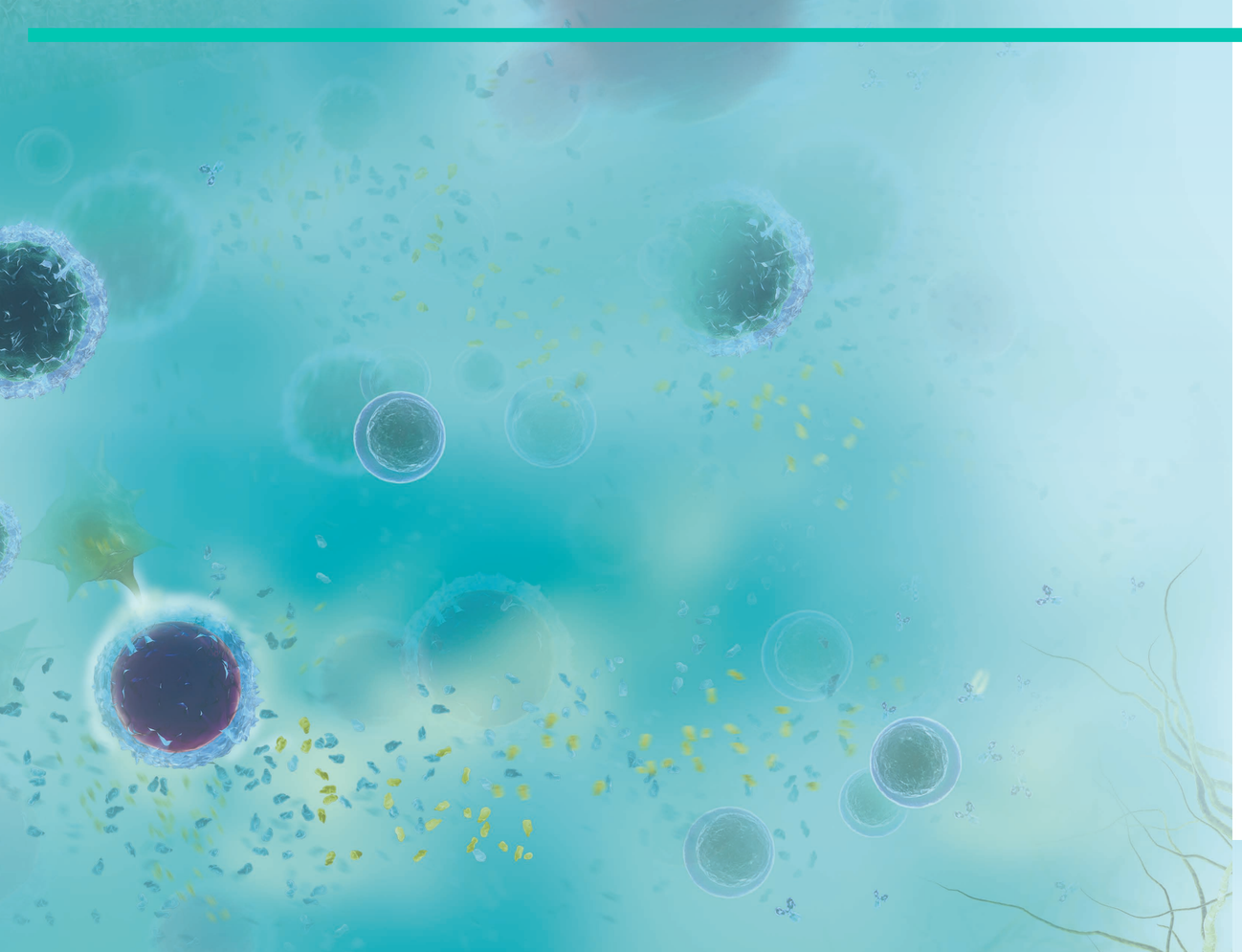


Figure 34 | Dogs returned to a normal level (VAS score < 2 cm) of pruritus with ongoing APOQUEL® therapy (US trial) – Veterinarian dermatitis and owner pruritus assessments during long-term continuation therapy with APOQUEL.





7 APOQUEL®(oclacitinib) Safety

IN THIS CHAPTER

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
- **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[30]

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). The data in Table 12 are findings obtained from the final study report; this population of dogs may be slightly different from the sub-set reported on local product labeling.

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[32]

Dogs were enrolled at 18 dermatology specialty veterinary practices in this placebo-controlled study to demonstrate the efficacy and safety of APOQUEL® for the treatment 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 same dose regimen. Treatment was administered for up to 112 days during the study period.

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.[10]

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.

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). The data in Table 14 are findings obtained from the US label; this population of dogs may be slightly different than the sub-set reported on local product labeling.

In the global clinical trials in 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).

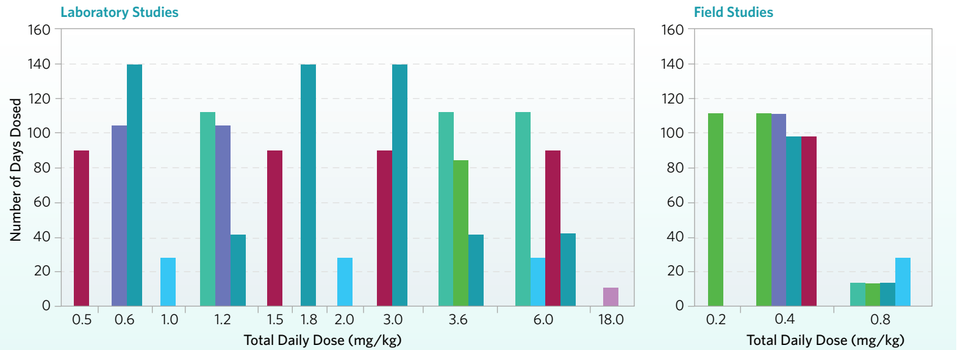
CONTINUATION THERAPY

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[18]

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
Opthalmologic 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

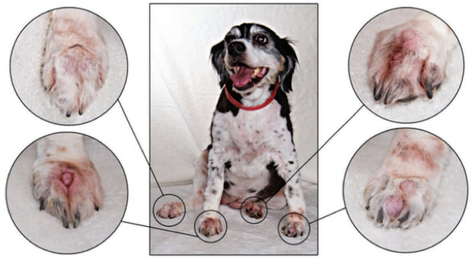
* Dermatitis term includes pododermatitis, interdigital cysts (IDC), moist dermatitis, swelling between toes, and ulcers on pads.

APOQUEL® (oclacitinib) 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 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.



Allergic pododermatitis

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) 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*

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 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 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

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

8 The APOQUEL® (oclacitinib) Difference

IMPACT OF ALLERGIC AND ATOPIC DISEASE

KEAURA'S LEGACY

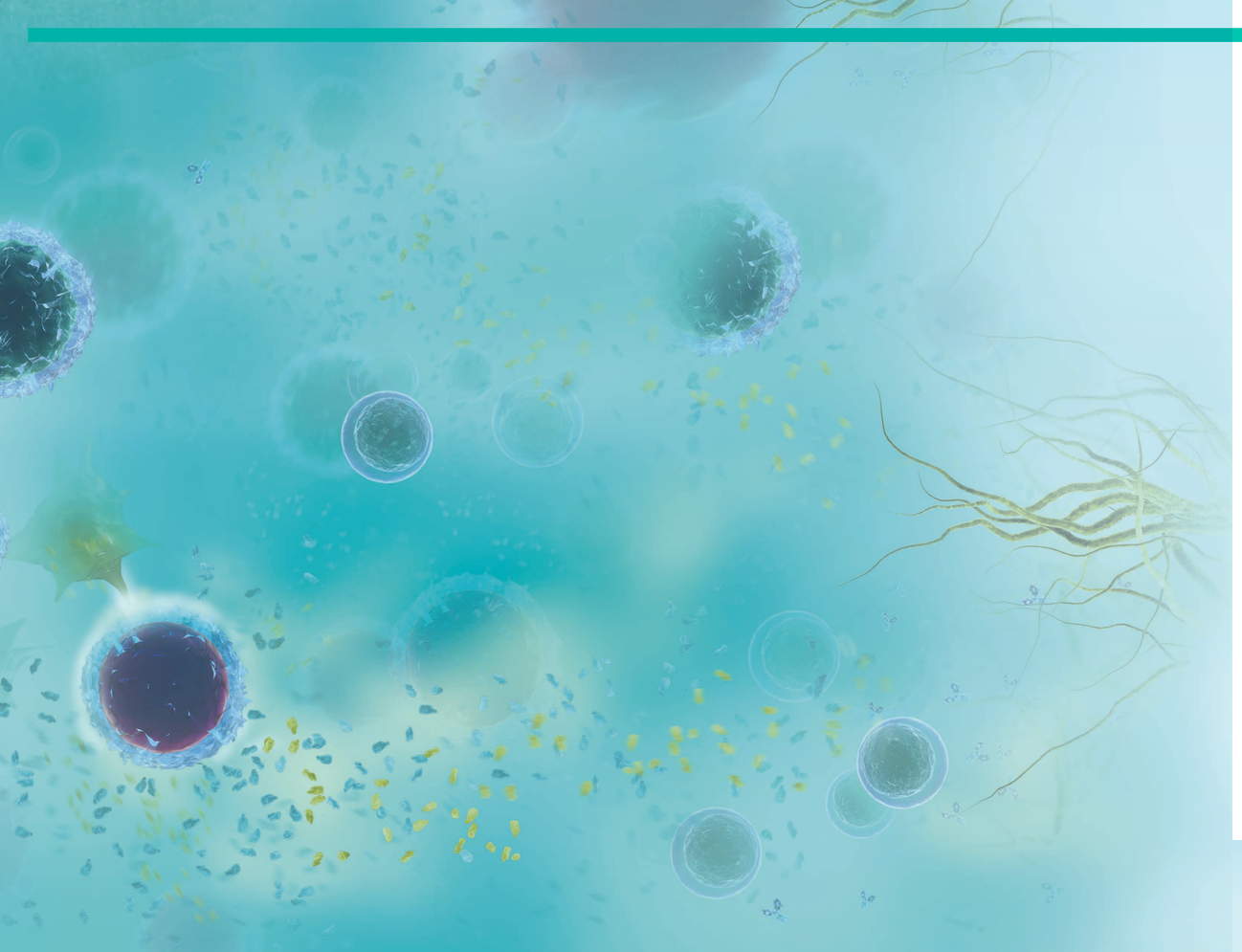
Allergic and atopic skin diseases take their toll on the dogs who suffer from them, as well as the families who love them. The itch and scratching, and the dermatitis associated with canine AD, disrupts lives - as do many of the therapies used to treat the disease such as corticosteroids, shampooing 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) 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 the10-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

Extremely Severe Dermatitis. Extensive evidence of chronic lesion and/or active infections/excoriations.

Severe Dermatitis.

Moderately Severe Dermatitis.

Moderate Dermatitis.

Mild Dermatitis.

Normal Dog. Dermatitis is not a problem

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 CONCURRENLTY USED THERAPIES FROM CLINICAL STUDIES[35]

APOQUEL® (oclacitinib)-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
Study 1462N-60-10-A29: **Margin of safety (MOS) study of APOQUEL® administered for 26 weeks to adult dogs**	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
Study 1462N-60-08-905: **MOS study of APOQUEL® administered for 26 weeks to adult dogs with recovery period**	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
Study 1462N-60-09-927: **The effect of oral APOQUEL® on the response to primary vaccination in dogs**	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

APPENDIX 7: SUMMARY OF PRODUCT SPECIFICS

ANNEX I, SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

APOQUEL 3.6 mg film-coated tablets for dogs
APOQUEL 5.4 mg film-coated tablets for dogs
APOQUEL 16 mg film-coated tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each film-coated tablet contains:

APOQUEL 3.6 mg	3.6 mg oclacitinib (as oclacitinib maleate)
APOQUEL 5.4 mg	5.4 mg oclacitinib (as oclacitinib maleate)
APOQUEL 16 mg	16 mg oclacitinib (as oclacitinib maleate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White to off-white, oblong shaped film-coated tablets with a score-line on both sides and marked with the letters "AQ" and "S", "M" or "L" on both sides. The letters "S", "M" and "L" refer to the different strengths of tablets: "S" is on the 3.6 mg tablets, "M" on the 5.4 mg tablets, and "L" on the 16 mg tablets.

The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Treatment of pruritus associated with allergic dermatitis in dogs.

Treatment of clinical manifestations of atopic dermatitis in dogs.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.

Do not use in dogs less than 12 months of age or less than 3 kg bodyweight.

Do not use in dogs with evidence of immune suppression, such as hyperadrenocorticism, or with evidence of progressive malignant neoplasia as the active substance has not been evaluated in these cases.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Oclacitinib modulates the immune system and may increase susceptibility to infection and exacerbate neoplastic conditions. Dogs receiving APOQUEL tablets should therefore be monitored for the development of infections and neoplasia.

When treating pruritus associated with allergic dermatitis with oclacitinib, investigate and treat any underlying causes (e.g. flea allergic dermatitis, contact dermatitis, food hypersensitivity). Furthermore, in cases of allergic dermatitis and atopic dermatitis, it is recommended to investigate and treat complicating factors, such as bacterial, fungal or parasitic infections/infestations (e.g. flea and mange).

Given the potential for effects on certain clinicopathological parameters (see section 4.6), periodic monitoring with complete blood counts and serum

biochemistry is recommended when dogs are on treatment long-term.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Wash hands after administration.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

The common adverse reactions seen up to day 16 of the field trials are listed in the following table and compared to placebo:

	ADVERSE REACTIONS OBSERVED IN ATOPIC DERMATITIS STUDY UP TO DAY 16		ADVERSE REACTIONS OBSERVED IN PRURITUS STUDY UP TO DAY 7	
	APOQUEL (n=152)	PLACEBO (n=147)	APOQUEL (n=216)	PLACEBO (n=220)
Diarrhea	4.6%	3.4%	2.3%	0.9%
Vomiting	3.9%	4.1%	2.3%	1.8%
Anorexia	2.6%	0%	1.4%	0%
New cutaneous or subcutaneous lumps	2.6%	2.7%	1.0%	0%
Lethargy	2.0%	1.4%	1.8%	1.4%
Polydipsia	0.7%	1.4%	1.4%	0%

After day 16, abnormal clinical signs, in addition to those clinical signs listed above and occurring in greater than 1% of the dogs receiving oclacitinib included pyoderma, non-specified dermal lumps, otitis, histiocytoma, cystitis, yeast skin infections, pododermatitis, lipoma, lymphadenopathy, nausea, increased appetite and aggression.

Treatment related clinical pathology changes were restricted to an increase in mean serum cholesterol and a decrease in mean leukocyte count, however, all mean values remained within the laboratory reference range. The decrease in mean leukocyte count observed in oclacitinib-treated dogs was not progressive, and affected all white blood cell counts (neutrophil, eosinophil and monocyte counts) except lymphocyte counts. Neither of these clinical pathology changes appeared clinically significant.

In a laboratory study, the development of papillomas was noted in a number of dogs.

Regarding susceptibility to infection and neoplastic conditions, see section 4.5.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation, or in breeding male dogs, therefore its use is not recommended during pregnancy, lactation or in dogs intended for breeding.

4.8 Interaction with other medicinal products and other forms of interaction

No drug interactions were observed in field studies where oclacitinib was administered concomitantly with veterinary medicinal products such as endo- and ectoparasiticides, antimicrobials and anti-inflammatories.

The impact of oclacitinib administration on vaccination with modified live vaccines, canine parvovirus (CPV), canine distemper virus (CDV) and canine parainfluenza (CPI) and inactivated rabies vaccine (RV), on 16 week old vaccine naïve puppies has been studied. An adequate immune response (serology) to CDV and CPV vaccination was achieved when puppies were administered oclacitinib at 1.8 mg/kg bodyweight (bw) twice daily for 84 days. However, the findings of this study indicated a reduction in serological response to vaccination with CPI and RV in puppies being treated with oclacitinib compared to untreated controls. The clinical relevance of these observed effects for animals vaccinated while being administered oclacitinib (in accordance with the recommended dosing regimen) is unclear.

4.9 Amounts to be administered and administration route

For oral use.

Dosage and treatment schedule:

The recommended initial dose is 0.4 to 0.6 mg oclacitinib/kg bodyweight, administered orally, twice daily for up to 14 days.

For maintenance therapy, the same dose (0.4 to 0.6 mg oclacitinib/kg bodyweight) should then be administered only once a day. The requirement for long-term maintenance therapy should be based on an individual benefit-risk assessment.

These tablets can be administered with or without food.

The dosing table below shows the number of tablets required. The tablets are breakable along the score line.

BODYWEIGHT (kg) OF DOG	STRENGTH AND NUMBER OF TABLETS TO BE ADMINISTERED:		
	APOQUEL 3.6 MG TABLETS	APOQUEL 5.4 MG TABLETS	APOQUEL 16 MG TABLETS
3.0-4.4	½	-	-
4.5-5.9	-	½	-
6.0-8.9	1	-	-
9.0-13.4	-	1	-
13.5-19.9	-	-	½
20.0-26.9	-	2	-
27.0-39.9	-	-	1
40.0-54.9	-	-	1 ½
55.0-80.0	-	-	2

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Oclacitinib tablets were administered to healthy, one year old Beagle dogs twice daily for 6 weeks, followed by once per day for 20 weeks, at 0.6 mg/kg bw, 1.8 mg/kg bw and 3.0 mg/kg bw for a total of 26 weeks.

Clinical observations that were considered likely to be related to oclacitinib treatment included: alopecia (local), papilloma, dermatitis, erythema, abrasions and scabbing/crusts, interdigital "cysts", and oedema of the feet. Dermatitis lesions were mostly secondary to the development of interdigital furunculosis on one or more feet during the study, with the number and frequency of observations increasing with increasing dose. Lymphadenopathy of peripheral nodes was noted in all groups, increasing in frequency with increasing dose, and was frequently associated with interdigital furunculosis.

Papilloma was considered treatment related, but not dose related.

There is no specific antidote and in case of signs of overdose the dog should be treated symptomatically.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Agents for dermatitis, excluding corticosteroids. ATCvet code: QD11AH90.

5.1 Pharmacodynamic properties

Oclacitinib is a Janus kinase (JAK) inhibitor. It can inhibit the function of a variety of cytokines dependent on JAK enzyme activity. For oclacitinib, the target cytokines are those that are proinflammatory or have a role in allergic responses/pruritis. However, oclacitinib may also exert effects on other cytokines (for example, those involved in host defence or haematopoiesis) with the potential for unwanted effects.

5.2 Pharmacokinetic particulars

Following oral administration in dogs, oclacitinib maleate is rapidly and well absorbed, with a time to peak plasma concentration (tmax) of less than 1 hour. The absolute bioavailability of oclacitinib maleate was 89%. The prandial state of the dog does not significantly affect the rate or extent of its absorption.

Total body oclacitinib clearance from plasma was low – 316 ml/h/kg bodyweight (5.3 ml/min/kg bodyweight), and the apparent volume of distribution at steady-state was 942 ml/kg bodyweight. Following intravenous and oral administration, the terminal t1/2s were similar at 3.5 and 4.1 hours respectively. Oclacitinib exhibits low protein binding with 66.3% to 69.7% bound in fortified canine plasma at nominal concentrations ranging from 10 to 1,000 ng/ml.

Oclacitinib is metabolised in the dog to multiple metabolites. 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 P450s is minimal with IC_{50s} 50-fold greater than the observed mean C_{max} (333 ng/ml or 0.997 μM) following 0.6 mg/kg bw oral administration in the target animal safety study. Therefore, the risk of metabolic drug-drug interactions due to oclacitinib inhibition is very low. No accumulation was observed in the blood of dogs treated for 6 months with oclacitinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Magnesium stearate
Sodium starch glycolate

Tablet coating:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400 (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

Any remaining half tablets should be discarded after 3 days.

6.4. Special precautions for storage

Store below 25 °C.

Any remaining half tablet should be placed back in the opened blister and stored (for a maximum of 3 days) in the original cardboard carton.

6.5 Nature and composition of immediate packaging

All tablets strengths are packaged in aluminium/PVC/Aclar blisters (each strip containing 10 film-coated tablets) packed into an outer cardboard box. Pack sizes of 20 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/154/001 (1 x 20 tablets, 3.6 mg)
EU/2/13/154/002 (1 x 100 tablets, 3.6 mg)
EU/2/13/154/003 (1 x 20 tablets, 5.4 mg)
EU/2/13/154/004 (1 x 100 tablets, 5.4 mg)
EU/2/13/154/005 (1 x 20 tablets, 16 mg)
EU/2/13/154/006 (1 x 100 tablets, 16 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Pfizer Italia S.R.L.
Via del Commercio 25/27
63100 Marino Del Tronto (AP)
ITALY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE CARDBOARD CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

APOQUEL 3.6 mg film-coated tablets for dogs
APOQUEL 5.4 mg film-coated tablets for dogs
APOQUEL 16 mg film-coated tablets for dogs

Oclacitinib

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Each tablet contains 3.6 mg oclacitinib (as oclacitinib maleate)
Each tablet contains 5.4 mg oclacitinib (as oclacitinib maleate)
Each tablet contains 16 mg oclacitinib (as oclacitinib maleate)

3. PHARMACEUTICAL FORM

Film-coated tablets

4. PACKAGE SIZE

20 tablets
100 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Any remaining half tablet should be stored in the blister and discarded if not used within 3 days.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium SA
Rue Laid Burniat
1 1348 Louvain-la-Neuve
BELGIUM

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/154/001 (1 x 20 tablets, 3.6 mg)
EU/2/13/154/002 (1 x 100 tablets, 3.6 mg)
EU/2/13/154/003 (1 x 20 tablets, 5.4 mg)
EU/2/13/154/004 (1 x 100 tablets, 5.4 mg)
EU/2/13/154/005 (1 x 20 tablets, 16 mg) E
U/2/13/154/006 (1 x 100 tablets, 16 mg)

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS BLISTER

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

APOQUEL 3.6 mg tablets for dogs
APOQUEL 5.4 mg tablets for dogs
APOQUEL 16 mg tablets for dogs

Oclacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Lot

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:

APOQUEL 3.6 mg film-coated tablets for dogs
APOQUEL 5.4 mg film-coated tablets for dogs
APOQUEL 16 mg film-coated tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
BELGIUM

Manufacturer responsible for batch release:
Pfizer Italia S.R.L.
Via del Commercio 25/27
63100 Marino Del Tronto (AP)
ITALY

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

APOQUEL 3.6 mg film-coated tablets for dogs
APOQUEL 5.4 mg film-coated tablets for dogs
APOQUEL 16 mg film-coated tablets for dogs

Olacitinib

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each film-coated tablet contains 3.6 mg, 5.4 mg or 16 mg oclacitinib (as oclacitinib maleate). White to off-white, oblong shaped film-coated tablets with a score-line on both sides and marked with the letters "AQ" and "S", "M" or "L" on both sides. The letters "S", "M" and "L" refer to the different

strengths of tablets: "S" is on the 3.6 mg tablets, "M" on the 5.4 mg tablets, and "L" on the 16 mg tablets. The tablets can be divided into equal halves.

4. INDICATION(S)

Treatment of pruritus associated with allergic dermatitis in dogs. Treatment of clinical manifestations of atopic dermatitis in dogs.

5. CONTRAINDICATIONS

Do not use in case of hypersensitivity to oclacitinib or to any of the excipients.

Do not use in dogs less than 12 months of age or less than 3 kg bodyweight.

Do not use in dogs with evidence of immune suppression such as hyperadrenocorticisim or with evidence of progressive malignant neoplasia as the active substance has not been evaluated in these cases.

6. ADVERSE REACTIONS

The common adverse reactions seen up to day 16 of the field trials are listed in the following table and compared to placebo:

	ADVERSE REACTIONS OBSERVED IN ATOPIC DERMATITIS STUDY UP TO DAY 16		ADVERSE REACTIONS OBSERVED IN PRURITUS STUDY UP TO DAY 7	
	APOQUEL (n=152)	PLACEBO (n=147)	APOQUEL (n=216)	PLACEBO (n=220)
Diarrhoea	4.6%	3.4%	2.3%	0.9%
Vomiting	3.9%	4.1%	2.3%	1.8%
Lack or loss of appetite (Anorexia)	2.6%	0%	1.4%	0%
New cutaneous or subcutaneous lumps	2.6%	2.7%	1.0%	0%
Weakness (Lethargy)	2.0%	1.4%	1.8%	1.4%
Excessive thirst (Polydipsia)	0.7%	1.4%	1.4%	0%

After day 16, abnormal clinical signs in addition to those clinical signs listed above and occurring in greater than 1% of the dogs receiving oclacitinib included pyoderma, non-specified dermal lumps, otitis, histiocytoma, cystitis, yeast skin infections, pododermatitis, lipoma, enlarged lymph nodes (lymphadenopathy), nausea, increased appetite and aggression.

Treatment related clinical pathology changes were restricted to an increase in mean serum cholesterol and a decrease in mean leukocyte count, however, all mean values remained within the laboratory reference range. The decrease in mean leukocyte count observed in oclacitinib-treated dogs was not progressive, and affected all white blood cell counts (neutrophil, eosinophil and monocyte counts) except lymphocyte counts. Neither of these clinical pathology changes appeared clinically significant.

In a laboratory study, the development of papillomas was noted in a number of dogs.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please, inform your veterinary surgeon.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For oral use.

Dosage and treatment schedule:

The recommended initial dose of APOQUEL tablets to be given to the dog is to achieve 0.4 to 0.6 mg oclacitinib/kg bodyweight, administered orally, twice daily for up to 14 days.

For maintenance therapy (after the initial 14 days of treatment), the same dose (0.4 to 0.6 mg oclacitinib/kg bodyweight) should then be administered only once a day. The requirement for long-term maintenance therapy should be based on an individual benefit-risk assessment by the responsible veterinarian.

These tablets can be administered with or without food.

Please see dosing table below for the number of tablets required to achieve the recommended dose. The tablets are breakable along the score line.

BODYWEIGHT (kg) OF DOG	STRENGTH AND NUMBER OF TABLETS TO BE ADMINISTERED:		
	APOQUEL 3.6 MG TABLETS	APOQUEL 5.4 MG TABLETS	APOQUEL 16 MG TABLETS
3.0-4.4	½	–	–
4.5-5.9	–	½	–
6.0-8.9	1	–	–
9.0-13.4	–	1	–
13.5-19.9	–	–	½
20.0-26.9	–	2	–
27.0-39.9	–	–	1
40.0-54.9	–	–	1 ½
55.0-80.0	–	–	2

9. ADVICE ON CORRECT ADMINISTRATION

Dogs should be carefully observed following administration to ensure that each tablet is swallowed.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store below 25 °C.

Any remaining half tablet should be placed back in the opened blister and stored (for a maximum of 3 days) in the original cardboard carton.

Do not use this veterinary medicinal product after the expiry date which is stated on the blister after EXP.

12. SPECIAL WARNING(S)

Special precautions for use in animals:

Oclacitinib modulates the immune system and may increase susceptibility to infection and exacerbate neoplastic conditions. Dogs receiving APOQUEL tablets should therefore be monitored for the development of infections and neoplasia.

When treating pruritus associated with allergic dermatitis with oclacitinib, investigate and treat any underlying causes (e.g., flea allergic dermatitis, contact dermatitis, food hypersensitivity). Furthermore, in cases of allergic dermatitis and atopic dermatitis, it is recommended to investigate and treat complicating factors, such as bacterial, fungal or parasitic infections/infestations (e.g. flea and mange).

Given the potential for effects on certain clinicopathological parameters (see section 6), periodic monitoring with complete blood counts and serum biochemistry is recommended when dogs are on treatment long-term.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Wash hands after administration.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician.

Use during pregnancy or lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation, or in breeding male dogs, therefore its use is not recommended during pregnancy, lactation or in dogs intended for breeding.

Interaction with other medicinal products and other forms of interaction:

No drug interactions were observed in field studies where oclacitinib was administered concomitantly with veterinary medicinal products such as endo- and ectoparasiticides, antimicrobials and anti-inflammatories.

The impact of oclacitinib administration on vaccination with modified live vaccines, canine parvovirus (CPV), canine distemper virus (CDV) and canine parainfluenza (CPI) and inactivated rabies vaccine (RV), on 16 week old vaccine naïve puppies has been studied. An adequate immune response (serology) to CDV and CPV vaccination was achieved when puppies were administered oclacitinib at 1.8 mg/kg bodyweight (bw) twice daily for 84 days. However, the findings of this study indicated a reduction in serological response to vaccination with CPI and RV in puppies being treated with oclacitinib compared to untreated controls. The clinical relevance of these observed effects for animals vaccinated while being administered oclacitinib (in accordance with the recommended dosing regimen) is unclear.

Overdose (symptoms, emergency procedures, antidotes):

Oclacitinib tablets were administered to healthy, one year old Beagle dogs twice daily for 6 weeks, followed by once per day for 20 weeks, at 0.6 mg/kg bw, 1.8 mg/kg bw and 3.0 mg/kg bw for a total of 26 weeks. Clinical observations that were considered likely to be related to oclacitinib treatment included: alopecia (local), papilloma, dermatitis, erythema, abrasions and scabbing/crusts, interdigital "cysts", and oedema of the feet.

Dermatitis lesions were mostly secondary to the development of interdigital furunculosis on one or more feet during the study with the number and frequency of observations increasing with increasing dose. Lymphadenopathy of peripheral nodes was noted in all groups, increasing in frequency with increasing dose, and was frequently associated with interdigital furunculosis.

Papilloma was considered treatment related, but not dose related.

There is no specific antidote and in case of signs of overdose the dog should be treated symptomatically.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

15. OTHER INFORMATION

APOQUEL tablets are supplied in blister packs with 20 or 100 tablets per pack. Not all pack sizes may be marketed.

Oclacitinib is a Janus kinase (JAK) inhibitor. It can inhibit the function of a variety of cytokines dependent on JAK enzyme activity. For oclacitinib, the target cytokines are those that are proinflammatory or have a role in allergic responses/pruritis. However, oclacitinib may also exert effects on other cytokines (for example, those involved in host defence or haematopoiesis) with the potential for unwanted effects.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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APOQUEL® (oclacitinib) Bibliography

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