

Canine Atopic Dermatitis Immunotherapeutic: A Caninized Anti-cIL-31 Monoclonal Antibody

U.S. FAQ's for External Use

GENERAL/ MODE OF ACTION

1. *What type of product is Canine Atopic Dermatitis Immunotherapeutic*?*

Answer: Canine Atopic Dermatitis Immunotherapeutic* is a caninized monoclonal antibody (mAb) that targets canine interleukin (IL)-31, a key cytokine responsible for pruritus in canine atopic dermatitis. Thus, it is an anti-cIL-31 mAb.

The preferred term for the use of mAbs is **Antibody Therapy**. The body's normal immunologic response to disease is to create antigen-specific antibodies that bind to and neutralize the disease agent. The term Antibody Therapy is used to reflect the fact that mAbs work in a way that mimics the body's natural response to disease. Some of the more common ways that mAbs work are by specific binding to a circulating protein (such as a cytokine) or a soluble receptor for that protein, or by binding to a receptor on the cell for that protein, neutralizing the protein's activity.

The therapeutic application of monoclonal antibodies has been variously referred to as: biological therapy, biotherapy/biotherapeutic therapy and immunotherapy.

Source:

Reference:

2. *Why is the cytokine IL-31 the chosen target?*

Answer: IL-31 has been identified as a key cytokine in the pathophysiology of atopic dermatitis (AD) in dogs. It has also been identified as a cytokine implicated in human atopic dermatitis. In a laboratory study involving laboratory Beagles, the injection of IL-31 via several routes (intravenous, subcutaneous or intradermal) caused transient episodes of pruritic behavior regardless of the route of administration. The intensity of pruritus ranged from a 2- to 10-fold increase above baseline and the dogs administered IL-31 exhibited a significant increase in pruritic behavior compared to those that received placebo. Some of the pruritic behaviors induced included scratching, licking, chewing, body rubbing, head shaking and scooting and tended to return to baseline within 24 hours.

In the same study, serum samples were obtained from laboratory dogs, healthy client-owned dogs and client-owned dogs with naturally occurring AD to measure and possibly compare serum IL-31 levels. IL-31 levels were detectable in 57% of dogs with naturally occurring AD (≥ 13 pg/mL) but were below limits of quantification (<13 pg/mL) in normal, healthy laboratory or client-owned animals.

Source: "Review of the Pathophysiology and Therapies for Canine Atopic Dermatitis..." slide deck, Dr. C. Sousa

Reference: Gonzales AJ, Humphrey WR, Messamore JE, Fleck TJ, Fici GJ, Shelly JA, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013 Feb; 24(1):48–53.e11-2.

***This product license is conditional. Safety and efficacy studies are in progress.**

3. How do monoclonal antibodies (mAbs) exert a therapeutic effect?

Answer: In antibody therapy, therapeutic mAbs can exert their effect by direct or indirect action. Examples of a direct effect of mAbs would be when they bind with high specificity and affinity to soluble targets, for example cytokines, in the blood or tissue to help prevent these molecules from binding with and activating their receptor. Alternatively, a therapeutic mAb can bind to a target cell-surface receptor to block its activation. These are described as antagonistic mAbs.

Indirect action of mAbs may occur where they induce several types of immune-based insult on their cellular target. For example, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis – these actions result in the destruction of the target cell, such as a virus or a malignant cell.

Source:

Reference:

1. Olivry T, Bainbridge G. Advances in Veterinary Medicine: Therapeutic Monoclonal Antibodies for Companion Animals. *Clinicians Brief* March 2015.
2. Keizer RJ, et al. Clinical Pharmacokinetics of Therapeutic Monoclonal Antibodies. *Clin Pharmacokinet* 2010;49 (6): 493-507.

4. How does Canine Atopic Dermatitis Immunotherapeutic* work – what is its mode of action?

Answer: Canine Atopic Dermatitis Immunotherapeutic* binds to canine interleukin (IL)-31, a key JAK1-dependent cytokine that drives and promotes pruritus and clinical signs in dogs with atopic dermatitis. As a result of the binding of Canine Atopic Dermatitis Immunotherapeutic* to cIL-31, the cytokine is prevented from binding to its target receptor. For example, IL-31 binds to IL-31 receptors on peripheral cutaneous sensory nerves that are critical in signaling the brain to the presence of allergic dermatitis and thus inducing pruritic behavior. By blocking IL-31 from binding to its receptor, the brain does not receive the signal from the skin and no pruritic behavior occurs.

Source: Gonzales A. Monoclonal Antibodies: A New Therapeutic Approach in Companion Animal. Presented 10.13.14

Reference: Gonzales A, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013; 24: 48–e12.

5. How does the mode of action of Canine Atopic Dermatitis Immunotherapeutic* differ from that of APOQUEL?

Answer: APOQUEL® is a small molecule pharmaceutical agent that is a selective Janus Kinase (JAK) inhibitor. As such, APOQUEL inhibits pruritogenic and pro-inflammatory cytokines, as well as cytokines involved in allergy that are dependent on JAK1 or JAK3 enzyme activity from inducing target cells to contribute to the allergic/inflammatory response; as a result the clinical signs of allergic dermatitis are controlled. APOQUEL does not bind to IL-31 or any other pruritogenic or pro-inflammatory cytokine – its site of action is the target cells of these cytokines.

Canine Atopic Dermatitis Immunotherapeutic*, an antibody therapy, is a therapeutic biologic

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agent, namely a monoclonal antibody, which binds specifically to cIL-31. As a result of this interaction, IL-31 is prevented from binding to its target receptor and driving the allergic inflammatory response. Canine Atopic Dermatitis Immunotherapeutic* does not inhibit JAK enzyme activity – its target is IL-31 before it binds to target cells.

Source: Gonzales A. Monoclonal Antibodies: A New Therapeutic Approach in Companion Animal. Presented 10.13.14

Reference:

1. APOQUEL PI
2. Gonzales AJ et al. Oclacitinib (APOQUEL) is a novel Janus kinase inhibitor with activity against cytokines involved in allergy. *J Vet Pharm Therap* 2014.

6. What physiologic mechanisms is IL-31 involved in? When IL-31 is blocked, what effects could be seen in dogs?

Answer: Human and mouse IL-31 receptor mRNA can be detected in skin, brain, lung, trachea, skeletal muscle, testis, ovary, prostate, placenta, spleen, thymus, bone marrow and blood leukocytes. IL-31 receptors have also been demonstrated on canine monocytes, keratinocytes and in the dorsal root ganglion. The precise role and function of IL-31 in each of these tissues is not fully known. *In vitro*, the effect of IL-31 on cell proliferation depends on the type of cell, cell density and cytokine concentration. Some functions of IL-31 demonstrated *in vitro* include regulation of cell proliferation (lung epithelium), regulation of hematopoiesis, and regulation of immune and inflammatory responses. For example, mice with a total deficiency of IL-31 **receptors** [Note – not the same as a total deficiency of IL-31] have reduced hematopoietic progenitor cells in their bone marrow but have normal circulating blood cell counts. It should be noted that the majority of the effects cited here were demonstrated *in vitro* studies; however, the *in vivo* processes require signals from other cells in order to create the desired biologic effect.

In dogs, administration of cIL-31 has been demonstrated to induce pruritic behavior, validating the role of IL-31 in itch. Further, specific caninized anti-cIL-31 mAb have been demonstrated to inhibit IL-31 induced pruritus in dogs without any additional adverse reactions.

There is clinical evidence that blocking cIL-31 activity in atopic dogs will inhibit pruritic behavior; but is not anticipated that this blockade will have other physiologic activity at the dose and dosing interval recommended on the product label. Under the conditional license, pharmacovigilance data will be collected and reported periodically USDA.

Source:

Reference:

1. Broxmeyer HE et al. Regulation of myeloid progenitor cell proliferation/survival by IL-31 receptor and IL-31. *Experimental Hematology* 35 (2007) 78-86.
2. Zhang Q et al. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine & Growth Factor Reviews* Volume 19, Issues 5–6, October–December 2008, Pages 347–356.
3. Dunham S et al. Evaluation of anti-interleukin-31 monoclonal antibodies in a model of interleukin-31-induced pruritus in beagle *dogs Abstract: ESVD Salzburg* 2014.
4. McCandless EE et al. Allergen-induced production of IL-31 by canine Th2 cells and identification of immune, skin, and neuronal target cells. *Vet Immunol Immunopathol* 157 (2014) 42–48.

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7. How does the use of Canine Atopic Dermatitis Immunotherapeutic* help improve inflammation?

Answer: IL-31 is a cytokine that has been demonstrated to induce pruritic behavior when injected into laboratory dogs, thus validating the role of IL-31 in itch. Canine Atopic Dermatitis Immunotherapeutic* binds to cIL-31 thus preventing this cytokine from binding to its receptor and stimulating itch and driving the allergic response. As a result, patients administered Canine Atopic Dermatitis Immunotherapeutic* are expected to experience reduced itch and consequently reduced self-trauma, thus a reduction of inflammation of the skin is likely.

In addition, it has been demonstrated *in vitro* that IL-31 has effects on epithelial tissue proliferation, induction of cytokines and chemokines, as well as regulation of immune and inflammatory responses. The precise mechanisms of these effects are uncertain and whether any are translated to *in vivo* changes that may result in reduced skin inflammation with Canine Atopic Dermatitis Immunotherapeutic* has not been evaluated.

In clinical trials, Canine Atopic Dermatitis Immunotherapeutic* administered at 2.0 mg/kg decreased pruritus inflammation in atopic patients. Skin inflammation in the form of erythema is one of the lesions assessed in CADESI-03.

Source:

Reference:

1. Gonzales A, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013; 24: 48–e12.
2. Zhang Q et al. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine & Growth Factor Reviews* Volume 19, Issues 5–6, October–December 2008, Pages 347–356.
3. Data on File, Study Report No. C863R-US-12-018, Zoetis Inc.

PRODUCT HANDLING/ STABILITY

8. What are the storage requirements for this product? How should the un-broached vials be stored?

Answer Canine Atopic Dermatitis Immunotherapeutic has no preservatives and should be stored upright at 2°- 8°C (35.6° – 46.4° F) in its original box. Prolonged exposure to higher temperatures and/or exposure to direct sunlight may adversely affect potency. Do not freeze punctured or unpunctured vials of Canine Atopic Dermatitis Immunotherapeutic RTU solution. Each vial is for single use only, and should be discarded after puncture. Any unused contents remaining after the vial is broached or punctured should be immediately discarded.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

9. Does temperature variability during shipping alter the product?

Answer: Canine Atopic Dermatitis Immunotherapeutic has no preservative and should be stored upright at 2°-8°C (35.6° – 46.4° F) in its original box. Prolonged exposure to higher temperatures and/or exposure to direct sunlight may adversely affect potency. The vials

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should not be frozen.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

10. Can the contents of a vial be split into several doses and saved for later use in this patient or another dog? (For example, can I split a 40 mg/mL vial and use it in 4 dogs that each weighs 10 kg?) Can the remaining content be frozen for later use?

Answer: Canine Atopic Dermatitis Immunotherapeutic* is packaged as a single-use dose and the entire volume should be used at one time for a dog within the dosing range for the vial size. This ensures that each dog will receive the minimum target dose of 2 mg/kg and no more than 4.3 mg/kg. There is no preservative in Canine Atopic Dermatitis Immunotherapeutic* and sterility cannot be guaranteed if the vial is broached more than once. Vials of Canine Atopic Dermatitis Immunotherapeutic* punctured or unpunctured should not be frozen.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

11. What is the shelf-life of an unbroached vial when stored as in the refrigerator?

Answer: The shelf-life following manufacture is 2 years when stored according to the label or product insert.

Source: Olivier Martinon, VMRD

Reference:

DOSING AND ADMINISTRATION

12. Can re-sterilized syringes be used to administer Canine Atopic Dermatitis Immunotherapeutic*?

Answer: Only new, sterile syringes and needles should be used to administer this product. Re-sterilized syringes and needles should not be used to administer the product. Traces of disinfectant used to chemically re-sterilize syringes or needles may inactivate the product.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

13. Why is the dose for Canine Atopic Dermatitis Immunotherapeutic* stated on the label as 'a minimum of 2.0 mg/kg' rather than referring to the dose range accommodated by the dose chart (between 2.0 and 4.3 mg/kg, based on weight)?

Answer: All recommendations by Zoetis for dosing of the Canine Atopic Dermatitis Immunotherapeutic* should be based on the dose chart contained in the package insert.

The label states the dose to be applied as 'a minimum of 2.0 mg/kg' because that is the dose

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applied in the dosage chart. The label dose chart only applies a dose of up to 4.3 mg/kg to dogs with weights at the lowest end of the 2.3-4.5 and 4.6-9.0 kg weight bands.

Source:

Reference:

14. Are there any limits to the age of a dog for this product to be administered to? A minimum age? A maximum age?

Answer: There is no minimum or maximum age for a dog to be treated with Canine Atopic Dermatitis Immunotherapeutic*. A diagnosis of atopic dermatitis should be made prior to use, as this is the label indication. Most but not all dogs diagnosed with atopic dermatitis are over one year of age.

Source:

Reference:

15. Is there any recommendation for a site on the dog's body that Canine Atopic Dermatitis Immunotherapeutic* should be administered?

Answer: In the studies that definitively described the injection site location, it was described as “between the shoulder blades” or “just behind the caudal aspect of the shoulder blade”. A directive of injection site location is not described on the label. However, since the product is not designed to induce an immune response, we would advise that it be administered in a different site than that of a concomitant vaccine administration.

Source:

Reference: Data on File, Study Report No. C166R-US-13-037, C860R-US-14-097, C961R-US-13-051, Zoetis Inc.

16. Does the site for injection of Canine Atopic Dermatitis Immunotherapeutic* need to be prepared in any special/specific/particular way?

Answer: Canine Atopic Dermatitis Immunotherapeutic* is administered at a minimum dose of 2 mg/kg by subcutaneous injection – the clinician is advised to consult the dosing chart in the package insert. If multiple vials are to be administered, the contents of each vial should be drawn up into a single syringe for administration subcutaneously as a single injection. The label does not prescribe any specific injection site preparation (such as shaving or clipping the hair, the use of a disinfectant such as alcohol, etc.) Clinicians are advised to administer Canine Atopic Dermatitis Immunotherapeutic* as they would a routine prophylactic vaccine. No specific injection site is prescribed on the label but it is advised to administer Canine Atopic Dermatitis Immunotherapeutic* at a different site to any other subcutaneous injections (such as allergen-specific immunotherapy) or vaccines.

Source: Dr. A. Hillier, Zoetis

Reference:

***This product license is conditional. Safety and efficacy studies are in progress.**

17. How long after an injection should I monitor a dog, particularly when looking for hypersensitivity reactions?

Answer: In the studies conducted to support global registration in which over 500 dogs were treated with at least one injection of Canine Atopic Dermatitis Immunotherapeutic*, there were no reports of acute hypersensitivity reactions or generalized anaphylaxis. Therefore, there were no recommendations provided by the USDA for monitoring a dog after an injection and no directives are on the package insert.

A general recommendation would include monitoring as you would for any injection or vaccine.

Canine Immunotherapeutic* should not be administered in the same syringe as a vaccine. A vaccine acts by stimulating an immunologic response and Canine Atopic Dermatitis Immunotherapeutic* is a caninized monoclonal antibody that mimics a natural antibody and is designed to not stimulate an immune response.

Source:

Reference:

SAFETY

18. What is the impact of Canine Atopic Dermatitis Immunotherapeutic* on the immune system?

Answer: Canine Atopic Dermatitis Immunotherapeutic* is a monoclonal antibody that will only bind to and “inactivate” a single cytokine, IL-31. It therefore has no impact on inhibition of any other parts of the immune system, such as innate immunity.

Source:

Reference:

19. What is the margin of safety of Canine Atopic Dermatitis Immunotherapeutic*?

Answer: There have been 2 laboratory safety studies completed with Canine Atopic Dermatitis Immunotherapeutic*, in addition to the safety assessments that were performed with the field trials in client-owned dogs with atopic dermatitis.

In the Exploratory Safety Margin Study, 6 laboratory Beagles were administered either 1 mg/kg, 3 mg/kg or 9 mg/kg of Canine Atopic Dermatitis Immunotherapeutic* subcutaneously for a total of 3 injections at 2 week intervals. The 2-week dose interval was considered ideal for eliciting an acquired immune response without compromising safety evaluation for the traditional target-associated end points. There were no hypersensitivity-related reactions observed in the study.

In the Safety Study, 12 laboratory Beagles were administered either 3.3 mg/kg or 10 mg/kg subcutaneously monthly for 7 months. There were no test article-related effects.

Source:

***This product license is conditional. Safety and efficacy studies are in progress.**

Reference: Data on File, Study Report No. 7462W-60-11-B43, C362N-US-13-042, Zoetis Inc.

20. Would pain on injection be expected with this product? (Injection site pain is one of the biggest 'side effects' reported with the use of human biologics like Humira® and Stelara®).

Answer: Injection site pain was not reported in the laboratory efficacy and safety studies or in the 2 field efficacy and safety studies.

In the Field Evaluation of the Safety of Canine Atopic Dermatitis Immunotherapeutic*, immediate reactions (animal discomfort) at administration were specifically measured and recorded. The study included an enrollment of 245 client-owned dogs that were randomly assigned to either the placebo group (T01) or the test article group (T02) at either 2-3.3 mg/kg (< 5 kg BW) or 1-2 mg/kg (≥ 5 kg BW) depending on the dog's weight. The parameters that were measured included vocalization (none, mild, moderate), scratching or biting at the injection site (none, mild, moderate) and aggressive or escape attempts ("yes"/"no" responses). Immediate reactions (animal discomfort at administration) were distributed approximately equally between dogs administered placebo (6.1%; 10/165) and dogs administered anti-IL-31 mAb (4.7%; 15/322) on both frequency and severity.

The results with a further breakdown by weight resulted in the findings that the frequency of immediate reactions in dogs weighing between 3.0-20.0 kg was 7.8% (T01, 7.3% (7/95); T02, 8.1% (11/135)) and the frequency of immediate reactions in dogs weighing >20.0 kg was 2.8% (T01, 4.3% (3/70); T02, 2.2% (4/181).

Source:

Reference: Data on File, Study Report Nos. 4962R-60-11-277, C863R-US-12-018, C961R-US-13-051, Zoetis Inc.

21. Should I expect to see injection site reactions when Canine Atopic Dermatitis Immunotherapeutic* is administered in my canine patients?

Answer: Injection site reactions with Canine Atopic Dermatitis Immunotherapeutic* would not be expected to be increased over what is typically observed with other injectable products.

In the laboratory efficacy studies, there were no injection site reactions reported. In the Exploratory Safety Margin lab study, 24 Beagles of either sex (intact females or neutered males), 7 to 8 months of age, and a weight >5 kg at dose initiation, were randomized to 4 treatment groups on a 1:1:1:1 basis comparing placebo to 3 doses ranges (1, 3 and 9 mg/kg). Three doses of the test article were administered subcutaneously at 2-week intervals, on Days 0, 14, and 28. On histopathology submitted on Day 31, there were some changes clearly related to treatment associated with the site of injection, where microscopic evaluation of injection sites revealed initial minimal to moderate tissue irritation that also demonstrated a normal progression toward resolution over the 31-day study. It was concluded that the tissue response was considered mild and typical for a subcutaneously administered product.

In a field safety study that enrolled 245 client-owned dogs, the safety was compared to placebo. A total of 2 injections were administered to each dog on Days 0 and 28. The study duration was 42 (+/- 3) days. There was one dog that had a possible injection site reaction and the details included the following:

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Case 0203 The 7.9 kg dog on Day 0 was reported to have “pruritus at the injection site” (scratching) for approximately 15 minutes following Test Article Administration. Injection site pain response was reported immediately post-dosing on Day 0 (moderate vocalization and scratching at the injection site). The pain response following Test Article Administration 2 (moderate vocalization) was less severe and no pruritus at the injection site was reported, although the same serial was administered.

Source:

Reference: Data on File, Study Report Nos. C863R-US-12-024, C166R-US-13-037, C860R-US-14-097, 7462W-60-11-B43, C362N-US-13-042, 4962R-60-11-277, C961R-US-13-051, Zoetis Inc.

22. What ‘adverse events’ are on the product label?

Answer: The draft package insert for conditional registration in the US of Canine Atopic Dermatitis Immunotherapeutic* does not delineate any specific adverse events and simply states: A field study has demonstrated Canine Atopic Dermatitis Immunotherapeutic* is well tolerated in dogs after subcutaneous injection.

The only elaboration on the draft package insert is:

In a study of 245 canine patients presented to veterinary hospitals and diagnosed with atopic dermatitis, dogs were administered Canine Atopic Dermatitis Immunotherapeutic* at a minimum dose of 1 mg/kg body weight or placebo by the subcutaneous route on Days 0 and 28. Signs of patient discomfort on administration and adverse events occurred at a similar frequency between treatment groups (Canine Atopic Dermatitis Immunotherapeutic* and placebo).

The most frequently observed abnormal clinical effects in dogs administered the mAb in laboratory and field studies were vomiting, diarrhea and lethargy. No clinically relevant differences were generally reported between dogs administered Canine Atopic Dermatitis Immunotherapeutic* and control dogs. For example, in study 4962R-60-11-277 where 2.0 mg/kg of caninized anti-cIL-31 mAb was dosed twice 2 weeks apart in client-owned dogs and compared to placebo adverse reactions the most commonly reported ADEs were:

<u>Clinical Sign</u>	<u>Placebo</u> (n=25)	<u>Canine Atopic Dermatitis Immunotherapeutic*</u> (n=53)
Vomiting	16%	15.1%
Diarrhea	4%	11.3%
Lethargy	4%	7.5%

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert Data on File, Study Report No. C-961R-US-13-051, Zoetis Inc.

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EFFICACY

23. How quickly do dogs administered Canine Atopic Dermatitis Immunotherapeutic* show a decrease in pruritus? What is the onset of the anti-pruritic effect? How does this compare to prednisolone/prednisone? To APOQUEL?

Answer: In clinical field trials the pruritus VAS was evaluated by owners as early as 1 day. With the use of 2 mg/kg mean pruritus scores were significantly decreased ($p \leq 0.05$) in that period of time.

In laboratory Beagles challenged with canine IL-31 (cIL-31), pruritus scores were significantly decreased ($p \leq 0.0001$) at 8 hours following administration of Canine Atopic Dermatitis Immunotherapeutic* at 1 mg/kg.

In laboratory Beagles challenged with cIL-31 and treated with APOQUEL at 0.5 mg/kg, a significant reduction in pruritus was noted between 1-3 hours.

In dogs with allergic dermatitis, both APOQUEL (0.4-0.6 mg/kg) and prednisolone (0.50-0.98 mg/kg) reduced pruritus by 4 hours.

Source: APOQUEL FTK slide deck

Reference: Data on File, Study Report Nos. 4962R-60-11-277, C863R-US-12-018, C860R-US-14-097, Zoetis Inc.

24. If a dog with atopic dermatitis did not respond to APOQUEL, will it respond to anti-IL-31 mAb? Is there any correlation with this?

Answer: Both Canine Atopic Dermatitis Immunotherapeutic* and APOQUEL work to inhibit cytokines involved in itch and inflammation associated with atopic dermatitis. APOQUEL works by binding to the JAK 1/3 enzymes associated with the receptors for some of these cytokines. Canine Atopic Dermatitis Immunotherapeutic* works by binding to and inactivating a single cytokine, IL-31.

Some of the client-owned dogs with atopic dermatitis that were entered into the Canine Atopic Dermatitis Immunotherapeutic* field trials had previously been treated with APOQUEL, but there is no data to suggest that these dogs did not respond to treatment with APOQUEL.

Source: See additional information in Q74, 83 and 84

Reference:

25. Can Canine Atopic Dermatitis Immunotherapeutic* be used for the itch associated with allergic dermatitis?

Answer: Canine Atopic Dermatitis Immunotherapeutic* is labeled as an aid in the reduction of clinical signs associated with atopic dermatitis in dogs. Unlike APOQUEL which has indications for allergic dermatitis and demonstrated efficacy in a number of different allergic conditions, the efficacy of Canine Atopic Dermatitis Immunotherapeutic* in helping reduce pruritus in dogs with flea allergy, food allergy or contact allergy has not been evaluated. A recent study showed elevations in serum IL-31 levels in ~50% of atopic dogs, but not in experimentally flea sensitized and flea infested mixed breed dogs. It is unknown if dogs with

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naturally occurring flea allergy, food allergy or contact allergy have elevated IL-31 levels in the serum or tissues and therefore if Canine Atopic Dermatitis Immunotherapeutic* would be effective.

Source:

Reference: Gonzales A, Humphrey W, Teel J, et al. IL-31: Its role in canine pruritus and prevalence in naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013, 24:48-e12.

26. Does efficacy diminish over time in dogs administered repeated doses of Canine Atopic Dermatitis Immunotherapeutic*?

Answer: None of the studies conducted to date has been specifically designed to compare the clinical response over time or with multiple doses of caninized anti-cIL-31 mAb. Safety and efficacy has been demonstrated in client-owned dogs that have been administered Canine Atopic Dermatitis Immunotherapeutic* for up to 56 days. No substantial decrease of clinical efficacy was reported by veterinary investigators or pet owners as an adverse event in any of these studies where dogs have received more than one injection over time in a dog with atopic dermatitis.

Source:

Reference: Data on File, Study Report Nos. 4962R-60-11-277, C863R-US-12-018, Zoetis Inc.

CONCOMITANT MEDICATIONS/ DRUG INTERACTIONS

27. Can Canine Atopic Dermatitis Immunotherapeutic* be used concurrently with APOQUEL? Short-term? Long-term?

Answer: In a field safety study that compared Canine Atopic Dermatitis Immunotherapeutic* to Placebo in 245 client-owned dogs, there was a wide variety of topical and systemic concomitant medications used safely, including parasiticides, antibiotics, antifungals, corticosteroids, vaccines, immunotherapy, antihistamines and antipruritics including oclacitinib (APOQUEL[®]) and cyclosporine (Atopica[®]).

53 dogs received Canine Atopic Dermatitis Immunotherapeutic* along with oclacitinib during the study. The study was 42 +/- 3 days in duration. There was one adverse event reported with the concurrent use of these 2 products and the details were the following:

Source:

Reference: Data on File, Study Report No. C961R-US-13-051, Zoetis Inc.

28. Is Canine Atopic Dermatitis Immunotherapeutic* safe to administer concurrently with other medications (NSAIDs, antibiotics, antifungals, antihistamines, ivermectin, high daily dose ivermectin, phenobarbital, behavior modification drugs, parasiticides, etc.)?

Answer: With reference to the US clinical field safety trial (study number C-961R-US-13-051), the safety section of the draft package insert states: A wide variety of concomitant medications were safely used, including parasiticides, antibiotics, antifungals, corticosteroids,

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vaccines, immunotherapy, antihistamines and other antipruritics, such as oclacitinib and cyclosporine. There is no need for any washout period for any product prior to using Canine Atopic Dermatitis Immunotherapeutic*.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert Data on File, Study Report No. C-961R-US-13-051, Zoetis Inc.

29. Is there a “wash out” period that should be followed when switching a dog with atopic dermatitis from any product to therapy with Canine Atopic Dermatitis Immunotherapeutic* or after administration of Canine Atopic Dermatitis Immunotherapeutic* to another product?

Answer: This has not been specifically studied, but due to the mechanism of action of Canine Atopic Dermatitis Immunotherapeutic* and other drugs that are used for atopic dermatitis in dogs, no washout period is suggested. Canine Atopic Dermatitis Immunotherapeutic* has been safely used in client-owned dogs with atopic dermatitis concomitantly with corticosteroids, cyclosporine, oclacitinib and allergen-specific immunotherapy.

Source:

Reference:

30. Can Canine Atopic Dermatitis Immunotherapeutic* be used at the same time as allergen-specific immunotherapy (ASIT)?

Answer: There is no theoretical reason to believe that Canine Atopic Dermatitis Immunotherapeutic* will interfere with allergen-specific immunotherapy due to the extreme specificity of anti-cIL-31 monoclonal antibody. Dogs enrolled in the clinical field efficacy and safety study were allowed to be treated concurrently with ASIT if they had been on this therapy for at least 8 months.

There is no contraindication for the co-administration of Canine Atopic Dermatitis Immunotherapeutic* and ASIT. Canine Atopic Dermatitis Immunotherapeutic* binds specifically to IL-31. Successful ASIT is suggested to involve development of tolerance associated with Treg lymphocytes and increased production of IL-10 and possibly TGF- β . Canine Atopic Dermatitis Immunotherapeutic* has no known or anticipated effects on these cytokines or Treg cells.

Source:

Reference: Lowenstein C, Mueller R. A review of allergen-specific immunotherapy in human and veterinary medicine. *Vet Dermatol* 2009; 20: 84-98.

CLINICAL USE

31. Is blood work required or recommended prior to starting this product?

Answer: Canine Atopic Dermatitis Immunotherapeutic* is licensed to aid in the reduction of clinical signs associated with atopic dermatitis in dogs. **A diagnosis of atopic dermatitis**

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should be made prior to the use of this product.

There are no recommendations or requirements on the product label that mandate pre-treatment blood work or other diagnostic testing. However, it is good medical practice to conduct a full physical examination and thorough patient evaluation including diagnostic work-up as indicated in all patients.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

32. Is there any specific monitoring required in dogs being administered Canine Atopic Dermatitis Immunotherapeutic*?

Answer: There are no recommendations or requirements on the label for Canine Atopic Dermatitis Immunotherapeutic* that mandate any specific monitoring tests or evaluations of any kind. However, it is good medical practice to monitor patients on any chronic therapy for a chronic or recurrent condition such as atopic dermatitis for continued response and possible side effects associated with therapy. If Canine Atopic Dermatitis Immunotherapeutic* is administered long term, annual examination of the patient and discussion of clinical response and any possible adverse effects should be conducted with the owner, and appropriate testing performed if indicated.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

33. Can circulating IL-31 levels in the blood be used as a diagnostic for atopic dermatitis?

Answer: In a study evaluating the role of IL-31 in canine pruritus, serum samples were collected from laboratory dogs, healthy client-owned dogs and client-owned dogs with naturally occurring atopic dermatitis (AD) and levels of IL-31 were measured. IL-31 levels were detectable in 57% of dogs with naturally occurring AD (≥ 13 pg/mL) but were below limits of quantification (<13 pg/mL) in normal, healthy laboratory or the client-owned animals.

Measuring circulating IL-31 levels may not be a reliable diagnostic as a large percentage of the animals with AD (43%) did not display detectable levels of IL-31 (<13 pg/mL). It was hypothesized that these animals may have had either circulating levels of IL-31 that were below the assay limits of detection or that the IL-31 levels were acting locally within target tissues and not released into circulation.

Source:

Reference: Gonzales AJ, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol.* 2013 Feb;24(1):48–53.e11-2.

***This product license is conditional. Safety and efficacy studies are in progress.**

EXTRA-LABEL USE

34. Is Canine Atopic Dermatitis Immunotherapeutic* safe to use in cats?

Answer: No. Canine Atopic Dermatitis Immunotherapeutic* is licensed for use only in dogs. Canine Atopic Dermatitis Immunotherapeutic* is a caninized anti-cIL-31 monoclonal antibody. When it was injected into cats the caninized mAb was highly immunogenic. 3/8 cats had large, persistent anti-mAb antibody responses.

Source:

Reference: Data on File, Study Report Nos. C481R-US-13-016, Zoetis Inc.

35. Can Canine Atopic Dermatitis Immunotherapeutic* be administered IV? IM?

Answer: No. Zoetis will only recommend use of Canine Atopic Dermatitis Immunotherapeutic* as per the label directions. The draft package insert states that caninized anti-cIL-31 mAb should be administered subcutaneously by injection. If the product is accidentally administered IV or IM the patient should be monitored for allergic or adverse reactions. Pre-clinical studies administering Canine Atopic Dermatitis Immunotherapeutic* IV were performed to determine such things as pharmacokinetics with no adverse effects noted. There is no data to suggest when the product can be re-administered after it has been administered IV or IM.

Source:

Reference: Canine Atopic Dermatitis Immunotherapeutic* conditional product package insert

36. Can Canine Atopic Dermatitis Immunotherapeutic* be administered orally?

Answer: No. Canine Atopic Dermatitis Immunotherapeutic* is a caninized anti-cIL-31 monoclonal antibody. Antibodies are proteins and therefore, if administered orally, will be degraded in the digestive tract before they can be absorbed.

Source:

Reference:

37. Can the contents of 2 vials be mixed in one syringe?

Answer: A single dose of Canine Atopic Dermatitis Immunotherapeutic* for dogs weighing more than 40 lb (18.1 kg) requires the full volume of TWO OR MORE 1-mL vials as indicated. The label states that the entire dose should be drawn into one syringe and administered as a single injection. If more than 1 vial is necessary, all of the product can be drawn into a single syringe.

Source:

Reference:

***This product license is conditional. Safety and efficacy studies are in progress.**

CONDITIONAL LICENSURE

38. What is a conditional license? How does it differ from a full license?

Answer: Veterinary biologics (such as a mAb like Canine Atopic Dermatitis Immunotherapeutic*) are regulated by the Center for Veterinary Biologics (CVB) in the Animal and Plant Health Inspection Service (APHIS), which is a branch of the USDA. In order for a veterinary biologic to be manufactured and sold, the company is required to attain 2 types of licenses; an establishment license and a product license, which are both granted by the CVB. Establishment licenses are only given when manufacturers are shown to have appropriate, inspected facilities and qualified persons to run the facilities.

Before the product license is issued, the biological must demonstrate:

- efficacy: the ability to produce the desired effect
- safety: no significant adverse events
- potency: confirms the product will be efficacious out to the end of the expiration date
- purity: freedom of extraneous agents

The USDA will grant conditional licenses to meet an emergency condition, limited market, local situation, or other special circumstance. The product must demonstrate the same safety and purity requirements as fully licensed products but only needs to have a “reasonable expectation” of efficacy.

The company must provide the following information in the application for a conditional license:

- proof from scientific journals or experts that there is urgent need in the field for the product
- evidence of a “reasonable expectation” of efficacy with data from studies of the product
- all requirements for safety and purity (same as fully licensed products)
- testing that shows consistency between batches of manufactured product (fully validated potency test may not be required)
- claim that is consistent with single-tier labeling rather than fully licensed product

Once a conditional license is granted, the company is expected to make progress toward completion of the full efficacy and safety data in order to obtain a full license. While under a conditional license, products may need additional authorization for distribution in each state. The product label must clearly state that the product license is conditional and no trade names may be used.

The USDA will grant a conditional license to Zoetis for Canine Atopic Dermatitis Immunotherapeutic*, a novel mAb therapy to help reduce clinical signs associated with atopic dermatitis in dogs. The USDA stated they would grant a conditional license for any company seeking to license such a product addressing the prevention of canine atopic dermatitis. During the conditional license, Zoetis will provide Canine Atopic Dermatitis Immunotherapeutic* to dermatology specialists and a small group of general practice veterinarians, which will allow Zoetis to gain experience with the product and help in the preparation for a full launch. This program will start during the second half of 2015 and continue until full license is received. Zoetis will work closely with the USDA to align expectations to secure a full license for this product, which is anticipated in 2016. Once full licensure is attained, Zoetis will make the product available to veterinarians nationwide.

***This product license is conditional. Safety and efficacy studies are in progress.**

For conditionally-licensed biologic products, purity and potency have been demonstrated, as has a reasonable expectation of efficacy.

Source:

Reference:

39. Since the Canine Atopic Dermatitis Immunotherapeutic* has a conditional license, are there any special instructions that I need to give to the dog owner?

Answer: The conditional license for Canine Atopic Dermatitis Immunotherapeutic* was granted by the USDA in July, 2015. For this conditionally-licensed biologic product, purity and potency have been demonstrated, as has a reasonable expectation of efficacy. Canine Atopic Dermatitis Immunotherapeutic* has been demonstrated to be safe and effective in helping decrease itching within one day and maintains efficacy for one month; dosing can be repeated monthly as necessary. The label information is not expected to change after the conditional license period while additional safety data is collected. There are no precautions or special instructions that need to be given to the owners of dogs with atopic dermatitis that are administered the product.

Source:

Reference:

CYT-00046

***This product license is conditional. Safety and efficacy studies are in progress.**