Lecture overview

- Introduction
- Dosage, administration, presentation
- Indications
- Mechanism of action
- Pharmacology
- Efficacy, safety, contraindications, cautions
- Monitoring
- Selection

Introduction

- The two “new kids on the block” for allergic dermatoses are oclacitinib (Apoquel™) and lokivetmab (Cytopoint®).
- These first-in-class medicines give veterinarians effective and safe additional options to customize atopic dermatitis treatment for canine patients.
- Though these treatments have similar indications, there are some substantial differences in their mechanism of action, administration, contraindications, safety profiles, and other details that require careful consideration when selecting them for different patients.
New therapies for use in dogs in Canada

Dosage, Administration, and Presentation

- **Apoquel™** is an orally-administered film-coated tablet containing oclacitinib maleate.
- It is available in 3 tablet strengths: 3.6 mg, 5.4 mg, and 16 mg.
- Marked with AQ and either S, M, or L on both sides.
- Non-flavoured tablets are scored in half for convenient dosing in dogs:
  - At least 12 months of age
  - Ranging from 3 to 80 kg
- Further division has not been evaluated.
- Packaged in bottles of 100 tablets.
- Administer orally at a dose of 0.4 to 0.6 mg/kg (according to the dosing table) q12h for up to 14 days followed by q24h for maintenance therapy.
- Can be given with or without food.
- Store at controlled room temperature between 20°C to 25°C.
Dosage, Administration, and Presentation

- Cytopoint® is a ready-to-use, sterile liquid containing lokivetmab.
- It is available in 1mL vials in four concentrations (10, 20, 30 or 40 mg).
- Packaged in a two-vial carton.
- Must be refrigerated. Store upright at 2°C to 8°C. Prolonged exposure to higher temperatures and/or direct sunlight may adversely affect potency. Do not freeze!
- Administer subcutaneously at a minimum dose of 2 mg/kg.
- For convenience, dosing tables may be used as a guideline.
- Repeat administration every 4-8 weeks as needed in individual patients.
- The product does not contain a preservative.
- Each vial is for single use only, and should be discarded after puncture.

Dosing tables

<table>
<thead>
<tr>
<th>Dog body weight (kg)</th>
<th>3.6 mg tablets</th>
<th>5.4 mg tablets</th>
<th>16 mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - 4.4</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 - 5.9</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>6 - 8.9</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 - 13.4</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13.5 - 19.9</td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>20 - 26.9</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>27 - 39.9</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>40 - 54.9</td>
<td></td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>55 - 80</td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
Dosing tables

Dogs weighing < 2.3 kg
Aseptically withdraw 0.2 mL/kg from a single, 10-mg (Sky) vial and administer subcutaneously.

Dogs weighing 2.3-18.1 kg
Aseptically withdraw the full volume of the appropriate vial according to the dosage table below and administer subcutaneously.

<table>
<thead>
<tr>
<th>Dog Body Weight (kg)</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (Sky)</td>
</tr>
<tr>
<td>2.3-4.5</td>
<td>1 vial</td>
</tr>
<tr>
<td>4.6-9.1</td>
<td></td>
</tr>
<tr>
<td>9.2-13.6</td>
<td></td>
</tr>
<tr>
<td>13.7-18.1</td>
<td></td>
</tr>
</tbody>
</table>

Dosing tables

Dogs weighing > 18.1 kg
A single dose requires a combination of vials, as outlined in the table below. Prior to administration, collect the number of vials indicated under each presentation according to the dog’s body weight. Aseptically draw the full volume from each vial into one syringe and administer subcutaneously as a single injection.

<table>
<thead>
<tr>
<th>Dog Body Weight (kg)</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (Sky)</td>
</tr>
<tr>
<td>18.2-22.7</td>
<td>1 vial</td>
</tr>
<tr>
<td>22.8-27.2</td>
<td></td>
</tr>
<tr>
<td>27.3-31.7</td>
<td></td>
</tr>
<tr>
<td>31.8-36.3</td>
<td></td>
</tr>
<tr>
<td>36.4-40.8</td>
<td>1 vial</td>
</tr>
<tr>
<td>40.9-45.4</td>
<td></td>
</tr>
<tr>
<td>45.5-49.9</td>
<td></td>
</tr>
<tr>
<td>50.0-54.4</td>
<td></td>
</tr>
<tr>
<td>54.5-59.0</td>
<td>1 vial</td>
</tr>
<tr>
<td>59.1-63.5</td>
<td></td>
</tr>
<tr>
<td>63.6-68.0</td>
<td></td>
</tr>
<tr>
<td>68.1-72.6</td>
<td></td>
</tr>
<tr>
<td>72.7-77.1</td>
<td>1 vial</td>
</tr>
<tr>
<td>77.2-81.6</td>
<td></td>
</tr>
<tr>
<td>81.7-86.2</td>
<td></td>
</tr>
<tr>
<td>86.3-90.7</td>
<td></td>
</tr>
</tbody>
</table>
Indications: Broad vs. Narrow

- BROAD: Apoquel™ is labelled for the control of pruritus associated with canine allergic dermatitis (atopic dermatitis, cutaneous adverse food reaction, flea allergy dermatitis, contact allergy). Short or long-term use.

- NARROW: Cytopoint® aids in the reduction of clinical signs of canine atopic dermatitis. Short or long-term use.

Neuroimmunology

- Pruritus is now understood to result from a complex interaction between the nervous system and the immune system.
- Pruritus results from stimulation of nonmyelinated nerve fibers located in the skin.
- Itch mediators stimulate receptors on itch-specific sensory neurons, which relay signals through the spinal cord to certain brain regions.
- Histamine does not have actually have a big impact!
What are cytokines?

- Cytokines are proteins produced by cells such as lymphocytes and keratinocytes.
- They are used 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 receptor it triggers specific intracellular signaling pathways, one of which is the JAK pathway.
- In the skin, cytokines regulate acute and chronic processes such as neuronal itch simulation and inflammation.

Cytokines involved in canine allergic skin disease

Review: Lymphocytes, cytokines, chemokines and the T-helper 1–T-helper 2 balance in canine atopic dermatitis

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Cytokines involved in canine allergic skin disease

Many cytokines implicated in canine allergic skin disease are secreted from activated T-lymphocytes. Each of these cytokines plays a specific role in the production of the clinical signs (pruritus and inflammation).

Interleukin-31 (IL-31)

- IL-31 is a recently identified cytokine implicated in pruritic skin conditions such as canine atopic dermatitis.
- IL-31 binds to a heterodimeric receptor complex. Upon ligand binding, signal transduction cascades such as the Janus kinase-signal transducer and activator of transcription (JAK/STAT) are activated.
- Interleukin-31 could be detected in >50% of serum samples in client-owned dogs with naturally occurring atopic dermatitis, but not in healthy dogs.
- Administration of IL-31 induced pruritus in laboratory beagles.

Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis

Janus kinase (JAK) enzymes

- There are 4 types of JAK enzymes: JAK1, JAK2, JAK3 and TYK2.
- JAK enzymes are attached to the intracellular region of cytokine receptors in various tissues in the body, including the skin and the nervous system.
- JAK1 is the isoenzyme form most closely associated with pro-allergic, pruritogenic and pro-inflammatory processes mediated by interleukins.
- Cytokine receptors occur in pairs, each corresponding to one of the 4 types of JAK receptors inside the cell.

![Diagram of cytokines and JAK enzymes](image)

Janus kinase (JAK) enzymes

- The name is taken from the two-faced Roman god of doorways *Janus*.
- JAKs possess two near-identical phosphate-transferring domains.
- One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first.
**JAK signaling pathway**

JAKs activate the intracellular proteins called Signal Transducer and Activator of Transcription (STAT) to induce gene transcription and biological responses.

**How does Apoquel™ work?**

**Selective JAK inhibitor (JAKi)**

Oclacitinib primarily inhibits JAK1 (the form of the isoenzyme involved in the action of cytokines associated with pruritus and inflammation) and JAK3, with minimal impact on JAK2 (the form of the isoenzyme associated with cytokines involved in hematopoiesis and innate immune function).

Not a systemic immunosupressant
Oclacitinib inhibits the activity of many cytokines (incl. IL-31)

Oclacitinib blocks the activity of pruritogenic and pro-inflammatory cytokines that utilize JAK 1/JAK3. Oclacitinib has both anti-pruritic and anti-inflammatory effects.

What are antibodies?

- Antibodies are Y-shaped proteins produced by mature B-cells (plasma cells).
- They are used by the immune system to identify and neutralize foreign substances.
- Five isotypes (classes) of immunoglobulins are recognized in mammals on the basis of their molecular weight and antigen binding capacity: IgA, IgD, IgE, IgG and IgM.
- Approximately 80% of all antibodies in humans and companion animals are of the IgG class.
**Antibody structure and epitope**

- All antibodies contain 2 heavy and 2 light chains.
- Each light chain contains 1 variable region and 1 constant region.
- Each heavy chain contains 1 variable region and 3 constant regions.
- An epitope is the region of an antigen that is recognized by the antibody.

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**What are monoclonal / therapeutic antibodies?**

- Monoclonal antibodies (mAbs) are a single pure homogeneous antibody preparation produced by a single lineage of B-cells.
- They all have the same sequence and recognize a single epitope.
- They can be designed to selectively bind different molecules to identify, neutralize or block their intended target.
- Biological therapy: therapeutic mAbs are used medically to block a patient’s soluble protein (e.g. a cytokine), a receptor on a cell, or infectious agents such as viruses or bacteria.
mAb nomenclature

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Target/Disease Infix</th>
<th>Source Infix</th>
<th>Suffix</th>
</tr>
</thead>
<tbody>
<tr>
<td>-k(l)-</td>
<td>interleukin</td>
<td>-o-</td>
<td>mouse</td>
</tr>
<tr>
<td>-l(l)-</td>
<td>immune system</td>
<td>-xi-</td>
<td>chimeric</td>
</tr>
<tr>
<td>-le(s)-</td>
<td>inflammatory lesions</td>
<td>-zu-</td>
<td>humanized</td>
</tr>
<tr>
<td>variable</td>
<td>-t(u)- tumor</td>
<td>-u-</td>
<td>human</td>
</tr>
<tr>
<td></td>
<td>-b(a)- bacterium</td>
<td>-vet-</td>
<td>veterinary</td>
</tr>
<tr>
<td></td>
<td>-f(u)- fungus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-v(l)- virus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WHO International Nonproprietary Names (INN)
United States Adopted Names (USAN)

What is lokivetmab?

- Lokivetmab is a “caninized” chimeric antibody.
- Only the antigen binding site is murine. The rest is canine.
- DO NOT USE IN CATS!
How does Cytopoint® work?

**Anti-IL-31 mAb**

Lokivetmab is a caninized monoclonal antibody, targeted specifically to a single cytokine: IL-31. It works by “soaking up” or neutralizing soluble circulating IL-31 produced by lymphocytes, preventing it from activating cell receptors and inducing pruritus.

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Absorption

- Apoquel™ has an ideal pharmacokinetic profile.
- Rapidly and well absorbed following oral administration in dogs.
- Average time to maximum plasma concentration ($T_{\text{max}}$) is < 1 hour.
- Terminal half-life ($t_{1/2}$) = 4.1 hours.
- High oral bioavailability (89%).
- Low protein binding (66.3%-69.7%).
- No significant impact of prandial state (can be given with or without food).

Mean oclacitinib plasma concentration - time profiles after IV and oral administration in dogs under fed and fasted conditions.
Metabolism

- Apoquel™ minimally inhibits cytochrome P450 isoenzymes therefore minimizing the potential for any clinically-relevant drug-drug interaction.
- Inhibitory concentrations (IC50s) are 50-fold greater than the observed maximum plasma concentration (Cmax) values at the labelled dose.

![In vitro inhibition of canine liver cytochrome P450 isoenzymes by oclacitinib.](image)

Clearance

- Major clearance route is metabolism with minor contributions from renal and biliary elimination.
- The main route of excretion is via the urine (51%), with a significant amount also excreted in the feces (38%).
- Transformed into one major metabolite, and several smaller metabolites.
- No accumulation.
Absorption and distribution

- Monoclonal antibodies have unique pharmacologic features.
- A subcutaneous injection deposits the mAb into the interstitial space.
- There is 50-100% bioavailability when the antibody is injected.
- The mAb is then transported out of the interstitial space into the bloodstream in one of several ways:
  - Via lymphatic circulation
  - Direct absorption into capillaries
  - By receptor-mediated cell uptake (endocytosis) and transfer to the bloodstream.
- mAbs are held in the bloodstream (low tissue distribution) by barriers to capillary diffusion and lymphatic transport back to the blood.
- In general, mAb targets are circulating in blood or on cell surfaces, not inside cells.

Catabolism and clearance

- mAbs are cleared from the body in several ways:
  - Through binding to their target
  - Via anti-mAb antibodies in circulation
  - By flow out of capillaries into the interstitial space, where they are taken up by cells.
- mAbs are catabolized (not metabolized) to peptides and amino acids within cells.
- mAbs that attach to the FcRn (Fc neonatal receptor) within the endosome are protected from catabolization and are recycled back into the blood or lymph which extends the half-life of the antibody.
- Hepatic and renal elimination is minimal. In a radiolabeled mAb study in mice, only 3.6% of the mAb was found in the liver, and 2-3% in the kidney.
- The kidneys can only filter molecules with a molecular weight cutoff of approximately 30-50 kDa, and mAbs, being large macromolecules, are not filtered.
mAbs are processed by the body through degradation

mAbs are recycled and reused by the body

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
## Apoquel™ vs. Cytopoint®

<table>
<thead>
<tr>
<th></th>
<th>Apoquel™</th>
<th>Cytopoint®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment type</strong></td>
<td>Traditional pharmaceutical (drug)</td>
<td>Biopharmaceutical (biological)</td>
</tr>
<tr>
<td><strong>Regulated by</strong></td>
<td>Health Canada</td>
<td>Canadian Food Inspection Agency (CFIA)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Small molecules</td>
<td>Large MW protein (macromolecule)</td>
</tr>
<tr>
<td><strong>Route/Frequency</strong></td>
<td>Oral Daily (short duration)</td>
<td>Injectable (SQ) Monthly or less often (long period of time)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Less targeted Blocks the activity of several cytokines</td>
<td>Single target Extreme specificity (IL-31 only)</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Intracellular (JAK enzymes)</td>
<td>Extracellular (circulating cytokine)</td>
</tr>
<tr>
<td><strong>Metabolism, clearance</strong></td>
<td>Hepatic, renal metabolism and elimination</td>
<td>Protein catabolism Minimal hepatic and renal elimination</td>
</tr>
</tbody>
</table>

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Dr. Vincent Defalque  
Diplomate of the American College of Veterinary Dermatology  
North West Veterinary Dermatology Services
Examples in human medicine

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>XELJANZ</td>
<td>Pfizer</td>
<td>JAK enzymes</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Xolair</td>
<td>Novartis</td>
<td>Immunoglobulin E</td>
<td>Allergic asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic idiopathic urticaria</td>
</tr>
</tbody>
</table>

Apoquel™ compared to placebo

299 client-owned atopic dogs, 18 practices
Apoquel™ compared to placebo for 4 weeks
Adverse effects reported
Study provides evidence of the effectiveness of oclacitinib compared to placebo

Source of funding:

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Apoquel™ compared to placebo

Visual analog scale (VAS) for placebo and oclactinib.
*Significant treatment difference at $P < 0.05$.

Adverse health events occurring in dogs in the placebo and oclactinib-treated groups.

<table>
<thead>
<tr>
<th>Adverse reactions observed during days 0–16 $^a$</th>
<th>Oclactinib $^{(n = 152)}$ [n (%)]</th>
<th>Placebo $^{(n = 147)}$ [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>7 (4.6)</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (3.9)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (2.6)</td>
<td>0</td>
</tr>
<tr>
<td>New dermal, epidermal or subcutaneous mass $^b$</td>
<td>4 (2.6)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (2.0)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>
Apoquel™ compared to prednisolone

123 client-owned allergic dogs, 12 practices
Apoquel™ compared to prednisolone 5 mg tablets (Delta-Cortef®, Zoetis) for 4 weeks
Adverse effects reported
Response in both treatment groups was rapid (4 hours)

Visual analog scale (VAS) for prednisolone and oclactinib.
*Significant treatment difference at $P < 0.05.$
Apoquel™ compared to prednisolone

<table>
<thead>
<tr>
<th>Abnormal clinical sign</th>
<th>Prednisolone-treated dogs (n=62; n%) (\uparrow)</th>
<th>Oclacitinib-treated dogs (n=61; n%) (\downarrow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyoderma, including folliculitis</td>
<td>6 (9.7)</td>
<td>6 (9.8)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3 (4.8)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Dermatohyposis</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1 (1.6)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Emesis</td>
<td>2 (3.2)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Lamelessness</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>3 (4.8)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Pruritus Intention</td>
<td>2 (3.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Adverse health events occurring in 2 or more dogs in the prednisolone and oclacitinib-treated groups.

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Apoquel™ compared to Atopica®

226 client-owned atopic dogs
Apoquel™ compared to Atopica® for 12 weeks
Adverse effects reported
Apoquel™ had a faster onset of action and less gastrointestinal side effects than Atopica®
Confidential Information - MARS INC.

Corneocyte

Visual analog scale (VAS) for ciclosporin and oclactinib.

*Significant treatment difference at $P < 0.05$.

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### Abnormal health events occurring in 2 or more dogs in the ciclosporin and oclactinib-treated groups.

<table>
<thead>
<tr>
<th>Abnormal health event</th>
<th>Ciclosporin (N=112) [n (%)]</th>
<th>Oclactinib (N=114) [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>49 (43.8)</td>
<td>16 (14.0)</td>
</tr>
<tr>
<td>Pyoderma</td>
<td>11 (11.7)</td>
<td>13 (11.4)</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>16 (14.3)</td>
<td>12 (10.5)</td>
</tr>
<tr>
<td>Unspecified skin lump</td>
<td>6 (5.4)</td>
<td>8 (7.0)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6 (5.4)</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Abnormal test result</td>
<td>3 (2.7)</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (15.2)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Fungal skin infection</td>
<td>4 (4.5)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Skin lesion NOS</td>
<td>5 (4.5)</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>9 (8.0)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>3 (2.7)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Erythema</td>
<td>5 (4.5)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Haematuria</td>
<td>3 (2.7)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>External parasite</td>
<td>2 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Urinary tract disorder NOS</td>
<td>2 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>6 (5.4)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Pinnal irritation</td>
<td>3 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Urinary bladder disorder NOS</td>
<td>3 (2.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

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Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
**Apoquel™ compared to Atopica®**

A retrospective study comparing the incidence of cutaneous histiocytoma development in atopic dogs treated with oclacitinib and ciclosporin

**E.J. HIGH, A.T.H. LAM, L. FERRER**

533 client-owned atopic dogs treated with Apoquel™
654 client-owned atopic dogs treated with Atopica®

Cutaneous histiocytoma development may be higher (2.6% versus 0.6%) in dogs treated with Apoquel™ compared to those treated with Atopica®.

Additional research is needed to determine a causal relationship and pathomechanisms between oclacitinib and cutaneous histiocytomas.

**Apoquel™ administration for > 6 months does not significantly increase incidence of malignancies**

Comparison of malignancies and nonmalignant skin masses in 339 allergic dogs receiving long-term (> 6 months) oclacitinib with age and breed matched control population

**B. LANCELLOTTI, J. ANGUS, H. EDGINTON, W. ROSENKRANTZ**

339 client-owned atopic dogs treated with Apoquel™ for > 180 days
321 client-owned allergic dogs NOT treated with Apoquel™

Minimum of 2 years of follow up or death/euthanasia within 2 years

Incidence of malignancies and skin masses in the oclacitinib group (16.2%, 57.2%, respectively) vs. controls (12.5%, 60.1%, respectively) not statistically different

Age of death in the oclacitinib group vs. controls not statistically different
Apoquel™ administration is not associated with increased risk of UTI or subclinical bacteriuria

**Veterinary Dermatology**

*Vet Dermatol 2017; 28: 485-e113*  
*DOI: 10.1111/vde.12450*

The frequency of urinary tract infection and subclinical bacteriuria in dogs with allergic dermatitis treated with oclacitinib: a prospective study

Andrew C. Simpson*, Jennifer R. Schissler*, Rod A.W. Rosychuk* and A Russell Moore+

47 client-owned atopic dogs  
Received Apoquel™ for > 180 days  
No lower urinary tract signs  
Negative urine bacterial cultures  
Gastrointestinal side effects noted in 7.3% of patients

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Cytopoint® compared to placebo

**Veterinary Dermatology**

*Vet Dermatol 2016; 27: 476-e129*  
*DOI: 10.1111/vde.12376*

A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis

Gina M. Michels*, Deborah S. Ramsey*, Kelly F. Walsh*, Olivier M. Martinon†, Sean P. Mahabir*, Jaqueline L. Hoovers*, Rodney R. Walters† and Steven A. Dunham†

211 client-owned atopic dogs, 15 practices  
A single Cytopoint® injection at 3 different dosages compared to placebo for 8 weeks  
Adverse effects reported  
Cytopoint® at minimum dose of 0.5 mg/kg reduced pruritus compared to placebo for at least 1 month  
Level and duration of response increased with increasing dose

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Cytopoint® compared to placebo

Visual analog scale (VAS) for placebo and lokivetmab.

*Significant treatment difference at $P < 0.05$.

Adverse health events occurring at least once in >2% of the placebo and lokivetmab-treated groups.
Cytopoint® compared to Atopica®

![Veterinary Dermatology](https://doi.org/10.1111/ede.12478)

A blinded, randomized clinical trial evaluating the efficacy and safety of lokivetmab compared to ciclosporin in client-owned dogs with atopic dermatitis

Hilde Moyaert*, Leen Van Brussel*, Stasie Borowski*, Monica Escalada*, Sean P. Mahabir†, Rodney R. Walters‡ and Michael R. Stegmann*  

| 274 client-owned atopic dogs, 40 practices, 4 countries | Monthly Cytopoint® injections compared to Atopica® for 12 weeks | Adverse effects reported | Cytopoint® is noninferior to Atopica® for pruritus reduction |

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Visual analog scale (VAS) for ciclosporin and lokivetmab.  
*Significant treatment difference at $P < 0.05$.  

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North West Veterinary Dermatology Services
Cytopoint® compared to Atopica®

<table>
<thead>
<tr>
<th>Study period</th>
<th>Ciclosporin (n = 132) [%]</th>
<th>Lokivetmab (n = 142) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0-D64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive tract disorders (65.3% versus 36.1% versus 19.8%)*</td>
<td>49 (37.1)</td>
<td>22 (15.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>47 (35.6)</td>
<td>19 (13.4)</td>
</tr>
<tr>
<td>Systemic disorders (12.9% versus 19.0% versus 8.6%)*</td>
<td>11 (8.3)</td>
<td>14 (10.9)</td>
</tr>
<tr>
<td>Lethargy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (3.8)</td>
<td>7 (4.9)</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Skin and appendage disorders (15.2% versus 16.3% versus 22.2%)*</td>
<td>10 (7.0)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Ectopic skin infection</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Dermatitis and eczema</td>
<td>6 (4.5)</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (6.8)</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (0.8)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0 (0.0)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders (8.3% versus 12.7% versus 12.4%)*</td>
<td>4 (3.0)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>4 (3.0)</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>External ear disorder NOS</td>
<td>1 (0.8)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Otitis NOS</td>
<td>1 (0.8)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Musculoskeletal disorders (0.8% versus 2.8% versus 3.7%)*</td>
<td>1 (0.8)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Lameness</td>
<td>1 (0.8)</td>
<td>3 (2.1)</td>
</tr>
</tbody>
</table>

Adverse health events occurring at least once in >2% of the ciclosporin and lokivetmab-treated groups.

Contraindications

▶ Apoquel™

Should not be given to dogs with known or suspected allergy or intolerance to oclacitinib maleate or any other components of this product.
Not for use in dogs less than 12 months of age.
Not for use in dogs with serious infections, evidence of immune suppression or evidence of malignant neoplasia.
Not for use in breeding dogs, pregnant or lactating bitches.

▶ Cytopoint®

DO NOT USE IN CATS
Cautions

▶ Apoquel™

Has not been evaluated:
- In dogs less than 3 kg.
- In combination with glucocorticoids, cyclosporine, or other immunosuppressive agents.

▶ Cytopoint®

Has not been tested in breeding dogs, pregnant or lactating bitches.

Monitoring

▶ Apoquel™

Rare development of leukopenia (neutropenia).
Complete blood count (for example at 2-3 months, at 6 months, then annually).
Occasional development of demodicosis and cutaneous histiocytoma.

▶ Cytopoint®

No monitoring necessary or recommended.
General considerations

- Apoquel™ and Cytopoint® work in ~70% of dogs.
- Lack of response to Apoquel™ does not mean Cytopoint® will not be effective, and vice-versa. It is a matter of trial and error.
- Work on allergic pruritus. Pruritus caused by other conditions such as infection may not respond.
- Anecdotally, may be less effective against the otitis component of allergy in some dogs.
- Not all-in-one miracle treatments. Must be used along with other elements of multimodal therapy such as infection and parasite control.

<table>
<thead>
<tr>
<th></th>
<th>Apoquel™</th>
<th>Cytopoint®</th>
</tr>
</thead>
</table>
| **Indication** | Control of pruritus associated with allergic dermatitis in dogs  
Control of atopic dermatitis in dogs | Aids in the reduction of clinical signs associated with atopic dermatitis in dogs |
| **Owner compliance** | Oral, once daily for maintenance | SQ injection, once every 4-8 weeks |
| **Owner preference** | Drug | Biological |
| **Age** | Dogs >1 year of age | Can be given to dogs of any age |
| **Contraindications** | Severe infections, neoplasia  
Immunocompromised patient | Can be given with any concurrent condition |
| **Caution** | Not studied with other immunomodulatory drugs | Can be given with any medication |

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General considerations

- Apoquel™ and Cytopoint® work in ~70% of dogs.
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- Not all-in-one miracle treatments. Must be used along with other elements of multimodal therapy such as infection and parasite control.

Identification and characterization of monoclonal antibodies targeting feline IL-31

T.J. Fleck*, G. Bammert*, S. Mahabir, C. Javens, B. Galvan, S. Steiniger, A. Gonzales*, S. Dunham*

*Veterinary Medicine Research and Development, Zoetis Inc., Kokomo, IN, USA

Abstract: The use of lokivetmab (Cytopoint®), a monoclonal antibody (mAb) targeting canine interleukin-31 (IL-31), for the treatment of canine allergic and atopic dermatitis has proven the therapeutic benefit of targeting IL-31 in canine disease. To evaluate the role of IL-31 in feline allergic and atopic dermatitis, we have generated monoclonal antibodies (mAbs) and speculated derivatives targeting feline IL-31. Each mAb was evaluated for its ability to bind feline IL-31 and inhibit IL-31-mediated signaling in a feline cell line. Several mAbs were found to bind and neutralize the function of feline IL-31. Here we present the affinity (sub nanomolar to low picomolar) and in vitro potency (IC50 = 3.7 – 15 ng/mL) of three progenitor antibodies and several speculated derivatives. We also explored the in vivo efficacy of one antibody in a feline model of IL-31-induced pruritus. In this model, eight cats per group were treated with either placebo or mAb (2 mg/kg, subcutaneously). Feline IL-31 was intravenously administered (1 mg/kg) prior to mAb administration and 7 days post mAb administration. Pruritic behavior was evaluated using a categorical scoring system in 1 min intervals over the course of 1 h after IL-31 injection. The results of this study demonstrated that a single 2 mg/kg subcutaneous dose resulted in statistically significant reduction of pruritus (P < 0.0001) for at least 1 week when compared to a placebo group administered mAb buffer. These data demonstrate the ability of anti-IL-31 antibodies to effectively inhibit IL-31-induced pruritus in a model of feline disease.

Sources of funding: Zoetis, Inc. funded this study.

Conflict of interest: The authors are employed by Zoetis, Inc.