

# APOQUEL - OCLACITINIB MALEATE

ALK TECHNICAL MEMO

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Apoquel® is the brand name of oclacitinib maleate, a drug produced by Zoetis that reduces itching in an average of 61% of dogs diagnosed with canine atopic dermatitis<sup>1</sup>. Apoquel® indirectly blocks the activity of interleukin-31 (IL-31), one of a dozen or more inflammatory mediators known to induce itch<sup>2</sup>. Produced by activated T<sub>H</sub>2 cells, IL-31 has been shown to induce pruritus in humans, dogs and mice<sup>3-5</sup>. Circulating IL-31 is detected in just over half (57%) of dogs with naturally-occurring atopic dermatitis<sup>6</sup>. IL-31 receptors are found on a wide variety of cell types and are abundant in dorsal ganglion root neurons, suggesting that IL-31 directly links T cell-mediated allergenic signals to sensory nerves responsible for the sensation of itch<sup>5,7</sup>.

IL-31 cannot enter the cell to induce itch without signaling assistance from a family of kinase enzymes. The Janus kinase (JAK) family has 4 members: JAK1, JAK2, JAK3 and TY2. JAKs transmit signals from IL-31 and other extracellular stimuli at the cell surface into the cell's nucleus, where transcription occurs and gene expression is regulated<sup>8</sup>. Many cytokines and growth factors rely on intracellular signal transduction mediated by JAK enzymes in order to function. Apoquel® blocks IL-31 activity by selectively targeting JAK1 (and JAK3 to a lesser extent), which transmits IL-31 signals in sensory nerve cells to the spinal cord and into the brain<sup>9</sup>. JAK signaling is vital to IL-31 activity, cell growth, immune cell differentiation, and also in protecting the body against infections and the formation of tumors, by supporting adaptive and innate immune responses<sup>8,9</sup>.

Apoquel® is FDA-approved for use in dogs aged 12 months or older<sup>1,10</sup>. It is contraindicated in dogs less than 1 year old, due to higher than acceptable levels of infections such as pneumonia, deep pyoderma and demodicosis<sup>10</sup>. Apoquel® is not approved for use in breeding, pregnant or lactating dogs, and should not be used in dogs with serious infections, due to increased susceptibility to infection as the result of immunosuppression by this drug.

Apoquel® is not approved for use in cats<sup>1,10</sup>.

Apoquel® formulated for oral use is available in 3.6, 5.4 and 16 mg tablets<sup>10</sup>. It is absorbed and metabolized within 4-6 hours and must be given daily to prevent a recurrence of symptoms. The approved protocol for this drug is twice daily administration for days 1-14, followed by once daily dosing thereafter<sup>10</sup>. Adverse events associated with Apoquel have been reported in approximately 5% of treated

dogs, and include vomiting, diarrhea, otitis, pyoderma, urinary tract infections and hyperlipidemia<sup>1,10</sup>.

Apoquel® has been shown to be an effective immunomodulatory drug for managing pruritus in atopic dogs. It is very useful for the short term management of acute flare ups, and has been shown to be effective for long-term use<sup>11</sup>. Use of this drug for extended periods to treat chronic atopic dermatitis should be accompanied by an awareness of the numerous ways that IL-31 affects atopy and innate immune responses. IL-31 affects regulation of the physical skin barrier in multiple ways that are incompletely understood<sup>12</sup>. It also stimulates the expression of anti-microbial peptides, which support innate immune responses in preventing bacterial growth on the skin<sup>12</sup>. This may explain why increased infection is observed as a side effect of Apoquel® use in some patients<sup>1,10</sup>.

Allergen-specific immunotherapy remains the safest option for the core treatment of atopy<sup>13</sup>. It is the only allergy treatment that improves symptoms by altering IgE-mediated immune responses to allergens, rather than by immunosuppressing the immune system or blunting clinical symptoms<sup>14,15</sup>. Apoquel® is an excellent adjunctive treatment method for managing pruritus in the initial stages of immunotherapy, during the 6-9 months before therapeutic immune system changes result in significant improvement in an affected dog's symptoms.

## Apoquel® FAQs

### Can a dog on Apoquel® therapy also be treated with ketoconazole or other azole-based parasiticides?

Yes. Apoquel® has little interaction with cytochrome P450 enzymes, which means that azole-based drugs are unaffected<sup>16</sup>.

### Can other immunosuppressive drugs, such as glucocorticoids and cyclosporine be co-administered with Apoquel®?

No. Safety of co-administration of Apoquel® with immunosuppressive drugs such as glucocorticoids and cyclosporine has not been evaluated for long-term use, and should be avoided. Short-term co-administration of Apoquel® and other immunosuppressive drugs should also be avoided, if possible<sup>16</sup>.

### What other drugs used to treat atopy are safe to use in combination with Apoquel®?

Apoquel® can be safely used with medications such as antibiotics and nonsteroidal anti-inflammatory drugs, and also with vaccinations.

### Does a dog being treated with Apoquel® require monitoring?

Yes. ACVD consensus from a 2015 NAVDF roundtable discussion recommends that a baseline complete blood count, serum chemistry profile and urinalysis be performed before starting the drug, repeated again in 30 to 60 days, and then, depending on the patient's age, every six to 12 months thereafter<sup>16</sup>. Zoetis also recommends that patients on Apoquel be monitored for infections and neoplasia<sup>10</sup>.

## References

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