Position Statement Regarding the Use of APOQUEL® (oclacitinib tablet) and the Risk of Neoplasia

This statement was drafted March, 2016, after consultation and with the help from a group of board-certified oncologists including Drs. Barbara Biller, Craig Clifford, Steven Dow, Ann Hohenhaus, Mary Klein, Cheryl London, Greg Ogilvy, Xuan Pan, and David Vail

No definitive causal relationship has been established between the administration of APOQUEL and the development of cancer in dogs.

- More than 1000 dogs were treated and actively monitored during the laboratory, field and continuation therapy studies, some for more than 2 years. The incidence of neoplasia as reported in literature suggests the incidence in the APOQUEL-treated dogs in the field and continuation therapy studies occurred no more frequently than that seen in the general population of dogs.
- Dogs with pre-existing, malignant neoplasia were not allowed to enroll in the studies conducted to support global registration. Thus, the relationship between APOQUEL and exacerbation of neoplasia has not been specifically studied.
- As suggested in available literature, the rate of neoplasia reported in the Continuation Therapy program in this middle-aged to older dog population (average age 9.3 years) was not greater than what would be expected in an aging population of dogs.
- Development of malignant neoplasia was not seen in the Target Animal Safety study where APOQUEL was administered to healthy, one-year-old Beagle dogs twice daily for 6 weeks, followed by once daily for 20 weeks, at 0.6 mg/kg (1X maximum exposure dose, 8 dogs), 1.8 mg/kg (3X, 8 dogs), and 3.0 mg/kg (5X, 8 dogs).
- Oclacitinib is not considered to have a mutagenic or genotoxic concern given the negative findings in a standard battery of tests required by VICH guideline GL23 (EMEA/CVMP/VICH/52600): two in vitro (a test for gene mutation in bacteria and a test for chromosomal effects in mammalian cells) and one in vivo (micronucleus assay).
- Carcinogenicity studies for oclacitinib were not conducted. The absence of carcinogenicity studies was justified on the basis that: oclacitinib was not mutagenic or genotoxic in a standard battery of tests; there were no proliferative changes in the 90-day oral rat toxicity study; and there were no structural alerts for carcinogenicity.

APOQUEL belongs to the immune modulating Janus kinase (JAK) inhibitor class of drugs, which exert their pharmacologic effect by modulating the activity of a variety of pruritogenic and proallergic inflammatory cytokines that drive intracellular signaling pathways. APOQUEL has been shown to modulate the activity of cytokines that utilize JAK 1 and JAK 3 enzymes. These effects should be considered when treating dogs with allergic skin disease. As such, it is good medical practice for the veterinarian to make an appropriate risk:benefit assessment for each individual patient when considering APOQUEL treatment based on the dog's current clinical condition, including the presence of existing neoplasms, history of past neoplastic conditions, tolerability of and/or response to other therapeutic interventions for, allergic dermatitis, and the impact on the quality of life of both the owner and the dog with the various therapeutic options.

Prescribing veterinarians and pet owners should consider the following:

- *Understanding how a class of drug exerts its pharmacologic effect*. For APOQUEL use in dogs, this is selective inhibition of JAK1 and JAK3 signaling pathways.

- *Noting reported adverse events observed with the drug during clinical field trials and post-marketing experience*.
- *Reviewing the animal safety studies in the target species.* For APOQUEL, the Target Animal Safety studies were conducted in one year old beagle dogs at 0.6, 1.8 and 3 mg/kg (8 dogs/group) for six months.
- *Noting the serious adverse events reported in treated dogs in the field safety and efficacy study, with the understanding that it is not always possible to establish a causal relationship to product exposure.* For APOQUEL, this includes 12 dogs, average age 9.3 years, of the 239 in the Continuation Therapy study that developed suspected or confirmed tumors after administration of APOQUEL for between 17 and 392 days.

APOQUEL is the first JAKi to be approved for use in dogs. Long term pharmacovigilance data will bring additional clarity on the causal relationship between product exposure and adverse events.

IMPORTANT SAFETY INFORMATION: Do not use APOQUEL in dogs less than 12 months of age or those with serious infections. APOQUEL may increase the chances of developing serious infections, and may cause existing parasitic skin infestations or pre-existing cancers to get worse. APOQUEL has not been tested in dogs receiving some medications including some commonly used to treat skin conditions such as corticosteroids and cyclosporines. Do not use in breeding, pregnant, or lactating dogs. Most common side effects are vomiting and diarrhea. APOQUEL has been used safely with many common medications including parasiticides, antibiotics and vaccines. See full Prescribing Information, attached.

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