Acceptance of Oclacitinib Maleate (Apoquel®) Chewable Tablets In Client-Owned Dogs With Allergic And Atopic Dermatitis.

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Abstract

Background: The oral acceptance of oclacitinib maleate (Apoquel®) chewable tablets administered twice daily for 7 days at the labeled dose range of 0.4-0.6 mg/kg was evaluated in 121 dogs treated at ten general practice veterinary clinics in the United States.

Results: Dogs that were enrolled in the study ranged were client-owned, from 1 to 14 years of age, weighed 3.7 to 60.7 kg, and required twice daily treatment with oclacitinib for allergic or atopic dermatitis. One hundred and twenty-one (121) dogs with 1,673 total dose administrations successfully completed the study and were included in the data summary. Out of a total number of 1673 administrations, 1533 (91.6%) were accepted voluntarily within 5 minutes, 134 (8%) were consumed with assistance (with food treats or by pilling) outside of the 5 minutes offering time and 6 (0.4%) doses were not consumed. The per dose percent acceptance rate for the 14 offered doses showed minimal variation ranging from 89.9% to 93.3%.

Conclusions: Client-owned dogs from the general veterinary patient population that required treatment with oclacitinib found the Chewable tablets to be very palatable and no aversion occurred with repeated dosing. Oclacitinib chewable tablets were well tolerated and is a palatable alternative to the film-coated tablet.

Background

Drug administration compliance can be a challenge with a patient not willing to consume the medication. Developing a palatable formulation enables the owner to administer the medication without the need to hide the item in food or treat item, or resort to “poking down” the medication increasing the risk of trauma and stress for both the owner and the pet. Development of a palatable, flavored, chewable formulation of medications that are approved for frequent administration is an approach commonly used by animal health companies to: (1) help pet owners ensure compliance; (2) reduce the stress on the pet and the pet owner associated with administering tableted formulations which can lead to a fracture in the owner-pet bond, and (3) make the overall medication experience more reminiscent of the pleasurable experience of giving the dog a treat. Examples extend across therapeutic categories and include monthly heartworm preventatives (e.g. Heartgard Plus), nonsteroidal anti-inflammatories (e.g. Rimadyl Chewables) and antiinfectives (Clavamox Chewable) among others.

Palatability is a product property, resulting in the product being pleasant or acceptable to taste. In veterinary medicine, this suggests that the product will be voluntarily consumed without the need to hide the product in a treat or food (cheese, bread etc). Palatability can be evaluated via one of two studies: acceptance or preference. In an acceptance study, the animal is offered the tablet for a set period of time and must consume the whole tablet within that time period (voluntary acceptance). For a product to be voluntarily consumed, the patient must spontaneously consume the product when offered from a bowl, the ground, or from the Owner’s hand(1). This can be used as a direct measurement of pet compliance. In

a preference study, two different dosage forms are offered simultaneously to the animal and the animal can choose which formulation to consume.

While the Federal Drug Administration Center for Veterinary Medicine (FDA CVM) does not provide criteria for a product to be considered palatable; in the European Union (EU), the Committee for Medicinal Products for Veterinary use (CVMP) “Guideline on the demonstration of palatability of veterinary medicinal products” defines a veterinary medicinal product to be palatable and hence allowing a palatability statement to be included in the Summary of Product Characteristics (SPC), if the voluntary acceptance rate in dogs within 2 minutes is at least 80% (2). The EU SPC of Apoquel Chewable (authorized in the EU on 13 December 2021) contains the palatability statement “Apoquel tablets are chewable, palatable and readily consumed by the majority of dogs” in the EU SPC.

Oclacitinib maleate is a Janus kinase (JAK)/ signal transducers and activators of transcription (STAT) inhibitor. Apoquel®, is approved globally for the control of pruritus due to allergic dermatitis and the control of atopic dermatitis in dogs. Inhibition of the JAK/STAT pathway results in the inhibition of IL-2, IL-4, IL-6, IL-13, and IL-31, pro-inflammatory cytokines associated with clinical signs of allergic and atopic dermatitis(3). The purpose of this study was to evaluate the acceptance of a chewable tablet containing oclacitinib maleate, a reformulated version of the original Apoquel® film-coated tablet, in client-owned dogs with allergic or atopic dermatitis.

Methods

This study was conducted as a non-randomized, unmasked, multi-centered clinical trial. Dogs were client-owned, and written informed consent was obtained prior to completion of any study activities. At the time of enrollment, dogs were at least 12 months of age, and weighed a minimum of 3.0 kg (6.6 lbs) and no more than 80.0 kg (175.9 lbs). The dogs were diagnosed with allergic dermatitis or atopic dermatitis and, per the Veterinarian, needed to receive Apoquel twice daily to manage clinical signs. Dogs with a diagnosed history or current diagnosis of malignant neoplasia, that were intended for breeding, pregnant or lactating, or had received Apoquel within 7 days prior to enrollment could not be enrolled in the study. A single blood sample for a complete blood count and serum biochemistry was collected to ensure dogs did not have any clinically significant clinical pathological abnormalities that would require withdrawal from study.

After enrollment, a minimum of 7 days of oclacitinib maleate chewable tablets were dispensed for administration twice daily at label dose. Dogs may have received up to 14 days if deemed appropriate by the Veterinarian. All doses were administered in the dog’s normal home environment. If additional medications were being administered on the same day as oclacitinib, the chewable tablets were to be administered first, and the owner was to wait a minimum of 30 minutes before any medications, treats, supplements or food was administered.

A 5-minute timer was started when the dog was given access to the chewable tablet(s). The entire dose was offered by placing the tablet(s) in the dog’s usual empty food bowl or in the palm/fingers of the

owner's hand. A single dose may have been comprised of more than one tablet. The tablet(s) was not broken, crumbled or crushed except for breaking a tablet in half as necessary to administer the correct dose (e.g., for dogs that require 0.5 or 1.5 tablets per dose). The owner observed the dog carefully during the whole five-minute period to assess whether the total dose was consumed. When the alarm timer sounded (indicating five minutes had elapsed) the owner recorded whether the dose was completely consumed or not. If the dog consumed the complete dose, it was recorded, and no further assessment was needed. If, while dosing the dog (within the five-minute assessment), the owner observed the dog vomiting, regurgitating or spitting out the tablet, the tablet was re-offered immediately either in the bowl or in the palm/fingers of the owner's hand. If necessary, a new tablet was offered. If the dose had not been completed consumed within the initial 5 minutes, the owner administered any unconsumed dose (or portion of the dose) to the dog, using either assisted administration (placing the dose in the dog's mouth or in the back of the dog's throat and closing the dog's mouth until the dose has been swallowed) or the dose may have been administered with food, treat or water. This additional offering ensured that the dog received the appropriate treatment for the underlying condition.

Data Summaries:

Data summaries were calculated (SAS/STAT User's Version 9.4, SAS Institute, Cary, NC). Hypothesis tests were not conducted for this study.

To evaluate overall voluntary acceptance, percentage of acceptance tests across the entire period of the study where the full dose of the product was voluntarily accepted, was computed for the 5-minute time period (Equation 1)

$$\frac{\text{Number of successful dosings}}{\text{Number of all dosings}} \times 100$$

Equation 1

The percentage of doses administered to the dogs via 'assisted administration (pilling) or treat' past the 5-minute voluntary intake period, was calculated (Equation 2).

$$\frac{\text{Number of dosings administered as assisted administration (pilling) or treat}}{\text{Number of all dosings}} \times 100$$

Equation 2

The percentage of doses that could not be administered to the dogs even with 'assisted administration (pilling) or treat', was calculated (Equation 3).

$$\frac{\text{Number of dosings that could not be administered}}{\text{Number of all dosings}} \times 100$$

Equation 3

The percentage of dogs that voluntarily accepted the dose at all 14 administrations, 13 administrations, 12 administrations etc. was also calculated.

Frequency distributions of breed, sex, and spayed/neutered were calculated. Descriptive statistics for age and initial body weight (mean, standard deviation, minimum and maximum) were calculated.

Results

A total of 121 dogs were enrolled in the study. Demographics are reported in Table 1. Out of total number of 1673 administrations, 1533 (91.6%) were accepted voluntarily within 5 minutes, 134 (8%) were consumed with assistance (with food treats or by pilling) outside of the 5 minutes offering time and 6 (0.4%) doses were not consumed (Table 2). Dogs did not appear to develop an aversion to the tablets over time, the 5-minute acceptance was 93.3% for the first dose and 91.6% for the last dose. The 5-minute acceptance at each dosing ranged from 89.9% - 93.3% (Table 3).

Table 1
Demographics of enrolled dogs

Breed	Age (yrs)	Weight (kg)	Sex	
Purebred n= 71; Crossbred n = 50	1-14	3.7-60.7	Female (n= 53)	spayed n = 50; intact n = 3
			Male (n = 68)	neutered n = 57; intact n = 11

Table 2
Summary of Average Acceptance

Acceptance Rate	Total Number	Overall Rate
Overall Voluntary Acceptance within 5 minutes	1533	91.6%
Overall Consumption with Assistance*	134	8.0%
Overall Non-consumption	6	0.4%
* if after the dog did not fully consume the offered dose within 5 minutes the remaining tablet(s) were administered in food, treat or by pilling		

Table 3
Average Voluntary Acceptance over Time

AM				PM		
Day	Number Consumed	Number of Doses	Voluntary Acceptance Rate (%)	Number Consumed	Number of Doses	Voluntary Acceptance Rate (%)
0	111	119	93.3	110	121	90.9
1	109	120	90.8	109	120	90.8
2	111	120	92.5	112	120	93.3
3	111	120	92.5	110	119	92.4
4	110	119	92.4	108	119	90.8
5	107	119	89.9	107	119	89.9
6	109	119	91.6	109	119	91.6

A summary of the number and percent of dogs that accepted 14 doses, 13 doses, 12 doses etc., to those dogs that did not accept any of the tablet(s) offered for five minutes is reported in Table 4. Ninety-nine dogs (81.8%) of dogs consumed all 14 doses voluntarily within 5 minutes, while 5 dogs (4.1%) did not voluntarily consume any of the offered doses within 5 minutes.

Table 4
Number of Times an Animal Voluntarily Consumed the Dose

Number of Times Dose Fully Consumed	All	
	n	%
0	5	4.1
1	1	0.8
3	1	0.8
4	1	0.8
6	2	1.7
7	1	0.8
8	2	1.7
9	2	1.7
10	1	0.8
11	1	0.8
13	5	4.1
14	99	81.8
All	121	100.0

Nine abnormal health events were observed in 6 dogs during the study. Adverse events included gastrointestinal upset (diarrhea, vomiting, and flatulence), lethargy, and one case of joint pain and lameness. Two dogs were withdrawn from the study due to an abnormal health event, one case of diarrhea and one case of an acute exposure. The enrolled dog, and potentially her housemate, consumed 50 tablets after gaining access to the chewable tablets. Follow-up did not report any adverse events due to the acute exposure.

Discussion

The overall voluntary acceptance within 5 minutes of offering of oclacitinib chewable tablets administered twice daily for 7 days was 91.6% in 121 client owned dogs with allergic or atopic dermatitis. The per dose percent acceptance rate for the 14 offered doses showed minimal variation ranging from 89.9–93.3%, indicating that no aversion occurred with repeated dosing. There is no research regarding the impact of dosing compliance on owner satisfaction and improvement in condition. In a human study assessing the compliance of patient who took their lipid-lowering medication reports that patient who received 75% or more of their prescribed medication reduce their risk from any cause by a third compared

to those who took their medication less than 75% of the time(4). In veterinary medicine, compliance is further complicated if the patient is reluctant to consume the medication. The use of palatable formulations therefore helps to improve compliance by decrease stress for both the owner and their pet, strengthening the human-animal bond, while ensuring the animal receives the appropriate treatment.

Abbreviations

CVMP	Committee for Medicinal Products for Veterinary use
EU	European Union
FDA CVM	Federal Drug Administration Center for Veterinary Medicine
JAK/STAT	Janus kinase/ signal transducers and activators of transcription
Kg	Kilogram
Lbs	pounds
SPC	Summary of Product Characteristics

Declarations

Ethics approval and consent to participate: The protocol was approved by Zoetis Ethical Review Board. Informed Owner Consent was obtained prior to any study activities occurring.

Consent for publication: All authors have reviewed the manuscript and consent to publication of the provided manuscript and associated tables.

Availability of data and material: No raw data beyond summarized tables in manuscript will be provided.

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Authors' contributions: Marike Visser and Laura Caneva wrote the manuscript and Marike Visser, Kelly Walsh and Vickie King prepared all tables. Marike Visser, Kelly Walsh, Gordon Sture and Vickie King designed and executed the study. All authors reviewed the manuscript.

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