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Safety of the Selective JAK1 Inhibitor Oclacitinib in Dogs

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ABSTRACT

Apoquel(oclacitinib maleate) as a film-coated tablet, a selective Janus kinase (JAK)1 inhibitor, was approved by the United States Food and Drug Administration (FDA) in 2013 for the control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age. The goal of this review is to describe the safety of oclacitinib in dogs based on data from investigational laboratory and field studies, independent directed studies, and an extensive postmarketing pharmacovigilance (PV) surveillance program. The safety of oclacitinib has been extensively evaluated in investigational and independent studies. In the oclacitinib postapproval PV surveillance, the types and rank order of frequency of reported adverse events were similar to the premarketing field studies, with diarrhea, anorexia, and lethargy being the most frequently reported adverse events. In the postmarketing PV continuous monitoring, adverse events for patients receiving oclacitinib are rarely reported and the individual clinical signs within the PV adverse event reports were considered "very rare" in frequency. An age- and breed-matched retrospective cohort study in dogs with allergic dermatitis showed no significant difference in incidence of neoplasia between dogs treated with oclacitinib and dogs treated with other systemic therapies. The extensive investigational and PV experience with oclacitinib shows that long-term or lifelong use per label instructions has a positive benefit–risk profile and is not associated with any cumulative safety risk.

1 | Introduction

Allergic and atopic dermatitis are common skin conditions and are causes of pruritus in dogs, affecting approximately 10%–15% of the canine population (Hillier and Griffin 2001). According to the American Veterinary Medical Association (AVMA), skin disorders and allergies were the third and fourth most commonly reported health issues by dog-owning households in the United States, respectively, in 2016 (*AVMA pet ownership and demographics sourcebook* 2017–2018). In a recent news article by the largest provider of pet health insurance in the United States, canine atopic or allergic dermatitis was the number one medical condition for which a claim was filed by pet health insurance members in 2022 (Nationwide Mutual Insurace Company n.d.).

Allergic and atopic dermatitis have a multifactorial basis, in which specific pro-inflammatory cytokines have significant roles. Cytokines are small protein molecules involved in intercellular communications that affect the behavior of nearby cells by binding to cell surface receptors (Borish and Steinke 2003). Numerous cytokines act through the JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway to induce biological effects by regulating gene transcription and expression (Hu et al. 2021; Rusinol and Puig 2023). The JAK/STAT pathway is evolutionarily conserved and includes 4 types of JAK enzymes (JAK1, JAK2, JAK3, and TYK2) that are recruited in pairs to the cytoplasmic portion of the cytokine receptor (Figure 1) (Hu et al. 2021; Rusinol and Puig 2023; Gonzales et al. 2013). The various pairings of JAK enzymes are illustrated in Figure 1.

In the early 2000s, pharmaceutical companies were developing JAK/STAT inhibitors for the treatment of human T-cell mediated inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, and psoriasis (Hu et al. 2021). Concurrently, researchers at Pfizer Animal Health (now Zoetis) were investigating treatments for T-cell mediated inflammatory diseases in animals, hypothesizing that inhibition of JAK1 may have therapeutic (safety and efficacy) advantages over other T-cell inhibitors, such as steroids and cyclosporine, the latter of which had recently been approved for the treatment of canine atopic dermatitis (U.S. Food and Drug Administration n.d.-a). Research showed that the pathophysiology of pruritus in dogs is a multifactorial process, with pro-inflammatory cytokines being a key contributor to itching (Gonzales et al. 2013; Marsella et al. 2012). The JAK1 enzyme was shown to play a key role in the signaling of pro-inflammatory, pro-allergic, and pro-pruritogenic cytokines, including interleukin (IL)-2, IL-4, IL-6, IL-12, and IL-31 (Figure 1) (Gonzales et al. 2013, 2014; Marsella et al. 2012). The JAK2, JAK3, and TYK2 enzymes are important mediators of hematopoiesis (JAK2 and JAK3) and proinflammatory signaling (JAK3 and TYK2) (Hu et al. 2021; Rusinol and Puig 2023). JAK2 inhibitors are being developed for hematologic disorders (Hu et al. 2021), JAK3 inhibitors for inflammatory and autoimmune disorders such as rheumatoid arthritis (Hu et al. 2021), and TYK2 inhibitors for inflammatory diseases such as psoriasis and psoriatic arthritis (Rusinol and Puig 2023). Oclacitinib, a selective JAK1 inhibitor, was developed to treat pruritus associated with allergic and atopic dermatitis in dogs (Hu et al. 2021). Apoquel (oclacitinib maleate) as a film-coated tablet was approved by the United States Food and Drug Administration (FDA) in 2013 for the control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age (U.S. Food and Drug Administration 2013) and by the European Medicines Agency (EMA) also in 2013 for the treatment of pruritus associated with allergic dermatitis and treatment of clinical manifestations of atopic dermatitis in dogs 12 months of age and older (European Medicines Agency n.d.-a).

Prior to the introduction of oclacitinib, the main pharmaceuticals used in the treatment of canine allergic and atopic dermatitis were systemic glucocorticoids and cyclosporine (Olivry and Baumer 2015; Olivry et al. 2010, 2003). Their clinical utility was limited because of their short– and long–term adverse events among other factors (Olivry and Baumer 2015; Olivry et al. 2010, 2003). In clinical trials of client-owned dogs, oclacitinib administration resulted in rapid onset of efficacy, with relief from itching within 24 h after the first oral dose (Cosgrove et al. 2013a) and a

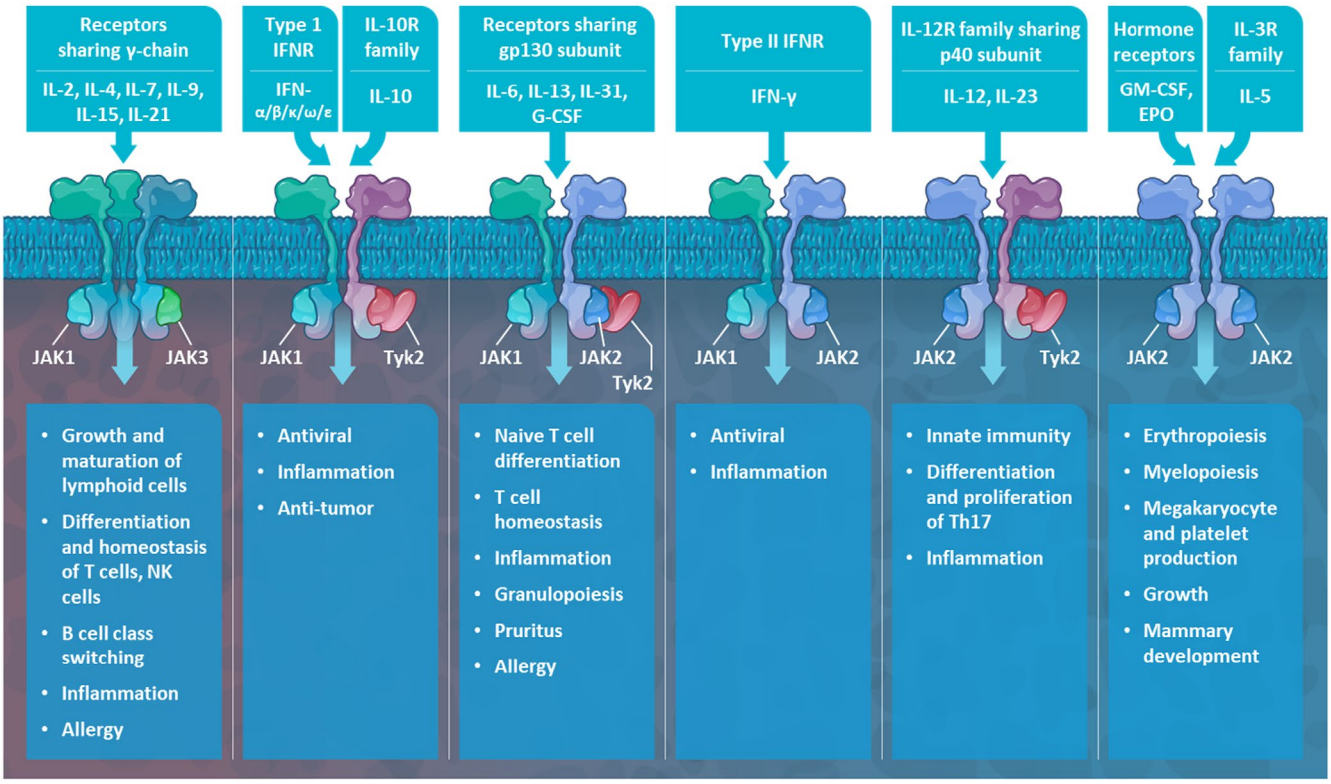

FIGURE 1 | Schematic representation of cytokine cell surface receptor families and associated receptor complexes that utilize intracellular JAK enzymes for signaling. The functional responses to receptor complex activation are listed. Many of the cytokines involved in allergy, inflammation, and pruritus bind to receptor complexes that utilize JAK1 as one of the obligate JAK partners. Oclacitinib was shown to inhibit JAK1-dependent cytokines involved in allergy, inflammation, and pruritus (IL-2, IL-4, IL-6, IL-13, and IL-31) (Hu et al. 2021; Rusinol and Puig 2023; Gonzales et al. 2013, 2014; Marsella et al. 2012). EPO, Erythropoietin; G-CSF, Granulocyte colony-stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; gp, Glycoprotein; IFN, Interferon; IFNR, Interferon receptor; IL, Interleukin; JAK, Janus kinase; NK, Natural killer cell; R, Receptor; Th, T helper cell; Tyk, Tyrosine kinase. EPO: Erythropoietin; G-CSF: Granulocyte colony-stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; gp: Glycoprotein; IFN: Interferon; IFNR: Interferon receptor; IL: Interleukin; JAK: Janus kinase; NK: Natural killer cell; R: Receptor; Th: T helper cell; Tyk: Tyrosine kinase.

faster onset of action compared to cyclosporine (Little et al. 2015). Veterinary patient studies also showed that the efficacy of oclacitinib in controlling canine pruritus is comparable to oral cyclosporine (Little et al. 2015) and oral prednisolone (Gadeyne et al. 2014), with continued efficacy of oclacitinib shown for up to nearly 2 years in one clinical trial (Cosgrove et al. 2015). Since its introduction, oclacitinib has been readily adopted for the management of canine allergies (American Veterinary Medical Association n.d.). Oclacitinib has become the most prescribed animal health therapeutic in the United States (American Veterinary Medical Association n.d.; Barron's n.d.), with veterinarians having treated over 15 million dogs with oclacitinib in the last 11 years (Zoetis n.d.-a, Zoetis n.d.-d).

This review describes the safety profile of oclacitinib in dogs. The safety of oclacitinib in dogs has been evaluated in premarketing laboratory and field studies (U.S. Food and Drug Administration n.d.-b, n.d.-c) as well as in independent-directed studies (Gotthelf 2017; Simpson et al. 2017) and postmarketing PV monitoring (Woodward 2009).

2 | Oclacitinib Pharmacology and Safety From Investigational/Independent Studies

Cytokine receptors can be grouped according to the types of JAKs that are recruited to the receptor complexes. Many cytokines involved in allergy, inflammation, and pruritus bind receptor complexes that utilize JAK1. For example, IL-2 and IL-4 bind receptor complexes that recruit JAK1 and JAK3, IL-6 and IL-13 bind receptors that engage JAK1, JAK2, and tyrosine kinase (TYK)2, and IL-31 will engage receptors that activate JAK1 and JAK2 (Gonzales et al. 2014). Dysregulation of cytokines that utilize the JAK1 enzyme has been implicated in atopic dermatitis and allergic skin disease (Gonzales et al. 2014).

Oclacitinib inhibits JAK1-dependent cytokines involved in inflammation and allergy (IL-2, IL-4, IL-6, and IL-13) as well as pruritus (IL-31), with minimal effects on cytokines that do not depend on JAK1 (Gonzales et al. 2014; Rugg et al. 2014). Oclacitinib plasma concentrations at higher than labeled dosing were considered to inhibit JAK2-dependent cytokines such as granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), IL-12 and IL-23, which are involved in hematopoiesis and the innate immune response (Marsella et al. 2023). Twice daily oral dosing of oclacitinib (0.6 mg/kg) for up to 14 days resulted in oclacitinib plasma levels that were above the threshold required to inhibit JAK1-dependent cytokines by 50% (IC_{50}). These plasma levels were also below the IC_{50} for JAK2-dependent cytokines (Figure 2), but were found to have an inadequate safety margin for long-term maintenance dosing. Switching after 2 weeks to a once-daily oclacitinib (0.6 mg/kg) maintenance regimen resulted in plasma concentrations below the IC_{50} for JAK2-dependent cytokines, but above the IC_{50} for JAK1-dependent cytokines for part of the day (Marsella et al. 2023). Once-daily oclacitinib dosing still provided good efficacy and a margin of safety between the inhibition of proinflammatory cytokines involved in the disease process versus those involved in normal functions such as hematopoiesis (Marsella et al. 2023). This points to both the relative selectivity of oclacitinib for JAK1-dependent cytokines and the chosen dosing interval as being contributing factors in the safety profile of oclacitinib when used in the broader patient population.

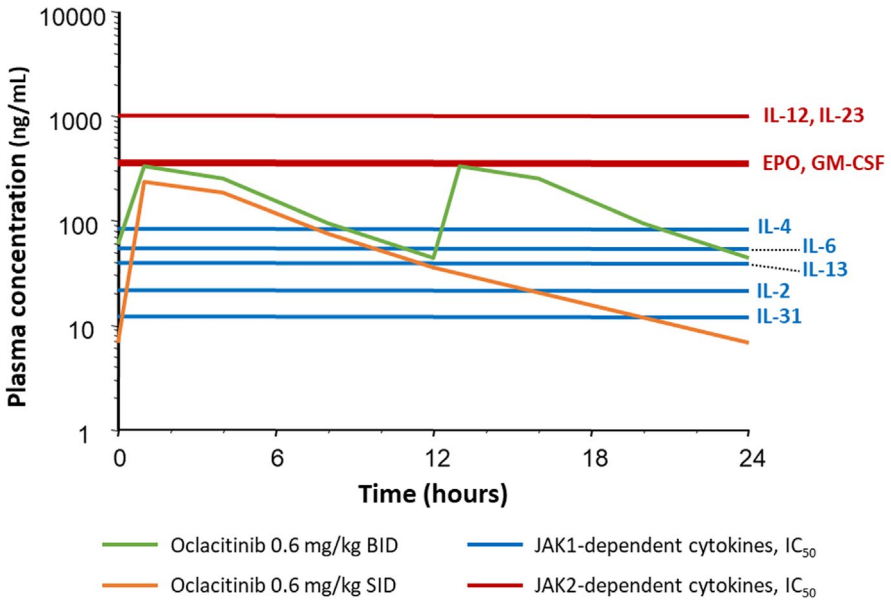

FIGURE 2 | Relationship between oclacitinib plasma concentration in dogs and inhibition of cytokine function. Oclacitinib (oral tablet) was administered once-daily (SID) or twice-daily (BID). JAK1-dependent cytokine IC_{50s} (plasma concentration required to inhibit cytokine activity by 50%) are shown in blue and JAK2-dependent cytokine IC_{50s} are shown in red. Oclacitinib at the recommended dose and regimen generates plasma concentrations that preferentially inhibit pruritogenic and pro-inflammatory JAK1-dependent cytokines while not inhibiting JAK2-dependent cytokines involved in hematopoiesis and immune function (Marsella et al. 2023). BID, Twice (two times) a day; EPO, Erythropoietin; GM-CSF, Granulocyte macrophage colony-stimulating factor; IC_{50}, Plasma concentration required to inhibit cytokine activity by 50%; IL, Interleukin; JAK, Janus kinase; SID, Once a day.

In assays measuring ex vivo T-cell proliferation, time above inhibitory concentration was the primary predictor of oclacitinib toxicity. This finding translated to safety evaluations, where the frequency of oclacitinib administration was shown to be as important as individual dose and total daily dose in producing toxicity (Zoetis n.d.-b). Exploratory in vitro and in vivo data demonstrated reversibility of oclacitinib primary and secondary pharmacology, except in cases where secondary effects of oclacitinib overdose-related immunosuppression were associated with systemic infections such as irreversible bacterial pneumonia and generalized demodectic mange infections (Zoetis n.d.-b).

Well-controlled efficacy and safety evaluations based on the above understanding of JAK biology and pharmacology were conducted to measure the investigational drug's effects across a range of doses. Data from in vitro, pharmacology and pharmacokinetic studies with oclacitinib (Gonzales et al. 2014; U.S. Food and Drug Administration n.d.-b; Rugg et al. 2014; Collard et al. 2014) were used to design larger-scale investigative in vivo studies showing dose titratability (U.S. Food and Drug Administration 2013; U.S. Food and Drug Administration n.d.-c), reversible primary pharmacology (Zoetis n.d.-b), consequences of persistent overdosing (U.S. Food and Drug Administration n.d.-b), a safety margin (Malpas et al. 2013), and clinical safety of the therapeutic dosage (Cosgrove et al. 2013a, 2015, 2012, 2013b, 2013c, 2013d).

Safety findings from the oclacitinib investigational laboratory and field studies supported the initial approval and label for oclacitinib (U.S. Food and Drug Administration 2013), and are summarized in the Center for Veterinary Medicine (CVM) Freedom of Information Summary (U.S. Food and Drug Administration n.d.-c), the US Food and Drug Administration (FDA) label (U.S. Food and Drug Administration 2013), and the European Medicines Agency's (EMA) European Public Assessment Report (EPAR) Annex 1: Summary of Product Characteristics (European Medicines Agency n.d.-a) for oclacitinib. Common to all laboratory studies with oclacitinib was the diligence of ensuring that assigned doses were administered at each scheduled time, with results showing predictable and dose-titratable changes in clinical pathology results for the immune and hematological systems (U.S. Food and Drug Administration n.d.-b). At supra-pharmacologic dosages of oclacitinib, where some instances of secondary demodicosis and bacterial pneumonia manifested, nonfatal cases showed gradual spontaneous recovery (Zoetis n.d.-b). In oclacitinib field studies (each conducted with the eventual approved dose), some of the adverse reactions such as diarrhea, anorexia, and lethargy, occurred at a slightly higher numeric frequency in oclacitinib-treated dogs versus negative controls and were not unusual for this patient population (U.S. Food and Drug Administration n.d.-b, n.d.-c). Additional adverse reactions with oclacitinib were listed due to their potential clinical significance, but the overall low frequency of these adverse reactions was too low to determine whether numeric differences between oclacitinib-treated and control groups were clinically meaningful. Independent-directed studies have subsequently been performed with oclacitinib. A single-arm, single-site study (Gotthelf 2017) of 13 client-owned dogs with otitis externa and allergic skin disease showed that coadministration of oclacitinib and enrofloxacin/silver sulfadiazine otic drops for 14 days was effective for the management of otitis externa in dogs with allergic skin disease, with no adverse events reported. A prospective, observational, single-center study (Simpson et al. 2017) of 55 client-owned dogs without a history of urinary tract disease or predisposition to urinary tract infections (UTIs) showed that administration of oclacitinib for 58–280 days (mean 195 days) did not lead to bacterial growth in any urine sample cultures. This finding is in contrast to the established risk of UTIs associated with cyclosporine and glucocorticoids (Ihrke et al. 1985; Peterson et al. 2012; Torres et al. 2005).

Risks of neoplasia with oclacitinib have previously been noted in the literature with a personal experience from an author of "...several young dogs receiving oclacitinib developing fast-growing histiocytomas...", but did not determine that oclacitinib was causal (Marsella et al. 2023). In a field study of 283 dogs receiving oclacitinib, histiocytomas developed in 3.9% of dogs (Cosgrove et al. 2013b). In contrast, an age- and breed- matched retrospective cohort study (Lancellotti et al. 2020) of 660 dogs found no differences in the cumulative incidence of masses or malignancies (including mast cell tumors and histiocytomas) between dogs with allergic dermatitis treated with oclacitinib for $\geq$6 months versus dogs with allergic dermatitis treated with other systemic therapies (e.g., glucocorticoids, cyclosporine, allergen-specific immunotherapy, or antihistamines). In this cohort study, 19 (5.6%) histiocytomas were detected in the oclacitinib-treated group compared with 14 (4.4%) in the control group ($p = 0.464$). The relative risk of histiocytoma for dogs who received oclacitinib compared with dogs who did not was not statistically significant (relative risk 1.3; 95% CI, 0.7 to 2.5) in this study (Lancellotti et al. 2020).

3 | Safety From Pharmacovigilance (PV) Continuous Monitoring

In the field of veterinary medicinal products (VMPs), PV is defined as the detection and investigation of the effects and the use of these products related to safety and efficacy in animals and safety in people exposed to the veterinary products (European Medicines Agency 2013). Participants involved in the veterinary PV process include pet owners, veterinarians, drug and device manufacturers, and regulatory authorities (World Organisation for Animal Health n.d.). Postmarketing PV monitoring involves multiple processes (Table 1) (European Commission n.d.; Beninger 2018) and is a primary mechanism for ensuring that the product label accurately summarizes a product's safety and efficacy profile (StatPearls Publishing n.d.). Postmarketing PV builds upon investigational information of a product by monitoring during long-term usage, with the possibility of identifying previously unrecognized sensitive sub-populations, discovering previously unknown pharmacology or pharmacologic interactions, and clinical, cultural, social, or environmental factors, any of which might become recognized as important to product usage. Although PV reporting is voluntary and data collected from PV monitoring require fundamentally different summarization and interpretation methods compared to investigational data, PV profiles eventually become the definitive reference for safety of a VMP in real world use because PV profiles reflect massive numbers of patients treated over long periods of time. Postapproval monitoring and analysis by product manufacturers

TABLE 1 | Primary components of the pharmacovigilance process (European Commission n.d.; Beninger 2018).

- Collection and management of drug safety data
- Safety data analysis for detection of "signals" (any new or changing safety issue)
- Safety data evaluation and decision- making regarding safety issues
- Pro-active risk management with the objective to minimize any potential associated risks
- Developing a safety profile for medically appropriate use of a new molecular entity and appropriate communication of safety information to all categories of relevant stakeholders
- Attending to surveillance activities through a set of signal management processes
- Monitoring the product through collaborative activities with manufacturing professionals

and regulatory agencies identify unexpected adverse events and other safety concerns that may arise with wider or longer-term use than noted clinical studies. The results of this review and analysis lead to updates in various sections of product labeling to ensure that veterinarians and pet owners are aware of new risks, usage guidelines, or additional contraindications beyond the initially approved labeling.

Product labels for VMPs can differ significantly between countries due to varying regulatory frameworks and local requirements. Each country or region has its own guidelines specifying what information must be included on the label or in the Summary of Product Characteristics. These guidelines cover key product details, such as composition, indications, and dosage, as well as safety information, the inclusion of reported adverse events which may include frequency or incidence rates, and updates to the risk benefit of product administration (European Medicines Agency 2013; World Organisation for Animal Health n.d.; European Commission 2009; European Commission n.d.; US Food and Drug Administration n.d.-a; European Medicine Agency n.d.; US Food and Drug Administration n.d.-e). Regulatory agencies make efforts to harmonize pharmacovigilance guidance with each other where regulations and industry guidelines allow.

In PV, adverse events are defined as undesirable or unintended events, symptoms, or disease that occur after use of a VMP (off- or on-label), regardless of causal relationship (European Medicines Agency 2013). Accumulation, categorization, and mathematical analysis of adverse event reports according to accepted PV procedures eventually reveals a PV profile that describes the relative proportions of each adverse event category. Once a PV profile has been established, it tends to remain stable over time. Monitoring the PV profile over time permits comparisons of the adverse events between different time intervals and with reference populations. Where individual signals are considered relatively disproportionate and follow-up suggests that the PV signal is drug-related, then the label can be updated if appropriate (Woodward 2009).

For oclacitinib, individual PV reports have been accumulated on an ongoing basis globally since its initial marketing approval in 2013. Each report has been summarized using a standardized format (European Commission 2009) (Table 2), using Veterinary Dictionary for Drug Related Affairs (VeDDRA) terminology (European Medicines Agency n.d.-b; European Medicines Agency 2023). The VeDDRA system is organized as a 4-level hierarchical structure, with the highest level being system organ class, followed by high level term, preferred term, and low level term at the lowest level (European Medicines Agency 2023). VeDDRA terminology has been applied to clinical, laboratory, and other findings from the individual PV case reports with oclacitinib (U.S. Food and Drug Administration n.d.-b; Khan et al. 2023; Zoetis n.d.-c).

A recently disclosed PV profile for oclacitinib summarizes adverse events for 2 time periods (2013 to 2020 and 2016 to 2021) (Table 3) (European Commission 2009; Khan et al. 2023; Zoetis n.d.-c; The European Agency for the Evaluation of Medicinal Products (Veterinary Medicines and Inspections) n.d.). The frequency of adverse event reports in the oclacitinib PV program was estimated using a standardized calculation method (European Medicines Agency n.d.-c). An estimated >91 million dogs received a standard treatment with oclacitinib (based on an average 20 kg dog and dosed for 28 days per label [0.4–0.6 mg/kg twice daily for 14 days and 0.4–0.6 mg/kg once daily for 14 days]) and 21,867 adverse events were reported to Zoetis (regardless of causal relationship), producing an adverse event frequency of 0.025% (2.5 per 10,000 treated animals) (Khan et al. 2023; Zoetis n.d.-c). This adverse event frequency is considered "rare" per European Commission definition (≥1/10,000 to <1/1000; between 1 and 10 reacting animals per 10,000 treated animals; Table 2) (European Commission 2009). Given that the frequency of adverse events combined was "rare", the frequency of any individual clinical sign was considered "very rare" (<1/10,000; Table 2) and none of the events indicated a previously unrecognized safety issue. Each of the time periods includes a large number of adverse event reports, with types of adverse events in both time intervals markedly similar and reported with similar frequencies, indicating a mature PV profile.

As expected, the 0.025% estimated frequency of adverse events for oclacitinib based on voluntary PV reporting is much lower (2 orders of magnitude) than frequencies reported in the investigational clinical trials, where each case was audited to ensure that all adverse events were captured. Voluntary adverse event reporting in PV is well known to be much lower and more variable than mandatory adverse event reporting in clinical trials. Pharmacovigilance data often follows a pattern over time known as the "Weber effect", which describes a high number of adverse event reports occurring in the first 2 years postregulatory approval and declining and subsequent stable rate of adverse event reports thereafter, often due to a reduction of reporting of clinically mild or trivial reactions (Weber 1987). It is likely that when a new VMP enters the market, users tend to report the first several adverse events, but as their familiarity and comfort level with the drug increases, they tend not to file additional reports unless an adverse event is unexpected,

TABLE 2 | Definitions of assessment of adverse reaction causality and frequency in pharmacovigilance reporting (European Commission 2009; The European Agency for the Evaluation of Medicinal Products (Veterinary Medicines and Inspections) n.d.).

Assessment of adverse reaction causality		
Category	**Assessment**	**Criteria**
A	Probable	• A reasonable association in time between the administration of the drug and onset and duration of the reported event • Description of the clinical phenomena should be consistent with, or at least plausible, the known pharmacology and toxicology of the drug • There should be no other equally plausible explanation(s) for the case
B	Possible	Causality is possible and plausible, but the data did not meet the criteria for inclusion on Category A
O	Unclassified	Cases where insufficient information was available to draw any conclusion
O1	Inconclusive	Cases where other factors prevent a conclusion from being drawn, but a product association cannot be discounted
N	Unlikely to be drug related	Cases where sufficient information was available and where investigation has established this beyond reasonable doubt
Assessment of adverse reaction frequency		
Grouping		Frequency (number of animals with adverse reaction/number of animals treated)
Very common		≥1/10
Common		≥1/100 to <1/10
Uncommon		≥1/1000 to <1/100
Rare		≥1/10,000 to <1/1000
Very rare		<1/10,000
Not known		Frequency cannot be estimated from the available data

TABLE 3 | Frequency of adverse reactions reported from pharmacovigilance monitoring of oclacitinib (U.S. Food and Drug Administration n.d.-b; Khan et al. 2023; Zoetis n.d.-c) using VeDDRA terminology (European Medicines Agency n.d.-b; European Medicines Agency 2023) during two time periods. The frequency of each adverse reaction was considered "very rare" (<1 animal reacting/10,000 animals treated) (Khan et al. 2023; Zoetis n.d.-c). Adverse reactions are listed in decreasing frequency of reporting, from top to bottom. The left column lists the 10 most commonly reported adverse reactions during a 6-year period (2016–2021) in terms of causality ("Probable" and "Possible"). The right column lists adverse reactions reported during an 8-year period (2013–2020) irrespective of causality (U.S. Food and Drug Administration n.d.-b).

Causality probable or possible (reported in the period 2016–2021) (Khan et al. 2023; Zoetis n.d.-c)	**Reported to FDA/CVM regardless of causality (reported in the period approximately 2013–2020) (U.S. Food and Drug Administration n.d.-b)**
Emesis	Emesis
Diarrhea	Lethargy
Lethargy	Anorexia
Suspected lack of efficacy or partial efficacy	Diarrhea
Anorexia	Elevated liver enzymes
Papilloma	Dermatitis (crusts, pododermatitis, pyoderma)
Leukopenia	Seizures
Aggression	Polydipsia
Neutropenia	Demodicosis
Skin Disorder NOS	

Abbreviations: CVM, Center for Veterinary Medicine; FDA, Food and Drug Administration; NOS, not otherwise specified.

unusual, severe, or otherwise exceptional. The "Weber effect" was first described in the literature in 2004 in connection with human PV data (Hartnell and Wilson 2004). It is not thought to be as pronounced or always consistently recognized, likely because of a large increase in the volume of adverse event reporting and a concerted communications effort by the FDA to increase awareness regarding the utility of postmarketing adverse event reporting (Hoffman et al. 2014). Interestingly, the frequency of PV reporting for oclacitinib in a number of global markets including the US, followed a typical "Weber effect" pattern (European Medicines Agency n.d.-d; US Food and Drug Administration n.d.-d).

4 | Oclacitinib US Label

The initial label for a newly-approved VMP is based on data from the investigational studies in a research and development program. After a VMP's approval and introduction into the market, its product label is expected to evolve over time as the product is used in a broader patient population of naturally-affected animals. The study designs in the investigational program are intended to demonstrate the effects of the investigational VMP in healthy laboratory animals under highly controlled conditions and in clinical field trial cases where patients are screened to ensure and enroll veterinary patients which have no or stable comorbidities so as not to interfere with safety and effectiveness of product use. Evolution of a label's contents over time provides additional insights into the degree to which the disease process and the VMP's pharmacology were originally understood, and the extent to which the investigational data collected in the research and development program were predictive of clinical usage of the marketed product in real world applications.

The addition of postapproval PV experience to a product label is a standard regulatory policy of the US CVM, with label changes expected to be made when sufficient PV data have accumulated to reveal a representative PV profile. For oclacitinib, the original US label (May 14, 2013) (U.S. Food and Drug Administration 2013) was updated in December 2020 (U.S. Food and Drug Administration n.d.-b). In this updated label, after having monitored postmarketing adverse events for 7 years, no changes were made to the "Precautions" section. The "Warnings" section in the most recent version contains additional statements regarding modulation of the immune system, observations of new neoplastic (benign and malignant) conditions, a patient-level risk/benefit recommendation, and a procedural note recommending storage of oclacitinib in a secure location to prevent accidental ingestion or overdose as well as a new section, "Post-Approval Experience", which summarizes adverse events of any cause that were observed concurrently with the use of oclacitinib (the label does not state causality) and reported during the PV monitoring process (Table 4) (U.S. Food and Drug Administration 2013; U.S. Food and Drug Administration n.d.-b). The adverse events listed in the "Post-Approval Experience" section of the current oclacitinib label (Table 4) (U.S. Food and Drug Administration n.d.-b) had been recognized in the oclacitinib investigational program and reported in the original label (U.S. Food and Drug Administration 2013). Interestingly, including causality (probable or possible) in the evaluation of PV reports during the period 2016–2021 had relatively little impact on the frequency (from highest to lowest) of adverse events reported (Table 3).

5 | Discussion

Oclacitinib was approved by the US FDA on May 14, 2013 for the control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age and by the EMA on September 12, 2013 for the treatment of pruritus associated with allergic dermatitis and treatment of clinical manifestations of atopic dermatitis in dogs (U.S. Food and Drug Administration n.d.-b). The safety profile of oclacitinib at the time of initial regulatory approval was based on investigational studies. Since that time, the safety of oclacitinib has been examined through independent studies and by PV monitoring and adverse event reporting, resulting in over 10 years of experience in dogs under conditions of use. During the 6-year period from 2016 to 2021, an estimated > 91 million dogs received a standard treatment with oclacitinib[1], with an estimated frequency of adverse events of 0.025%, which is considered "rare", with a "very rare" rate of any individual adverse event (European Commission 2009). The PV profile of oclacitinib during this time period did not reveal any previously unrecognized safety issues. The PV safety profile of oclacitinib also did not indicate any concerns related to the objectives of independent investigations (otitis externa, neoplasia, etc.) described in Section 2 of this review.

Licensing and initial clinical usage of any new therapeutic class of drugs that target a disease process not already understood involves the potential for discovering unique subpopulations and previously unknown pharmacology of the drug. Investigational efficacy and safety studies are tailored to the major foreseeable conditions of clinical usage, but it is not possible for studies involving hundreds of animals to reflect the conditions of usage that occur with tens of millions of cases, across diverse cultural, social, and other environments. For products intended for chronic administration, even trials as long as 1 year in duration may not reveal all consequences of lifelong treatment. For these and other reasons, many regulatory authorities require implementation of postmarketing PV monitoring programs for veterinary (European Medicines Agency 2013; US Food and Drug Administration n.d.-a) and human products (European Medicine Agency n.d.; US Food and Drug Administration n.d.-e).

The utility of drug safety data recorded in a PV program differs from safety data recorded in research studies in several ways. For example, in a PV program, the causal relationship between an adverse event and a drug is difficult to ascertain because of the uncontrolled environment of PV reporting. Thus, adverse events recorded in a PV program should be interpreted differently from research studies. With appropriate analyses, PV data can inform clinical decision making and help to ensure that VMP safety labeling remains current. Over time, since PV reporting essentially reflects all conditions of clinical usage, properly managed and interpreted PV data eventually become the definitive reference for safety of a VMP in a real-world setting.

The combination of investigational-phase results, PV profile, and additional supporting information from independent

TABLE 4 | Comparison of the current (2020) and original (at-launch) oclacitinib label (US FDA/CVM) contents (U.S. Food and Drug Administration 2013; U.S. Food and Drug Administration n.d.-b).

Label Section	Contents at launch (2013) (U.S. Food and Drug Administration 2013)	Contents in current label (2020) (U.S. Food and Drug Administration n.d.-b)	Basis for change
Warnings	Not for use in dogs less than 12 months of age Not for use in dogs with serious infections May increase susceptibility to infection, including demodicosis, and exacerbate neoplastic conditions	No change No change No change [new points added] APOQUEL modulates the immune system New neoplastic conditions (benign and malignant) were observed in dogs treated with APOQUEL during clinical studies and have been reported in the postapproval period Consider the risks and benefits of treatment prior to initiating APOQUEL in dogs with a history of recurrent serious infections or recurrent demodicosis or neoplasia Keep APOQUEL in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose	NA NA NA Clarifications of existing data
Precautions	Not for use in breeding dogs, or pregnant or lactating bitches Not evaluated in combination with glucocorticoids, cyclosporine, or other systemic immunosuppressive agents Patients should be monitored for the development of infections, including demodicosis, and neoplasia	No change No change No change	NA NA NA
PostApproval Experience (2020)	[new section added]	The following adverse events reported in dogs are listed in decreasing order of reporting frequency. Vomiting, lethargy, anorexia, diarrhea, elevated liver enzymes, dermatitis (i.e., crusts, pododermatitis, pyoderma), seizures, polydipsia, and demodicosis Benign, malignant, and unclassified neoplasms, dermal masses (including papillomas and histiocytomas), lymphoma and other cancers have been reported Death (including euthanasia) has been reported	Data recorded in the pharmacovigilance process after launch. Statement in the label: "The following adverse events are based on postapproval adverse drug experience reporting for APOQUEL. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data"

Abbreviations: CVM, Center for Veterinary Medicine; FDA, Food and Drug Administration; NA, not applicable.

studies allow for a comprehensive description of the safety profile of oclacitinib in dogs. The overlapping types of adverse events in the investigational studies and PV program suggest that the adverse event profile of oclacitinib was well-defined at the time of regulatory approval. Furthermore, PV reporting of oclacitinib suggests that the investigational studies had utilized the biological safety endpoints and specific observations that comprehensively characterized oclacitinib's safety profile in dogs. In the postapproval PV surveillance program, the estimated frequency of adverse events was lower than in the

investigational studies. However, the types of adverse events reported in PV surveillance were the same rank order of frequency as in investigational studies. The markedly lower frequency of adverse events and appearance of some new adverse events in PV are as expected. The relatively few adverse events considered to have "probable" or "possible" VMP causality based on individual case reviews in the PV program suggest that many of the adverse events listed in the "Post-Approval Experience" section of the current oclacitinib US label are typical findings in the population of dogs with atopic/allergic dermatitis.

A chewable form of oclacitinib (Apoquel Chewable) was introduced to the market in 2023 (U.S. Food and Drug Administration 2023) to optimize compliance and improve the ease of administration of oclacitinib in dogs requiring long-term therapy. The safety of the chewable form of oclacitinib was established by pharmacokinetic data comparing oclacitinib film-coated tablets to oclacitinib chewable tablets (U.S. Food and Drug Administration 2023). Pharmacovigilance reports are being collected for this newly introduced chewable formulation and comprehensive analysis of these data is not available at this time due to the limited time in the market. However, pharmacologically, the chewable product appears to have a similar PV safety and efficacy profile to the original oclacitinib film-coated tablet as would be expected as the active ingredient, oclacitinib, is the same, the only differences between the products are the excipients.

On September 19, 2024, the US FDA approved an additional animal health JAK inhibitor. Zenrelia (ilunocitinib) (U.S. Food and Drug Administration 2024) has the same indication for use as Apoquel: to control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age. However, ilunocitinib is categorized by the U.S. FDA as a non-selective Janus kinase (JAK) inhibitor and includes additional safety concerns related to vaccine safety and risk of infections as noted in the Dear Veterinarian Letter regarding important safety information associated with the use of Zenrelia (ilunocitinib tablets) for controlling pruritus associated with allergic dermatitis and atopic dermatitis in dogs published by the U.S. FDA (FDA n.d.). Elanco, the manufacturer of Zenrelia, includes important safety information on their Zenrelia product information website (Elanco n.d.) for users to read the entire package insert before using this drug, including the Boxed Warning due to warnings listed by the U.S. FDA related to vaccine induced disease and inadequate response to vaccines (FDA n.d.).

6 | Conclusions

Oclacitinib, a JAK1 selective inhibitor, has become widely used in the treatment of allergic and atopic dermatitis in dogs since it was first marketed in 2013. To date, extensive PV reporting for oclacitinib has not revealed any unusual effects in demographic subgroups, rare pharmacologic effects, consequences of atypical metabolism, toxicity, or other unforeseeable outcomes when used as directed. Furthermore, important new information, not discernible at the time of the oclacitinib investigational program, is that long-term or lifelong usage of oclacitinib does not incur any cumulative safety risk different to what is already understood. The constancy of adverse event categories over time shows that oclacitinib was thoroughly characterized during the investigational stage of development. The desired and undesired effects of oclacitinib usage are clinically manageable. The risk/benefit profile for oclacitinib at the level of individual patients remains positive. Due to the novelty of the new oclacitinib chewable formulation, its PV profile is not yet known, but is not expected to be different from the PV profile of the original oclacitinib film-coated tablet.

Author Contributions

S.M.N., M.J.K. and J.M. contributed to the design, the analysis of the results and to the writing and editing of the manuscript.

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Conflicts of Interest

Steven M. Nederveld: current employee of Zoetis. Matthew J. Krautmann: previous employee of Zoetis (retired); has served in the past year as a paid consultant for Zoetis. John Mitchell: current employee of Zoetis.

Data Availability Statement

This manuscript does not report original results of a clinical trial or secondary results of clinical trial data. All references can be provided upon request to the corresponding author.

Animal Welfare Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as no animals were used.

Endnotes

[1] Based on an average 20 kg dog and dosed for 28 days per label (0.4–0.6 mg/kg twice daily for 14 days and 0.4–0.6 mg/kg once daily for 14 days).

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