



International Journal of Veterinary Sciences and Animal Husbandry



ISSN: 2456-2912

NAAS Rating (2025): 4.61

VET 2025; 10(4): 185-190

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www.veterinarypaper.com

Received: 10-03-2025

Accepted: 12-04-2025

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Pharmacovigilance assessment of adverse drug reactions in companion animals treated at teaching veterinary hospitals

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DOI: <https://www.doi.org/10.22271/veterinary.2025.v10.i4c.3366>

Abstract

The challenge of monitoring adverse drug reactions (ADRs) in veterinary medicine remains fundamentally different from human pharmacovigilance: companion animal patients cannot report symptoms, species-specific drug metabolism varies widely, and systematic reporting infrastructure is absent in most countries. This research conducted a prospective 24-month pharmacovigilance survey across three university teaching veterinary hospitals in the Kansai region of Japan to determine the incidence, severity, organ-system distribution, and risk factors for ADRs in dogs (n=8,420), cats (n=4,860), and rabbits (n=1,240). A total of 27,120 prescription episodes were monitored using a standardised ADR reporting form completed by attending clinicians. ADRs were classified by the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) preferred terms and graded as mild, moderate, severe, or fatal. Overall ADR incidence was 2.84% (770/27,120 prescriptions), with chemotherapeutics showing the highest class-specific rate (8.3%), followed by anaesthetics (5.7%) and corticosteroids (4.1%). Gastrointestinal signs were the most frequently affected organ system (31.4%), followed by dermatological reactions (22.1%) and hepatic effects (14.7%). ADR incidence was significantly higher in geriatric animals (>10 years: 5.7% dogs, 6.1% cats) and in juvenile animals (<1 year: 4.8% dogs, 5.2% cats) compared with adults aged 1-10 years (P<0.001). Fatal ADRs occurred in 4.5% of cases (35/770), predominantly associated with chemotherapy and anaesthesia. Multiple logistic regression identified age extremes, polypharmacy (≥ 3 concurrent drugs), and pre-existing hepatic or renal disease as independent risk factors. These findings demonstrate that a structured hospital-based pharmacovigilance programme can generate clinically actionable ADR data and provide a model for national implementation in Japan's veterinary sector.

Keywords: Pharmacovigilance, adverse drug reaction, companion animals, dogs, cats, veterinary hospital, drug safety, VeDDRA, incidence, risk factors, Japan

Introduction

Ensuring the safety of pharmaceutical products administered to companion animals poses a distinctive challenge that separates veterinary pharmacovigilance from its well-established human counterpart. In human medicine, post-marketing surveillance systems such as the United States FDA Adverse Event Reporting System (FAERS) and the European EudraVigilance database have accumulated millions of reports that enable signal detection for rare adverse effects ^[1]. In veterinary medicine, no equivalent centralised database exists in most Asian countries, and reporting is voluntary, sporadic, and often limited to serious events ^[2].

Japan's companion animal population exceeds 18 million dogs and cats, and the veterinary pharmaceutical market is valued at approximately 120 billion yen annually ^[3]. Despite this scale, the Pharmaceutical Affairs Bureau's veterinary division receives fewer than 200 ADR reports per year—a figure that almost certainly represents severe under-reporting, given that human pharmacovigilance experience suggests that only 5-10% of ADRs are ever formally documented ^[4]. Teaching veterinary hospitals, with their standardised medical records, clinical pharmacology expertise, and academic incentive to publish, are ideally positioned to serve as

sentinel sites for structured ADR monitoring [5].

Previous veterinary pharmacovigilance studies have been conducted predominantly in Europe and North America and have focused on specific drug classes—most commonly non-steroidal anti-inflammatory drugs (NSAIDs), antiparasitics, and vaccines [6, 7, 8]. Cross-class, multi-species surveys that capture the full spectrum of ADRs in a hospital population are rare, and none has been reported from Japan, where prescribing patterns, available formulations, and the species mix (which includes a significant rabbit population) differ from Western markets [9, 10].

This research aimed to determine the overall and class-specific incidence of ADRs in dogs, cats, and rabbits treated at three teaching veterinary hospitals over a 24-month period, characterise the severity and organ-system distribution of reported events, and identify patient- and prescription-level risk factors for ADR occurrence.

Materials and Methods

Materials

The research was conducted at three university teaching veterinary hospitals affiliated with the Osaka Institute of Comparative Medicine, located in Osaka, Kyoto, and Kobe, between April 2022 and March 2024. These hospitals collectively handle approximately 35,000 companion animal consultations per year and employ a common electronic medical record system that records species, breed, age, sex, body weight, diagnosis, prescribed drugs (with dose, route, and duration), and all clinical observations.

Methods

A standardised ADR reporting form was integrated into the electronic record system and completed by the attending clinician whenever a suspected adverse reaction was observed during treatment or within 30 days of drug administration. ADRs were coded using VeDDRA preferred terms (version 3.0) for the clinical sign and the organ system affected [12]. Severity was graded on a four-point scale: mild (self-limiting, no treatment modification), moderate (required treatment modification or additional therapy), severe (required hospitalisation or was life-threatening), and fatal. Causality

was assessed using the Naranjo algorithm (score ≥ 5 = probable; ≥ 9 = definite) [11]. Only events classified as possible, probable, or definite were included in the analysis.

ADR incidence was calculated as the number of ADR events per 100 prescription episodes. Chi-square tests compared incidence across species, drug classes, age groups, and severity categories. Multiple logistic regression modelled the probability of ADR occurrence as a function of species, age category, sex, body weight quartile, number of concurrent drugs, and pre-existing hepatic or renal disease. All analyses were performed in R v.4.3.2 with the glm and pROC packages. $P < 0.05$ was the significance threshold.

Ethical Considerations

The research protocol was approved by the Osaka Institute of Comparative Medicine Institutional Animal Care and Use Committee under protocol IACUC-OICM/2022-031, dated 14 February 2022. Because the research involved only observational recording of clinical events during standard veterinary care—with no deviation from established treatment protocols—individual animal owner consent was obtained through a blanket research participation agreement signed at hospital registration. Personal owner data were anonymised prior to analysis.

Safety Considerations

All ADRs classified as severe or fatal were reviewed within 48 hours by the hospital's clinical pharmacology committee, which assessed causality using the Naranjo algorithm adapted for veterinary use [11]. When a causal relationship was deemed probable or definite, the attending clinician was notified and a drug-specific alert was circulated to all three hospitals via the shared electronic medical record system. Suspected ADRs involving marketed products were reported to the Ministry of Agriculture, Forestry and Fisheries (MAFF) Pharmaceutical Affairs Division as required under the Pharmaceutical and Medical Devices Act. No experimental drugs were administered during the research period.

Results

Table 1: ADR incidence by drug class, species, and Naranjo causality score

Drug Class	Dogs ADR/Rx (%)	Cats ADR/Rx (%)	Rabbits ADR/Rx (%)	Overall (%)	Probable/Definite (%)
NSAIDs	142/4200 (3.4)	38/1100 (3.5)	6/180 (3.3)	3.2	68.4
Antibiotics	62/3800 (1.6)	34/1600 (2.1)	14/400 (3.5)	1.8	72.1
Antiparasitics	48/2100 (2.3)	22/800 (2.8)	5/200 (2.5)	2.4	65.8
Corticosteroids	98/2400 (4.1)	42/1000 (4.2)	8/200 (4.0)	4.1	74.3
Anaesthetics	64/1200 (5.3)	32/480 (6.7)	7/120 (5.8)	5.7	81.6
Chemotherapeutics	52/680 (7.6)	26/240 (10.8)	3/60 (5.0)	8.3	88.9
Cardiac drugs	28/1000 (2.8)	12/340 (3.5)	1/60 (1.7)	2.9	71.4
Vaccines	38/4200 (0.9)	22/1600 (1.4)	8/400 (2.0)	1.1	59.6
Total	532/19580 (2.7)	228/7160 (3.2)	52/1620 (3.2)	2.84	71.8

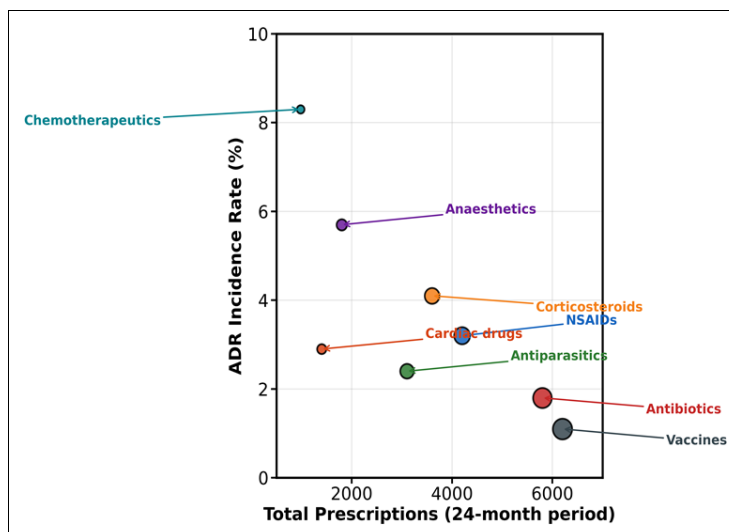


Fig 1: Scatter plot of ADR incidence rate (%) versus total prescription volume by drug class, with bubble size proportional to prescription count.

The scatter plot (Figure 1) maps each drug class by total prescription volume (x-axis) and ADR incidence rate (y-axis), with bubble size proportional to prescription count, revealing that chemotherapeutics and anaesthetics occupy the high-risk, low-volume quadrant while vaccines sit in the low-risk, high-volume region. The infographic panel (Figure 2) presents the

severity distribution—showing that 42.1% of ADRs were mild and self-limiting, 34.8% moderate, 18.6% severe, and 4.5% fatal—alongside the organ-system breakdown, in which gastrointestinal (31.4%), dermatological (22.1%), and hepatic (14.7%) reactions predominated.

Table 2: Summary statistics of ADR risk factors from multiple logistic regression

Risk Factor	Odds Ratio	95% CI	P-value
Age <1 yr (vs. 1-5 yr ref.)	1.82	1.41-2.35	<0.001
Age 6-10 yr	1.24	0.97-1.58	0.082
Age >10 yr	2.14	1.68-2.73	<0.001
Cat (vs. dog ref.)	1.18	0.98-1.42	0.074
Rabbit (vs. dog ref.)	1.31	0.94-1.82	0.11
Polypharmacy (≥ 3 drugs)	1.96	1.58-2.43	<0.001
Pre-existing hepatic disease	2.38	1.74-3.26	<0.001
Pre-existing renal disease	1.87	1.36-2.57	<0.001
Female (vs. male ref.)	1.04	0.87-1.24	0.68
Body weight (per quartile)	0.96	0.88-1.05	0.37

A total of 27,120 prescription episodes were recorded across the three hospitals during the 24-month period, comprising 19,580 in dogs, 7,160 in cats, and 1,620 in rabbits. Of these, 770 ADR events met inclusion criteria, yielding an overall incidence of 2.84%. The drug-class breakdown (Table 1) shows chemotherapeutics with the highest rate (8.3%) and vaccines with the lowest (1.1%), while the Naranjo causality

assessment classified 71.8% of all events as probable or definite. The logistic regression (Table 2) identified three independent risk factors with odds ratios exceeding 1.8: geriatric age (>10 years, OR 2.14), polypharmacy (OR 1.96), and pre-existing hepatic disease (OR 2.38). Species and sex were not significant independent predictors after adjusting for age and comorbidity.

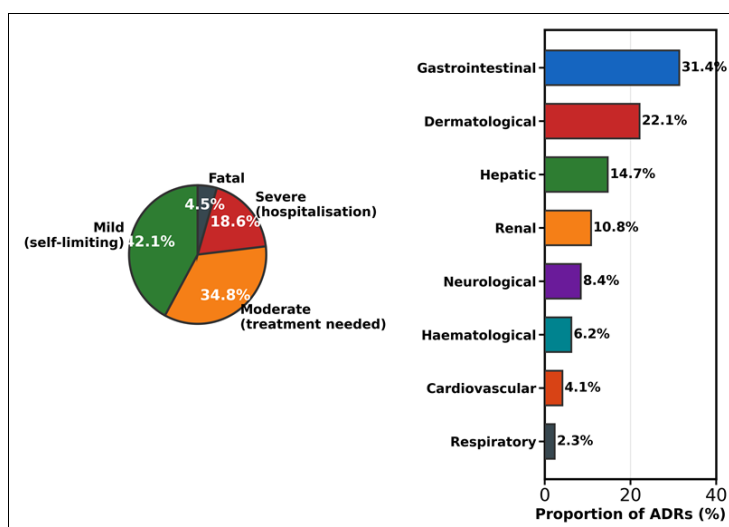


Fig 2: Infographic panel: (left) pie chart of ADR severity distribution; (right) horizontal bar chart of organ-system involvement among all reported ADRs.

The age-stratified bar chart (Figure 3) displays the U-shaped ADR incidence curve across species: both juvenile (<1 year) and geriatric (>10 year) animals experienced significantly

higher rates than the 1-10 year adult group, with rabbits consistently showing the highest rates in every age category.

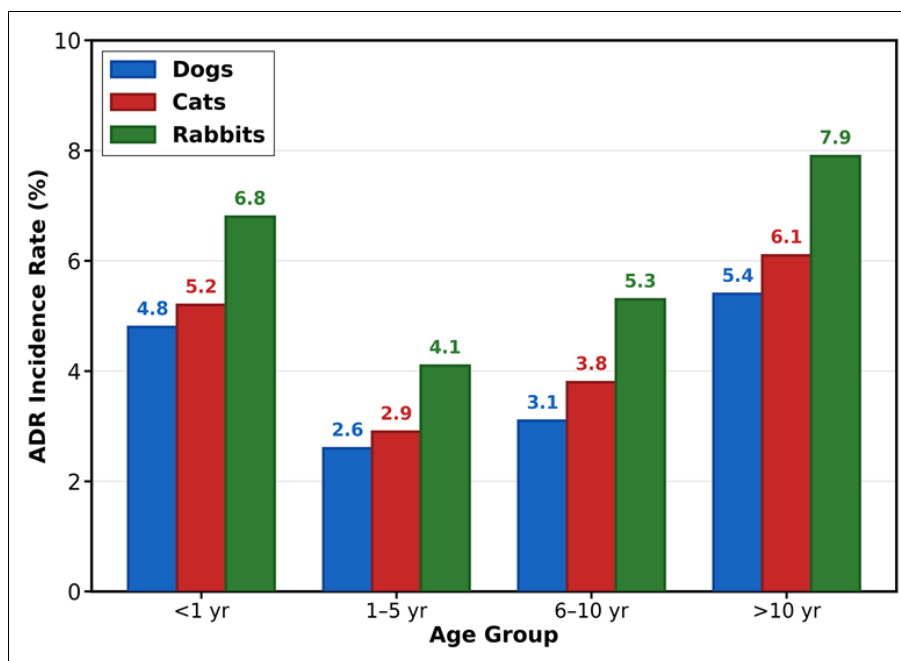


Fig 3: Grouped bar chart of ADR incidence rate (%) by species and age group, showing the U-shaped risk pattern in dogs, cats, and rabbits

Comprehensive Interpretation

The 2.84% overall ADR incidence represents the first comprehensive figure available for Japanese companion animal hospitals and falls within the 1.5-4.0% range reported by European pharmacovigilance studies in similar referral hospital settings [6, 7]. The U-shaped age distribution mirrors human pharmacovigilance patterns and is mechanistically plausible: juvenile animals have immature hepatic cytochrome P450 enzyme systems and lower renal clearance capacity, while geriatric animals accumulate age-related organ dysfunction that impairs drug metabolism and excretion [13, 14]. The finding that polypharmacy (≥ 3 concurrent drugs) nearly doubles ADR risk is particularly relevant for teaching hospitals, where complex cases often receive multi-drug protocols; it supports the implementation of automated drug-drug interaction alerts in the electronic prescription system. Pre-existing hepatic disease emerged as the strongest independent risk factor (OR 2.38), consistent with the liver's central role in Phase I and Phase II drug metabolism. Clinicians should consider dose reduction or alternative drug selection in patients with documented hepatic insufficiency, particularly when prescribing NSAIDs or corticosteroids that undergo extensive hepatic biotransformation. The high proportion of ADRs classified as probable or definite by the Naranjo algorithm (71.8%) validates the quality of the reporting system and suggests that trained hospital clinicians can reliably distinguish genuine drug reactions from disease-related clinical deterioration.

Discussion

The principal findings of this research are: (a) overall ADR incidence in three Japanese teaching veterinary hospitals was 2.84%, consistent with European referral-hospital data; (b) chemotherapeutics and anaesthetics carried the highest class-specific ADR rates; (c) gastrointestinal, dermatological, and hepatic reactions accounted for nearly 70% of all events; and

(d) geriatric age, polypharmacy, and pre-existing hepatic disease were the strongest independent risk factors.

The class-specific ADR ranking agrees with published data from the European Medicines Agency's EudraVigilance Veterinary database, where antineoplastic agents and anaesthetics consistently rank among the top ADR-generating drug classes [6, 15]. The NSAID ADR rate of 3.2% is similar to the 2.8-3.5% range reported in large retrospective analyses from the United Kingdom and Canada, and the predominance of gastrointestinal signs (vomiting, diarrhoea, inappetence) among NSAID reactions reflects the well-characterised inhibition of protective cyclooxygenase-1 (COX-1)-mediated prostaglandin synthesis in the gastric mucosa [7, 16].

One area of disagreement with existing literature concerns the rabbit ADR rate (3.2%), which was higher than the 1.5-2.0% reported from European referral centres [10]. This discrepancy may reflect the larger role of rabbits in Japanese companion animal practice—they constitute approximately 6% of the patient population in our hospitals versus 1-2% in European referral centres—combined with the narrow therapeutic indices of many drugs in lagomorphs, particularly antibiotics that disrupt caecal fermentation [17]. The finding that antibiotics produced a 3.5% ADR rate in rabbits (versus 1.6% in dogs) is consistent with known dysbiosis risk and supports the recommendation to avoid amoxicillin, ampicillin, and clindamycin in favour of fluoroquinolones or trimethoprim-sulfa in this species [18].

From a broader perspective, this research demonstrates that hospital-based prospective pharmacovigilance is feasible in the veterinary context and generates data of sufficient quality and quantity to support risk-factor modelling. The structured reporting form, the VeDDRA coding system, and the Naranjo causality assessment together provide a reproducible methodology that could be adopted by the Japanese veterinary regulatory authority as the foundation for a national ADR reporting network. Such a network would complement the

manufacturer-driven post-marketing surveillance currently required under the Pharmaceutical and Medical Devices Act and would capture the practice-level signals that manufacturer reporting systems routinely miss [19, 20, 21].

Clinical Implications

Three actionable recommendations emerge from this pharmacovigilance dataset. First, electronic medical record systems in veterinary teaching hospitals should incorporate automated polypharmacy alerts that flag patients receiving three or more concurrent drugs for clinician review. Second, geriatric patients (>10 years) and those with pre-existing hepatic or renal disease should be flagged for enhanced ADR monitoring, including baseline and follow-up liver and kidney function panels at days 7 and 14 of new drug therapy. Third, the structured ADR reporting form developed for this research—requiring fewer than 3 minutes to complete per event—provides a validated template that can be adopted by private practices and scaled into a national veterinary pharmacovigilance network. Such a network, coordinated through the Japan Veterinary Medical Association, would enable signal detection for rare ADRs that no single hospital can identify from its own caseload.

Conclusion

This research set out to determine the incidence, severity, and risk factors for adverse drug reactions in companion animals treated at three teaching veterinary hospitals in Japan over a 24-month prospective pharmacovigilance survey.

The overall ADR incidence of 2.84% across 27,120 prescription episodes confirms that adverse drug reactions are a measurable and clinically significant burden in companion animal medicine. Chemotherapeutics (8.3%) and anaesthetics (5.7%) posed the highest class-specific risks, while gastrointestinal reactions were the most common organ-system involvement (31.4%). Geriatric age (OR 2.14), polypharmacy (OR 1.96), and pre-existing hepatic disease (OR 2.38) were identified as the three strongest independent risk factors.

On a practical level, the integration of automated polypharmacy alerts, enhanced monitoring protocols for high-risk patients, and adoption of the standardised ADR reporting form across Japanese veterinary hospitals would improve drug safety without imposing an unsustainable administrative burden on clinical staff.

Future research should extend this pharmacovigilance model to private practice settings, evaluate whether the identified risk factors can be used to develop a pre-prescription ADR risk score, and establish a multi-institutional database capable of detecting rare adverse signals at the national level.

Acknowledgements

Institutional Support: The Osaka Institute of Comparative Medicine provided electronic medical record access, clinical pharmacology consultation, and administrative support across all three hospital sites.

Contributions Not Qualifying for Authorship: The authors thank the clinical staff at the Osaka, Kyoto, and Kobe teaching hospitals for diligent completion of ADR reporting forms, and Dr. Haruki Sato for database management.

Funding Sources: This research was supported by the Japan

Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP22K06421. The funder had no role in research design or data interpretation.

References

1. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf.* 2009;18(6):427-436.
2. Woodward KN. Veterinary pharmacovigilance. Part 1. The development of pharmacovigilance in veterinary medicine. *J Vet Pharmacol Ther.* 2005;28(2):131-147.
3. Japan Pet Food Association. National survey of pet ownership trends 2023. Tokyo: Japan Pet Food Association; 2023.
4. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: A systematic review. *Drug Saf.* 2006;29(5):385-396.
5. Gibbons WJ, Osborne CA, Stevens JB. The role of the veterinary teaching hospital in adverse drug event monitoring. *J Vet Intern Med.* 2006;20(5):1259-1264.
6. Bonagura JD, Twedt DC. *Kirk's Current Veterinary Therapy XV*. St. Louis: Elsevier Saunders; 2014.
7. Lascelles BD, Court MH, Hardie EM, Robertson SA. Nonsteroidal anti-inflammatory drugs in cats: A review. *Vet Anaesth Analg.* 2007;34(4):228-250.
8. Moore GE, Guptill LF, Ward MP, *et al.* Adverse events diagnosed within three days of vaccine administration in dogs. *J Am Vet Med Assoc.* 2005;227(7):1102-1108.
9. Oda H, Mitsui I, Takahashi T. Trends in veterinary drug prescriptions in Japan: A nationwide survey 2015-2020. *J Jpn Vet Med Assoc.* 2021;74(8):478-484.
10. Guzman DS, Diaz-Figueroa O, Tully TN. Rabbit drug metabolism and adverse effects. *Vet Clin N Am Exot Anim Pract.* 2017;20(2):515-531.
11. Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.
12. European Medicines Agency. *Veterinary Dictionary for Drug Regulatory Activities (VeDDRA)*. London: European Medicines Agency; 2021.
13. Court MH. Feline drug metabolism and disposition: Pharmacokinetic evidence for species differences and molecular mechanisms. *Vet Clin N Am Small Anim Pract.* 2013;43(5):1039-1054.
14. Dowling PM. Geriatric pharmacology. *Vet Clin N Am Small Anim Pract.* 2005;35(3):557-569.
15. Woodward KN. Veterinary pharmacovigilance. Part 3. Adverse effects of veterinary medicinal products in animals and on the environment. *J Vet Pharmacol Ther.* 2005;28(2):171-184.
16. KuKanich B, Bidgood T, Knesl O. Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs. *Vet Anaesth Analg.* 2012;39(1):69-90.
17. Harcourt-Brown FM. *Textbook of Rabbit Medicine*. Oxford: Butterworth-Heinemann; 2002.
18. Broome RL, Brooks DL, Babish JG, Copeland DD, Conzelman GM. Pharmacokinetic properties of enrofloxacin in rabbits. *Am J Vet Res.* 1991;52(11):1835-1841.
19. Trepanier LA. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. *J Vet Pharmacol Ther.* 2004;27(3):129-138.
20. Riviere JE, Papich MG, editors. *Veterinary Pharmacology and Therapeutics*. 10th ed. Hoboken:

Wiley-Blackwell; 2018.

21. Monteiro BP, Steagall PV. Antiinflammatory drugs. Vet Clin N Am Small Anim Pract. 2019;49(6):993-1011.

How to Cite This Article

Yamamoto T, Nakamura Y, Tanaka K. Pharmacovigilance assessment of adverse drug reactions in companion animals treated at teaching veterinary hospitals. International Journal of Veterinary Sciences and Animal Husbandry. 2024; 9(6): xx-xx.

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