

**“Much as they do in managing their own health care, people need to weigh the benefits and risks of a drug prescribed for their pet.”**

–Bren, Linda. Prescriptions for Healthier Animals: Pets and People Frequently Fight Disease with Similar Drugs. FDA Consumer Magazine, Nov-Dec 2000.

“In recent years, the demand for drugs for companion animals - in particular, dogs and cats - has significantly increased, driven in part by an ageing pet population and a greater willingness of owners to pay for effective treatments. (In fact, of the seven drugs with annual sales greater than US \$100 million introduced in the past decade, five are for companion animals.) This has created opportunities both for novel drug development and for the crossover of drugs developed for humans... The use of non-steroidal anti-inflammatory drugs for canine arthritis is an example of how animal drug development can mirror new drug development for humans. Today, more than half of all commercially led pharmaceutical research and development in the veterinary field is focused on developing products for companion animals, and the emphasis on this sector looks likely to increase in coming years, as companion animals live longer, and more diseases of old age are being diagnosed and treated.”

–Lathers, Claire M. Challenges and opportunities in animal drug development, Nature Reviews Drug Discovery, 2003 Nov; 2(11): 915-18.

## **IN SEARCH OF: VETERINARY DRUG INFORMATION**

### **Sources of veterinary drug information**

#### **VETERINARIAN**

Verbal information; manufacturer provided FDA CVM approved Client Information Sheet (for drugs which CVM requires manufacturers to provide a CIS); veterinary clinic's own information sheet or information printed from a web resource or purchased drug reference; package insert or prescribing information.

#### **FDA**

**“It is paradoxical that products as potentially hazardous as prescription medications are often dispensed with little more than a ‘use as directed’ statement on the product label.”**

–Food and Drug Administration

A search of the FDA website by brand or generic drug name will yield several types of information, such as Freedom of Information (FOI) Summaries, Dear Doctor letters, CVM (Center for Veterinary Medicine) Updates, and regulatory or warning letters to drug manufacturers. Some drug labels and Client Information Sheets are also available at the FDA website, as well as the Cumulative Adverse Drug Event (ADE) report. Information not available on the website may be requested by filing a formal FOI request (for example - scored ADE reports for a particular drug).

The FOI Summary for a drug contains summaries of safety, effectiveness, and toxicity studies for the drug, as well as its US approval date. Dear Doctor letters and CVM Updates contain important safety information about a drug which has been learned since its approval date. Regulatory letters or warning letters may be issued for various offenses, such as the dissemination of misleading promotional materials or the failure of the manufacturer to comply

with CVM's adverse drug event reporting requirements. The Cumulative ADE Report contains the adverse events and deaths reported to FDA CVM for each animal drug. All included reports have been evaluated and judged by a review team of FDA veterinarians to be possibly, probably, or definitely related to a drug. No reports scored as remotely related or about which no conclusion could be drawn are included.

### **FDA Home**

<http://www.fda.gov>

### **Labels/Client Information Sheets**

<http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/DrugLabels/ucm050105.htm>

### **NSAID Page**

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055434.htm>

### **NSAID Brochure (Treating Pain in Your Dog)**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm047987.htm>

### **Adverse Drug Experience Reports Lead to Label Changes, Other Actions for Safer Animal Drugs**

<http://www.fda.gov/downloads/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM063046.pdf>

### **How CVM Uses Adverse Drug Experiences Reports System**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm093739.htm>

### **What veterinarians should tell clients about pain control and their pets**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm093572.htm>

### **Advice to dog owners whose pets take NSAIDS**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm093573.htm>

### **Important Safety Information (Dear Doctor letters)**

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055433.htm>

### **CVM Updates and Other Safety Notifications**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/default.htm>

### **Update on Rimadyl®**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm129408.htm>

## **Report a Drug Reaction**

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm>

## **Advisory Action Letters**

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/ucm042132.htm>

## **FOIA Drug Summaries**

<http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm>

## **Warning Letters**

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

## **Warning Letter Example**

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075865.htm>

## **Cumulative ADE Report**

“...These reports include domestic adverse drug experience reports submitted to the Center for Veterinary Medicine (CVM or the Center) that CVM has determined to be at least ‘possibly’ drug related. Since 2000, only serious and unexpected ADEs in Periodic Reports are included in the database. The on-line database is expected to be updated monthly for expedited (fifteen day) reports for drugs approved within the previous three years, but not more than yearly for periodic (annual) reports...”

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055394.htm>

## **ADE Report Disclaimer**

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055369.htm>

## **CVM Improves Its Cumulative Adverse Drug Experience Summaries Website**

<http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm092835.htm>

## **CVM FOIA Electronic Reading Room**

(To file a written FOIA request see link in menu “How To Make a FOIA Request”)

<http://www.fda.gov/AboutFDA/CentersOffices/CVM/CVMFOIAElectronicReadingRoom/default.htm>

## **Report of FDA CVM to VMAC concerning ProHeart6®**

[www.fda.gov/downloads/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM127121.pdf](http://www.fda.gov/downloads/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM127121.pdf)

## **CVM Announces the Return of Fort Dodge Animal Health’s ProHeart6®**

(Links on this page to CIS, label, frequently asked questions, and other information.)

<http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm047945.htm>

## **MANUFACTURER**

Veterinary drug information may be found at the drug manufacturer's website or a website set up for the drug by the manufacturer. The Package Insert (also known as Professional Insert, Product Label, Product Insert, or US Prescribing Information) and any FDA approved Client Information Sheet (also known as Pet Owner Information or Dog Owner Information) should be available on the site. At this time, FDA requested, manufacturer provided Client Information Sheets exist for only a limited number of drugs with special safety considerations, such as the veterinary NSAIDS. Other materials on the manufacturer's website may be highly promotional in nature.

Example of manufacturer provided drug website:

<http://www.adequan.com/>

## **US PHARMACOPEIA VETERINARY DRUG INFORMATION**

U.S.P. currently has veterinary drug information monographs available online for antibiotics, anti-inflammatory drugs, anthelmintics, and compounded medications. The U.S.P. monographs are in-depth and evidence-based, and decisions on their scientific content are made by the U.S.P. Veterinary Medicine Information Expert Committee. A free, one-time registration is required to view the veterinary drug monographs.

<http://www.usp.org/audiences/veterinary/>

## **VETERINARY PARTNER AND VETERINARY CLINIC PHARMACIES ONLINE**

Note that drug information monographs written for consumers vary in quality and may or may not be updated regularly.

### **Veterinary Partner**

<http://www.veterinarypartner.com/>

Other examples:

### **Marvista Vet**

[http://www.marvistavet.com/html/pharmacy\\_center.html](http://www.marvistavet.com/html/pharmacy_center.html)

### **Drs. Foster & Smith**

<http://www.peteducation.com/>

## **DRUGS.COM**

The Drugs.Com site now has a veterinary product database.

<http://www.drugs.com/vet/>

## **BOOKSTORE**

Plumb's Veterinary Drug Handbook by Pharmacist Donald C. Plumb includes information on human drugs used off-label in animals. Taber's Cyclopedic Medical Dictionary is useful when reading technical drug monographs if one is not familiar with medical terminology.

## **PUBMED**

PubMed is a service of the National Library of Medicine that includes over 15 million citations from MEDLINE and other life science journals for biomedical articles dating back to the 1950's. The full text of articles that are available only as abstracts may be purchased at low cost by setting up a Loansome Doc account with any of several medical libraries.

<http://www.ncbi.nlm.nih.gov/pubmed/>

## **UNIVERSITY COLLEGES OF VETERINARY MEDICINE**

Various types of information relating to drugs may be found. For example, Washington State University of Veterinary Medicine has a page about the gene responsible for hypersensitivity to ivermectin, immodium, and some other drugs, and offers a test to pet guardians which will detect the gene.

<http://www.vetmed.wsu.edu/depts-vcpl/>

## **ASPCA POISON CONTROL CENTER**

ASPCA Animal Poison Control Center veterinarians have a wide range of information specific to animal poisonings involving pesticide, drug, plant, metal, and other exposures in companion animals. If an animal needs veterinary care the APCC will direct the guardian to their veterinarian and provide the veterinarian with a detailed diagnostic and treatment protocol.

<http://www.aspca.org/pet-care/poison-control/>

## **INTERNET PET-RELATED WEBSITES, DISCUSSION GROUPS, BREEDER WEBSITES, INTERNET SEARCH, POPULAR PUBLICATIONS ONLINE, ETC.**

Readers will need to judge the quality and verify the correctness of information given in discussion groups and on internet web sites. Unfortunately, pet guardians even need to be wary of articles written by veterinarians in popular publications which give only benefit information for a drug and are accompanied by no references. Often these articles are no more than drug advertisements, and a type which cannot be regulated by FDA CVM. A good, balanced information article about a veterinary drug will communicate RISKS as well as BENEFITS.

Example of a group which discusses animal drugs online:

Doghealth2: Be Aware of Canine Drug Dangers

<http://pets.groups.yahoo.com/group/doghealth2/>

Website examples:

<http://www.dogsadversereactions.com>

<http://www.vetnsaids.com>

**“We have many effective and potent drugs available in our armamentarium. As the activity and potency of drugs increased, so has the risk of serious adverse effects, especially serious toxicity, and the ability to recognize adverse effects. Do not dismiss an unexplained disorder in a patient until a drug-induced cause has been ruled out. The Greek physician Hippocrates (440-375 BC) provided an ethical basis for the practice of therapeutics. He recognized that a physician sometimes does more harm than good. (This applies to veterinarians as well.) The advice of Hippocrates ‘primum non nocere’ (translated: above all, do no harm) reminds us that it is better to administer no therapy at all than to administer therapy that might be harmful.”**

–Papich, Mark G., DACVCP. Adverse Drug Events of Clinical Significance. 2003 CVC Proceedings.

## **Why veterinary drug information?**

The first consideration in administering any drug is whether or not the condition truly requires its use. The possible benefits to be gained from a medication must be balanced with its potential risks. In order to assess the risk vs. benefit for any drug prescribed for a pet, the pet guardian must seek the best available drug information.

According to the FDA, “a safe medical product is one that has reasonable risks, given the magnitude of the benefits expected and the alternatives available.” (1) The FDA, in considering what drugs should be available to the population as a whole, must sometimes approve drugs with severe side effects. A drug may be the only effective treatment for a life threatening condition, or may be needed as a second or last choice treatment if a less dangerous drug is not effective. Since all drugs are not perfectly fine, safe, and appropriate in any circumstance in which they might be used, and some require more information to be used safely than others, drug labels carry approved usages, precautions, contraindications, drug interaction information, different strengths of warning information, and sometimes Medication Guides (human) or Client Information Sheets (animal).

The prescribing information or package insert, a part of a drug’s label, is provided for the use of the veterinarian in making complicated risk vs. benefit decisions for individual animals. Per the FDA:

“The Agency approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use... Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk and benefit to the healthcare community and patients. Once medical products are on the market, however, ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information

to select and use products wisely, thereby minimizing adverse events.” (1)

Steven M. Fox, in Clinical Perspectives on Current and Future Options in Canine NSAID Therapy, had this to say about the value of the drug label:

“Product labeling is an excellent primary source of safety data because this is the basis for drug approval. Prelicensing safety studies for NSAIDs will include multi-dose toxicity test, long-term toxicity tests, or both. **If toxicity occurs experimentally at multi-dose levels, that’s important because those toxic reactions will eventually show up clinically, even when the drug is used at the recommended dose.** Labeling data is a good start for assessing product safety.” (2)

Any chosen treatment’s outcomes (i.e., its risks and benefits) should be shared by the veterinarian with the pet guardian, preferably in the form of both verbal and printed information. The guardian plays the final role in assessing risk vs. benefit based on personal values, and has a need and a right to enough information to make informed decisions about the use of a drug product. If information about the risks of a drug is not forthcoming, then the pet guardian must ask. As an article from the American Veterinary Medical Association states:

“Communication is the key to good health whether you are working with a family physician, pediatrician, or veterinarian.” (3)

The FDA, after an extensive review of research related to written drug information, concluded that written information is beneficial in the following ways:

- 1) Patients who receive written materials about medications have increased knowledge about the use and effects of the medications;
- 2) Patients who receive written information show more knowledge about side effects and are better able to attribute adverse reactions to the medications they are taking;
- 3) Patients can more easily discriminate adverse reactions due to medication from other clinical events;
- 4) There is increased compliance with the treatment regimen;
- 5) Patients are more able to communicate about their medications and more knowledgeable inquiries of health professionals. (4)

While these conclusions apply to written drug information for human patients, it is even more important for pet guardians to receive the benefits of information about drugs for pets. Because animals cannot complain, it is vitally important that pet guardians have enough information to identify adverse effects, and identify them early. According to the professional services staff of Novartis Animal Health:

“The pet owner sees the dog every day and is more likely to detect improvements or problems, but only if he or she knows what to watch for. Educated consumers who have a good understanding of the medication are more likely to be both responsible and compliant.” (5)

Other important differences (besides the fact that animals cannot complain) exist between human drug use and the use of drugs in animals. While humans may survive severe adverse

reactions due to advanced diagnostics and medical procedures usually paid for by insurance benefits, most pet guardians cannot travel, many times out of state, to veterinary university facilities which offer state of the art care, nor afford extended hospitalization. In addition, many treatments available to humans are still investigational for pets. For these reasons, many pets very ill from adverse drug effects are euthanized. Finally, the intermediary available to provide drug counseling to humans, the pharmacist, does not exist in veterinary medicine.

Much in particular has been written about the need to provide pet guardians with information about the veterinary NSAIDs. In a discussion of the NSAIDs in *Veterinary Practice News*, the former president of the American Animal Hospital Association Daniel Aja had this to say:

“If I could get all veterinarians to do one thing when it comes to NSAIDs, it would be to seriously heed the recommendations from the drug companies to explain the potential side effects to the clients... Vets get in trouble by not explaining the side effects and not emphasizing the importance of follow-up care... It is part of our duty to inform the client.” Aja also stated that he often hears from clients that the veterinarian never mentioned side effects. (6)

All of the veterinary NSAID labels state that the Client Information Sheet should be provided to pet guardians, and the FDA has in addition written several articles asking that pet guardians be given the CIS. In the article *Adverse Drug Experience Reports Lead to Label Changes, Other Actions for Safer Animal Drugs*, Thomas Moskal stated that “The Client Information Sheet can be as important as the drug’s label to ensure the safe and proper use of the drug.” (7) The professional services staff of Novartis Animal Health advised veterinarians in the 2005 Deramaxx ® Update:

“As recommended by the FDA, clients should receive a Client Information Sheet when Deramaxx ® is prescribed for their dogs. The information helps dog owners to properly dose their dogs and identify potential signs of intolerance.” (5)

Elderly animals are a group who require particular consideration and caution when administering medications. From Johnny D. Hoskins, DVM, PhD, DACVIM, in the book *Geriatrics and Gerontology of the Dog and Cat*:

“Choose initial drug dose based on the aphorism ‘Start low and go slow.’ Monitor drug therapy for efficacy and adverse effects. Drug therapy in older dogs and cats is often a double-edged sword. In geriatric humans, rates of adverse drug reactions are reported to be two to three times those seen in younger patients. There is no reason to believe that the same thing does not occur in older dogs and cats. Because often more than one disease is being treated and multiple drugs are being used, an increased potential for adverse drug interactions exists. Use therapeutic drug monitoring for drugs with narrow therapeutic windows. Avoid polypharmacy - using more drugs than are necessary - in older dogs and cats. Polypharmacy is a problem not only in human medicine but also in veterinary medicine. Polypharmacy may lead to increased morbidity and mortality secondary to drug-drug interactions, it may result in increased adverse effects, or the cost of therapy may lead to premature euthanasia.” (8)

The decision to use a brand new animal drug must be considered carefully, as new and unknown adverse events will inevitably surface in the first several years of use. Some reasons this is true include:

- 1) The size of clinical trials for animal drugs is limited, and rare or idiosyncratic adverse events

that only occur, for example, in 1 in 2000 animals will not be discovered;

2) The trials typically exclude the young, the old, animals with multiple or complicated medical conditions, and those receiving multiple drugs - groups that have a higher risk for experiencing an ADE;

3) Clinical trials are generally too short to detect delayed reactions or those resulting from long term use.

According to veterinary pharmacologist Dawn Boothe re veterinary NSAIDs:

“Pre and post-licensing studies are, of course, important in establishing NSAID safety, but mass usage is the ultimate test. Only then will the product’s safety profile fully emerge. Prelicensing and other experimental studies focus on dose-dependent effects and target a relatively small test population. It is not until a drug is placed in widespread clinical use that we see the idiosyncratic and other more subtle toxicities that are potentially serious.” (9)

From Monitoring of Responses: Pharmacovigilance:

“It is generally believed that testing of veterinary medicinal products during pre-marketing development programs, and review of data by regulatory authorities in licensing these products, does not guarantee absolute safety and effectiveness due in part to the inherent limitations of pre-marketing development programs. Due to the limited size and controlled nature of pre-marketing clinical trials, only the most common adverse events will be observed and included in product labeling at the time of product approval. Following marketing of a new product, the number and variety of animals exposed to the product increase greatly. In addition, patients with multiple medical conditions or that are receiving multiple concomitant veterinary medical products are exposed to the new product. Thus the patient base will be much broader than that from development studies.” (10)

The veterinary drug information which reaches pet guardians is generally focused on how to administer a medication, with little precautionary or adverse drug event information provided. Risk vs. benefit cannot be adequately assessed by the pet guardian if the existence of any risk is unknown, nor can the guardian monitor the animal appropriately for adverse effects. In the case of veterinary drugs with Client Information Sheets, the FDA has judged that the drug cannot be used with an acceptable level of risk without provision of this information. If it is not given to the client the likelihood that the drug will be used in the safest manner decreases. While the veterinarian should be the major source for Client Information Sheets and other drug information, pet guardians would be well-advised to conduct their own research, in order to protect the safety of their pets.

**“All drugs are poisons. Compounds such as strychnine, mercury, arsenic, and snake venom were once considered useful drugs capable of curing a variety of ailments. Today, medical personnel know that these compounds, if given in sufficient quantities, can kill an animal or a person. Although today’s drugs are much safer, they can be just as deadly as strychnine or snake venom if given in excessive amounts or if administered inappropriately. Only proper administration determines whether a compound is beneficial or deadly.”**

--Bill, Robert L. When Good Drugs Go Bad: Adverse Event Reactions and How to Avoid Them. 2005 CVC Proceedings.

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