

Nice, France; September 28, 2009

The European Commission
D.G. Enterprises and Industries
Health and Consumer Protection
B/1049 Brussels, Belgium

Gentlemen,

The Friends of Guenady is an animal defense association, based in Nice, France, with, for one of its stated objectives, the intention to contribute to improving understanding between consumers of veterinary medicine and veterinarians.

Making reference to the EU general safety requirement, we write to inform the Commission that our association, over the eight years of its existence, has received various reports concerning adverse drug events (ADEs) relating to veterinarian-prescribed medicines. In addition to the ADEs themselves, the reports point to a general, but not systematic, lack of appropriate information regarding medicines prescribed, whether in the availability (or lack) of Client Information Sheets (« Notices ») accompanying the medicines, or in the advice and information provided (most often only orally) by the veterinarian at the moment the prescription is written.

We bring this information to the attention of the European Union (Health and Consumer Protection) because the victims of these ADEs report a consistent refusal by veterinary pharmacovigilance authorities in France to take ADE reports seriously. Clearly, the probability of 'under-reporting' of ADEs is heightened by either the refusal to consider reports of ADEs or the summary dismissal of such reports, to the entire dissatisfaction of the consumer who has been subjected, through a beloved animal, to the pain and suffering of an adverse drug event, sometimes resulting in injury or death.

Why does it seem that a discrepancy exists between the stated aims of pharmacovigilance and the practical functioning of the Pharmacovigilance Agency in France? Certainly, one can imagine that the pharmaceutical establishment is allowed too much influence and control in the treatment of ADE reports.

We applaud the EU's intention to release pharmaceutical products information to the general public. (See <http://www.emea.europa.eu>, then vet docs.) At the same time, we observe that certain pharmaceutical products sold in France seem to be slipping under the wire of the EU's critical observation, and thus contributing to ADEs which are, too often, under-reported or dismissed (as already observed). And yet, in order to protect consumer health and safety, Community law stipulates that producers may place only safe products on the market.

In passing, we mention that we also deplore the exclusivity which

veterinarians enjoy in France in regard to domestic animal therapies and treatments which, outside accepted pharmaceutical treatments, stifle and suppress alternative therapies of all sorts, globally referred to as 'holistic veterinary medicine', a fast-growing sector of veterinary practice in, for example, the USA. Democratic institutions, as well as the principle of freedom of information and choice in medical matters, ethically require the pharmaceutical industry and veterinarians who rely on it, to tolerate other approaches to animal health and well-being, with consumers being the ultimate decision-makers for treatments used to restore and maintain pet health.

With all these points in mind, we write to the Health and Consumer Protection Division of the European Commission to ask that it undertake a comparison of 'notices' (i.e., Client Information Sheets - CISs, or Package Inserts, PIs) which accompany, or fail to accompany, veterinary medicines sold in France, and this with the correct, known properties of each pharmaceutical substance, particularly in regard to Counter-Indications and Undesirable Side Effects, in order to ensure a consistently accurate and reliable correlation between the two, as well as to take every precaution to avoid ADEs.

The provision of such information is the prerequisite for an informed choice on the part of consumers, and indeed the provision of such information is a principle enshrined in French public opinion and law. Unfortunately, due to the withdrawal of the « Code Déontologique des Vétérinaires » from public access (at least, we are no longer able to find public access to this document), we are no longer able to affirm the practicing veterinarian's obligation to inform and advise clients regarding pharmaceutical products prescribed. Nevertheless, the logic of this obligation is so strong that we take it for granted that the European Medicines Agency also recognizes this obligation, and shares our concerns about the provision of accurate information, to allow an informed choice regarding treatments on the part of the consumer.

In order to reinforce our request for such a systematic comparison, we point to two notable examples of discrepancies between known pharmaceutical substance information and the 'Notice' (CIS or PI) for two pharmaceutical medicines marketed for dogs in France, Carprofen and Ketoconazole.

I. CARPROFEN

Carprofen, a non-steroidal anti-inflammatory drug, was originally developed and sold in the US for human use against arthritis pain. Early on, carprofen was withdrawn from the market, according to the manufacturer, for commercial reasons. Quite possibly, there may have been too many ADEs that captured too much public attention. Whatever, Carprofen was then repackaged and sold for use against arthritis pain in dogs.

Dr Carolyn Dean wrote, in 2005, about the history of carprofen for dogs, marketed under the brand name, Rimadyl.

« As for putting animals at risk to the dangers of modern medicine, I even wrote about an example of a crossover drug [N.B. a drug that is developed for humans, then repackaged and sold as veterinary medicine] that Pfizer, one of the members of the “strategic partnership” [N.B. National Commission on Veterinary Economic Issues (NCVEI)] was so anxious to sell. It was its animal arthritis pain killer drug, Rimadyl, which was promoted through a Christmas card \$10 discount coupon campaign...

...Rimadyl, a Vioxx-type drug, had big problems from the get go. According to a report put together by The Senior Dog Project, The FDA’s Center for Veterinary Medicine reported that by May 1, 2003, 2,133 dogs had died as a result of using Rimadyl since its introduction in 1997.

An even more alarming article published in USA Today reported that through November of 2004, the FDA received almost 13,000 adverse-event reports about Rimadyl, which was much higher than any other dog pain reliever. USA Today also reported that another dog drug in the same Vioxx-type class as Rimadyl, is Dermamaxx, developed by another of the American Veterinary Medical Association’s “strategic partners”, Novartis. Since its launch in 2002, the FDA has had 2,813 adverse event reports including 630 deaths.

The market for dog arthritis pain meds tops \$130 million a year and, according to USA Today, it is growing about 13% a year. However according to the FDA, 3,200 dogs have died and records show there have been almost 19,000 adverse reaction to them... »

Dr. Carolyn Dean, MD, ND and Elissa Meininger

October 13, 2005

« BIG PHARMA JUST BOUGHT YOUR DOG AND MIGHT PUT YOU IN JAIL? » See : NewsWithViews.com

The class of drugs that Dr Dean refers to here is known as NSAIDs (AINS in French), Non-Steroidal Anti-Inflammatory Drugs. As there is no reason to believe that dogs in France are biologically different from dogs elsewhere, it does seem that information is lacking on the « notice » (see copy attached to the present) of possible deadly side effects, and probably ADEs in France are significantly under -reported :

Translated from French : (see attachment)

« Counter-indications

...Do not use in case of :

- severe hepatic or renal ailments
 - gastro-intestinal ulceration or bleeding
 - any hemorrhagic syndrome
 - hyper-sensitivity to NSAIDs
- ...

« Undesirable side effects

In rare cases, cutaneous eruptions, vomiting, loose stools or tearing have been observed.

Ulcerations of the gastro-intestinal tract linked to the administration of carprofen in dogs are rare at therapeutic doses. Hepatic or renal effects of the idiosyncrasic type have been observed during administration of this specialty to dogs. In the event of such trouble, treatment should be stopped... »

Clients of veterinarians have contacted us to protest that carprofen has been given to them by veterinarians in blister (or bubble) packets with no « notice » or CIS or PI, and no verbal information or warning, either, and for problems as slight as pain associated with tooth extraction! Certain dogs have died from NSAID treatments, sometimes after as little as one dose! In that case, the consumer hasn't got time to see the adverse event, and react. Contacted about this frightening lapse in the duty to provide information about the treatment proposed, veterinarians invariably reply that they have been using the drug for years and have never had an adverse reaction. Informed of this, their clients tell us that veterinarians will immediately claim, in the event of an ADE, « The animal was already borderline something-or-other (reference to a malady); it's just a coincidence that this previously undetected illness has manifested during this drug treatment. »

Of course, these observations remain anecdotal given the pressure exerted on consumers by veterinarians, laboratories doing blood and specimen analyses, and the pharmacovigilance authorities to dismiss reports of ADEs.

Let us for a moment briefly consider another of the same class of veterinary drugs, NSAIDs. Metacam (meloxicam) is marketed in France with a (reasonably) informative « notice »:

[Translated from French]

« What are the undesirable side effects of Metacam?

« In dogs and cats, the undesirable effects produced by Metacam are those observed with NSAIDs, in particular loss of appetite, vomiting, diarrhea, blood in stools and apathy (absence of vitality). In dogs, these side effects occur generally during the first week of treatment and are most of the time transitory (temporary). They disappear after the end of treatment, but can be serious or deadly in certain very rare cases.

...

**« Other information relative to Metacam :
« The European Commission delivered a marketing authorization valid in all the European Union for Metacam from Boehringer Ingelheim Vetmedica – Germany, on January 7, 1998. Information relating to the prescription of this product figures on the packaging label... »**

**See « Rapport Européen Public d'Evaluation - Metacam » at
« www.emea.europa.eu »**

In conclusion, in regard to carprofen (Rimadyl), we ask that the EU Commission intervene to ensure that not only is this product, marketed in France accompanied by a 'notice' which properly corresponds to the dangers associated with this drug (including mention of the 'wash-out' period, which should intervene between administration of one NSAID and any other, as well as with certain drugs of other classes). We ask as well that veterinarians be formally informed of these dangers so that they can alert their patients each and every time they prescribe this drug, informing the client of the symptoms to watch for which indicate 'hypersensitivity to NSAIDs'.

N.B. It should always be remembered that, when informing consumers of the dangers associated with pharmaceutical drugs, the veterinarian's duty to inform is primordial, as most consumers trust their vet and do not even read the 'notice'-- until after something has gone wrong.

II. KETOCONAZOLE

Info from Janssen Pharmaceutica, USA (see attachment) :

« NIZORAL (KETOCONAZOLE) TABLETS

NIZORAL TABLETS ARE NOT APPROVED FOR VETERINARY USE, CONSEQUENTLY WE CAN NOT RECOMMEND THE USE OF OUR PRODUCT IN THE MANAGEMENT OF DISEASES IN THE ANIMAL POPULATION; »

We compare this statement with this text, taken from the KETOFUNGOL Oral-Antimycotic-for-Dogs Client Info supplied by Janssen-Cilag in France :

**(Translated from French) (see 'notice' attached) :
KETOFUNGOL200 mg is an oral antimycotic of systemic activity with for active substance ketoconazole, a synthetic derivative of imidazole-dioxolanne which after oral administration, exercises wide activity on dermatophytes.**

Dosage : 200mg per 20 kilos of body weight (=10mg/kg) daily for 3 to 4 consecutive weeks.

Secondary effects : KETOFLUNGOL 200mg is very well tolerated. In rare cases, vomiting may occur immediately after administration.

Precautions for user : Keep out of the reach of children.]

Returning to info supplied by Janssen USA (see attached), we read :

WARNING / WHEN USED ORALLY, KETOCONAZOLE HAS BEEN ASSOCIATED WITH HEPATIC TOXICITY, INCLUDING SOME FATALITIES. PATIENTS RECEIVING THIS DRUG SHOULD BE INFORMED BY THE PHYSICIAN OF THE RISK AND SHOULD BE CLOSELY MONITORED...

Hepatotoxicity, primarily of the hepatocellular type, has been associated with the use of Nizoral (ketoconazole) tablets, including rare fatalities. The reported incidence of hepatotoxicity has been about 1:10,000 exposed patients, but this probably represents some degree of under-reporting, as is the case of most reported adverse reactions to drugs. The median duration of NIZORAL Tablet therapy in patients who developed symptomatic hepatotoxicity was about 28 days, although the range extended to as low as 3 days. The hepatic injury has usually, but not always, been reversible upon discontinuation of NIZORAL tablet treatment. Several cases of hepatitis have been reported in children...

Information for Patients :

Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools...

In two cases brought to our attention, dogs died as a result of ketoconazole treatment, according to the conviction of their owners. Neither could get pharmacovigilance authorities to take their ADE reports seriously. Both felt that they had been fobbed off (one recounts how he was told by a veterinarian at his « Laboratoire Vétérinaire Départemental », 'If we took every case like yours seriously, why we wouldn't be able to treat at all anymore!'). The other dog owner recounted how he had been obliged to insist on a necropsy for his dog, in the face of the resistance of the Departmental Laboratory habilitated to perform necropsies. 'There's a dog shelter just down the road', he was told. 'Why don't you go get yourself another dog, and let us get on with our work!'

We also ask the Commission to note the following :

LIVER TOXICITY AND THE USE OF ORAL KETOCONAZOLE (NIZORAL) FOR FUNGAL INFECTIONS

March 3, 2008 - The March issue of Drug Safety Update published by the British counterpart of the Saudi Food and Drug Authority (SFDA),

the Medicines and Healthcare products Regulatory Agency (MHRA), reported that because of the risk of liver toxicity the approved uses of oral ketoconazole (Nizoral) have been restricted in Great Britain. The British authorities have received reports of serious liver toxicity associated with the use of the drug, including cases resulting in death or that required liver transplantation...

[http: // www. sfda. gov. Sa / En / Drug / News / 270-en-10-3.htm](http://www.sfda.gov.Sa/En/Drug/News/270-en-10-3.htm)

In light of these two recent rulings, we ask the European Commission to not only consider requiring KETOFUNGOL (ketoconazole) veterinary medicine to include the proper warnings on the information supplied to consumers who buy this drug but, even more, to consider suspending the right to prescribe this drug, which is (it seems) not approved for veterinary use in any other country of the European Union, just as it is not approved for veterinary use in the USA.

Ketoconazole, packaged and sold for human consumption, can still be prescribed off-label in Europe (unless the Commission decides otherwise) in which case the Nizoral CIS or PI or 'notice' delivers proper information to the consumer (see copy enclosed) regarding symptoms of possible adverse reaction and the injunction to stop treatment in the event of one or more symptoms and immediately consult one's doctor.

The present total absence of appropriate consumer information and warnings on the KETOFUNGOL veterinary medicine CIS and PI, or 'notice' is, in our opinion, a grave breach of public trust and a state of affairs which we hope the Commission will quickly and wisely bring to an end.

Before concluding this correspondence, we wish to make reference to other types of veterinary medicines which escape the vigilance of consumers : those which are administered directly by veterinarians, often without explaining what they are administering or why they have chosen to administer it (after all, informed consent is a sacred principle to the enlightened consumer, and ought to be respected as well when the veterinary medicine is administered by the veterinarian).

III. Zoletil

One consumer contacted us concerning the death of his female labrador following administration by a veterinarian of zoletil, a tranquilizer, before taking x-rays of one of the dog's hind legs.

The veterinarian's treatment report, written in a state of stress just after the dog's death is auto-incriminating. He indicates that he injected, at 3:00 pm a proper dose of the product, that the x-raying went smoothly, and that the labrador awoke (translated from French, see attachment) 'without problem

because at 4:30 pm the dog was sitting up in her cage barking loudly...

The only reaction this barking elicited from the veterinarian, he admits was annoyance. He writes that he and his staff considered calling the owner to come get the dog earlier than arranged. The loud barking continued up to about 5:40 pm when ' ... one of my nurses, going to get another animal in the cage room, noticed that the labrador was convulsing and alerted me right away...'

The veterinarian reports that he immediately carried out an electrocardiogram, to discover that the dog was in cardiac arrest with ventricular fibrillation.

According to the MERCK online Manual on ventricular fibrillation: '...if the disorder is not rapidly treated, death follows... Cardiopulmonary resuscitation (CPR) must be started within a few minutes, and it must be followed by defibrillation (an electrical shock delivered to the chest) to restore normal heart rhythm... It [ventricular fibrillation] is fatal unless treated immediately... The most common cause of ventricular fibrillation is inadequate blood flow to the heart muscle due to coronary artery disease, as occurs during a heart attack. Other causes include the following : Shock (very low blood pressure...)... Electrical shock... Drowning... Very low levels of potassium in the blood (hypokalemia)... Drugs that affect electrical currents in the heart...'

The veterinarian continues, 'One injection of adrenalin by IV and intra cardiac with a series of cardiac massages did not revive the dog after 20 minutes... I myself proposed to the owner of the dog to carry out an autopsy by an expert colleague, or at the veterinary school at ==, before incinerating the animal, when I saw lack of belief in my statement on the part of the owner's sons, as I concluded in the existence of underlying heart disease, undetected and undetectable, to provoke lethal cardiac trouble with 1 cc of zoletil 100 given intravenously 2 1/2 hours after its injection!! » (emphasis his)

Having spent precious minutes on the electrocardiogram, the veterinarian finally began heart massage, which he says he kept up for twenty minutes, but which failed. We can hazard a guess as to the amount of time wasted at the critical moments when every second counted...

Should the veterinarian have started CPR (resuscitation) immediately, given the condition of the animal, without needing an ECG to confirm what seems to have been clearly apparent? Still more pertinent, should the veterinarian have reacted earlier, hearing the loud and insistant barking (which is one of the recognized signs of overdose with zoletil – see product info attached), and should he have at least gone to check on the animal in the cage room? The answers to these questions do not figure in the veterinarian's written report.

Instead, he gives a full paragraph to HIS surprise and anger that the son of Talia's owner, witness to the scene, expressed disbelief in the veterinarian's immediate explanation for Talia's death, that is, 'an undetected and undetectable(!)' heart disease which was responsible for the reaction to the drug. And yet, laymen that we are, when we consult the Client Information

Sheet, we read (see attached, translated from French, emphasis ours) :

Zolétil - In strong doses -Excessive salivation (reduced by atropine) -- muscular spasms --vomiting --nervousness, BARKING --short periods of apnea --high blood pressure --tachycardia. A RESPIRATORY DEPRESSION MAY BE INDUCED AFTER ADMINISTRATION OF HIGH DOSES. IF THIS DEPRESSION BECOMES TOO GREAT, THE ANIMAL CAN BECOME CYANOTIC [NB : discolored due to lack of oxygen in the blood]. REANIMATION MEASURES MUST THEN BE IMMEDIATELY TAKEN, SUCH AS ARTIFICIAL RESPIRATION OR THE USE OF OXYGEN...'

In the veterinarian's report, he expresses righteous indignation that the son of Talia's owner, witness to the failed attempt at cardiac massage, did not believe his conclusion that the dog had a previous undetected, and UNDETECTABLE, heart disease... The veterinarian counseled the family, he writes, to have an autopsy done BY A FRIEND OF HIS or at a veterinary school, FOLLOWED BY INCINERATION. We change nothing in the advice given by this veterinarian : an autopsy carried out by someone he recommended, followed by incineration... Why the recommendation of someone he knew to carry out the autopsy? Why the inclusion of the advice to incinerate immediately after the autopsy? Why would it come to this veterinarian's mind at such a moment to advise the rapid destruction of the corpse?

Faced with the son's frank refusal to believe the veterinarian's explanation for Talia's death, the family nevertheless followed this advice, and the autopsy was carried out by the pathologist recommended. The conclusion? The family was right, Talia did not die of a previously undetected and UNDETECTABLE, heart disease... She died of a previously undetected brain condition... Also undetectable? We can ask ourselves many questions... But there will never be formal answers, for Talia was incinerated, according to the veterinarian's advice.

Conclusion

Clearly, many veterinarians and many manufacturers of veterinary medicines do not respect the principle of informed consent, whether by design or by incompetence hardly matters. What matters is to change 'the way things are done', instituting checks and balances into the treatment process, so as to be sure to respect the duty to inform, as well as to respect the duty of the veterinarian to BE informed about the pharmaceutical products s/he prescribes..

In the last cited case, certainly we can and do deplore the apparent ignorance of this veterinarian when it came to the signs of adverse reactions to the drug zolétil. What can the consumer do to protect himself, or rather his animal, from negligent veterinary practice? We feel that this question can only find an answer within the veterinary associations, and we hope that raising this concern at the level of the Commission will result in a more serious attitude on the part of the profession to inform itself about new drugs and new drug therapies, while checking to be sure not to sluff off information about other

therapies regularly used.

If the health and the lives of our animal companions are worth the high cost we pay for veterinary care, then the veterinarian owes not only to consumers, but to himself and his profession as well, to be up-to-date in his knowledge of the pharmaceutical products he employs or prescribes, or else s/he should refrain from prescribing and using them.

In the meantime, we request that veterinary products administered directly by veterinarians be included in the procedures about which the consumer should be informed and subsequently to which s/he should give consent.

We hope that the European Commission will give serious consideration to our request for a study/comparison between information contained in the CISs, PIs and 'notices' with the known product information about each individual veterinary medicine, so as to ensure that the information is accurate and up-to-date.

We thank the Commission for its time and serious consideration of our request. We also remain at the disposal of the Commission for any further information we might be able to provide.

**The Friends of Guenady Association
Janne Sieben
Marie Isaia
Hannah Straite**

**7 rue Lamartine
06000 Nice, France
33 4 93 85 59 50**