

# Deramaxx<sup>®</sup>: Smart Drug or Clever Marketing?

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Jeff Levine's long-time, constant companion Rudy, a 9 year old Golden Retriever, died from internal bleeding after he had been administered a single dose of the new non-steroidal anti-inflammatory drug (NSAID) Deramaxx<sup>®</sup> (Novartis Animal Health Products). The bleeding was caused by severe ulceration of the stomach. This is not an isolated case. Other dogs on Deramaxx<sup>®</sup> have died possibly numbering the hundreds already.

The Food and Drug Administration's Center for Veterinary Medicine has received 108 Adverse Event Reports as of mid-February 2003 according to Victoria Hampshire DVM, the coordinator of Adverse Event Reporting. Dr. Hampshire notes that death is now the 8<sup>th</sup> leading sign of a problem with Deramaxx . If you add in euthanasia, it becomes the 3<sup>rd</sup> most common "sign."

## Reported Adverse Drug Reactions Deramaxx (deracoxib)

	Sign	Number	Percent
1	VOMITING	33	31
2	ANOREXIA	28	26
3	BUN HI, BLD	24	22
4	DEPRESSION/LETHARGY	22	20
5	SGPT/ALT HI, BLD	19	18
6	CREATININE HI, BLD	18	17
7	ALK PHOS HI, BLD	17	16
8	DEATH	17	16
9	ANEMIA	15	14
10	WBC HI, BLD	15	14
11	MELENA	12	11
12	INTERACTION, DRUG(S)	11	10
13	P HI, BLD	11	10
14	WEAKNESS	11	10
15	DEATH(EUTHANIZED)	10	9

Source: Center for Veterinary Medicine, Food and Drug Administration. February 24, 2003.  
[http://www.fda.gov/cvm/index/ade/ade\\_web\\_rpts.htm](http://www.fda.gov/cvm/index/ade/ade_web_rpts.htm)

Deramaxx<sup>®</sup> has been promoted as a miracle pain reliever, something every owner of a dog in pain wants. Novartis specifically terms Deramaxx<sup>®</sup> a "smarter" drug and tout s the

benefits of the drug's COX-2 (cyclooxygenase-2) specificity. It is a non-steroidal anti-inflammatory drug (NSAID) whose activity is similar to that of Celebrex<sup>®</sup>, a widely used human NSAID. COX-2 is an enzyme involved in the body's inflammatory response to injury which is a major source of pain.

Some dogs have benefited from Deramaxx<sup>®</sup>, perhaps the majority who have received it. For other dogs, the drug has been ineffective. And some dogs have become seriously ill or died after having been administered Deramaxx<sup>®</sup>.

The drug is widely promoted by veterinarians for pain relief

## **What's the problem?**

Pain relief is important. Most of us would rather suffer ourselves than see our animals in pain and many veterinarians feel the same way.

There are three choices available in the veterinary pharmacy for dealing with pain: steroids, NSAIDs and narcotics.

Steroids suppress pain because they suppress the body's response to injury. They can have serious side effects, including diabetes mellitus. Several studies have indicated that as many as half of all diabetes cases in dogs are caused by long-term steroid use.

Narcotics are effective pain relievers, but so effective that they need to be managed carefully in a clinical setting.

That leaves NSAIDs. There are two types: COX-1 inhibitors and COX-2 inhibitors. COX is the abbreviation for the enzyme cyclooxygenase. There are two forms (isoforms) of this enzyme called isozymes. Both are involved in the body's response to injury, particularly the inflammatory response which is largely responsible pain.

COX-1 and COX-2 isozymes are versatile. They are also involved in other processes in the body, not just the inflammatory response. COX-1 helps the body protect the lining of the stomach from acids needed to digest food. COX-2 enzymes are involved in various kidney functions, particularly regulation of chemicals (electrolytes) in the body.

No drug is perfect. If a medicine could be developed that only targeted specific causes of pain, side effects theoretically would be minimized. But when the causes of pain, in this case the products of COX-2 enzymatic reactions, are involved in other vital bodily functions, there are side effects--side effects that include death.

## **It's in the genes.**

NSAIDs are widely taken and have been extensively studied. A key issue with any drug is how it is metabolized. To be effective, a certain level of the drug's main ingredient(s)

has to end up in the blood stream. Celebrex<sup>®</sup>, a widely prescribed human COX-2 inhibitor similar to Deramaxx<sup>®</sup>, is metabolized in the liver by a metabolic pathway known as CYP 450.

Because dogs are used extensively in clinical testing of human drugs, there has been considerable research into how dogs metabolize Celebrex<sup>®</sup>. (While structurally different, the two drugs vary from each other by a single atom.)

Researchers have found that one of the key enzymes involved in the CYP 450 metabolic pathway determines how fast drugs such as Celebrex<sup>®</sup> are metabolized. Variations (polymorphisms) in the gene that expresses this enzyme cause some dogs to be Fast Metabolizers and others Slow Metabolizers. About half the dogs fall into one category, half in the other.

Fast Metabolizers quickly metabolize Celebrex<sup>®</sup> clearing it from the body in a few hours. In the case of Slow Metabolizers, the drug is broken down slowly; consequently, drug levels in the blood are elevated because the rate of excretion is reduced.

## **The Key Question**

Fast Metabolizers are generally not at risk for adverse side effects. Since the drug is cleared quickly, the relief they receive may be limited to a few hours, but they are for the most part not in danger of adverse side effects.

The opposite is true for the Slow Metabolizers. The drug slowly builds up and can reach toxic levels. In some cases, there is a high level of the drug in the blood when the second dose is administered, sending the drug level even higher.

While this variation in metabolic rate is an issue with many of the NSAIDs, it is clearly not the only problem. Dogs with compromised kidneys, livers, heart problems or pre-existing gastro-intestinal ulceration are at risk, even if they are Fast Metabolizers.

## **Deramaxx<sup>®</sup> Side Effects**

When a COX-2 drug goes above a certain level in a dog's system, three documented adverse reactions can occur:

1. Kidney damage and secondary effects on the heart.
2. Gastro-intestinal ulceration
3. Liver damage

The degree of damage and danger varies, but can include death.

In the case of the kidneys, NSAIDs can upset the body's ability to regulate electrolytes

such as sodium and potassium, leading to sky-rocketing increases in blood pressure and the kidneys themselves can be damaged leading to other problems.

The table above shows that high levels of BUN and Creatinine are frequently associated with Deramaxx<sup>®</sup>. Adverse event reports further suggest that Deramaxx<sup>®</sup> can cause irreparable kidney damage. Many dogs continue to have abnormal blood values indicative of kidney damage long after Deramaxx<sup>®</sup> has been discontinued.

Novartis has been less than straightforward when it comes to gastro-intestinal effects of Deramaxx<sup>®</sup>. Veterinarians have been led to believe that COX-2 inhibitors spare the stomach, despite the fact that it has been documented that this is not the case when a COX-2 inhibitor drug reaches high levels.

Research into new drugs aimed at making them more COX-2 specific has shown that highly COX-2 specific drugs have gastro-intestinal effects that are not unlike those seen with traditional COX-1 inhibitors such as aspirin.

Just as COX-2 is involved in the basic functions of the kidneys, it is also involved in protecting the stomach from the body's own digestive fluids. A review of reported adverse effects, including endoscopy and tissue biopsies indicates that Deramaxx<sup>®</sup> can lead to massive gastric ulcerations as happened to Rudy. Signs and symptoms include vomiting, diarrhea and dark bloody stools.

Excessive levels of COX-2 inhibitors can be toxic to the liver as well as shown by the frequency of high levels of SGPT/ALT and ALK PHOS in the adverse event reports. In addition, the liver produces coagulation factors that are involved in wound healing, specifically the coagulation of blood. This can be a double whammy. Bleeding caused by ulceration of the stomach cannot be stopped because the liver is not producing coagulation factors necessary to stop the bleeding.

This appears to be what happened to Rudy who was on Deramaxx<sup>®</sup> for only a single day.

Precisely how drugs like Deramaxx<sup>®</sup> damage the liver is not well understood. However, we do know that the damage is caused by toxic levels of the drug in the blood and that this is common sign of dogs who have reacted badly to Deramaxx<sup>®</sup>.

## **Play It Safe — Do No Harm.**

There are many reasons dogs need pain relief. This makes finding a safe, effective analgesic critical. An NSAID used wisely can be beneficial. But it needs to be used wisely.

A general rule in using an NSAID is to use no more than the absolute minimum necessary to *manage* the pain. The key word is **MANAGE**. This does not mean obliterating the pain. It means reducing it so that the quality of life is not significantly diminished.

Your pet cannot tell you when he has enough medicine to get by and enjoy life. It is up to you to make that decision. Give your dog enough analgesic to make him comfortable, not oblivious. Strong, long-term pain medication can mask underlying disorders or disorders that develop during the course of analgesic therapy. Of course, these disorders are not necessarily caused by the analgesic. Such disorders may be serious enough to require the attention of a veterinarian. If a pet is asymptomatic because of strong analgesic therapy administered for an unrelated clinical condition, then even the most attentive owner may miss the disorder early on. Try not to overdo the analgesia. Your pet's life may depend on it. Play it safe.

The manufacturers of Deramaxx<sup>®</sup> and other NSAIDs need to develop a screening procedure that identifies Slow Metabolizers, the dogs who are most likely to experience adverse reactions. The science of characterizing dogs as Fast or Slow metabolizers is well established, the trick is getting this technology into the clinic.

Until a screening test becomes available, there are three things an owner and veterinarian need to do when prescribing an NSAID such as Deramaxx<sup>®</sup>.

### **1. Screening**

The dog should be screened for kidney and liver problems. This will not tell you whether your dog is a Fast or Slow Metabolizer, but it will tell you *in advance* whether your dog is likely to suffer adverse effects from Deramaxx<sup>®</sup> if he or she is a Slow Metabolizer.

Dogs with impaired kidney or liver function are not good candidates for NSAIDs — period.

Dogs with heart problems are in danger of heart failure because of the effects of COX-2 inhibitors' on the kidneys. These dogs should not be given Deramaxx<sup>®</sup>.

The stool should be checked for blood. If gastrointestinal bleeding is present, Deramaxx<sup>®</sup> administration is contraindicated: toxic levels in a Slow Metabolizer could produce life-threatening hemorrhage. We will never know whether Rudy had an asymptomatic stomach ulcer before receiving Deramaxx<sup>®</sup> or whether he was a Slow Metabolizer. If a stool test had been performed and had been positive for blood, then Deramaxx<sup>®</sup> should never have been administered.

### **2. Concomitants**

Adverse reactions have been linked with insufficient time between administration of one drug and beginning Deramaxx<sup>®</sup>. The time that needs to elapse between administering Deramaxx<sup>®</sup> after having received another NSAID has not been established. It is hoped that either Novartis or the FDA will research this further and provide guidelines.

### **3. Careful Observation**

This one is tough. There are a large number of cases in the adverse event reports and reports from owners who have not formally reported the reaction in which the dog has

died or almost died after receiving a single dose of Deramaxx®.

In general, with Deramaxx® or any other NSAID, the drug should be stopped at the first sign of an adverse reaction. In most cases, stopping the drug is enough to prevent permanent damage and the symptoms quickly resolve.

Veterinarians and owners should be alert for signs and symptoms of gastrointestinal problems such as vomiting, diarrhea, dark or bloody stools or changes in appetite or drinking.

Liver and kidney problems are more difficult to spot. Look for changes in the frequency or amount of urination and drinking (fluid and electrolyte imbalance), yellowing of the whites of the eyes (jaundice) or any behavioral change such as aggression or lethargy (hepatic psychosis).

Reports have suggested that Deramaxx® can affect a dog's central nervous system. In many cases, symptoms have occurred post-operatively and can be attributed to the anesthetic or post-operative pain. Aggression, disorientation, staring off into space, circling, lack of coordination when walking, lethargy or hyperactivity have been documented.

No scientific study has investigated whether Deramaxx® is tumorigenic (can cause tumors, benign or malignant). Any long-term intervention in the inflammatory response can affect tumor growth, pro or con. This topic is currently under research with respect to Celebrex®, a widely prescribed human COX-2 inhibitor. Different tumors respond differently to COX-2 inhibitors. Does Deramaxx® accelerate the growth of preexisting tumors or cause them to shrink?

## **What should be done if there is a negative reaction?**

**STOP ADMINISTERING DERAMAXX®.** Get to your veterinarian as soon as possible. Because damage can be serious and immediate, *any* sign of NSAID toxicity should be treated as an **EMERGENCY**. Do not wait to see how your dog does.

A full blood panel test should be obtained to determine whether there is kidney or liver damage. Stool and urine samples should be obtained to determine if there is blood in the stool (gastrointestinal hemorrhaging) or if the kidneys have been damaged (changes in the specific gravity of the urine).

Your veterinarian needs to review the case with the veterinarians at Novartis by calling 1-800-332-2761. Novartis veterinarians will help plan appropriate treatment, will log this reaction and will report it to the FDA's Center for Veterinary Medicine (CVM) to help establish guidelines for the use of Deramaxx®.

The CVM's Dr. Hampshire notes that immediate, aggressive treatment can make the

difference between life and death when warranted by blood tests and other signs of distress.

Simply stopping the drug is not enough in some cases. The drug must be cleared from the system as quickly as possible, as would be done with any poisoning. Further intervention with steroids and antihistamines may be required.

Tests and treatment can be expensive. Novartis has been generous in paying for both as a part of its program to monitor adverse reactions to the drug and collect as much information as possible about what caused the reaction.

## **Helping Others**

Drugs such as Deramaxx<sup>®</sup> are regulated by the FDA. Six full-time employees are monitoring reactions to Deramaxx, an unprecedented level of involvement by CVM in a new drug.

Without follow-up reporting by your veterinarian of what happened with your dog, including submitting copies of all laboratory tests and clinical notes on the case, vital information will be missing from the record. Novartis and the FDA rely on this record to ensure that Deramaxx<sup>®</sup> is prescribed safely.

There are situations in which veterinarians have been at odds with pet owners over the cause of a reaction. Some veterinarians may be concerned that they will be held liable for problems that arose after prescribing Deramaxx<sup>®</sup>. In other cases, it is simply that in their medical judgment, they believe what happened was not linked to Deramaxx

Remind the veterinarian that the jury is not yet in on the safety of Deramaxx<sup>®</sup>. It is best to consider all the possibilities until research and experience have clearly indicated what is and is not pertinent. Epidemiologic studies have documented that seemingly irrelevant information — even if it is counterintuitive — can end up being statistically significant. If data within the report ends up irrelevant, so be it. No harm will have been done. If data are dismissed as irrelevant at the outset and are not subjected to statistical analysis, none of us will be the wiser. The best science questions the obvious. Remind your veterinarian of this fact.

Novartis is not eager to attribute adverse events to Deramaxx<sup>®</sup>, especially if the treating veterinarian does not see the link.

In these cases, it is a simple matter for owner to report the case directly to the FDA either by phone (1-888-FDA-VETS) or by filing a Form 1932 Adverse Event Report available on line at:

<http://www.fda.gov/cvm/index/ade/adereporting.htm>

CVM officials will take a report on your case and let you know what documentation they need and where to send it.

It is vitally important that the FDA get these reports backed with laboratory data and clinical notes so they can assess what steps are needed to protect our pets while providing them with pain relief.

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