



Your Vet for Life since 1955

## Evaluation of the FDA's information on Librela (post release adverse events)

### WPVH Medical Director Caitrine Hellenga DVM

Dear Pet Parent:

The FDA did a standard evaluation of the adverse event reporting after the launch of Librela. I read the full 32 page report and I have concerns about the evaluation process and conclusions of the FDA. We have seen the FDA make a mistake in the veterinary space in the past. For example, in a previous drug injection evaluation, the FDA counted a dog who leapt out of the back of a pickup truck as a death associated with an injectable drug. So I looked at their conclusions carefully.

**With more than 21 million doses distributed globally, no individual adverse event sign is reported at a rate higher than rare, as defined by the European Medicines Agency (EMA) as <10 per 10,000 treated animals.**

Here is a longer summary and my interpretation of the data.

Statistical analysis methodology:

- The FDA did a statistical analysis to determine whether the adverse events were being reported in the same proportion as adverse events to other drugs for arthritis (NSAIDs such as Vetprofen, Meloxicam and drugs such as Gabapentin).
- If the Librela had an adverse event reported at a higher rate than other arthritis drugs, then that symptom was labelled as being possibly or probably caused by Librela.

There are a couple problems with the analysis:

1. Librela is being used in really old dogs who likely have other health problems or other causes for the signs if you look at the numbers of reporting by age category
2. There was no medical workup reporting
  - This means statistics comparing very different drugs was used to decide cause and effect. Medical testing was not used to determine if Librela caused a problem.
  - None of the case reports included an MRI or a necropsy to show that Librela was the cause (as opposed to a spinal disease in an older dog with disk disease or spinal tumor).

- The reporting done by veterinarians assumes that the veterinarian made an accurate diagnosis of arthritis, see point 3 below which describes the difficulty in making a diagnosis for a veterinarian compared to a physician.
3. Veterinarians can't easily tell arthritis from a disease of the nervous system
    - We can't ask our patients if they hurt, and if so, where? What does it feel like? Is there burning, pinching, numbness, tingling?
    - Dogs get an adrenaline rush coming to the vet, so they hide where they hurt
    - Telling if your geriatric dog has arthritis (probably does) and NOT pain from a pinched nerve is very hard. Even with radiographs proving that there is arthritis, that doesn't mean that the arthritis is the cause of the trouble walking. For Example, Dr Hess, the owner of WPVH, had a Rottie mix named Tank. Tank was seen by a specialist and had a spinal MRI done. The specialist diagnosed a bone problem in the hips and did a total hip replacement. But it turned out that Tank had a degenerative spinal disease that can't be diagnosed on imaging, and the problem was really in his spine and not the hips.
    - All of this means that if we are giving Librela, which is a time and money commitment, there is a significant problem.
    - The case reports I read of geriatric dogs being given Librela and then having a nervous system problem (ataxia, paralysis) are hard to interpret. My first response is that without an MRI, how do you know what you are treating? I as a vet will reach for Librela if I can't tell, rather than say that every geriatric dog with lameness needs to be referred to a neurologist and go under general anesthesia for an MRI and a spinal tap. So if a geriatric dog has more trouble walking after Librela, maybe the vet was treating arthritis but should have been treating disk disease in the spine and/or brain tumors. Are these cases of Librela causing trouble walking? Or are these cases where Librela didn't work, the underlying disease was never diagnosed initially and then it progressed, and then the dog was never referred for an MRI post Librela?
  4. Lameness (the very reason you give Librela) had a probability score indicating that Librela causes lameness.
    - Librela is used to treat lameness, so that means that lameness is not an "adverse event", it is a symptom
    - It is interesting that statistical (rather than medical) analysis is showing that lameness is caused by Librela. Just a flaw in the analysis that the FDA themselves pointed out.
  5. Case reports included information as if the dog was totally normal and then something bad happened after Librela. Again, Librela is only given because there is significant medical disease including lameness, trouble walking, and pain. These are NOT "normal" dogs with nothing wrong getting a random injection.

For example:

- The youngest case example was a 9 year old St. Bernard who developed a front leg lameness and loss of nerve function, typical of a spinal compression in the neck. This St. Bernard did not receive an MRI to look for an underlying spinal disease. I wouldn't be putting my very geriatric giant breed dog through an MRI to see if he needs surgery so I don't question the lack of this test. It's just that

without the MRI, no one actually knows what the diagnosis was or what disease the vet thought he/she was treating (arthritis versus spinal disease).

- A 10 year old Mastiff on gabapentin, prednisone, tramadol, and amantadine: this is an intensive drug protocol used for a dog that has spinal problems (prednisone instead of a non-steroidal drug indicates the veterinarian was diagnosing spinal disease). Four days after the Librela, this Mastiff couldn't walk anymore. That is sad and yet a geriatric giant breed dog on prednisone (used for spinal nerve compression) and 3 pain drugs for the spine and who can't walk is probably suffering from a spine disease and not a Librela side effect. No MRI to diagnose spinal disease.
  - A 15 year old lab was unable to bear weight on his front limbs and had loss of nerve function in the front legs 24 hours after the Librela injection. To me it is more likely that a 15 year old lab was given Librela for the pain associated with a spine problem and not just arthritis. No MRI to diagnose spinal disease.
  - Another case report was a 12 year old Golden, four days after the first Librela injection was recumbent and couldn't lift his head and then died 6 days later. I would be very sad if this was my dog. And I would also think that my 12 year old Golden had an underlying medical cause rather than a reaction to Librela. No medical workup such as an MRI to show it was or wasn't Librela.
  - Another case was an 11 year old lab that was lame 5 days post Librela. I have to think this lab received Librela because of the lameness, because that is why you would give it.
  - A 10 year old mixed breed dog with paresis (weak legs) and possible stroke. Where is the MRI? Was this a brain tumor?
6. Librela is a novel drug in the class of arthritis treatments, and is not being Rx'd in the same way as Vetprofen/Rimadyl, Metacam, and Gabapentin.
- Librela adverse events are mainly in geriatric dogs unlike other drug reporting. Other drugs show higher side effects in the 1-5 year old age range.
  - This shows that veterinarians may be prescribing Librela to a different population of dogs than the other drug category and that the more geriatric population has more underlying diseases (such as spinal disease)
  - This means that comparing Librela to Vetprofen/Rimadyl is a bit like comparing apples and oranges

My review of the FDA information shows that we need to continue reporting anything that could be an adverse event, and that pet parents know that there is a very rare chance of an adverse event. I don't think the FDA analysis gives enough information to state any conclusions about cause and effect other than being on guard and watching for these signs. My advice is that if there is more trouble walking after giving Librela, that Librela may not be the answer and that further testing is necessary to get to a diagnosis. I also think that the benefits of Librela generally outweigh the rare risk, and at the end of the day that is a decision between you and your doctor. I am planning to continue giving Librela to my 7 year old chihuahua-pug mix Ivy.

Caitrine Hellenga, DVM  
Medical Director

