Veterinarians weigh benefits, risks of new osteoarthritis drugs

Treatments branded Librela for dogs, Solensia for cats seen as alternative to NSAIDs

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Veterinarians increasingly are weighing the largely positive results they're seeing from new osteoarthritis drugs for dogs and cats with the risk of side effects like neurological disease, following submissions to regulators of thousands of adverse incident reports associated with the popular products.

The drugs' manufacturer, Zoetis, maintains the adverse event reports about Librela for dogs and Solensia for cats represent only a small fraction of the millions of doses that have been administered to date. Both were first introduced in 2021, in Europe.

"We remain confident in the safety and effectiveness of Librela and Solensia for controlling osteoarthritis pain in dogs and cats, respectively, when used according to the label," Zoetis said in a statement to the VIN News Service.

Photo by Dr. Diane Walker

Beemer is now more active after her veterinarian owner, Dr. Diane Walker, gave her Librela, a new treatment for osteoarthritis in dogs.

Safety concerns were stoked in April by a Wall Street Journal story that highlighted the adverse incident reports and documented anecdotal accounts of pets suffering from serious health issues after taking the drugs, such as loss of mobility and kidney failure, that sometimes led them to be euthanized. Pet owners also have been airing safety concerns in forums dedicated to the drugs on social media platforms such as Facebook.

Osteoarthritis is a common condition in which cartilage in joints wears down. As the condition worsens, bones may rub together, causing pain and decreased mobility.

Librela and Solensia are administered via monthly injections. Their active ingredients are monoclonal antibodies, a relatively new class of drugs that can block, among other things, nerve growth factor (NGF), a protein associated with the formation of nerves and also with pain

generation.

Monoclonal antibodies that target NGF are seen as a potentially safer alternative to nonsteroidal anti-inflammatory drugs (NSAIDs), which can cause side effects ranging from vomiting and diarrhea to stomach ulcers and kidney disease.

Today, Librela and Solensia are available in countries around the world, such as Australia, Brazil, Canada and Japan. In the United States, the U.S. Food and Drug Administration approved Solensia in 2022 and Librela in 2023.

According to the European Union's database of suspected adverse drug reaction reports, 15,233 have been submitted there about Librela and 8,653 about Solensia since 2021. In the U.S., the FDA had received 3,359 adverse incident reports on Librela and 3,264 reports on Solensia as of March 31, according to the agency.

In dogs, some of the most frequently reported side effects in both jurisdictions are lethargy, neurological disorders like a loss of control of body movements (ataxia), renal and urinary disorders, and disorders of the digestive tract like vomiting.

In cats, skin disorders are among the most frequently reported adverse events. Some reports also cite lethargy, disorders of the digestive tract and neurological disorders.

Zoetis has distributed more than 14 million doses of Librela and 4 million doses of Solensia since the drugs debuted in 2021, the company told VIN News. It added that the estimated rate of adverse events "continues to be low with only 0.18% reported for Librela and 0.33% for Solensia" as of March 2024. Overall, no single type of adverse event is considered more than rare, Zoetis said, citing the European Medicines Agency's categorization of "rare" as more than one but fewer than 10 out of 10,000 animals treated.

In brief

* More than 18 million doses of new drugs that treat osteoarthritis in dogs and cats have been administered globally since they were initially approved in Europe, in 2021.

* Veterinarians largely are reporting positive experiences from Librela for dogs and Solensia for cats, though they are becoming increasingly cognizant of possible side effects like neurological disease as the drugs reach a larger number of patients.

* Safety concerns have grown following the submission of thousands of adverse events reports to regulators. Product manufacturer Zoetis maintains the drugs are safe and effective when used as recommended.

* Some veterinarians are encouraging colleagues to be wary of using the drugs in patients with certain comorbidities or only mild or suspected osteoarthritis until more research into potential side effects is conducted.

"The majority of the feedback we have received from vets and pet owners continues to be positive," Zoetis said. "Pet owners should always consult with their veterinarian to review their pet's medical history as they are best placed to determine if a product is appropriate for their pet."

For its part, the EMA told VIN News it has reviewed the adverse event reports "as per standard practice," and would continue to monitor them. The regulator noted adverse reactions sometimes are clinical signs of underlying disease rather than a reaction to a given drug. Or they may be reactions to another medication the patient is taking.

The FDA, meanwhile, said it is "diligently reviewing" the adverse event reports and will provide further information when available. "The FDA requires drug sponsors to report information about adverse drug events to the agency and encourages veterinarians, pet owners and animal producers to also share information," FDA spokesperson Siobhan DeLancey said in an email.

The FDA in November sent a letter to Zoetis saying it had made "false or misleading" claims about Librela's efficacy on a website promoting the drug. The company subsequently changed the promotional materials to the FDA's satisfaction.

How the drugs work — and how they might cause side effects

Monoclonal antibodies are a type of protein cloned in a laboratory that are designed to bind to a single target in the body. With names ending in "mab," they can be used to diagnose and treat various diseases and conditions in humans and other animals such as cancer, autoimmune disease, viruses and inflammation.

The active ingredients in Librela and Solensia — bedinvetmab and frunevetmab, respectively — are monoclonal antibodies that target nerve growth factor. They bind to NGF, stopping it from interacting with pain receptors.

Monoclonal antibodies that target NGF have not been approved for use in humans, following the emergence during clinical trials of side effects like peripheral nerve damage and worsening osteoarthritis. Zoetis designed Librela and Solensia specifically for dogs and cats and didn't encounter the same safety concerns during its trials on those animals.

NGF is essential for the development of nerve cells in fetuses, while in growing and adult animals, it plays a greater role in pain generation. NGF also contributes to healing, raising the possibility that anything that neutralizes NGF could hinder the body's ability to recover from certain diseases.

"I think part of what's happening here, but we don't know for sure, is that when you're trying to repair damaged nerves, NGF plays a good role, not a bad role," said Dr. Dawn Boothe, a veterinary clinical pharmacologist and internal medicine specialist in Auburn, Alabama.

"So for animals using these drugs where there's multiple complaints of ‘Now my dog can't walk, the lameness is worsening,' what may be going on is that we're using them in a situation where the body's still needing that repair factor."

Dr. David Dycus, an orthopedic surgeon in Severn, Maryland, concurs that the risk of patients suffering from side effects may be higher if they have other conditions in conjunction with osteoarthritis, such as neurological disease, for which the body may need NGF for repair.

"Like any new drug that hits the market, once it gets to the masses, we're going to see things come up that maybe weren't noted initially, or that weren't necessarily thought were going to occur," Dycus said.

"And something a lot of people have missed the boat on here is that in Zoetis's safety studies, the animals really didn't have comorbidities. So we can't say that we know what the outcome would be in all animals because some have certain disease conditions that the treatment was never studied in."

Studies by Zoetis to assess the efficacy and safety of Librela and Solensia applied various exclusion criteria. Studies on Librela in Europe and the U.S., for instance, excluded dogs with lameness associated with a primary neurologic disorder, as well as dogs with a history of injury resulting in neurologic deficits.

Osteoarthritis is more common in older animals, which, due to their age, are more likely to have a range of health problems — the emergence of which may not necessarily be linked to taking Librela or Solensia. Still, the existence of so many potential comorbidities means more research is needed to determine the drugs' overall safety profile, Boothe and Dycus agreed.

"One of the things that people always say is, 'Well, these dogs are already old, and these things could have happened, anyways,' " Dycus said. "I think using that as an excuse is kind of a cop-out that really ignores the bigger picture and the need to put our research-scientist caps on to see what the trade-offs really are with these drugs."

Practitioners watchful

Veterinarians largely are seeing positive results from both Librela and Solensia, judging by dozens of posts to message boards of the Veterinary Information Network, an online community for the profession and parent of the VIN News Service. Still, a few practitioners, Dycus among them, started warning of potential neurological side effects associated with Librela in a VIN discussion last July.

Among those who posted to that discussion is Dr. Diane Walker, a general practice veterinarian in Ottawa, Ontario. At the time, she said she'd given Librela to several patients with pleasing results, including in her own 11-year-old Australian shepherd mix, Beemer.

"It worked great on her," Walker said in an interview. "I live on a lake here and she started jumping off the dock again. She became much more active."

Beemer, now 12, took Librela for only three months, which resulted in what appear to be extended helpful effects. "It just seemed to give her that little bridge," Walker said. She now gives the dog meloxicam, a type of NSAID, on an as-needed basis, such as when the dog is accompanying her on long hikes.

Walker isn't surprised by the number of adverse incident reports on Librela and Solensia, figuring that with any popular new drugs, such reports tend to increase in volume over time. She's still recommending the drugs to many clients; her practice has given Librela, for example, to 58 dogs and counting.

Things haven't always gone smoothly, though, and Walker has grown a little more cautious about using the drugs in certain circumstances.

Walker stopped using Solensia on her own cat after the animal, now 17 years old, developed a bout of pruritus (itchy skin). Two dogs seen in her practice stopped taking Librela after developing urinary incontinence — cases that Walker reported to Zoetis. She said she was instructed by the company to discontinue treatment and wait 60 days. Both dogs recovered and are no longer on Librela.

The veterinarian would still consider administering Librela or Solensia in a patient that developed incontinence, provided the owner tolerated the side effect.

But with patients that have a pre-existing nervous-system condition, Walker is wary of using the drugs, given increasing evidence of potential neurological side effects.

"I am torn with that," Walker said — torn because when she gave Librela to a friend's neurologically compromised Jack Russell terrier almost a year ago, the dog dramatically improved.

The dog, named Spike, was so weak in his hind legs that he couldn't walk, wasn't adapting to a cart and tired easily — prompting his owner to consider euthanasia. Now, Spike doesn't need a cart and can even run up stairs. Librela, Walker said, "has changed his life."

What might veterinarians consider?

Boothe and Dycus, who are clinical pharmacology and orthopedic consultants, respectively, for VIN, both stressed that veterinarians shouldn't lose sight of the benefits that anti-NGF monoclonal antibodies can provide — for the right patients.

Boothe recalls a backlash that occurred a few decades ago to new-at-the-time NSAIDs like carprofen that promised to be safer than older ones like aspirin. As the drugs started being used on large numbers of pets, side effects began to emerge, and some people felt duped.

"I think we're at that stage with this class of drugs, as well, because we don't understand everything that's going to happen with them — and that's true for most drugs," Boothe said. "So my biggest concern is that we're going to disregard these drugs .... I think they're going to be an important way to control pain safely in a lot of animals."

Her advice to veterinarians, at least for now, is to only give the drugs to osteoarthritis patients that align with the inclusion and exclusion criteria of Zoetis's trials.

Dycus is concerned that anti-NGF monoclonal antibodies are being used too liberally, whether as general pain medications or to treat mild cases of osteoarthritis or suspected cases without clinical signs.

"It's gotten to the point now where I'm seeing two to three cases a week of dogs that come to me for ACL [anterior cruciate ligament] tears or have some hip arthritic changes on an x-ray, and they're now getting Librela," he said. "And I also think veterinarians really struggle with identifying what would be called radiographic osteoarthritis — meaning a dog has arthritic change on an x-ray but no clinical signs — versus clinical osteoarthritis."

Alternative strategies for managing suspected or mild osteoarthritis need not involve drugs. Weight loss, controlled daily exercise and feeding animals omega-3 fatty acids, which can ease joint inflammation, can be effective, Dycus said.

To treat more serious flare-ups, he added, oral NSAIDs could be used temporarily, say, for up to four months, or even daily for life with close monitoring. Other approaches are physical therapy; or, in cases of more painful osteoarthritis, injections of any of a variety of medications or substances directly into the joint. If all that fails, Dycus said, he'd administer Librela for two or three months at a time.

"In other words," he elaborated, "I would try to use Librela to break that flare-up cycle of pain perception rather than just putting them on Librela every month for the rest of their lives."

As to whether anti-NGF monoclonal antibodies are appropriate for young patients, Boothe notes that Librela and Solensia are not recommended for dogs under 12 months old and cats under 7 months old. She is hopeful, however, that in young animals beyond those age thresholds, the drugs could limit damage done to joint cartilage by the body's inflammatory response. "In some respects, young patients may be the very candidate that would benefit from them because by the time we see those older animals with osteoarthritis, the damage has been done by all those pain mediators."

Dycus, however, doesn't recommend giving the drugs to younger patients due to concerns they could worsen the progression of osteoarthritis over time. In human medicine, anti-NGF monoclonal antibodies have been linked in a small number of cases to a condition known as "rapid progression of osteoarthritis," in which the joint essentially goes into meltdown.

The condition hasn't been identified in nonhuman animals. But Dycus stresses that, in the context of veterinary medicine, he's referring to the risk of a more subtle worsening of osteoarthritis that has been demonstrated in several studies involving animal subjects, including one published in 2017.

"Several of our colleagues on the orthopedic side have seen patients having accelerated arthritic changes after receiving anti-NGF antibodies," he said. "And I think it's very important to understand that rapid progression of OA [osteoarthritis] is a disease condition, but more accelerated changes in the joint is very different. We're talking about two separate things, even though the terminology sounds very similar."

Both Dycus and Boothe re-emphasized that — as with all new drugs that hit the market — more research could help determine how factors like age, breed, cat versus dog, concurrent use of other medications like NSAIDs and the existence of various comorbidities influence the drugs' safety and efficacy.

"It's one of the reasons I push veterinarians to please report, please report," Boothe said. "We could maybe start making more sense out of this if we had a large enough data pool of animals with adverse events to start finding these risk factors."

Clarification: This story has been changed to no longer describe a letter the FDA sent to Zoetis as a warning letter. Although the letter signaled a law violation, it was not a "Warning Letter" as technically defined by the FDA's compliance framework, but an "Untitled Letter."

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