Food and Drug Administration
Center for Veterinary Medicine
Office of Surveillance and Compliance
Division of Pharmacovigilance and Surveillance

STANDARD ADVERSE EVENT REVIEW

Date:	September 10, 2024
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Through:	Renee Shibukawa-Kent, Branch Chief, DPS, HFV-242
Subject:	Pharmacovigilance Review
To:	Linda Walter-Grimm, Division Director, DPS, HFV-240
Drug Name:	Librela™ (bedinvetmab injection)
Dosage Form:	Injectable solution
File Number:	NADA 141-562
Sponsor:	Zoetis Inc.
DPS Consult #:	DVPS-2024-141

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1. BACKGROUND

1.1 Purpose of the Review

This is a comprehensive review of adverse event reports for Librela (bedinvetmab injection), N141-562, from approval, 5/5/2023 through March 31, 2024. Librela was first marketed on 7/14/2023 and the first adverse drug event submission was received by CVM on 9/8/2023.

1.2 Regulatory History

Librela, sponsored by Zoetic Inc., was approved for the control of pain associated with osteoarthritis in dogs on May 5, 2023, under NADA 141-562. On 7/1/2024, CVM recommended labeling revisions to Librela based on new safety information acquired following drug approval. The newly acquired safety information will be covered in this review.

1.3 Product Labeling

Librela is a sterile injectable solution administered subcutaneously (SC) once a month to target a minimum dose of 0.23 mg/lb (0.5 mg/kg) body weight. It is available as a 5, 10, 15, 20, or 30 mg/ml solution.

Proprietary name(s):	**Librela**
Chemical name(s):	bedinvetmab
A/NADA(s):	N 141-562
Approval date:	5/5/2023
Approved species:	dogs
Sponsor(s):	Zoetis Inc.
Dosage form(s):	Injectable solution
Approved strength(s):	5, 10, 15, 20, and 30 mg/ml
Route(s) of administration	Subcutaneous
Approved indication(s)*	For control of pain associated with osteoarthritis in dogs.
Pharmaceutical Classification (internal):	Monoclonal antibody

The following safety related information is taken from the current product package insert and was based upon information known at the time of approval:

PRECAUTIONS

Administration of monoclonal antibodies may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

The safe use of this product with other monoclonal antibodies has not been evaluated. Use with caution in dogs with known hypersensitivity to other immunoglobulin therapy.

Evaluations were not made to determine if interactions occurred between LIBRELA and veterinary vaccines.

Treatment with LIBRELA may result in the formation of anti-bedinvetmab antibodies and potentially the loss of product effectiveness (see **IMMUNOGENICITY**).

The safe use of anti-NGF monoclonal antibodies with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in dogs. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a

small number of patients receiving humanized anti-NGF monoclonal antibody therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF monoclonal antibody. RPOA has not been characterized or reported in dogs.

The safety and effectiveness of LIBRELA has not been evaluated in dogs less than 12 months of age.

LIBRELA has not been studied in dogs that have a history of cruciate ligament rupture within six months before initial product use as these cases were excluded from the field studies.

Long term effects which may occur more than 9 months after the use of LIBRELA have not been evaluated.

NGF is expressed within the heart and vasculature, and the long-term effects of reduced NGF in dogs with cardiac disease are unknown.

Primates receiving high doses of anti-NGF monoclonal antibodies had anatomical changes in postganglionic cell bodies (reduced size and number of neurons). The change in cell body size returned to normal after anti-NGF monoclonal antibody administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of LIBRELA in young growing dogs.

ADVERSE REACTIONS

The safety of LIBRELA was assessed in a masked, controlled 84-day US field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 272 dogs, 135 dogs treated with LIBRELA and 137 dogs treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17 years old), weighed between 1.8 to 62.7 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 2 below.

Table 2. Number (%) of Dogs with Adverse Reactions Reported in the US Field Study

Adverse Reaction*	LIBRELA n (%) (Total N = 135)	Negative Control n (%) (Total N = 137)
Urinary tract infection	15 (11.1)	11 (8.0)
Bacterial skin infection	11 (8.1)	9 (6.6)
Dermatitis	10 (7.4)	8 (5.8)
Dermal mass	8 (5.9)	5 (3.6)
Erythema	6 (4.4)	5 (3.6)
Dermal cyst(s)	4 (3.0)	2 (1.5)
Pain on injection	4 (3.0)	2 (1.5)
Inappropriate urination**	4 (3.0)	1 (0.7)
Histiocytoma	3 (2.2)	0 (0.0)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Of these, two dogs treated with LIBRELA were among those reported with a urinary tract infection.

The safety of LIBRELA was also evaluated in a masked, controlled 84-day European field study evaluating the effectiveness of LIBRELA for the control of pain associated with osteoarthritis. Enrollment included 281 dogs, 138 dogs were treated with LIBRELA and 143 treated with a negative control (sterile saline). The enrolled dogs were at least 1 year of age (1 to 17.5 years old), weighed between 1.7 to 66 kg and were of various breeds or non-purebred. Dogs were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the study are summarized in Table 3 below.

Table 3. Number (%) of dogs with Adverse Reactions Reported in the European Field Study

Adverse Event Reported*	LIBRELA n (%) (Total N = 138)	Negative Control n (%) (Total N = 143)
Increased Blood Urea Nitrogen (BUN)**	19 (13.8)	7 (4.9)
Lethargy	5 (3.6)	0 (0.0)
Emesis	4 (2.9)	1 (0.7)
Anorexia	3 (2.2)	0 (0.0)
Lameness	3 (2.2)	1 (0.7)
Cough	3 (2.2)	1 (0.7)

*An adverse reaction may have occurred more than once in a dog; only the first occurrence was counted.
** Two dogs treated with LIBRELA suffered serious adverse events and were euthanized during or after study completion: A 13-year old Bichon Frise had pre-existing increased urine protein-creatinine ratio and heart failure that worsened during study; the dog also had an increase in creatinine during the study and was diagnosed with renal failure and was euthanized 3 days after completing the study. An 8-year-old mixed breed dog had pancreatitis and was euthanized on Day 74. The remainder of the dogs that had elevations in the BUN did not have any obvious adverse events associated with this finding.

One dog in the LIBRELA group was diagnosed with pyelonephritis on Day 15; this dog had pre-existing increased serum BUN and creatinine and a recent history of urinary tract infection that was not confirmed resolved prior to enrollment. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen were initiated on Day 7 for osteoarthritis-associated joint pain but NSAIDs were discontinued on Day 10 due to anorexia and gastroenteritis; azotemia worsened at Day 13 and the dog received no further LIBRELA treatment.

One dog in the LIBRELA group with a history of atopy, developed mild alopecia and mild erythema on the injection site on Days 5 and 23. Both episodes of alopecia and erythema resolved with treatment.

A total of 89 dogs were enrolled in a 6-month, single arm, open labeled, uncontrolled continuation of the EU field study and received monthly subcutaneous injections of LIBRELA. The study provided additional field safety information.
One dog experienced acute gastroenteritis and recovered following treatment for abdominal pain, fever, vomiting, and anorexia. One large breed dog enrolled for stifle osteoarthritis developed acute forelimb lameness that was diagnosed as elbow dysplasia. Two dogs presented with rear limb paresis of unknown etiology, one of whom responded to ongoing NSAID treatment and one who did not.

The labeling used for this review can be found in the promotional section of DER submission 6, section 13. Section file name: 141562-000006-0623-L-SPECIAL-Special_Promotional

A copy of the labeling used for the purposes of this review has been included as a supporting document with this work activity in (b) (5)

1.4 Freedom of Information (FOI)

An FOI Summary summarizes the safety and effectiveness information submitted by the sponsor in support of the approval of their original or supplemental (A)NADA. It forms the basis for the agency's approval of an (A)NADA. FOIs for original and supplemental approvals are public documents and are available online at animaldrugs@fda or through FOIA requests. The FOI summary for Librela™ is available at:
https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/15226

2. METHODS AND MATERIALS

2.1 Database Overview

See APPENDIX I for full description.

2.2 Selection of Cases from Database

Search specifications*

Date of search:	April 18, 2024
Database application:	PV-Analyser
Date range:	All through March 31, 2024
NADA:	141-562

*See Appendix I for a description of the PV-Works/PV-Analyser databases

2.3 Other Databases

No other databases were searched for the purposes of this review.

2.4 Analyses Performed

Descriptive analyses

The following trends were assessed for cases received in dogs for Librela™ from approval through March 31, 2024, as of April 18, 2024:

- monthly distribution of cases received for Librela™
- age distribution of cases received for Librela™ compared to all other products in CVM's database
  - cases were categorized by the age of the affected dog into the following age groupings:
    - < 1 year
    - 1 year through 5 years (1 years ≤ age < 6 years)
    - 6 years to 10 years (6 years ≤ age < 10 years)
    - ≥ 10 years
  - distribution of cases received by reporter type and the attending veterinarian's level of suspicion regarding association of clinical signs with Librela™
  - clinical sign reporting frequencies for the most frequently reported signs.

Disproportionality analysis

Disproportionality analysis (DPA) was performed to assess whether the relative reporting frequency for selected signs was higher for Librela™ compared to other products in the database.

The following four DPA runs were performed:

Run Identifiers	**#1 Librela Standard Run / #2 Librela Stratified**
Date of runs	April 18, 2024
Cases received dates	All through March 31, 2024
Problem types	All except Lack of efficacy
Species	Dogs
Denominator products	All products
Denominator signs	All except those under HLT Lack of Efficacy; PT Emesis; SOCs Product defects, Med error, Med dev, IGA Animal, Other events
Target product	N141562
Target signs	HFV-241 severe signs for small animals and product-specific signs of interest
Interacting products	None
Results product level	MA number
Results VeDDRA level	Preferred term (PT)
Stratification	#1 None / #2 Age group categories (defined above)
Denominator data	Number of cases

Run Identifiers	**#3 Librela vs OA/ #4 Librela vs OS Stratified**
Date of runs	April 23, 2024
Cases received dates	All through March 31, 2024
Problem types	All except Lack of efficacy
Species	Dogs
Denominator products	All products approved for use in dogs for the control of pain associated with osteoarthritis
Denominator signs	All except those under HLT Lack of Efficacy; PT Emesis; SOCs Product defects, Med error, Med dev, IGA Animal, Other events
Target product	N141562
Target signs	HFV-241 severe signs for small animals and product-specific signs of interest
Interacting products	None
Results product level	MA number
Results VeDDRA level	PT
Stratification	#3 None / #4 Age group categories (defined above)
Denominator data	Number of cases

The proportional reporting ratio (PRR) is defined as the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for all drugs in the comparison group (relative to all adverse events for drugs in the comparison group). PRRs greater than 1 indicate that the sign is more frequently reported for the Librela™ than for the comparator products in a specific DPA run.

The information coefficient (IC) of the Bayesian confidence propagation neural network (BCPNN) and the Empirical Bayes geometric mean (EBGM) are the signal scores computed for the Bayesian confidence propagation neural network (BCPNN) and the Multi-item Gamma Poisson Shrinker (MGPS) respectively. These algorithms provide adjustment towards zero of the observed to expected number of ADE reports especially when number of events is small. The EB05 is the most conservative of the algorithms.

A preferred term is considered disproportionally reported for Librela™ if any of the following algorithms signal:

- PRR, ChiSq - signals if # of cases for LibrelaTM with the PT (A) ≥ 3, the PRR ≥2, and the Chi-Square value ≥ 4
- IC Floor – signals if the IC floor, defined as the lower 95% confidence limit of the information coefficient, is greater than or equal to 0
- EB05 – signals if the EB05, defined as the lower 90% confidence limit of the EBGM, is greater than or equal to 2.

Case series

Case series evaluations were performed for the following signs of concern for cases received through February 3, 2024:

- Ataxia
- Convulsion
- Paresis
- Proprioception abnormality
- Paralysis
- Recumbency
- Muscle weakness
- Muscle tremors
- Lameness
- Collapse NOS (Not otherwise specified)
- Immune-mediated PTs (IMHA, IMTP, IMPA)
- Pancreatitis
- Death

Due to large number of cases received for the following signs, only cases which included at least two of the signs of concern were assessed for causality: ataxia, convulsion, lameness, muscle tremor, muscle weakness, paresis, proprioception abnormality, recumbency, and death.

For all other signs of concern, all cases including the signs were assessed for causality.

Regarding causality assessment, there are several factors that are considered when assessing adverse drug event reports for potential drug association. Some of these factors include:

- previous experience (labeled sign or previously reported sign),
- alternative etiologies such as concomitant medications and/or concomitant medical conditions,
- timing of the event,
- evidence of overdose,
- dechallenge, and
- rechallenge.

Based on these and other factors, reported signs may be assessed as probably drug-related, possibly drug-related, or unlikely to be drug-related. In some cases there is insufficient information to make an assessment. Based on the modified Kramer algorithm used by the Division of Pharmacovigilance and Surveillance (DPS) for causality assessments of reported signs, signs considered 'probably' drug-related receive a score of 3, 4, or 5, and a sign that is considered 'possibly' drug-related receives a causality score of 0, 1, or 2. Signs considered unlikely to be drug-related receive a negative causality score.

3. RESULTS

3.1 Results of Analyses

As of April 18, 2024, CVM's database included 3,674 cases associated with Librela™ which had been received through March 31, 2024. Of these 3,674 total cases, 3,637 were reported in dogs.

Descriptive analyses

Figure 3.1.1. Monthly distribution of Librela™ cases in dogs through March 31, 2024

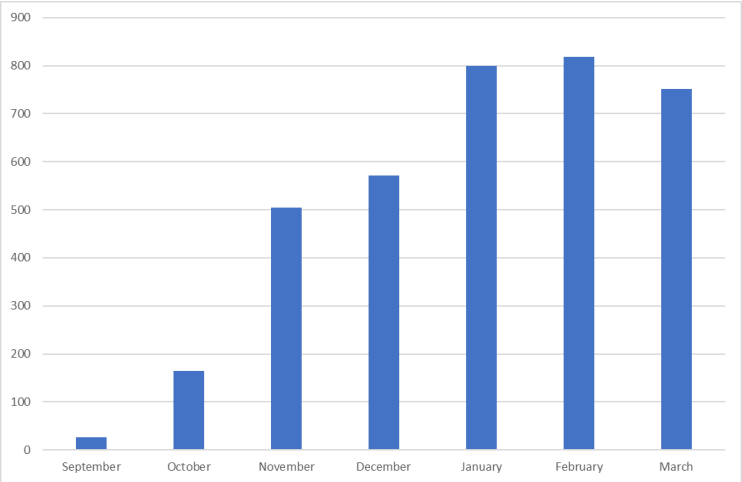

Table 3.1.1./Figure 3.1.2 Age distribution for Librela™ compared to all other cases reported in dogs

	Librela™		All other cases	
Age group category	# of cases	% of cases	# of cases	% of cases
Unknown	348	9.6%	66,358	7.6%
< 1 year	5	0.1%	94,040	10.8%
1 through 5 years	108	3.0%	377,720	43.2%
6 to 10 years	524	14.4%	181,505	20.8%
≥ 10 years	2,652	72.9%	154,450	17.7%
Grand Total	3,637		874,073	

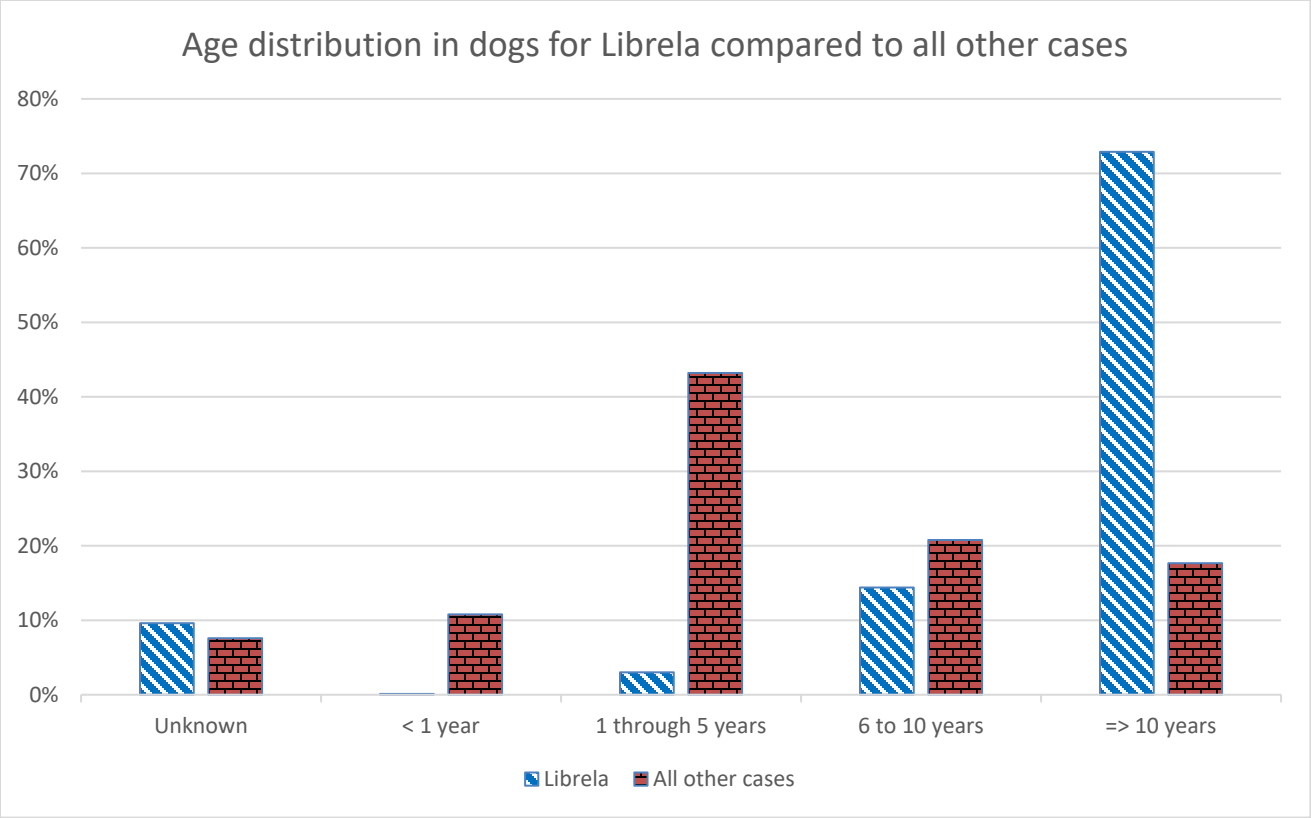
Age distribution in dogs for Librela compared to all other cases
80%
70%
60%
50%
40%
30%
20%
10%
0%
Unknown
< 1 year
1 through 5 years
6 to 10 years
=> 10 years
Librela
All other cases

Table 3.1.3. Cases by reporter role and attending veterinarian's level of suspicion for involvement of Librela™ with clinical signs

		Attending Veterinarian's Level of Suspicion					
Reporter Role	# of cases	Probable/High- A	Possible/Medium – B	Unlikely/Low – N	No Attending Vet	Unknown	(blank)
Veterinarian	1927	45	1619	236	5	4	18
Other health care professional	1307	33	1164	92	9	2	7
Animal owner	382		40	24	305	9	4
Other	19	1	11		5	1	1
Physician	2				2		
Grand Total	**3637**	**79**	**2834**	**352**	**326**	**16**	**30**

Table 3.1.4. Most frequently reported clinical signs (PT) in dogs in

Preferred term (PT)	**# of cases**	**Reporting frequency (N=3,637)**
Ataxia	634	17.4%
Anorexia	567	15.6%
Lethargy	501	13.8%
Polydipsia	477	13.1%
Emesis	468	12.9%
Polyuria/pollakiuria	462	12.7%
Death	458	12.6%
Diarrhoea	374	10.3%
Lack of efficacy**	352	9.7%
Urinary incontinence	296	8.1%
Muscle weakness	270	7.4%
Convulsion	224	6.2%
Urinary tract infection	196	5.4%
Musculoskeletal disorder NOS	189	5.2%
Recumbency	182	5.0%
Paresis	180	4.9%
Increased blood urea nitrogen (BUN) or creatinine	176	4.8%
Tachypnoea	167	4.6%
Muscle tremor	146	4.0%
Elevated liver enzymes	146	4.0%
Hyperactivity	144	4.0%
Inappropriate urination	143	3.9%
Behavioural disorder NOS	142	3.9%
Proprioception abnormality	141	3.9%
Decreased urine concentration	137	3.8%
Lameness	123	3.4%
Vocalisation	110	3.0%

* Signs in bold font indicate a labeled sign or considered related to a labeled sign

** Loss of expected efficacy is discussed on the labeling

Disproportionality analysis

Due to the low numbers of cases received for dogs less than a year old, DPA results for this age group are not included in this report.

Table 3.1.5. DPA results (positive signals) – unstratified

	Compared to All Products					**Compared to OA Products**			
Preferred Term	# of cases with sign	PRR	IC Floor	EB05		# of cases with sign	PRR	IC Floor	EB05
Ataxia	634	**2.41**	**1.12**	**2.41**		641	**2.65**	**1.15**	**2.38**
Polyuria/pollakiuria	462	**6.90**	**2.55**	**7.27**		467	**3.61**	**1.52**	**7.15**
Muscle weakness	270	**3.47**	**1.57**	**25.58**		276	**2.48**	**1.01**	**25.24**
Recumbency	203	**3.75**	**1.65**	**2.74**		208	**2.50**	**0.99**	**2.77**
Musculoskeletal disorder NOS	189	**3.58**	**1.57**	**2.45**		191	**4.12**	**1.59**	**2.42**
Paresis	180	**6.45**	**2.36**	**6.10**		183	**3.02**	**1.22**	**6.04**
Proprioception abnormality	141	**8.93**	**2.75**	**7.34**		146	**5.33**	**1.84**	**7.41**
Lameness	123	**3.37**	**1.43**	**2.72**		127	**3.19**	**1.23**	**2.74**
Paralysis	60	**4.61**	**1.71**	**3.69**		60	**2.65**	**0.88**	**3.59**
Nystagmus	55	**2.91**	**1.08**	**2.32**		56	1.95	**0.48**	**2.31**
Neuromuscular disorder NOS	15	**5.81**	**1.39**	**2.23**		15	**7.73**	**1.40**	**2.18**
Syncope	12	**2.99**	**0.55**	**12.84**		12	**3.97**	**0.72**	**12.53**
Focal seizure	11	**8.80**	**1.53**	**2.98**		11	**40.81**	**1.85**	**2.88**
Non-regenerative anaemia	9	**3.28**	**0.48**	**4.94**		9	**2.29**	**0.02**	**4.71**
Central nervous system disorder NOS	56	**4.39**	**1.63**	1.48		57	**6.82**	**1.90**	1.47
Neurological disorder NOS	53	**2.17**	**0.68**	1.71		56	**2.61**	**0.84**	1.77
Collapse NOS	42	**2.21**	**0.64**	1.49		42	**4.45**	**1.38**	1.46
Epileptic seizure	25	**2.71**	**0.76**	1.82		25	**12.88**	**2.07**	1.78
Splenic neoplasm NOS	15	**3.40**	**0.82**	1.79		Did not signal			
Immune mediated thrombocytopenia	11	**2.69**	**0.39**	1.36		11	**2.72**	**0.30**	1.33
Osteosarcoma	4	**5.21**	**0.18**	1.19		4	**4.95**	**0.01**	1.18
Death	456	1.34	**0.27**	1.30		Did not signal			
Disorientation	95	1.65	**0.40**	1.48		99	1.56	**0.30**	1.51
Elevated pancreatic enzymes	52	1.60	**0.25**	1.16		Did not signal			
Impaired consciousness	38	1.94	**0.45**	1.45		39	**7.46**	**1.86**	1.45
Diabetes mellitus	25	1.81	**0.24**	1.36		25	1.67	**0.08**	1.33
Lymphoma	13	1.92	**0.06**	1.19		13	**2.01**	**0.06**	1.16
Encephalitis	3	**4.03**	-0.27	0.89		3	**7.95**	-0.09	0.88

Table 3.1.6. DPA results (positive signal) – stratified by age group

		≥ 10 years old			6 to 10 years old			1 to 5 years old		
Preferred Term	Comparator Products	#	PRR	ICF	#	PRR	ICF	#	PRR	ICF
Ataxia	All	501	**2.08**	**0.87**	82	**2.27**	**0.79**	16	**2.39**	**0.33**
	OA	508	**2.36**	**0.94**		**2.52**	**0.88**		**3.08**	**0.61**
Polyuria/pollakiuria	All	385	**4.99**	**2.02**	44	**3.42**	**1.21**	9	**7.31**	**1.15**
	OA	389	**3.86**	**1.48**	45	**2.21**	**0.60**		**2.75**	**0.20**
Muscle weakness	All	224	**2.46**	**1.03**	30	**2.54**	**0.71**	did not signal		
	OA	230	**2.37**	**0.88**		1.84	**0.26**			
Recumbency	All	165	**3.21**	**1.35**	26	**3.16**	**0.95**	4	**2.74**	-0.34
	OA	170	**2.59**	**0.95**		**2.04**	**0.35**		did not signal	
Musculoskeletal disorder NOS	All	151	**3.15**	**1.32**	25	**2.74**	**0.75**	did not signal		
	OA	153	**4.52**	**1.55**		**3.70**	**1.05**			
Paresis	All	132	**3.79**	**1.54**	26	**5.90**	**1.70**	6	**10.34**	**0.98**
	OA	135	**2.40**	**0.84**		**3.07**	**0.85**		**4.98**	**0.46**
Proprioception abnormality	All	121	**6.68**	**2.24**	16	**6.14**	**1.48**	did not signal		
	OA	126	**5.06**	**1.64**		**4.72**	**1.11**			
Lameness	All	83	**2.94**	**1.14**	26	**3.82**	**1.18**	4	**4.16**	-0.01
	OA	87	**3.61**	**1.23**		**4.23**	**1.22**		**2.76**	-0.35
Nystagmus	All	49	**2.06**	**0.56**	did not signal			did not signal		
	OA	50	1.81	**0.33**						
CNS disorder NOS	All	47	**3.64**	**1.28**	6	**3.46**	**0.23**	did not signal		
	OA	48	**6.12**	**1.60**		**6.03**	**0.59**			
Paralysis	All	36	**2.76**	**0.86**	10	**5.05**	**0.97**	did not signal		
	OA		1.89	**0.31**		**2.95**	**0.36**			
Impaired consciousness	All	29	**2.52**	**0.68**	6	**2.36**	-0.13	did not signal		
	OA	30	**7.33**	**1.58**		**12.07**	**0.95**			
Epileptic seizure	All	18	**2.93**	**0.69**	6	**4.14**	**0.39**	did not signal		
	OA		**16.24**	**1.77**	did not signal					
Neuromuscular disorder NOS	All	12	**3.94**	**0.80**	did not signal			did not signal		
	OA		**7.04**	**1.05**						
Focal seizure	All	9	**8.25**	**1.21**	did not signal			did not signal		
	OA		**35.18**	**1.39**						
Neurological disorder NOS	All	38	1.99	**0.46**	did not signal			did not signal		
	OA	40	**2.50**	**0.65**						
Collapse NOS	All	33	1.92	**0.37**	6	**2.50**	-0.08	did not signal		
	OA		**5.03**	**1.30**		**3.80**	**0.25**			
Anaphylaxis	All	28	1.72	**0.18**	did not signal			did not signal		
	OA		**4.62**	**1.17**	8	**2.79**	**0.18**			
IMTP	All	did not signal			5	**5.05**	**0.38**	did not signal		
	OA					**5.34**	**0.34**			
Lymphoma	All	did not signal			5	**3.09**	-0.01	did not signal		
	OA					**4.17**	**0.17**			
Thrombocytopenia	All	did not signal			did not signal			5	**3.34**	**0.01**
	OT							did not signal		
Elevated pancreatic enzymes	All	did not signal			did not signal			3	**4.59**	-0.23
	OT							did not signal		

3.2 Case Series

Case series evaluations were performed for the following signs of concern:

- Ataxia
- Death
- Recumbency
- Muscle weakness
- Paresis
- Proprioception abnormality
- Convulsions

- Lameness
- Muscle tremor
- Paralysis
- Collapse NOS
- Immune-mediated (IMHA, IMTP, IMPA)
- Pancreatitis

There were 766 cases received which included at least one of these clinical signs as of February 3, 2024. Due to large number of cases received for the following signs, only cases which included at least two of the signs of concern were assessed for causality: ataxia, convulsion, lameness, muscle tremor, muscle weakness, paresis, proprioception abnormality, recumbency, and death. For all other signs of concern, all cases including the signs were assessed for causality.

In total, 363 cases were included for the case series evaluations for these signs.

Table 3.2.1. Causality assessment summary for signs of concern

Preferred Term	Cases assessed	Causality score 0 or higher	Assessed as probably-associated	
			Total	Subset with positive rechallenge
Ataxia	160	159	27	3
Death	121	120	26	N/A
Recumbency	106	104	34	5
Muscle weakness	81	80	23	1
Paresis	64	64	17	3
Proprioception abnormality	60	60	10	0
Convulsions	42	42	7	1
Lameness	29	27	10	1
Muscle tremor	28	28	9	0
Paralysis	24	24	3	0
Collapse NOS	23	23	3	0
Immune-mediated	15	15	0	0
Pancreatitis	11	11	0	0

The remainder of this section will include data from the 360 cases with causality scores of 0 or greater.

Figure 3.2.1.a. Time to onset of clinical signs – all cases combined (N=360)

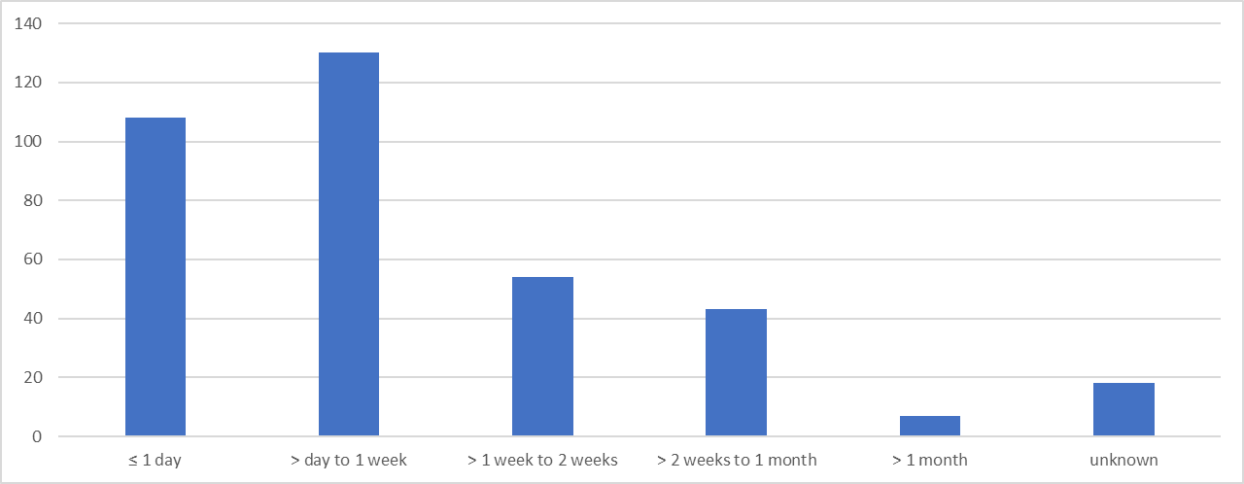

Figure 3.2.1.b. Time to onset of clinical signs – by specific preferred term

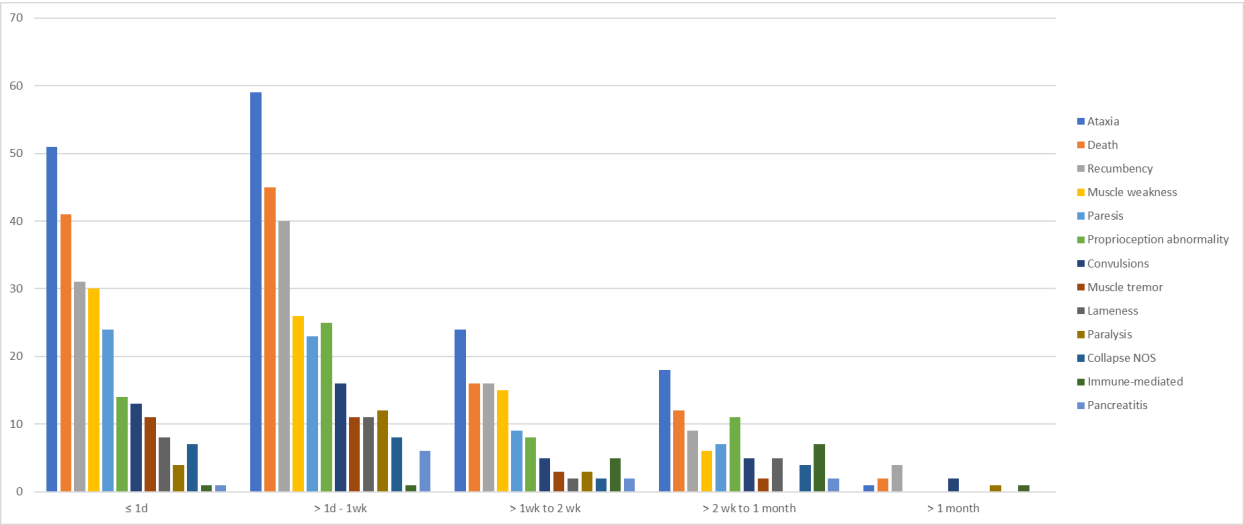

Table 3.2.2. Summary of time to onset for cases with clinical signs of concern

		Time to onset					
Preferred Term	# cases	≤1d	>1d – 1wk	>1wk – 2 wk	>2 wk – 1 month	> 1 month	Unknown
Ataxia	159	51	59	24	18	1	6
Death	120	41	45	16	12	2	4
Recumbency	104	31	40	16	9	4	4
Muscle weakness	80	30	26	15	6		3
Paresis	64	24	23	9	7		1
Proprioception abnormality	60	14	25	8	11		2
Convulsions	42	13	16	5	5	2	1
Muscle tremor	28	11	11	3	2		1
Lameness	27	8	11	2	5		1
Paralysis	24	4	12	3	0	1	4
Collapse NOS	23	7	8	2	4		2
Immune-mediated	15	1	1	5	7	1	
Pancreatitis	11	1	6	2	2		

Figure 3.2.2. Distribution of cases with clinical signs after first Librela™ dose (N=360)

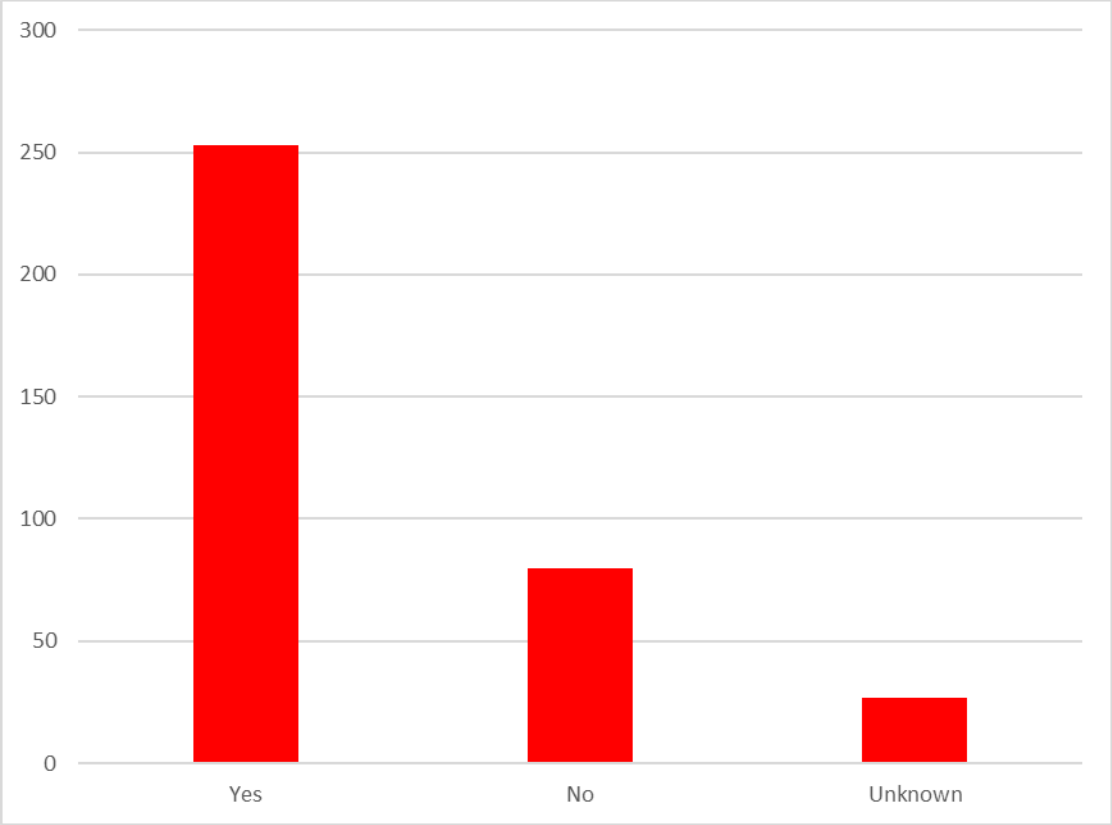

Figure 3.2.3. Distribution of cases with concomitant products (N=360)

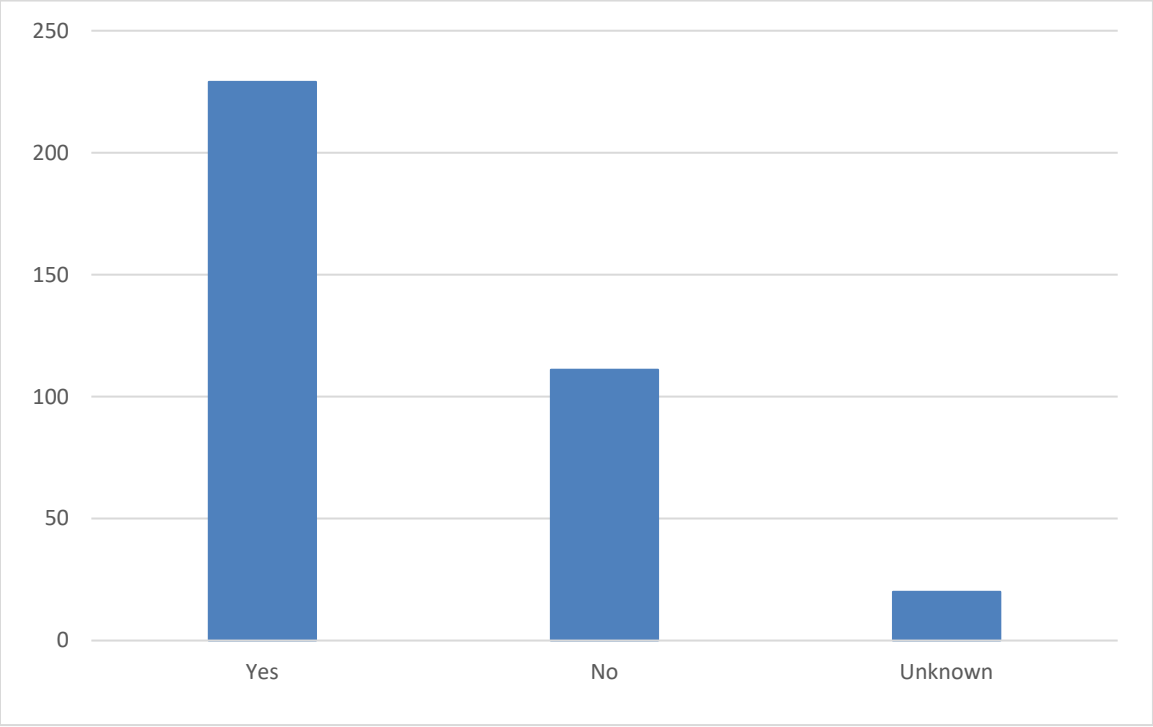

Table 3.2.3. Summary of cases with signs after initial dose of Librela™ and cases with concomitant products

	Sign(s) after initial Librela™ dose			Concomitant product use reported		
Preferred Term	Yes	No	Unknown	Yes	No	Unknown
Ataxia	113	32	14	111	42	6
Death	94	19	7	82	32	6
Recumbency	75	26	3	70	31	3
Muscle weakness	50	23	7	51	27	2
Paresis	47	14	2	41	17	5
Proprioception abnormality	42	14	3	41	15	3
Convulsions	30	6	6	26	14	2
Muscle tremor	20	7	1	12	12	4
Lameness	19	6	2	15	10	2
Paralysis	16	4	4	14	4	6
Collapse NOS	15	5	3	15	8	
Immune-mediated	12	3		12	2	1
Pancreatitis	10	1		8	3	

Of the 229 cases which have concomitant product use reported, 172 (75%) have clinical signs reported after the initial Librela™ dose with 56 cases reporting signs within the first day and 59 more reporting signs after the first day but within the first week of the initial Librela™ dose.

Table 3.2.4. Summary of time of onset for cases with concomitant product use and signs reported after the initial Librela™ dose by individual PT

	Cases with concomitant products		Time to onset for cases with concomitant product use and signs after 1st Librela™ dose		
Preferred Term	# of cases	# of cases with signs after first dose (%)	≤ 1 day	> 1 day to 1 week	> 1 week
Any sign of concern	229	172 (75%)	56	59	49
Ataxia	111	83 (75%)	34	25	24
Death	82	66 (80%)	24	23	19
Recumbency	70	52 (74%)	15	20	17
Muscle weakness	51	35 (69%)	11	12	12
Paresis	41	32 (78%)	9	10	13
Proprioception abnormality	41	32 (78%)	7	13	12
Convulsions	26	20 (77%)	6	9	5
Muscle tremor	12	11 (92%)	6	5	
Lameness	15	10 (67%)	2	4	4
Paralysis	14	12 (86%)	2	9	1
Collapse NOS	15	10 (67%)	5	3	2
Immune-mediated	12	10 (83%)			10
Pancreatitis	8	7 (88%)	1	4	2

Of the 360 cases assessed, 87 (24%) include a report of concomitant gabapentin use. For the 159 cases assessed which included PT Ataxia, 40 (25%) cases include a report of concomitant gabapentin use.

Figure 3.2.4. Distribution of outcome in cases with signs of concern (N=360)

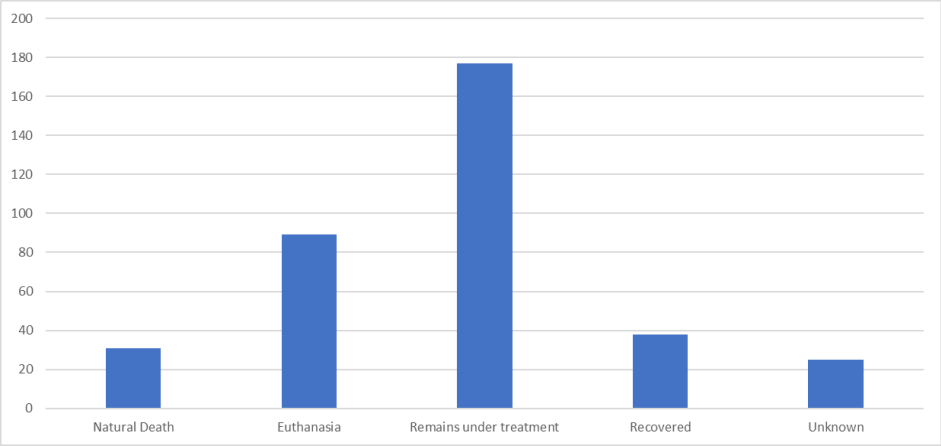

Table 3.2.5. Summary of the outcome in cases with signs of concern by individual PT

Preferred Term	Natural death	Euthanasia	Under treatment	Recovered	Unknown
Any sign of concern	31	89	177	38	25
Ataxia	8	31	97	14	9
Recumbency	4	18	35	10	8
Muscle weakness	5	12	49	6	7
Paresis	3	15	35	9	1
Proprioception abnormality	3	9	44	3	
Convulsions	5	16	12	7	2
Muscle tremor	2	6	13	4	2
Lameness	4	3	14	3	3
Paralysis	4	6	7	2	5
Collapse NOS	4	5	7	6	1
Immune-mediated	1	2	12		
Pancreatitis	1		9	1	

3.3 Results of Other Database Searches

No other databases were searched for the purposes of this review.

3.4 Results of Literature Search

Anderson, K.L., O'Neill, D.G., Brodbelt, D.C. *et al.* Prevalence, duration and risk factors for appendicular osteoarthritis in a UK dog population under primary veterinary care. *Sci Rep* **8**, 5641 (2018). https://doi.org/10.1038/s41598-018-23940-z

Jin K, Hoffman JM, Creevy KE, O'Neill DG, Promislow DE. Multiple morbidities in companion dogs: a novel model for investigating age-related disease. Pathobiol Aging Age Relat Dis. 2016 Nov 21;6:33276. Doi: 10.3402/pba.v6.33276. PMID: 27876455; PMCID: PMC5120387.

McKenzie BA, Chen FL, Gruen ME, Olby NJ. Canine Geriatric Syndrome: A Framework for Advancing Research in Veterinary Geroscience. Front Vet Sci. 2022 Apr 21;9:853743. Doi: 10.3389/fvets.2022.853743. PMID: 35529834; PMCID: PMC9069128.

4. DISCUSSION

Aging is the single most important risk factor for a wide variety of superficially unrelated diseases, including neoplasia, osteoarthritis, cardiac disease neurodegenerative disease, and many others. (McKenzie et al.)

The number of diagnoses increases significantly with age in dogs (Jin et al.), thus it would not be unusual that many recipients of Librela™ would have pre-existing medical conditions and concomitant medications.

With the average age of osteoarthritis diagnosis being 8 – 13 years of age (Anderson et al.), it is not unusual to see that most dogs using this product fell within the 6yr – ≥ 10yr old age range.

Of the pool of cases evaluated, 3234 of 3637 (88.9%) were reported by a veterinarian or other health care professional.

Current references from the sponsor list the most common clinical signs reported in a clinical study as urinary tract infection, bacterial skin infections and dermatitis. Post approval adverse drug experiences as of 2/1/2024 (n=1529) report the three most reported clinical signs as ataxia, anorexia, and lethargy. Falling lower in the clinical sign frequency list are urinary tract infection (#13), bacterial skin infection (#41) and dermatitis (#32). As of 5/31/2024 (n=5301), the three most reported clinical signs were ataxia, anorexia, and death. Again, urinary tract infection (#15), bacterial skin infection (#45) and dermatitis (#36) were listed lower on the clinical sign frequency list.

Of the 66 cases that reported concomitant gabapentin use, 1 case reported gabapentin as treatment for clinical signs occurring after the use of Librela™ and 1 case reported starting gabapentin concurrently with administration of Librela™ . The remaining cases stated it being unknown as to how long the pet had been on gabapentin or stated a known length of time the pet had been on gabapentin prior to Librela™ administration. Seven cases stated a specific amount of time for gabapentin use prior to Librela™ administration (ranging from 8 days prior to Librela™ administration to "the last several years"). For cases that simply stated that the pet was also on gabapentin, it was reasonable to deduce from the

information provided that the pet had consistently been on gabapentin (with or without other concomitant medications) prior to Librela™ administration.

Descriptive analyses

As of April 18, 2024, CVM's database included 3,674 cases reported in association with Librela™ which had been received through March 31, 2024. Most of these cases (99%) were reported in dogs, the species for which the drug is indicated. Small numbers of cases were received starting in September 2023, with large monthly increases from October through January 2024, after which the number of cases received per month stabilized through March 2024.

The age distribution of dogs in the cases received for Librela™, which is approved for the control of pain associated with osteoarthritis is dogs, is skewed with greater numbers of cases reported for dogs in older age groups (73% of cases are reported in dogs ≥ 10 years old) compared to the other cases in CVM's database (18% of cases are reported in dogs ≥ 10 years). This is not surprising as osteoarthritis is a disease that is most commonly diagnosed in older dogs.

A concern expressed by the sponsor is that the large amount of reporting for this product is "overreporting" due to negative social media activity about the product. (DER Submission Filename: 141562-000233-0424-L-SPECIAL-Special_Other) CVM does not believe that there is overreporting, as it is generally accepted that underreporting of adverse events is significant in spontaneous reporting systems, including serious or severe adverse drug events and there is no evidence that the cases being reported are not true cases associated with Librela™. Current evidence in CVM's database suggests that veterinarians and other health care professionals are involved in most of the cases being reported for Librela™. The majority (89%) of the cases reported for Librela™ were reported by a veterinarian (53%) or other health care professional (36%), usually a veterinary technician, and only 10% were reported by the animal owner. For all other cases in dogs reported during this period, 55% were reported by a veterinarian (22%) or other health care professional (32%), and 30% were reported by the animal owner.

The attending veterinarian's level of suspicion for Librela™ being a causal factor in the reported adverse events was reported as "probable/high" or "possible/medium" in 80% of the cases. It was considered "unlikely/low" in 10% of the cases and in 9% of the cases there was no attending veterinarian. About 1% of the cases indicated the level of suspicion was unknown or the field was left blank.

In comparison, for all other cases reported during this time period associated with other drug products and involving dogs, the attending veterinarian's level of suspicion was reported as "probable/high" or "possible/medium" in 32% of the cases. Level of suspicion was considered "unlikely/low" in about 5% of cases and in 18% of the cases there was no attending veterinarian. Level of suspicion was reported as unknown in about 45% of the cases and was blank in 3%.

These differences could indicate differences in both veterinary involvement in cases associated with reported ADEs, as well as level of information procurement from reporters by the drug sponsors, with both being higher for Librela™ relative to other cases received during this time period.

Many of the most frequently reported signs for Librela™ are not currently on the product labeling, including the most frequently reported sign, ataxia, which is reported in 17% of cases so far received. Other frequently reported preferred terms which are unlabeled include polydipsia, death, diarrhea, muscle weakness, convulsion, recumbency, and paresis.

Frequency is not the only parameter considered when determining clinical signs of concern. Severity of a sign is also considered. There may be severe signs such as anaphylaxis which are not reported frequently but have important consequences. Therefore, these severe signs are also monitored, reviewed, and analyzed and may be determined important to include in a post-approval experience (PAE) section.

Disproportionality analysis

Disproportionality analysis for Librela™ includes standard DPA runs, as well as targeted runs against other products approved for control of pain for osteoarthritis. Additionally, as the age distribution for Librela™ is skewed relative to many other products in CVM's database, age-group stratified runs were also performed to control for potential age-related adverse events. Due to the very low numbers of cases for the youngest age-groups, as expected based on Librela™'s indication, discussion will be focused on the two oldest age-group categories. However, it should be noted that both ataxia and paresis signal for the 1 to 5 years-old category for both the standard and targeted runs.

The following severe signs of concern signal for disproportionality for both the standard DPA and targeted runs and in the two oldest age group categories in both age stratified runs:

- Ataxia
- Recumbency
- Polyuria/pollakiuria
- Muscle weakness
- Musculoskeletal disorder
- Paresis
- Proprioception abnormality
- Lameness
- Paralysis
- CNS disorder NOS
- Collapse NOS
- Impaired consciousness.

The only labeled sign among those listed above is polyuria/pollakiuria. Lameness is associated with Librela™'s indication; however, it is interesting that it is disproportionately reported compared to other products with the same indication.

CVM has considered that negative social media activity may stimulate ADE reporting which could affect disproportionality analysis. However, disproportionality analysis is used as hypothesis generating and identified signals are evaluated by in-depth case review.

Case series

Case series evaluations were performed for the following signs of concern:

- Ataxia
- Convulsion
- Paresis
- Proprioception abnormality
- Paralysis
- Recumbency
- Muscle weakness
- Muscle tremors
- Lameness
- Collapse NOS
- Immune-mediated PTs (IMHA, IMTP, IMPA)
- Pancreatitis
- Death (incorporated into individual clinical signs)

Signs selected for case series were chosen with consideration of severity, reporting frequency, unexpectedness, disproportionality, and/or impressions from initial case review.

There were 766 cases received which included at least one of these clinical signs as of February 3, 2024. Due to large number of cases received for the following signs, only cases which included at least two of the signs of concern were assessed for causality: ataxia, convulsion, lameness, muscle tremor, muscle weakness, paresis, proprioception abnormality, recumbency, and death. For all other signs of concern, all cases including the signs were assessed for causality.

In total, 363 cases were included for the case series evaluations for these signs. All but three of these cases have causality scores of at least 0, indicating that there is evidence suggestive of at least a possible causal association between the sign(s) and Librela™ in the other 360 cases. The evidence is considered stronger in 80 of these cases in which the signs are considered probably-associated with Librela™, including 7 cases with positive rechallenge on a subsequent Librela™ dose. The narratives of many cases describe the adverse event (or events) occurring within a week of Librela™ administration, often with no other reasonable explanation for the adverse event in terms of concomitant medication or comorbidities. For cases with dogs on concomitant medications, many indicate a stable dosing history on these other medications prior to introduction of Librela™. Many dogs developed the clinical sign or signs of concern after their initial Librela™ dose. The commonality across cases was that the dogs received a Librela™ injection.

Two-thirds of the assessed cases report signs which occurred within the first week after Librela™ administration, with signs occurring within the first day in 30% of the cases. Signs

occurred after the initial dose of Librela™ in 70% of the cases assessed. No concomitant product use is reported in just over 30% of the assessed cases.

Any concomitant product use and concomitant gabapentin use is reported in 63% (n=229) and 24% (n=87) of the assessed cases, respectively. Of the cases which report any concomitant product use, 75% (n=172) report signs after the first dose of Librela™ and 65% (n=150) report signs occurred within the first week of Librela™ administration. Concomitant product use is not unusual as osteoarthritis may be managed with a variety of products. The population of dogs with osteoarthritis is generally older, and as such is likely to have additional age-related comorbidities requiring treatment.

At the time the cases were pulled from the database for evaluation, death, including euthanasia (n=89), was reported in 120 (33%) cases, recovery was reported in 38 (11%) cases, and "under treatment" was reported in 177 (49%) cases. Outcome was reported as unknown in 25 (7%) of the cases.

Ataxia

Of the 160 cases of Ataxia assessed, 159 have causality scores of zero or greater, indicating possible causality. Twenty-seven cases are considered probably associated, with 3 of these having positive rechallenge on subsequent Librela™ dose(s). Ataxia occurred within the first week for about 70% (n=110) and after the first dose in 113 cases (70%). No concomitant product use is reported in about 25% (n=42) of the ataxia cases.

Any concomitant product use and concomitant gabapentin use is reported in 70% (n=111) and 25% (n=40) of the assessed cases, respectively. Of the cases which report any concomitant product use, 75% (n=83) report signs after the first dose of Librela™ and 71% (n=59) report that signs occurred within the first week of Librela™ administration. Ataxia is a known side effect of gabapentin and has been proposed as being responsible for the ataxia seen with Librela™ use. However, the majority (75%) of the cases assessed for this review do not report gabapentin use.

At the time the cases were pulled for evaluation death, including euthanasia (n=31), was reported in 39 (25%) cases, recovery was reported in 14 (9%) cases, and under treatment was reported in 97 (61%) cases.

In a reported case, an 11-year-old Yorkshire Terrier was administered Librela™ with no concomitant medications. Later that same day, the pet experienced ataxia, muscle weakness, and recumbency. The pet, who had a skin condition prior to drug administration, also experienced purulent drainage from the injection site.

Convulsions

All 42 convulsion cases are assessed with causality scores of zero or greater, indicating possible causality. Seven cases are considered probably associated, with 1 of these having positive rechallenge on subsequent Librela™ dose(s). Convulsions occurred within the first week for 69% (n=29) and after the first dose in 30 cases (71%). No concomitant product use is reported in 33% (n=14) of the convulsion cases.

Any concomitant product use is reported in 62% (n=26) of the assessed convulsions cases. Of the cases which report any concomitant product use, 77% (n=20) report signs after the first dose of Librela™ and 58% (n=15) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=16), was reported in 21 (50%) cases, recovery was reported in 7 (17%) cases, and under treatment was reported in 12 (28%) cases.

A case report describes a 14-year-old Chihuahua receiving Librela™ for the first time, with no concomitants, experiencing 3 seizures within 48 hours of drug administration. The pet continued to decline and was euthanized 4 days post drug administration.

Paresis

All 64 cases of paresis are assessed with causality score of 0 or greater. Seventeen cases are considered probably associated, with 3 of these having positive rechallenge on subsequent Librela™ dose(s). Paresis occurred within the first week for about 74% (n=47) and after the first dose in 47 cases (74%). No concomitant product use is reported in 26% (n=17) of the paresis cases.

Any concomitant product use is reported in 64% (n=41) of the assessed cases. Of the cases which report any concomitant product use, 78% (n=32) report signs after the first dose of Librela™ and 49% (n=19) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=15), was reported in 18 (28%) cases, recovery was reported in 9 (14%) cases, and under treatment was reported in 35 (55%) cases.

A case report describes a 10-year-old cross breed, with no concomitant medications, being euthanized after experiencing paresis and a "stroke" 24 hours after Librela™ administration.

A case report describes a 13-year-old Labrador Retriever, with no concomitant medications, dragging its hind limbs the same day after receiving its first Librela™ injection. The same pet experienced hind limb weakness 13 days after receiving it's second Librela™ injection.

A case report describes a 10-year-old Mastiff, concomitantly taking gabapentin, Proin, tramadol, amantadine, and prednisone, experiencing ataxia and hindlimb paresis at an unknown time after the first injection and the inability to walk with no pain responses approximately 4 hours after the second Librela™ injection.

Proprioception abnormality

All 60 cases of proprioception abnormality are assessed with causality scores of zero or greater, indicating possible causality. Ten cases are considered probably associated. Proprioception abnormality occurred within the first week for 65% (n=39) and after the first

dose in 42 cases (70%). No concomitant product use is reported in 25% (n=15) of the proprioception abnormality cases.

Any concomitant product use is reported in 68% (n=41) of the assessed proprioception abnormality cases. Of the cases which report any concomitant product use, 78% (n=32) report signs after the first dose of Librela™ and 49% (n=20) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=12), was reported in 12 (20%) cases, recovery was reported in 3 (5%) cases, and under treatment was reported in 44 (73%) cases.

Cases often do not describe neurologic signs or concerns prior to receiving the product but after receiving the injection, proprioceptive issues were seen.

A case report describes a 14-year-old Miniature Poodle receiving two injections of Librela™ with no concomitants with each administration. After the first injection, the pet experienced anorexia and pruritus. After the second injection, the pet developed proprioception deficits and paralysis a few days after drug administration.

Paralysis

All 24 cases of paralysis are assessed with causality score of 0 or greater. Three cases are considered probably associated. Paralysis occurred within the first week for 67% (n=16) and after the first dose in 16 cases (67%). No concomitant product use is reported in 17% (n=4) of the paralysis cases.

Any concomitant product use is reported in 58% (n=14) of the assessed cases. Of the cases which report any concomitant product use, 86% (n=12) report signs after the first dose of Librela™ and 79% (n=11) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=6), was reported in 10 (42%) cases, recovery was reported in 2 (8%) cases, and under treatment was reported in 7 (29%) cases.

A case report describes a 14-year-old Labrador Retriever receiving Librela™ with no concomitant medications. Later that day, the hind limbs were described as paralyzed. Six hours after the described hind limb paralysis, the pet recovered.

Another case report describes a 10-year-old Great Pyrenes, also on Previcox as needed, experiencing ataxia about an hour post drug administration. Within 24 hours, the pet also experienced both urinary and fecal incontinence and hindlimb lameness, which progressed to the forelimbs. By 48 hours post drug administration, the pet was described as paralyzed. Four days post drug administration, the pet died.

Recumbency

Of the 106 cases of recumbency assessed, 104 have causality scores of zero or greater, indicating possible causality. Thirty-four cases are considered probably associated, with 5 of these having positive rechallenge after subsequent Librela™ dosing. Recumbency occurred within the first week after Librela™ administration in 68% (n=71) of the possible cases and after the initial Librela™ dose in 75 cases (72%).

Any concomitant product use is reported in 67% (n=70) of the assessed recumbency cases. Of the cases which report concomitant product use, 74% (n=52) report signs after the first dose of Librela™, and 67% (n=46) report signs occurred within the first week of Librela™ administration.

A case report describes 12-year-old Golden Retriever, with no concomitant products, receiving Librela™ for the first time. Four days after Librela™ administration, the patient was laterally recumbent and unable to lift his head. Six days after drug administration, the patient died. A necropsy was not performed

Muscle weakness

Of the 81 cases of muscle weakness assessed, 80 have causality scores of zero or greater, indicating possible causality. Twenty-three cases are considered probably associated, with 1 of these having positive rechallenge on subsequent Librela™ dose(s). Muscle weakness occurred within the first week for 70% (n=56) and after the first dose in 50 cases (62%). No concomitant product use is reported in 34% (n=27) of the muscle weakness cases.

Any concomitant product use is reported in 64% (n=51) of the assessed muscle weakness cases. Of the cases which report any concomitant product use, 69% (n=35) report signs after the first dose of Librela™ and 45% (n=23) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=12), was reported in 17 (21%) cases, recovery was reported in 6 (8%) cases, and under treatment was reported in 49 (61%) cases.

A case report described a 12-year-old Italian Greyhound, receiving no concomitant medications, experiencing hind end weakness and ataxia 5 days after Librela™ administration.

Muscle tremor

All 28 muscle tremor cases are assessed with causality scores of zero or greater, indicating possible causality. Nine cases are considered probably associated. Muscle tremors occurred within the first week for 78% (n=22) and after the first dose in 20 cases (71%). No concomitant product use is reported in 43% (n=12) of the muscle tremor cases.

Any concomitant product use is reported in 43% (n=12) of the assessed muscle tremor cases. Of the cases which report any concomitant product use, 92% (n=11) report signs after the first dose of Librela™ and 92% (n=11) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=2), was reported in 8 (30%) cases, recovery was reported in 4 (15%) cases, and under treatment was reported in 13 (48%) cases.

A case report describes a 15-year-old Shetland Sheepdog, receiving two injections of Librela™ with no concomitant medications. The pet had no reaction after the first dose of Librela™ . Twenty-four hours after the second dose of Librela™ , the pet developed hind limb ataxia, hind limb weakness, and hind limb muscle tremors. The pet recovered 5 days post drug administration.

Lameness

Twenty-seven of the 29 lameness cases are assessed with causality scores of zero or greater, indicating possible causality. Ten cases are considered probably associated with Librela™ administration, with one case having positive rechallenge after a subsequent dose. Lameness occurred within the first week for 70% (n=19) and after the first dose in 19 cases (70%). No concomitant product use is reported in 37% (n=10) of the lameness cases.

Any concomitant product use is reported in 56% (n=15) of the assessed lameness cases. Of the cases which report any concomitant product use, 67% (n=10) report signs after the first dose of Librela™ and 67% (n=10) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=3), was reported in 7 (26%) cases, recovery was reported in 3 (11%) cases, and under treatment was reported in 13 (52%) cases.

A case report describes an 11-year-old Labrador Retriever receiving its first Librela dose with no concomitant medications. The pet developed lethargy and shaking 4 days post injection followed by lameness 5 days post injection.

A case report describes a 15-year-Labrodor Retriever that had received Librela previously without issue. There were no concomitant medications administered with the most current Librela dose. Twenty-four hours post injection, the pet was unable to bear weight on its forelimbs and proprioceptive deficits were present.

A case report describes a 9-year-old Saint Bernard receiving its second dose of Librela with no concomitant medications. Six days post injection, the pet developed acute knuckling and was non-weight bearing on the left forelimb. The pet died 9 days post injection.

Collapse NOS

All 23 cases of collapse are assessed with causality score of 0 or greater. Three cases are considered probably associated. Collapse occurred within the first week for about 65% (n=15) and after the first dose in 15 cases (65%). No concomitant product use is reported in 35% (n=8) of the collapse cases.

Any concomitant product use is reported in 65% (n=15) of the assessed cases. Of the cases which report any concomitant product use, 67% (n=10) report signs after the first dose of Librela™ and 53% (n=8) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=5), was reported in 9 (39%) cases, recovery was reported in 6 (26%) cases, and under treatment was reported in 7 (30%) cases.

A case reports describes a dog of unknown age and breed, with no concomitant medications, experiencing 2 episodes of collapse within 9 days of Librela™ administration.

Immune-mediated cases

All 15 cases involving immune-mediated events (IMHA, IMTP, IMPA) are assessed with causality score of 0 or greater. Signs occurred within the first week for about 13% (n=2) and after the first dose in 12 cases (80%). No concomitant product use is reported in 13% (n=2) of the immune-mediated cases.

Any concomitant product use is reported in 80% (n=12) of the assessed cases. Of the cases which report any concomitant product use 83% (n=10) report signs after the first dose of Librela™ and all cases occurred after the first week post-administration.

At the time the cases were pulled for evaluation death, including euthanasia (n=2), was reported in 3 (20%) cases, recovery was not reported in any of the cases, and under treatment was reported in 12 (80%) cases.

A case report describes a 9-year-old German Pointer, with no concomitant medications, receiving Librela for the first time and being euthanized after being diagnosed with immune mediated hemolytic anemia 2 weeks after drug administration.

Pancreatitis

All 11 cases of pancreatitis are assessed with causality score of 0 or greater. Pancreatitis occurred within the first week for about 63% (n=7) and after the first dose in 10 cases (91%). No concomitant product use is reported in 27% (n=3) of the pancreatitis cases.

Any concomitant product use is reported in 73% (n=8) of the assessed cases. Of the cases which report any concomitant product use 88%, (n=7) report signs after the first dose of Librela™ and 62% (n=5) report signs occurred within the first week of Librela™ administration.

At the time the cases were pulled for evaluation death was reported in 1 case, recovery was reported in 1 case, and under treatment was reported in 9 cases.

A case report describes an 11-year-old unknown breed, with no concomitant medications, developing pancreatitis and acute renal failure 2 weeks after receiving Librela.

5. CONCLUSION AND RECOMMENDATIONS

Based on the evaluation and analysis of the reports and signs seen for Librela, the recommendation is to add a Post Approval Experience (PAE) section to the current label:

Post Approval Experience Section (2024)
The following adverse events are based on post-approval adverse drug experience reporting for LIBRELA. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.
The following adverse events in dogs are categorized in order of decreasing reporting frequency by body system and in decreasing order of reporting frequency within each body system:
Neurologic: ataxia, seizures, paresis, proprioceptive deficits, paralysis
General: anorexia, lethargy, recumbency
Renal/Urinary: polydipsia, polyuria/pollakiuria, urinary incontinence
Gastrointestinal: vomiting, diarrhea
Musculoskeletal: muscle weakness, muscle tremors, lameness
In some cases, death (including euthanasia) has been reported as an outcome of the adverse events listed above.

In addition, we suggest that owners be advised of the adverse reactions that may occur following administration of Librela.

While there is concern regarding other signs assessed in this review (Collapse NOS, immune-mediated signs, and Pancreatitis), the evidence for an association is not as strong as for the signs being included in the PAE section. Therefore, at this time these signs will continue to be monitored and may be considered for future safety-related labeling updates depending on the evidence in additional cases which may be received.

6. REFERENCES

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Appendix I. Database Overview

PV-Works and PV-Analyser are pharmacovigilance database applications maintained and utilized by FDA-CVM to support CVM's post-marketing safety surveillance program for animal drugs and devices. They contain reports of adverse drug events (ADEs), lack of effectiveness, and product defects. PV-Analyser is complementary to PV-Works and serves as a data querying, analysis, and trending tool for CVM's pharmacovigilance data which resides in PV-Works. ADE reports are imported from PV-Works to PV-Analyser on a weekly basis. Reporting of adverse drug events to CVM by veterinary health care providers or by the public is voluntary in the United States. Adverse events may be reported to the product's manufacturer, which is required to send adverse event reports to FDA-CVM, as specified by regulations (21 CFR 514.80). CVM uses this database to monitor for adverse events, product defects and medication errors that are seen under actual conditions of use, and which may not have been seen during pre-market testing. CVM can use this information to evaluate trends and relative frequencies of reported adverse drug experiences.

Adverse event data have limitations, and for any given case report, it is rarely possible to know with a high-level of certainty whether the event was caused by the product. Adverse event reporting systems are subject to a number of reporting biases (e.g., reporting stimulated by publicity or litigation), as well as confounders (e.g., concomitant medications and comorbidities), which are considered when CVM evaluates adverse event reports. ADE data may also be affected by the submission of incomplete or duplicate reports, and underreporting. In addition, since there is not an accurate way to determine the total number of animals exposed to the drug, accumulated ADE reports cannot be used to calculate incidence rates or other estimates of risk. There may be more ADEs for a particular drug that is used widely to treat certain conditions than for another drug that is not used as often. This does not imply that the first drug is more unsafe than the second and may be related to many other factors besides drug safety (e.g., disparate size and/or characteristics of the populations using the two drugs).

Signal detection may be employed within a pharmacovigilance database as a hypothesis-generating method and may be useful for assessing patterns of reporting and time trends. It is not a tool for establishing causal relationships between products and adverse events. Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. Such comparisons are however subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, comparisons of two or more reporting rates should be viewed with a clear understanding of the inherent statistical limitations and considered exploratory or hypothesis-generating. Further investigation is required in order to assess whether a true safety signal exists.

As part of CVM's ADE review process, reported clinical signs are verified and edited as appropriate. Clinical sign coding is accomplished using the Veterinary Medical Dictionary for Drug Regulatory Authorities (VeDDRA). The VeDDRA dictionary has a hierarchical coding schema, from the System Organ Class (SOC) down to the High Level Term (HLT), Preferred Term (PT), and Low Level Term (LLT). This allows searching for groups of signs at a more or less specific level.