



Summary of Studies Supporting USDA Product Licensure

Establishment Name	Elanco US Inc.
USDA Vet Biologics Establishment Number	196
Product Code	2668.02
True Name	Leptospira Canicola-Grippotyphosa-Icterohaemorrhagiae-Pomona Bacterial Extract
Tradename(s) / Distributor or Subsidiary (if different from manufacturer)	Elanco US Inc. Ultra Duramune 4L - Elanco US Inc.
Date of Compilation Summary	December 19, 2019

Disclaimer: Do not use the following studies to compare one product to another. Slight differences in study design and execution can render the comparisons meaningless.

Study Type	Efficacy
Pertaining to	<i>Leptospira canicola</i>
Study Purpose	To demonstrate effectiveness against <i>Leptospira canicola</i> in 6 week old dogs.
Product Administration	Two doses were administered subcutaneously (SC) 3 weeks apart.
Study Animals	Twenty-three (23) 6 week old puppies serologically negative for <i>Leptospira</i> were randomized into one group of 11 SC vaccinates and one group of 12 controls.
Challenge Description	Twenty-one (21) days after second vaccination all animals were challenged with <i>Leptospira canicola</i> organisms.
Interval observed after challenge	Dogs were observed daily for 21 days after challenge for clinical signs associated with <i>L. canicola</i> . Blood samples were collected through 14 days after challenge.
Results	<p>Efficacy was determined by comparing vaccinates versus controls in clinical signs, thrombocytopenia, and leukopenia.</p> <p>A dog was considered to have thrombocytopenia if the platelet count dropped below 200 k/μL and the count was less than 50% of the baseline value.</p> <p>A dog was considered to have leukopenia if the platelet count dropped below 6 k/μL and the count was less than 50% of the baseline value.</p> <p>Data tables are appended to the end of this summary.</p>
USDA Approval Date	April 3, 1998

Leptospira canicola White Blood Cell Count Post Challenge

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	SC Vaccinates													
		1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
12	22.1	25.8	15.1	17	20.3	19.3	20	20.7	16.5	19.4	19.3	10.7	17.2	19.6	16.6
13	12.3	12.4	9.3	9.6	10.5	9	8	12.5	11.8	10.4	8.8	12.7	10.2	9.7	9.1
14	21.7	19.8	12.3	12.9	14	15.5	13.6	17.4	19.2	19.3	16.9	15.3	14	23.2	15.7
15	13.3	8.8	9.6	12.7	8.2	11.5	12.2	13.1	11.8	8.5	8.5	13.1	9.2	10.2	9.4
16	14	13.2	9.5	7.6	8.4	10.1	10.2	9.4	11.4	9.7	11.3	9.3	10.1	10.8	10.5
17	14.3	16.1	12.8	11.8	12.2	10.7	13.2	12.5	9.8	7.3	8.8	9.5	10.3	9.9	12.3
18	11	11.4	10.6	10.1	10.2	9.4	11.7	9.7	9.3	9.3	9.1	11.6	11.7	17.2	17.6
19	8.9	8.4	8	9.1	8.4	6.6	7.2	7.5	6.4	8.2	7	8.8	7.3	12.3	13.4
20	11.2	15.8	10.7	9.1	7.6	8	9	9.2	10.5	11.4	7	13	9.3	7.6	12.7
21	11	10.5	9.5	15.1	14.6	14.1	13.9	13.4	20.7	14.9	11.7	16.5	13.2	14.7	21.7
22	10.2	15.6	9.4	12.1	9.5	12.7	11	7.3	8.3	11.7	7.7	10.2	9.2	11	11.5

DPC = Day post-challenge. Values reported as k/ μ L.

Leptospira canicola White Blood Cell Count Post Challenge

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	Controls															
		1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC		
23	18.3	21.7	14.2	7.4	21.7
24	16.1	20	16.7	6.1	11.5	14.6	20.5										
25	17.1	11.3	13	8.3	10	13.6	17	26	28.1	36.6	36.7	26.2	29.4	21.9			
26	9	7.9	9.6	5.6	5.7	6.7	8	11.7	13.8	16.6	9.6	11.5	12.7	13.9			
27	10.4	8.9	5.5	4.1	5.2	8.6	19.4	21	16.2	11.3	13.9	15	11.5	13.3			
28	9.6	18.4	6.4	3.9	7	19.4	13.2										
29	12.2	19.4	7.8	4.2	5	5.3	17.5										
30	9.5	11.9	9.5	3.2	6.1	7.9	10.6	11.1	10.4	11.4	9.2	12.69	16.7	12.2			
31	8.9	10.6	6.4	4	6	10.3											
32	11.9	12.2	11.5	5.3	6	6.6	15.8										
33	11.8	17.5	6.1	2.6	5.3	4.4	8.7	13	22.8	20.5	31.5	26.3	17.4	16.9			
34	7	9.6	10.1	3.4	5.6	3.8	6	12	12.6	15.3	10.9	15.7	15.9	20.2			

DPC = Day post-challenge. Values reported as k/ μ L.

Leptospira canicola Platelet Counts Post Challenge

SC Vaccinates

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
12	444.3	538	480	452	473	512	531	582	478	631	512	381	483	511	470
13	551.3	679	559	573	576	539	467	636	565	470	501	616	550	510	467
14	473.3	571	452	505	444	536	497	604	693	695	567	568	508	802	640
15	459.7	407	381	543	421	503	612	633	576	497	482	560	438	463	461
16	477.3	377	409	452	456	492	555	558	655	512	519	302	428	399	390
17	318	243	247	311	324	329	389	351	314	288	270	261	232	257	278
18	425.7	331	356	381	398	453	542	247	463	483	405	480	406	554	572
19	348.7	330	353	324	403	375	376	375	379	476	381	414	418	516	524
20	555.3	494	497	530	483	523	538	706	704	662	493	601	462	464	469
21	378.3	332	354	476	447	469	441	514	650	581	501	521	429	474	583
22	469.3	413	455	581	478	576	517	469	473	597	492	500	497	495	593

DPC = Day post-challenge. Values reported as k/ μ L.

Leptospira canicola Platelet Counts Post Challenge

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	Controls															
		1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC		
23	300	238	148	11	7.7	D	D	D	D	D	D	D	D	D	D	D	D
24	342	204	161	64.1	40.5	123	207	D	D	D	D	D	D	D	D	D	D
25	519.7	267	213	187	134	117	285	160	497	710	714	823	738	810	717		
26	404.7	278	279	196	150	172	ND	194	302	441	721	648	599	590	588		
27	482.7	281	225	119	55	49.9	157	100	405	455	492	552	528	428	435		
28	242.3	209	60.4	45.9	3.9	11.1	D	11.3	D	D	D	D	D	D	D	D	D
29	529.7	521	305	195	37.6	15.8	D	42.2	D	D	D	D	D	D	D	D	D
30	329.3	292	167	107	61.7	81.6	242	122	412	518	697	504	632	596	551		
31	432.7	327	150	80.2	38	14	D	D	D	D	D	D	D	D	D	D	D
32	395.7	329	195	103	33.3	14.2	D	44.1	D	D	D	D	D	D	D	D	D
33	563.7	409	182	115	67.1	8.5	11.4	2.4	87.1	235	417	744	701	726	714		
34	232.7	174	150	64.5	41.6	8.3	82.8	6.8	142	273	310	383	479	475	564		
ND= No Data																	
D = dead																	

DPC = Day post-challenge. Values reported as k/ μ L.

Study Type	Efficacy
Pertaining to	<i>Leptospira grippotyphosa</i>
Study Purpose	To demonstrate effectiveness against <i>Leptospira grippotyphosa</i> in 6-week-old dogs.
Product Administration	Two doses were administered subcutaneously (SC) 3 weeks apart.
Study Animals	Twenty (20) 6-week-old puppies were randomized into one group of 10 SC vaccinates and one group of 10 controls.
Challenge Description	Fifteen (15) days after second vaccination all animals were challenged with <i>Leptospira grippotyphosa</i> organisms.
Interval observed after challenge	Dogs were observed daily for 21 days after challenge
Results	<p>Efficacy was based on the reduction in spirochetemia in vaccinates when compared to controls.</p> <p>A data table is appended to the end of this summary.</p>
USDA Approval Date	January 12, 1999

Isolation of Leptospira from Blood Collected from Dogs Post Challenge

Control Animals													
Dog	0DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
1						+							
2					+		+	+					
3				+	+								
4					+	+							
5				+	+	+							
6						+	+	+	+	+	NA	NA	NA
7				+	+	+	+	+	+	NA	NA	NA	NA
8					+	+	+	+	+	+	NA	NA	NA
9				+	+	+	+	+	+	+	NA	NA	NA
10					+	+	+	+	+	+	NA	NA	NA

NA - Animal Dead or euthanized / no sample taken

+ - Positive for Leptospira

*Leptospira was not isolated in any of the SC vaccinates

Study Type	Efficacy
Pertaining to	<i>Leptospira icterohaemorrhagiae</i>
Study Purpose	To demonstrate effectiveness against <i>Leptospira icterohaemorrhagiae</i> in 6 week old dogs.
Product Administration	Two doses were administered subcutaneously (SC) 3 weeks apart.
Study Animals	Twenty-two (22) 6 week old puppies serologically negative for <i>Leptospira icterohaemorrhagiae</i> were randomized into one group of 10 SC vaccinates and one group of 12 controls.
Challenge Description	Twenty-one (21) days after second vaccination all animals were challenged with <i>Leptospira icterohaemorrhagiae</i> organisms.
Interval observed after challenge	Dogs were observed daily for 21 days after challenge for clinical signs associated with <i>L. icterohaemorrhagiae</i> . Blood samples were collected through 14 days after challenge.
Results	<p>Efficacy was determined by comparing vaccinates versus controls in clinical signs, thrombocytopenia, and leukopenia.</p> <p>A dog was considered to have thrombocytopenia if the platelet count dropped below 200 k/μL and the count was less than 50% of the baseline value.</p> <p>A dog was considered to have leukopenia if the platelet count dropped below 6 k/μL and the count was less than 50% of the baseline value.</p> <p>Data tables are appended to the end of this summary.</p>
USDA Approval Date	March 31, 1998

Leptospira Ictero Clinical Signs Observed Post Challenge

Dog	SC Vaccinates																							
	0DPC	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC	15DPC	16DPC	17DPC	18DPC	19DPC	20DPC	21DPC		
11							A																	
12																								
13				E		D								E				E		D			E	
14				E			E		F											D		E	E	
15		A,E							E															
16																								
17																								
18																								
19																								
20			D	D		D	D													D		E		
A-inappetance																								
B-Vomiting																								
C-Depression/Lethargy																								
D-Ocular Discharge Serous																								
E-Ocular Discharge Mucoïd																								
F-Nasal Discharge Serous																								
G-Nasal Discharge Mucoïd																								
H-Diarrhea Mild (loose stool)																								
I-Diarrhea Moderate (Watery stool)																								
J-Diarrhea Severe (bloody stool)																								

DPC = Day post-challenge

Leptospira Ictero Clinical Signs Observed Post Challenge

Controls																															
Dog	0DPC	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC	15DPC	16DPC	17DPC	18DPC	19DPC	20DPC	21DPC									
21					F		A																								
22					F					B												E									
23			L	L								E			E	E	E														
24			L	L																											
25																															
26																															
27			L	D	D	E		J	A				E			D															
28			L,E	K	A,C,D,J						M																				
29			L			D																		D							
30				L,D	A,E						M																				
31			L	E			A					E					E							D							
32							E																	B							
A-inappetance																															
B-Vomiting																															
C-Depression/Lethargy																															
D-Ocular Discharge Serous																															
E-Ocular Discharge Mucoid																															
F - Nasal Discharge Serous																															
G - Nasal Discharge Mucoid																															
H- Diarrhea Mild (loose stool)																															
I- Diarrhea Moderate (Watery stool)																															
J- Diarrhea Severe (bloody stool)																															
K - Bloody Urine																															
L - Fever >103.0°F																															
M - Death																															
Blank - no clinical sign observed																															

DPC = Day post-challenge

Leptospira ictero White Blood Cell Count Post Challenge

SC Vaccinates

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
11	7.2	7.3	12.4	7.9	6.8	10.1	6.4	6.4	6.4	8.5	8.9	9.7	9.6	7.2	6.4
12	10	13.9	10.4	8.9	9.1	12.4	15.2	8.2	11.1	8.6	7.7	10.2	9	9.1	12.3
13	7.6	15.4	9.6	13.2	9.1	14.2	8.8	9.2	9.6	8.3	10.6	6.7	7.8	7.8	8.4
14	13.4	7.6	12.6	8.2	12.6	11.3	9.3	7.3	11.8	8	13.2	9.8	10	12.8	9.1
15	9.8	11.4	9.8	9	8	8.3	11.2	10.2	8	7.5	10.4	7.7	11.1	7.5	10.9
16	9.1	8.8	9.5	6.8	8.1	9.1	9.4	8.4	10.1	7.7	8.7	9.5	10	8.3	8.3
17	9.1	7.1	7.8	8.1	7.5	7.2	10.5	9.4	11.4	7.6	11.7	7.1	10.2	7.5	7.3
18	7.2	7.7	10.5	9.1	6.6	7.3	7.1	8.4	7.4	8	9	8.1	6.5	7.8	6.4
19	9.5	13.8	8.4	11.7	11.7	8.7	6.7	10.5	7.5	8.2	7.7	7.8	7	8.8	6.7
20	13.1	9.9	5.3	9.1	11.9	14.8	14.4	6.4	9.1	8.7	12.5	12.6	7.6	8.1	8.9

DPC = Day post-challenge. Values reported as k/ μ L.

Leptospira ictero White Blood Cell Count Post Challenge

Controls															
Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
21	7.4	6.6	9.6	6.7	8.2	6.2	8.6	6.7	6.5	8.1	10.4	6.4	8.5	6.5	6.2
22	7.4	8.5	9.3	8.2	6.5	7.3	13.4	9.4	7.2	8.2	13.4	10.1	7.7	7.6	9.4
23	9.3	12.2	9.4	11.6	7.1	9	10	7	6.5	7.1	11.9	7	9.6	11	11.8
24	13.7	19.6	10.6	7.8	11.8	15.3	16.7	19.8	16	13.7	19.2	24.9	13.3	24.4	12.3
25	10	13.9	8.5	6.9	9.1	7	10.9	12.8	9.6	10	13.9	9.4	8.3	9	7.1
26	8.4	8.6	9	3.9	11.8	12.2	15.4	11.3	11.8	9	10.2	13.3	8.6	8.9	10.5
27	7.8	7.5	9.4	15.8	14.6	10.7	9.8	7.5	8.6	12.1	8.6	8.3	11.4	7.4	9.5
28	7.8	8.8	6.7	4.5	7.3	7.3	8.8	14.7	10	11.6	11.7	14	8.3	7.8	7.7
29	7.8	6.7	5.8	4.1	26.4										
30	8.8	7.6	5	7.2	7.8	7.5	7.8	6.2	9.9	8	10.3	10.1	9.9	9.4	9.6
31	11	8.1	8.3	4.2	19										
32	8.3	9.3	6.2	5	10.7	12.6	10.6	13.5	14.5	9.6	14.1	9.9	10	10.1	9.3
D = dead															

DPC = Day post-challenge. Values reported as k/ μ L.

Leptospira ictero Platelet Counts Post Challenge

Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	SC Vaccinates													
		1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
11	449.7	432	619	476	440	667	457	447	488	442	591	586	536	471	359
12	518.3	475	456	447	428	526	645	435	480	505	487	453	473	461	517
13	489.3	595	425	560	424	580	445	517	416	508	522	415	347	337	349
14	451.7	258	413	349	457	374	344	335	376	331	431	330	263	351	281
15	357.7	380	297	286	275	282	435	400	314	285	388	288	401	290	369
16	369	264	298	217	264	278	308	268	281	253	316	258	286	284	294
17	473.7	407	400	386	332	214	542	457	513	436	529	417	498	373	381
18	506	482	569	392	397	351	393	419	327	424	406	388	283	391	287
19	477	467	386	552	529	417	459	500	378	489	356	383	331	406	352
20	502.3	412	506	483	525	515	555	352	392	358	488	501	325	340	378

DPC = Day post-challenge. Values reported as k/μL.

Leptospira ictero Platelet Counts Post Challenge

Controls															
Dog	Baseline (Avg -2DPC, -1DPC, 0DPC)	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
21	534.3	291	315	207	301	341	545	506	529	537	575	434	399	414	410
22	428.7	238	250	168	126	184	261	288	340	412	520	421	369	386	367
23	411.3	374	307	265	289	362	393	361	369	447	546	444	422	583	535
24	344.7	251	130	99.5	116	189	312	497	440	480	618	635	461	658	451
25	566	401	220	146	189	288	483	611	458	466	660	519	427	432	409
26	392	302	213	94.9	84.5	210	361	381	421	444	467	578	513	452	388
27	475.7	399	423	483	413	335	386	437	465	575	469	461	540	372	474
28	411.7	214	93.5	60.5	128	213	307	332	467	612	622	618	495	467	383
29	332	136	101	6.7	11.2										
30	421.9	204	80.9	53.9	119	231	379	512	549	516	642	494	411	421	427
31	319.3	163	94.4	36.7	11.9										
32	267	184	55	7.7	88.8	196	257	347	525	430	529	360	337	287	301
D = Dead															

DPC = Day post-challenge. Values reported as k/ μ L.

Study Type	Efficacy
Pertaining to	<i>Leptospira pomona</i>
Study Purpose	To demonstrate effectiveness against <i>Leptospira pomona</i> in 6 week old dogs.
Product Administration	Two doses were administered subcutaneously (SC) 3 weeks apart.
Study Animals	Twenty (20) 6 week old puppies serologically negative for <i>Leptospira</i> were randomized into one group of 10 SC vaccinates and one group of 10 controls.
Challenge Description	Twenty-five (25) days after second vaccination all animals were challenged with <i>Leptospira pomona</i> organisms.
Interval observed after challenge	Dogs were observed daily for 21 days after challenge. Blood samples were collected through 14 days after challenge.
Results	<p>Efficacy was based on the reduction in spirochetemia in vaccinates when compared to controls.</p> <p>A Data table is appended to the end of this summary.</p>
USDA Approval Date	January 12, 1999

Isolation of Leptospira from Blood Collected from Dogs Post Challenge

Control Animals															
Dog	0DPC	1DPC	2DPC	3DPC	4DPC	5DPC	6DPC	7DPC	8DPC	9DPC	10DPC	11DPC	12DPC	13DPC	14DPC
1			+	+	+	+									
2															
3			+	+	+										
4				+	+										
5			+	+	+	+									
6			+	+											
7		+	+	+											
8			+	+	+										
9		+	+	+	+										
10		+		+	+										

DPC= Day post challenge

*Leptospira was not isolated from blood in any of the SC vaccinates

Study Type	Safety																																							
Pertaining to	ALL																																							
Study Purpose	Demonstrate safety of product under typical use conditions																																							
Product Administration	Two doses were administered subcutaneously approximately two weeks apart.																																							
Study Animals	A total of 675 dogs, privately owned and from commercial kennels were enrolled in the study. From these dogs 234 were 6 weeks of age or younger, at first vaccination. Three geographical sites were represented.																																							
Challenge Description	NA																																							
Interval observed after challenge	Animals were observed 30 minutes after each vaccination and daily for two (2) weeks after each vaccination.																																							
Results	<p>Frequency of adverse events:</p> <table border="1" data-bbox="616 887 1401 1599"> <thead> <tr> <th></th> <th>Number of Animals</th> <th>Percent of Animals</th> </tr> </thead> <tbody> <tr> <td>No observed adverse events</td> <td>628</td> <td>93.0%</td> </tr> <tr> <td>Injection Site Lesion</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Diarrhea-one day of loose stools</td> <td>23</td> <td>3.4%</td> </tr> <tr> <td>Heavy Breathing</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Death-Hit by Car *</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Death-depression,decreased appetite, weight loss **</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Lameness (leg cramp) *</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Decreased appetite, weight loss, diarrhea, and dehydration *</td> <td>4</td> <td>0.6%</td> </tr> <tr> <td>Gastroenteritis (vomiting) *</td> <td>2</td> <td>0.3%</td> </tr> <tr> <td>Laceration *</td> <td>1</td> <td>0.1%</td> </tr> <tr> <td>Prolapsed nictitan gland *</td> <td>7</td> <td>1.0%</td> </tr> <tr> <td>Pyoderma *</td> <td>5</td> <td>0.7%</td> </tr> </tbody> </table> <p>*Affirmed by study investigator to have cause other than vaccination **Cause of death was not determined by study investigator. Signs appeared 4 days after vaccination and death 8 days later.</p> <p>The injection site lesion was detected after the second vaccination and resolved within 15 days.</p>		Number of Animals	Percent of Animals	No observed adverse events	628	93.0%	Injection Site Lesion	1	0.1%	Diarrhea-one day of loose stools	23	3.4%	Heavy Breathing	1	0.1%	Death-Hit by Car *	1	0.1%	Death-depression,decreased appetite, weight loss **	1	0.1%	Lameness (leg cramp) *	1	0.1%	Decreased appetite, weight loss, diarrhea, and dehydration *	4	0.6%	Gastroenteritis (vomiting) *	2	0.3%	Laceration *	1	0.1%	Prolapsed nictitan gland *	7	1.0%	Pyoderma *	5	0.7%
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