Experior®

(lubabegron Type A medicated article)

Understanding the FOI Summary

PM-US-20-1029 (2)

Freedom of Information (FOI) Summary

The Freedom of Information Act (FOIA) mandates publicly accessible information.

The FOI summary for Experior provides an overview of information used by the Food and Drug Administration (FDA) to approve the new animal drug application (NADA 141-508).

Summary is prepared and published by the FDA's Center for Veterinary Medicine (CVM).

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General Information

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General Information

Experior (lubabegron Type A medicated article)

Beta-adrenergic agonist/antagonist

Type A contains 10 g per kg (4.54 g per lb)

How Supplied: 10 kg bag

Label Indication: For reduction of ammonia gas emissions per pound of live weight (LW) and hot carcass weight (HCW) in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

Directions for Use: Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% Dry Matter (DM) basis) to provide 13 - 90 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

General Information: Additional Indication Information

Effectiveness has not been demonstrated when fed for less than 14 days.

Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.

Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.

Effectiveness

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Effectiveness

Dose Characterization (3)

Three studies conducted to characterize emissions for NH_3, N_20, H_2S, CH_4, and CO_2

Substantial Evidence: (Clinical Program)

Emission Studies (2)

One study – 91 day duration

One study – 14 day duration

Studies conducted to estimate gaseous emissions for NH_3, N_20, H_2S, CH_4, and CO_2

Field Studies (4)

Two studies – 91 day duration

Two studies – 14 day duration

Studies conducted to demonstrate the safety and impact on production and meat quality of Experior under expected conditions of use.

Effectiveness: Conclusions*

- These studies support the use of Experior for the reduction of NH_3 gas emissions per pound of LW and HCW at the doses evaluated. Experior did not affect N_20, H_2S, CH_4, or CO_2 gas emissions per lb of LW and HCW at the doses evaluated.
- The approved dose range is 1.25 to 4.54 g/ton on a 90% DM basis.
- The approved consumption range is 13-90 mg lubabegron/head/day.
- Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
- To clearly differentiate its effects from other Type A medicated articles with beta-adrenergic activity approved for use in medicated feeds for beef steers and heifers fed in confinement for slaughter, the Indications for Use section includes the following statement: “Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.”

* Experior FOI. FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 18-19

Effectiveness: Dose Characterization Studies

Study	Duration, day	Animals, n (n trt)	Individual or Group	Lubabegron[a]	Result
1	28	12 (6)	Individual	200 (mg/hd/day)	Cumulative NH_3 gas emissions standardized for LW were reduced for the 14 – 27 day period.
2	42	12 (4)	Individual	12.5 and 50 (mg/hd/day)	Cumulative NH_3 gas emissions were reduced for the 50 mg/hd/day dose at 1 – 7, 8 – 14, 1 – 14, 29 – 41, and 1 – 41 day periods. Cumulative NH_3 gas emissions standardized for LW were lower for both non-zero dose groups for the 8 – 14 and 1 – 14 day periods.
3	93	56 (28)	Group	1.25 (g/ton DM)	Cumulative NH_3 gas emissions standardized for LW and HCW were significantly lower for the 1.25 g/ton treatment group.

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM) to provide 13-90 mg of lubabegron/hd/day during the last 14-91 days on feed.

Effectiveness: Dose Characterization Studies Conclusions

Results supported testing Experior at a dose range of 1.25 to 20 g of lubabegron/ton of Type C medicated feed on a 100% DM basis fed for 14 to 91 days in the clinical effectiveness program.

Effectiveness: Gas Emission Studies – Facilities

MICHIGAN	CALIFORNIA

Facility:
• MSU Animal Air Quality Facility
• 12 Individual animal chambers
  ○ 100% concrete chambers
• 7 ft x 13 ft x 8.5 ft (91 ft^2/animal)
• Animals tethered in an elevated platform
	Facility:
	• UCD Beef Cattle research facility
	• 8 cattle pen enclosures (CPEs)
	  ○ Dirt-floored
	• 185 m^2 pens (CPEs); 14 animals/CPE
	• 13 m^2 concrete feed bunk

Study Dates: • March 2014 to March 2015	**Study Dates:** • April 2014 to March 2015
Study Duration: • 14 day	**Study Duration:** • 91 day
Experimental unit: • Individual animal	**Experimental unit:** • Pen

Effectiveness: Gas Emission Studies – Design

Doses:

Dose: grams of Lubabegron/ton				
100% DM	0	1.25	5.0	20
90% DM	0	1.13	4.5	18

Gender: Steers and Heifers

Biological Cattle Type: British and Continental crossbreds

No Concomitant Therapies: No Concomitant Therapies

Gas Emissions Measured* NH_3, N_2O, H_2S, CH_4, CO_2

*Note the only statistical impact was for reduction of NH_3 ammonia gas emissions.

Effectiveness: 91 Day Gas Emissions – Results

	Lubabegron Dose, g/ton (100% DM)[ab]				
Variable	0	1.25	5.0	20.0	P-value
NH_3 emissions, g/hd	7783	7093 (P=0.076)b	6860 (P=0.023)	6751 (P=0.013)	0.052
NH_3/lb LW, g/lb	6.18	5.51 (P=0.009)	5.32 (P=0.002)	5.26 (P<0.001)	0.004
NH_3/lb HCW, g/lb	10.1	8.83 (P=0.004)	8.49 (P<0.001)	8.40 (P<0.001)	0.001
Initial weight, lb	994	1001	1004	996	0.937
Final weight, lb	1250	1286	1283	1282	0.257

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)
[b]*P*-value for the contrast between 0 g/ton and each dose level

Effectiveness:
91 Day Gas Emissions – Summary

- Mean cumulative NH_3 gas emissions per lb of LW and HCW were significantly lower for all dose levels tested.
- Main effect of dose was significant with the lowest effective dose being 1.25 g/ton.
- No evidence was found that the mean at 5 g/ton was different from that at 20 g/ton.
- There was no Dose x Gender interaction.
- Experior did not negatively affect average daily gain (ADG), feed efficiency (FE), liver abscess scores, or carcass characteristics.
- Experior resulted in a slight increase in Warner-Bratzler Shear Force (WBSF), but at a level unlikely to be distinguishable by consumers.

Effectiveness: 14 Day Gas Emissions – Results

Lubabegron Dose, g/ton (100% DM)[a]					
Variable	0	1.25	5.0	20.0	P-value
NH_3 emissions, g/hd	823	763	744	701	0.113
NH_3/lb LW, g/lb	0.642	0.594	0.582	0.551	0.130
NH_3/lb HCW, g/lb	1.00	0.917	0.900	0.852	0.093
Initial weight, lb	1237	1238	1226	1232	0.669
Final weight, lb	1277	1273	1268	1267	0.843
HCW, lb	819	828	823	821	0.798

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)

Effectiveness:
14 Day Gas Emissions – Summary

- None of the gases (NH_3, N_20, H_2S, CH_4, and CO_2) were significantly affected by dose for the 0-14 day period.
- Analysis of the 7-14 day treatment period showed a significant association between treatment and the mean cumulative NH_3 gas emissions per lb of LW and HCW.
- Analysis excluding outliers indicated that gas emissions standardized to LW and HCW were significantly different and numerically reduced for all non-zero treatments compared to controls in the 14 day period.
- Experior did not have any negative effects on ADG, FE, or carcass characteristics.
- There was a slight increase in WBSF, but this is unlikely to be noticed by consumers.

Effectiveness:
14 Day Gas Emissions – Additional Evidence
14 Day NH_3 (g/hd) from other studies

		Lubabegron Dose, g/ton (100% DM)[a]			
Location	**Study Duration[b]**	**0**	**1.25**	**5.0**	**20.0**
Michigan	14	823	763	744	701
California	91	953	835	801	699
Michigan	28	171	NA	NA	150
Michigan	42	494	397	355	NA
California	93	1301	1177	NA	NA

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)
[b]Lubabegron is approved to be fed during the final 14 to 91 days on feed

Effectiveness: Weight of Evidence at 14 Days

- Additional studies were considered in evaluating effectiveness of Experior at 14 days.
  - Mean cumulative NH_3 gas emissions and emissions per lb of LW were numerically lower at 14 days of treatment in previous studies.
  - Given consistency of response to Experior across additional studies (5), FDA concluded that effectiveness at the minimum duration of 14 days is supported.

Effectiveness: Field Studies – Facilities

NEBRASKA	IDAHO
Facility: • 100% concrete pens • 75 ft^2/animal, 1.56 ft/animal of bunk space • 125 ft^2 shade **Study Dates:** • July to October 2014 **Study Duration:** • 14 and 91 day **Transport and Slaughter:** • Distance: 70 miles (~ 2 hr) • Lairage: ~ 17 hr	**Facility:** • Predominately dirt (concrete apron at feed bunk) • 219 ft^2/animal, 3.1 ft/animal of bunk space **Study Dates:** • September to December 2014 **Study Duration:** • 14 and 91 day **Transport and Slaughter:** • Distance: 313 miles (~ 5 to 10 hr) • Lairage: ~ 11 to 14 hr

Effectiveness: Field Studies – Design

Number of Studies:
Two studies – 91 day duration
Two studies – 14 day duration

Doses:

Dose: grams of Lubabegron/ton				
100% DM	0	1.25	5.0	20
90% DM	0	1.13	4.5	18

Study Design:
8 head/pen
4 pens/block
5 blocks per gender (10 blocks)
320 head (160 steers and 160 heifers)

Gender: Steers and Heifers

Biological Cattle Type: British and Continental crossbreds

No Concurrent Therapies: No Concomitant Therapies

Effectiveness: Conclusions*

- These studies support the use of Experior for the reduction of NH_3 gas emissions per pound of LW and HCW at the doses evaluated. Experior did not affect N_20, H_2S, CH_4, or CO_2 gas emissions per lb of LW and HCW at the doses evaluated.
- The approved dose range is 1.25 to 4.54 g/ton on a 90% DM basis.
- The approved consumption range is 13-90 mg lubabegron/head/day.
- Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
- To clearly differentiate its effects from other Type A medicated articles with beta-adrenergic activity approved for use in medicated feeds for beef steers and heifers fed in confinement for slaughter, the Indications for Use section includes the following statement: “Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.”

* Experior FOI, summarized from pages 18-19

Effectiveness: Field Studies Conclusions*

- Animal performance measures (ADG, FE, HCW) were not negatively affected by Experior at any dose.
- No consistent negative effects of Experior were detected for skeletal maturity, lean maturity, and overall maturity.
- No consistent dose related effects were observed for marbling score or WBSF across the four field studies.
- No evidence of a difference in dark cutters was observed.
- Of the sensory traits evaluated by trained panelists, tenderness and chewiness were most frequently impacted, but these changes in sensory variables were deemed acceptable and unlikely to be noticed by consumers.

*Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 16-18

Target Animal Safety

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Target Animal Safety

Animal safety information evaluated in 4,240 animals across 15 studies.

Animal safety evaluated in:

Margin of Safety Study (1)

Emission Studies (2)

Field Studies (4)

Additional Development Studies (8)

Target Animal Safety: Conclusions*

- Experior was tested in cattle fed up to 1300 mg of lubabegron/hd/day (131 g/ton DM).
- Experior was also evaluated for its' effect on animal lameness when fed up to 20 gm/ton DM
  - Experior did not affect animal lameness.
  - Lameness issues in the studies appeared to be related to nutritional management and pen conditions.
  - Most cases resolved while the animals were still receiving Experior, indicating that the lameness was not test article related.
- Experior was found to be safe to the target animal when administered for the reduction of NH_3 gas emissions per lb of LW and HCW in beef steers and heifers fed in confinement during the last 14 to 91 days on feed.
- A caution statement is included on the label: “A decrease in dry matter intake may be noticed in some animals.”

* Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 19-32

Target Animal Safety: Margin of Safety

	Dose[ab]			
Lubabegron, mg/hd/day (gm/ton DM)	0 (0)	260 (24.9)	780 (71.9)	1300 (131.3)
No. Animals	10	10	10	10
Initial Weight, lb	1010.5	979.8	952.6	980.8
Final Weight, lb	1306.4	1304.4	1265.2	1273.1
Daily Gain, lb/day	3.2	3.5	3.4	3.2
DM Intake, lb/day	22.7	20.9	21.7	19.8
Feed Efficiency, gain/DMI	0.14	0.17	0.16	0.16

[a]Lubabegron was top-dressed to achieve intakes of 0, 260, 780, and 1300 mg/hd/day. Based on actual DM intake, lubabegron levels were 0, 24.9, 71.9, and 131.3 gm/ton DM, respectively. The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM).

[b]Study conducted for 95-99 days. Lubabegron is approved to be used for 14-91 days on feed.

Elanco Animal Health. Data on file.

Target Animal Safety: Margin of Safety Conclusions

- No clinically or biologically significant differences in hematology values, clinical pathology values, coagulation values, urinalysis, or physical examination findings.
  - Serum urea nitrogen was decreased while creatinine and phosphorus levels were increased.
  - Changes were not considered treatment related.
- Study demonstrated that Experior when fed according to label is safe to the animal.
  - The Type C approval for Experior is between 1.25 and 4.54 g/ton (90% DM) for the final 14 to 91 days on feed. Thus, the actual level fed was over 20X the maximum approved inclusion level.

Target Animal Safety: Lameness in Clinical Studies

			Lubabegron Dose, g/ton (100% DM)[a]					
Study Type	Location	Duration, day	0	1.25	5.0	20.0	Lame, n	Lame, %
Emissions	Michigan	14	0	1	2	1	4	3.3
Field Safety	Idaho	14	1	1	2	3	7	2.2
Field Safety	Nebraska	14	5	2	3	3	13	4.1
Emissions	California*	91	6	13	23[b]	17	59	17.6
Field Safety	Idaho	91	11	9	15	11	46	14.4
Field Safety	Nebraska	91	12	2[c]	8	7	29	9.1
Lame, n			35	28	53	43		
Lame, %			8.1	6.5	12.2	9.7		

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)
[b]Different from Control during treatment (P=0.018) and unloading (P=0.035)
[c]Different from Control during treatment (P=0.009), loading, unloading and ante-mortem (P=0.014)

*Several animals in California study were observed with interdigital dermatitis (foot rot) likely due to muddy conditions in the pens during the first cycle. Medicated foot baths were used which reduced lameness in the subsequent cycles.

Target Animal Safety: Unresolved Lameness in Clinical Studies

			Lubabegron Dose, g/ton (100% DM)[a]				
Study Type	Location	Duration, day	0	1.25	5.0	20.0	Lame, n
Emissions	Michigan	14	0	0	0	0	0
Field Safety	Idaho	14	0	0	0	0	0
Field Safety	Nebraska	14	3	0	2	2	7
Emissions	California	91	0	0	0	0	0
Field Safety	Idaho	91	0	1	1	1	3
Field Safety	Nebraska	91	7	0	6	4	17
Lame, n			10	1	9	7	

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)

Target Animal Safety: Lameness in Clinical Studies Conclusions

- The incidence of lameness varied by study:
  - In 91 day California study, some cattle were observed with interdigital dermatitis (foot rot) due to muddy conditions in the pens during the first cycle. Medicated foot baths were used which reduced lameness in the subsequent cycles.
- Most cases of lameness resolved during the study.
- Unresolved lameness was observed at similar levels across all treatment groups and at a smaller incidence rate in Experior groups compared to the control group.
- Lameness was not considered to be test-article related.
- No animals were non-ambulatory following transportation to slaughter.

Target Animal Safety: Adverse Events (AE) from the 8 Additional Studies

		Lubabegron Dose, g/ton (100% DM)[a]					
	No Head	0	1.25	2.5	5	10	20
Total Number	2504	665	641	318	354	120	406
Total AE (%)	39 (1.6)	10 (1.5)	10 (1.6)	0 (0)	13 (3.7)	1 (1.2)	5 (1.2)
Injuries	15	3	5	0	4	1	2
Lameness/ Foot Rot	4	3	0	0	1	0	0
Gastrointestinal	10	3	1	0	5	0	1
Respiratory	4	1	2	0	0	0	1

[a]The Type C approval for lubabegron is between 1.25 and 4.54 g/ton (90% DM)

Target Animal Safety: Adverse Events (AE) from the 8 Additional Studies Conclusions

- Most common adverse events reported were related to:
  - Injuries (n=15)
  - Gastrointestinal issues (n=10)
  - Lameness associated with injury (n=4)
  - Respiratory (n=4)
- No pattern was found across dose levels.
- Increasing Experior dosage did not appear to increase the incidence of AE.

Target Animal Safety: Conclusions*

- Experior was tested in cattle fed up to 1300 mg of lubabegron/hd/day (131 g/ton DM).
- Experior was also evaluated for its effect on animal lameness when fed up to 20 gm/ton DM
- Special attention was paid on Experior's effect on animal lameness.
  - Experior did not affect animal lameness.
  - Lameness issues in the studies appeared to be related to nutritional management and pen conditions.
  - Most cases resolved while the animals were still receiving Experior, indicating that the lameness was not test article related.
- Experior was found to be safe to the target animal when administered for the reduction of NH_3 gas emissions per lb of LW and HCW in beef steers and heifers fed in confinement during the last 14 to 91 days on feed.
- A caution statement is included on the label: "A decrease in dry matter intake may be noticed in some animals."

* Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 19-32

Human Food Safety

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Human Food Safety: Conclusions*

- The data support the assignment of a zero-day withdrawal period for doses up to 5 g/ton (4.54 g/ton on a 90% DM basis).
- Tissue residue:
  - The target tissue is the liver with a 10 ppb tolerance established.
  - Experior achieves steady state between 36-60 h post dose.
  - Experior was below detectable levels in muscle, fat, liver, and kidney (1.0ppb) following 72 hour withdrawal.
- The Acceptable Daily Intake (ADI) of Experior is 3 µg/kg BW/day.
- The NOEL (no-observed-effect-level) for Experior is 0.16 mg/kg BW/day.
- Experior has been tested for potential effects on acute toxicity, subchronic and chronic toxicity, reproductive and developmental toxicity, and genotoxicity.
- Experior does not have antimicrobial activity.

* Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 32-53

Human Food Safety Section: ^{14}C Lubabegron Residue in Tissue

	Tissue[a]			
Withdrawal Time, h	Muscle, ppb	Liver, ppb	Kidney, ppb	Fat, ppb
12	0 ± 1	1088 ± 219	374 ± 50	5 ± 4
24	2 ± 3	1011 ± 202	401 ± 79	5 ± 7
48	2 ± 2	1014 ± 108	479 ± 111	145 ± 277
72	10 ± 7	890 ± 183	459 ± 83	102 ± 173

[a]Steers and Heifers dosed with 0.4 mg/kg BW/day ^{14}C lubabegron for 5 days.
Note: Values represent total radioactive residues (not parent lubabegron)

Human Food Safety: Parent Lubabegron Residue in Tissue

	Tissue[a]			
Withdrawal Time, h	Muscle, ppb	Liver, ppb	Kidney, ppb	Fat, ppb
12	1.51 ± 0.19	6.16 ± 1.78	4.40 ± 0.65	1.30 ± 0.13
24	1.38 ± 0.13	6.61 ± 4.73	2.96 ± 0.34	1.21 ± 0.14
48	<LLOQ	1.55 ± 0.35	1.63 ± 0.38	<LLOQ
72	<LLOQ	<LLOQ	<LLOQ	<LLOQ

[a]Steers and Heifers dosed with 0.4 mg/kg BW/day ^{14}C lubabegron for 5 days. This is 4X the drug intake expected with the 4.54 g/ton (90% DM) maximum dosing level.
<LLOQ-lowest point on calibration curve = 0.963ppb

Human Food Safety Section: Parent Lubabegron Residues in Tissues

	Tissue[ab]			
Withdrawal Time, h	Muscle, ppb	Liver, ppb	Kidney, ppb	Fat, ppb
10-12	1.41	2.23	2.30	BCR
22-24	1.32	2.17	2.51	1.27
46-48	BCR	BCR	1.16	BCR
70-72	BCR	BCR	BCR	BCR

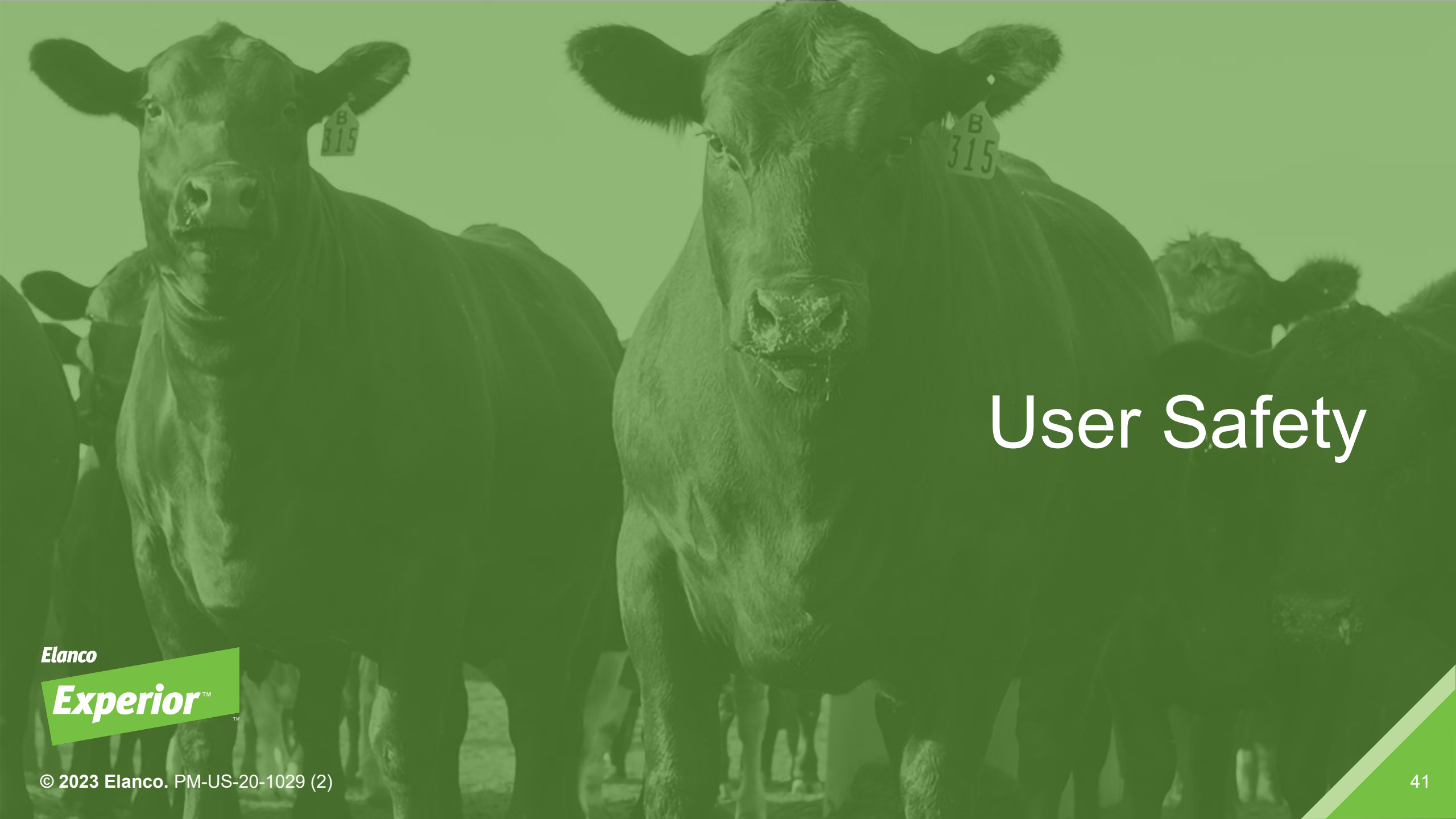
[a]Steers and heifers dosed with 13.0 gm/ton lubabegron for 10 days. Average consumption was 0.29 to 0.35 mg/kg BW/day. This is approximately 3X the drug intake expected with the 4.54 g/ton (90% DM) maximum dosing level.

[b]BCR-below calibration range = 1.2 ppb

Human Food Safety: Conclusions*

- The data support the assignment of a zero-day withdrawal period for doses up to 5 g/ton (4.54 g/ton on a 90% DM basis).
- Tissue residue:
  - The target tissue is the liver with a 10 ppb tolerance established.
  - Experior achieves steady state between 36-60 h post dose.
  - Experior was below detectable levels in muscle, fat, liver, and kidney (1.0ppb) following 72 hour withdrawal.
- The Acceptable Daily Intake (ADI) of Experior is 3 µg/kg BW/day.
- The NOEL (no-observed-effect-level) for Experior is 0.16 mg/kg BW/day.
- Experior has been tested for potential effects on acute toxicity, subchronic and chronic toxicity, reproductive and developmental toxicity, and genotoxicity.
- Experior does not have antimicrobial activity.

*Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from pages 32-53



User Safety

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User Safety: Conclusions*

USER SAFETY WARNING:

- Individuals with cardiovascular disease should exercise special caution to avoid exposure.
- Not for human use.
- Keep out of reach of children.
- When mixing and handling Experior, use protective clothing, impervious gloves, protective eye wear, and a National Institute of Occupational Safety and Health (NIOSH) approved dusk mask.
- Operators should wash thoroughly with soap and water after use.
- If accidental eye contact occurs, immediately rinse with water. If wearing contacts, rinse eyes first, then remove contacts and continue to rinse for 5-20 minutes.

*Experior FOI, FDA FOI NADA 141-508 Experior 2018 (v1.0), summarized from page 54

Adverse Event Reporting

All adverse events should be reported to Elanco US Inc at:

1-800-428-4441

Adverse events can also be submitted directly to the FDA at

1-888-FDA-VETS

http://www.fda.gov/reportanimalae

Agency Conclusions

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Agency Conclusions

- Experior, when used according to the label, is safe and effective for reduction of ammonia gas emissions per lb of LW and HCW in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.
- Data demonstrates residues in food products from species treated with Experior will not present a public health concern when the product is used according to the label.

Experior FONSI

(Findings of No Significant Impact)

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Finding of No Significant Impact (FONSI)

- "If CVM determines that the drug will not significantly impact the environment based on the information in the Environmental Assessment (EA), the center writes what is called a "Finding of No Significant Impact," or "FONSI" for short. If CVM determines that the drug will significantly impact the environment, the center writes an Environmental Impact Statement (EIS)."[1]
- This information is prepared and published by the CVM.
- The Experior FONSI concludes that the product will not have a significant adverse impact on the quality of the human environment.[2]

[1]FDA. FDA: From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process. 2019 (v1.0). Available at https://www.fda.gov/animal-veterinary/animal-health-literacy/idea-marketplace-journey-animal-drug-through-approval-process#environmental

[2] Experior FONSI, summarized from page 1

FONSI: General Information*

- Agricultural sources (which include livestock) are the largest known source of ammonia gas emissions in the United States.[1]
- Ammonia gas is thought to be a significant contributor to the eutrophication of waterways and the formation of atmospheric haze and noxious odors.
- The use of lubabegron is intended to reduce ammonia emissions from beef steers and heifers fed in confinement for slaughter for the last 14-91 days on feed.

* Experior FONSI, summarized from page 3

[1] EPA. EPA 2014 National Emissions Inventory (NEI) Data Accessed 2019 (v1.0)

FONSI: Reduction in Ammonia Emissions*

- Experior is thought to act by increasing nitrogen (amino acid) uptake in beef cattle and increasing the amount of nitrogen retained in the animal as protein, thereby reducing the amount of urea excreted and contained in manure (urine and feces combined).
- The urea in manure is rapidly converted by an enzyme, urease, to ammonia and ammonium. Subsequently, this ammonia is volatilized (i.e., released as a gas) to the atmosphere.
- Thus, the reduction in excreted urea from the animal results in a reduction in ammonia gas emissions to the environment.

*Experior FONSI, summarized from page 1

FONSI: Conclusions*

Based on the information in the Environmental Assessment (EA), no significant adverse environmental impacts are expected from the use of Experior for reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

* Experior FONSI, summarized from page 4

Experior Label

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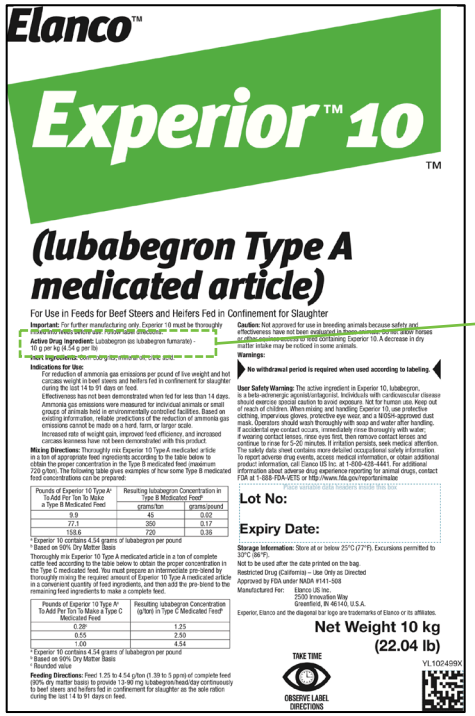
Experior Label: Active Drug Ingredient


Elanco™

Experior™ 10 ™

(lubabegron Type A medicated article)

For Use in Feeds for Beef Steers and Heifers Fed in Confinement for Slaughter

Important: For further manufacturing only. Experior 10 must be thoroughly mixed into feeds before use. Do not feed undiluted.

Active Drug Ingredient: Lubabegron (as lubabegron fumarate) - 10 g per kg (4.54 g per lb)

Inert Ingredients: Corn cob dry, mineral oil, and silica.

Indications for Use:
For reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.
Effectiveness has not been demonstrated when fed for less than 14 days.
Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.

Mixing Directions: Thoroughly mix Experior 10 Type A medicated article in a ton of appropriate feed ingredients according to the table below to obtain the proper concentration in the Type B medicated feed (maximum 720 g/ton). The following table gives examples of how some Type B medicated feed concentrations can be prepared:

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type B Medicated Feed	Resulting lubabegron Concentration in Type B Medicated Feed†	
	grams/ton	grams/pound
9.9	45	0.02
77.1	350	0.17
158.6	720	0.36

* Experior 10 contains 4.54 grams of lubabegron per pound
† Based on 90% Dry Matter Basis

Thoroughly mix Experior 10 Type A medicated article in a ton of complete cattle feed according to the table below to obtain the proper concentration in the Type C medicated feed. You must prepare an intermediate pre-blend by thoroughly mixing the required amount of Experior 10 Type A medicated article in a convenient quantity of feed ingredients, and then add the pre-blend to the remaining feed ingredients to make a complete feed.

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type C Medicated Feed	Resulting lubabegron Concentration (g/Ton) in Type C Medicated Feed†
0.28	1.25
0.55	2.50
1.00	4.54

* Experior 10 contains 4.54 grams of lubabegron per pound
† Based on 90% Dry Matter Basis
‡ Rounded value

Feeding Directions: Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13-96 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

Caution: Not approved for use in breeding animals because safety and effectiveness have not been evaluated in these animals or for dairy calves or other horses or other species or animals fed feed containing Experior 10. A decrease in dry matter intake may be reduced in some animals.

Warnings:

No withdrawal period is required when used according to labeling.

User Safety Warning: The active ingredient in Experior 10, lubabegron, is a beta-adrenergic agonist/antagonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for human use. Keep out of reach of children. When mixing and handling Experior 10, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water; if wearing contact lenses, rinse eyes first, then remove contact lenses and continue to rinse for 5–20 minutes. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information. To report adverse drug events, access medical information, or obtain additional product information, call Elanco US Inc. at 1-888-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Lot No:

Expiry Date:

Storage Information: Store at or below 25°C (77°F). Excursions permitted to 30°C (86°F).

Not to be used after the date printed on the bag.

Restricted Drug (California) — Use Only as Directed

Approved by FDA under NADA #141-508

Manufactured For: Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140, U.S.A.

Experior, Elanco and the diagonal bar logo are trademarks of Elanco or its affiliates.

Net Weight 10 kg (22.04 lb)

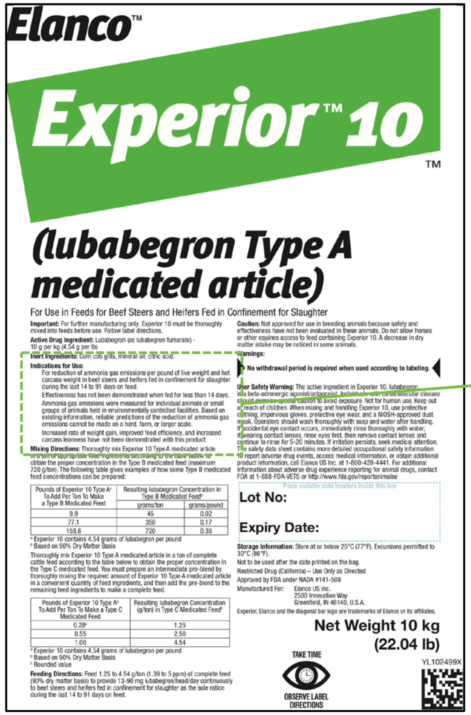
TAKE TIME

OBSERVE LABEL DIRECTIONS

YL102499X

Active Drug Ingredient:
Lubabegron (as lubabegron fumarate) - 10 g per kg (4.54 g per lb)

Experior Label: Indications for Use



Indications for Use:
For reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.

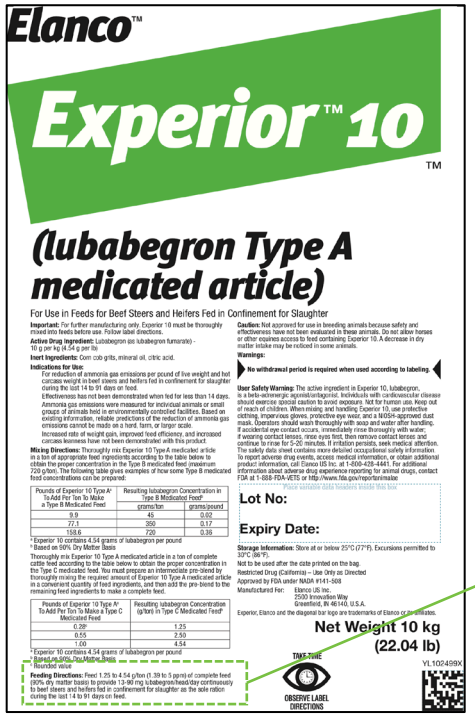
Effectiveness has not been demonstrated when fed for less than 14 days.

Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.

Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.

PM-US-20-1029 (2)

Experior Label: Feeding Directions


Elanco™

Experior™ 10™

(lubabegron Type A medicated article)

For Use in Feeds for Beef Steers and Heifers Fed in Confinement for Slaughter

Important: For further manufacturing only. Experior 10 must be thoroughly mixed into feeds before use. Follow label directions.

Active Drug Ingredient: Lubabegron (as lubabegron fumarate) - 10 g per kg (4.54 g per lb)

Inert Ingredients: Corn cob grits, mineral oil, citric acid.

Indications for Use:
For reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.
Effectiveness has not been demonstrated when fed for less than 14 days.
Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product

Mixing Directions: Thoroughly mix Experior 10 Type A medicated article in a ton of appropriate feed ingredients according to the table below to obtain the proper concentration in the Type B medicated feed (maximum 720 g/ton). The following table gives examples of how some Type B medicated feed concentrations can be prepared:

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type B Medicated Feed	Resulting lubabegron Concentration in Type B Medicated Feed*	
	grams/ton	grams/pound
9.9	45	0.02
77.1	350	0.17
158.6	720	0.39

* Experior 10 contains 4.54 grams of lubabegron per pound
* Based on 90% Dry Matter Basis

Thoroughly mix Experior 10 Type A medicated article in a ton of complete cattle feed according to the table below to obtain the proper concentration in the Type C medicated feed. You must prepare an intermediate pre-blend by thoroughly mixing the required amount of Experior 10 Type A medicated article in a convenient quantity of feed ingredients, and then add the pre-blend to the remaining feed ingredients to make a complete feed.

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type C Medicated Feed	Resulting lubabegron Concentration (g/ton) in Type C Medicated Feed*
0.28	1.25
0.55	2.50
1.00	4.54

* Experior 10 contains 4.54 grams of lubabegron per pound
* Based on 90% Dry Matter Basis
** Rounded value

Feeding Directions: Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13-90 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

Caution: Not approved for use in breeding animals because safety and effectiveness have not been evaluated in these animals. Do not allow horses or other equines access to feed containing Experior 10. A decrease in dry matter intake may be noticed in some animals.

Warnings:

No withdrawal period is required when used according to labeling.

User Safety Warning: The active ingredient in Experior 10, lubabegron, is a beta-adrenergic agonist/antagonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for human use. Keep out of reach of children. When mixing and handling Experior 10, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water; if wearing contact lenses, rinse eyes first, then remove contact lenses and continue to rinse for 5–20 minutes. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information. To report adverse drug events, access medical information, or obtain additional product information, call Elanco US Inc. at 1-800-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

Lot No:

Expiry Date:

Storage Information: Store at or below 25°C (77°F). Excursions permitted to 30°C (86°F).

Not to be used after the date printed on the bag.

Restricted Drug (California) – Use Only as Directed

Approved by FDA under NADA #141-508

Manufactured For: Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140, U.S.A.

Experior, Elanco and the diagonal bar logo are trademarks of Elanco or its affiliates.

Net Weight 10 kg (22.04 lb)

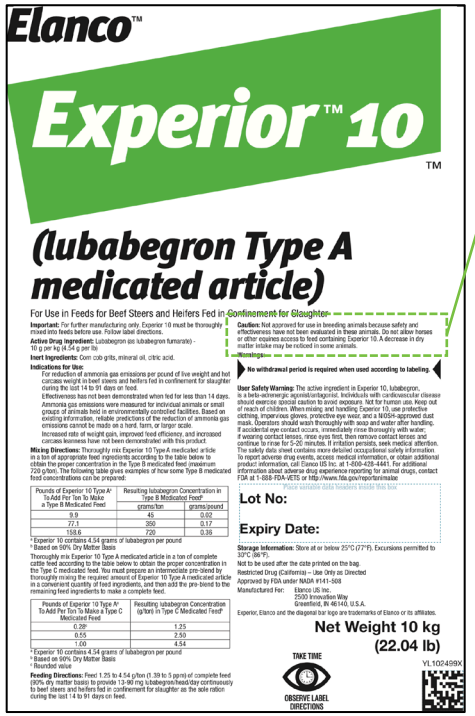
TAKE-TIME

OBSERVE LABEL DIRECTIONS

YL102499X

Feeding Directions:
Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13-90 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

Experior Label: Caution


Elanco™

Experior™ 10 ™

(lubabegron Type A medicated article)

For Use in Feeds for Beef Steers and Heifers Fed in Confinement for Slaughter

Important: For further manufacturing only. Experior 10 must be thoroughly mixed into feeds before use. Follow label directions.

Active Drug Ingredient: Lubabegron (as lubabegron fumarate) - 10 g per kg (4.54 g per lb)

Inert Ingredients: Corn cob grits, mineral oil, citric acid.

Indications for Use:
For reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.
Effectiveness has not been demonstrated when fed for less than 14 days.
Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.

Mixing Directions: Thoroughly mix Experior 10 Type A medicated article in a ton of appropriate feed ingredients according to the table below to obtain the proper concentration in the Type B medicated feed (maximum 720 g/ton). The following table gives examples of how some Type B medicated feed concentrations can be prepared:

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type B Medicated Feed	Resulting lubabegron Concentration in Type B Medicated Feed†	
	grams/ton	grams/pound
9.9	45	0.02
77.1	350	0.17
158.6	720	0.36

* Experior 10 contains 4.54 grams of lubabegron per pound
† Based on 90% Dry Matter Basis

Thoroughly mix Experior 10 Type A medicated article in a ton of complete cattle feed according to the table below to obtain the proper concentration in the Type C medicated feed. You must prepare an intermediate pre-blend by thoroughly mixing the required amount of Experior 10 Type A medicated article in a convenient quantity of feed ingredients, and then add the pre-blend to the remaining feed ingredients to make a complete feed.

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type C Medicated Feed	Resulting lubabegron Concentration (g/Ton) in Type C Medicated Feed†
0.28	1.25
0.55	2.50
1.00	4.54

* Experior 10 contains 4.54 grams of lubabegron per pound
† Based on 90% Dry Matter Basis
‡ Rounded value

Feeding Directions: Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13-90 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

Caution: Not approved for use in breeding animals because safety and effectiveness have not been evaluated in these animals. Do not allow horses or other equines access to feed containing Experior 10. A decrease in dry matter intake may be noticed in some animals.

Warnings:

No withdrawal period is required when used according to labeling.

User Safety Warning: The active ingredient in Experior 10, lubabegron, is a beta-adrenergic agonist/antagonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for human use. Keep out of reach of children. When mixing and handling Experior 10, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water; if wearing contact lenses, rinse eyes first, then remove contact lenses and continue to rinse for 5–20 minutes. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information. To report adverse drug events, access medical information, or obtain additional product information, call Elanco US Inc. at 1-888-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

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Lot No:

Expiry Date:

Storage Information: Store at or below 25°C (77°F). Excursions permitted to 30°C (86°F).

Not to be used after the date printed on the bag.

Restricted Drug (California) – Use Only as Directed

Approved by FDA under NADA #141-508

Manufactured For: Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140, U.S.A.

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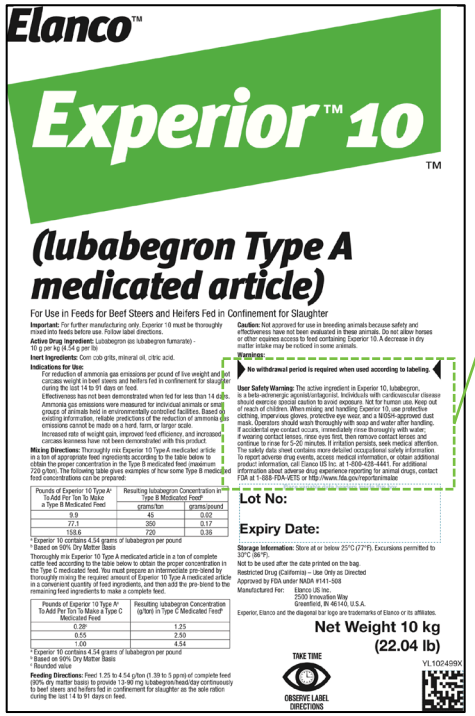
Net Weight 10 kg (22.04 lb)

TAKE TIME

OBSERVE LABEL DIRECTIONS

YL102499X

Experior Label: User Safety Warning


Elanco™

Experior™ 10 ™

(lubabegron Type A medicated article)

For Use in Feeds for Beef Steers and Heifers Fed in Confinement for Slaughter

Important: For further manufacturing only. Experior 10 must be thoroughly mixed into feeds before use. Follow label directions.

Active Drug Ingredient: Lubabegron (as lubabegron fumarate) - 10 g per kg (4.54 g per lb)

Inert Ingredients: Corn cob grits, mineral oil, citric acid.

Indications for Use:
For reduction of ammonia gas emissions per pound of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 days on feed.
Effectiveness has not been demonstrated when fed for less than 14 days.
Ammonia gas emissions were measured for individual animals or small groups of animals held in environmentally controlled facilities. Based on existing information, reliable predictions of the reduction of ammonia gas emissions cannot be made on a herd, farm, or larger scale.
Increased rate of weight gain, improved feed efficiency, and increased carcass leanness have not been demonstrated with this product.

Mixing Directions: Thoroughly mix Experior 10 Type A medicated article in a ton of appropriate feed ingredients according to the table below to obtain the proper concentration in the Type B medicated feed (maximum 720 g/ton). The following table gives examples of how some Type B medicated feed concentrations can be prepared:

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158.6	720	0.39

* Experior 10 contains 4.54 grams of lubabegron per pound
* Based on 90% Dry Matter Basis

Thoroughly mix Experior 10 Type A medicated article in a ton of complete cattle feed according to the table below to obtain the proper concentration in the Type C medicated feed. You must prepare an intermediate pre-blend by thoroughly mixing the required amount of Experior 10 Type A medicated article in a convenient quantity of feed ingredients, and then add the pre-blend to the remaining feed ingredients to make a complete feed.

Pounds of Experior 10 Type A* To Add Per Ton To Make a Type C Medicated Feed	Resulting lubabegron Concentration (g/ton) in Type C Medicated Feed*
0.28	1.25
0.55	2.50
1.00	4.54

* Experior 10 contains 4.54 grams of lubabegron per pound
* Based on 90% Dry Matter Basis
* Rounded value

Feeding Directions: Feed 1.25 to 4.54 g/ton (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13-90 mg lubabegron/head/day continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 days on feed.

No withdrawal period is required when used according to labeling.

User Safety Warning: The active ingredient in Experior 10, lubabegron, is a beta-adrenergic agonist/antagonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for human use. Keep out of reach of children. When mixing and handling Experior 10, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water; if wearing contact lenses, rinse eyes first, then remove contact lenses and continue to rinse for 5-20 minutes. If irritation persists, seek medical attention. The safety data sheet contains more detailed occupational safety information. To report adverse drug events, access medical information, or obtain additional product information, call Elanco US Inc. at 1-800-428-4441. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

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Net Weight 10 kg (22.04 lb)

TAKE TIME

OBSERVE LABEL DIRECTIONS

YL102499X

Thank You

Elanco

Experior™