Experior™ Lubabegron fumarate

Mechanism of Action

Overview

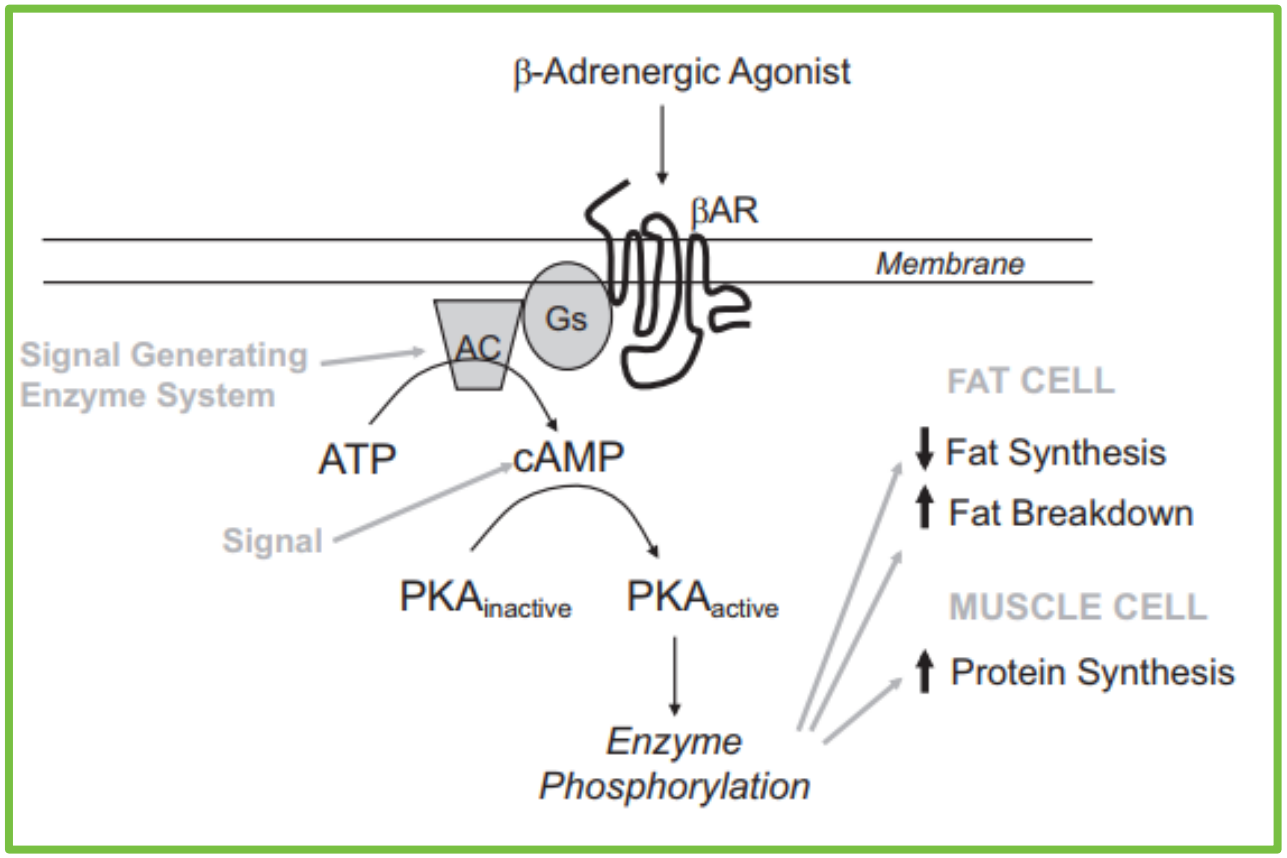
√ β-ligand basics

√ Lubabegron characteristics and action

√ Physiology from metabolic profiling

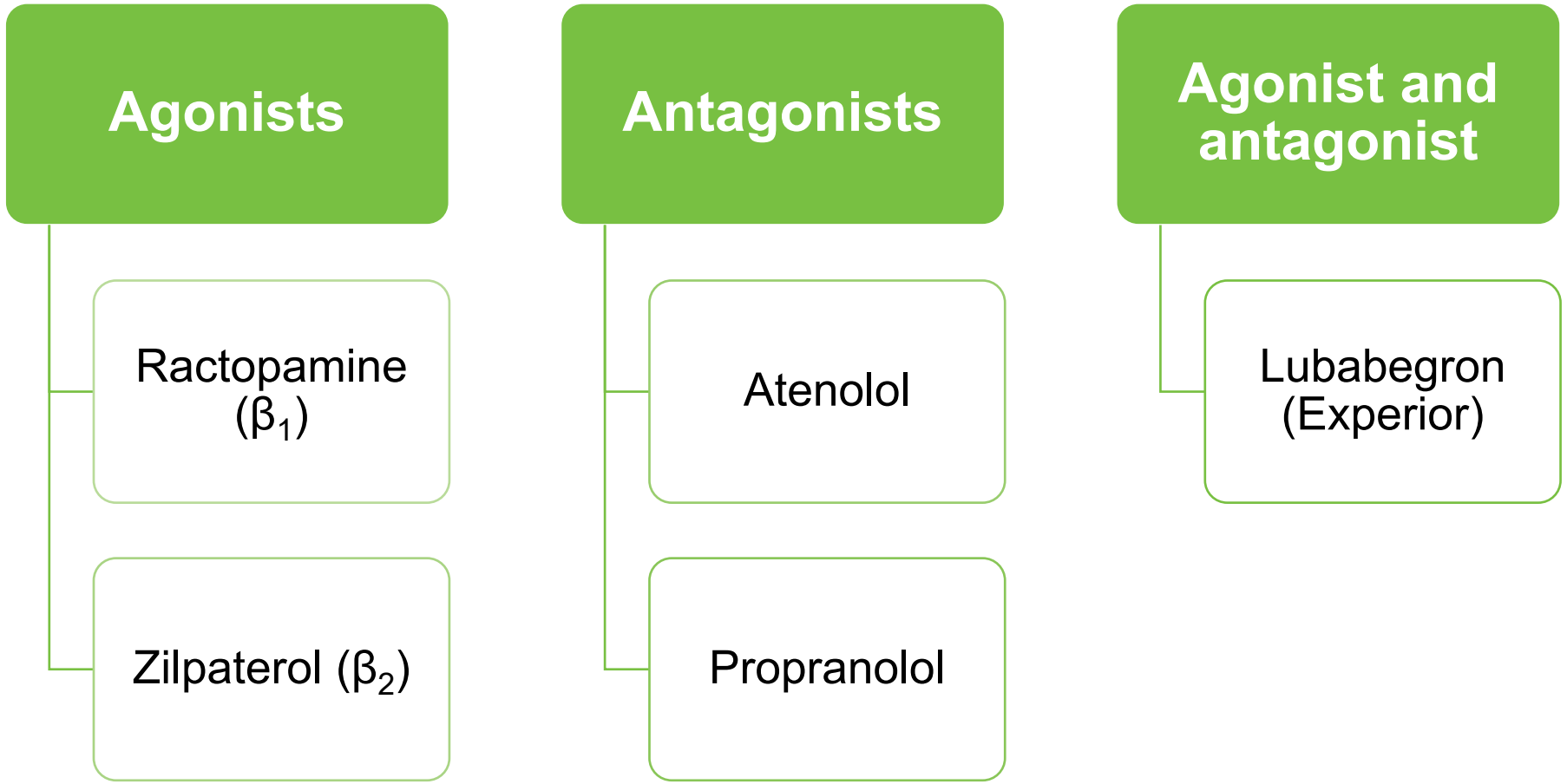
Adrenergic receptors[1]

- A class of G protein-coupled receptors that are targets of the endogenous catecholamines, epinephrine and norepinephrine
  - Two types: α and β
  - Agonistic binding stimulates the sympathetic nervous system



[1] Figure derived from: Anderson DB, Moody DE, Hancock DL. Beta-adrenergic agonists. In: Pond WG, Bell AW, editors. Pond WG, Bell AW, Editor. Encyclopedia of Animal Science. NY: Marcel Dekker, Inc., 2000. p. 104-107.

β-ligand nomenclature



Classification of β-adrenergic receptors

- β-adrenoceptors were first discovered in the mid 1900's and were originally only classified into the β_1 and β_2 subtypes[2,3]

Receptor	Characteristics
β-adrenergic	Vasodilation, inhibition of uterine contraction, myocardial stimulation
β_1 subtype	Fatty acid mobilization from adipose tissue, cardiac stimulation
β_2 subtype	Bronchodilation, vasodilation

[2] Wachter SB, Gilbert EM. Beta-adrenergic receptors, from their discovery through their manipulation and beneficial clinical application. Cardiology. 2012, 122(2):104-112.
[3] Minneman KP, Pittman, RN, Molinoff PB. Beta-adrenergic receptor subtypes: properties, distribution, and regulation. Annual Review of Neuroscience. 1981, 4:419-461.

Tissue distribution

- The density and distribution of β receptor subtypes varies between species and among tissues within a species
  - Heart = predominately β_1 subtype
  - Lung = predominately β_2 subtype[4]
  - Skeletal muscle = β_1 (swine) vs β_2 (cattle) predominance[5,6]
  - β_3 receptor originally believed to be present in human brown adipose tissue – present in heart, lung, skeletal muscle and subcutaneous adipose of cattle[7]

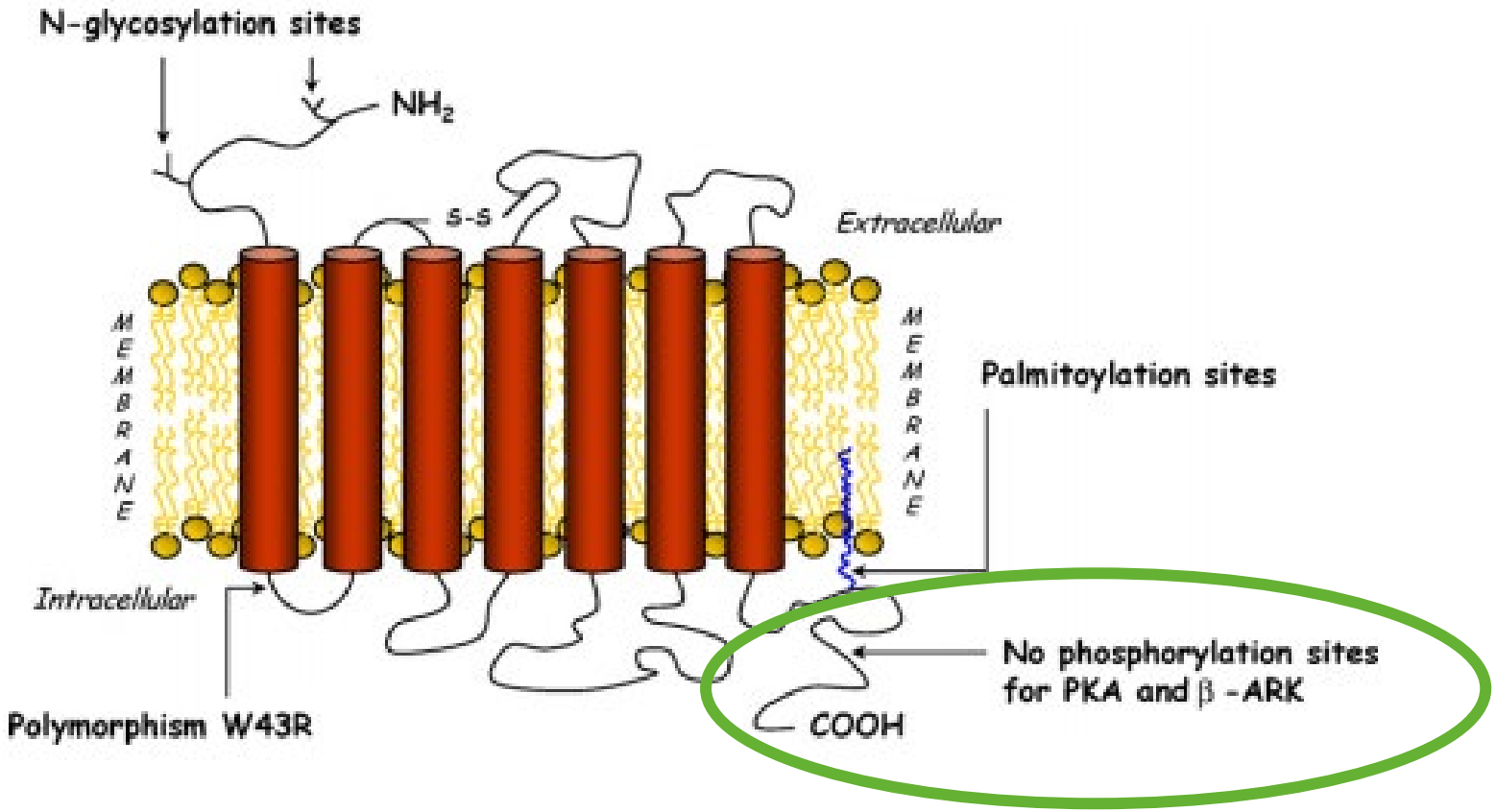
[4] Minneman KP, Hegstrand LR, Molinoff PB. The pharmacologic specificity of beta-1 and beta-2 adrenergic receptors in rat heart and lung in vitro. Molecular Pharmacology. 1979, 16(1):21-33.
[5] Sillence MN, Matthews ML. Classical and atypical binding sites for beta-adrenergic ligands and activation of adenylyl cyclase in bovine skeletal muscle and adipose tissue membranes. British Journal of Pharmacology. 1994, 111:866-872.
[6] Sillence MN, Hooper J, Zhou GH, Liu Q, Munn KJ. Characterization of porcine B1- and B2-adrenergic receptors in heart, skeletal muscle, and adipose tissue, and the identification of an atypical B-adrenergic binding site. Journal of Animal Science. 2005, 83:2339-2348.
[7] Elanco Animal Health. Data on file.

The β_3 is unique

- The β_3 subtype was first discovered in the 1980's in rat adipose tissue[8]
- Stimulation of the β_3 receptor induces an increase in cAMP similar to the other receptor subtypes
- Structurally unique - does not contain a phosphorylation site believed to be involved in down-regulation

[8] Ursino MG, Vasina V, Raschi E, Crema F, De Ponti F. The beta-3-adrenoreceptor as a therapeutic target: current perspectives. Pharmacological Research. 2009, 59:221–234.

β_3 regulation is unique[8]



[8] Ursino MG, Vasina V, Raschi E, Crema F, De Ponti F. The beta-3-adrenoreceptor as a therapeutic target: current perspectives. Pharmacological Research. 2009, 59:221–234.

β-ligand summary

- The β-adrenergic receptor is part of the G-protein family, with 3 known subtypes
- Prior technologies (Optaflexx, Zilmax) have been agonists at β_1 and β_2 receptor subtypes, respectively
- The β_3 receptor lacks a phosphorylation site that may be involved with downregulation and desensitization

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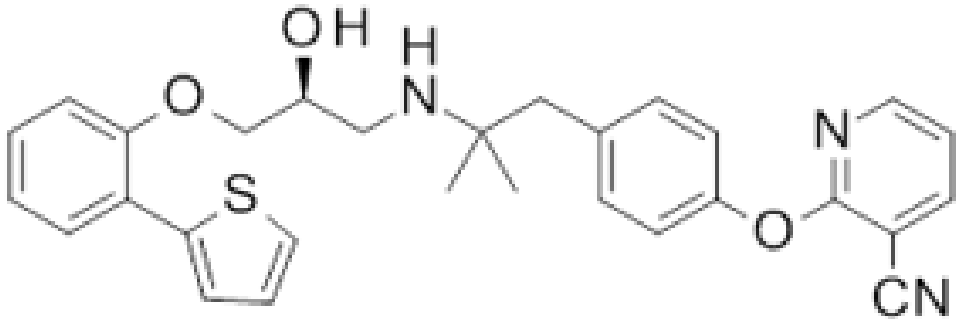
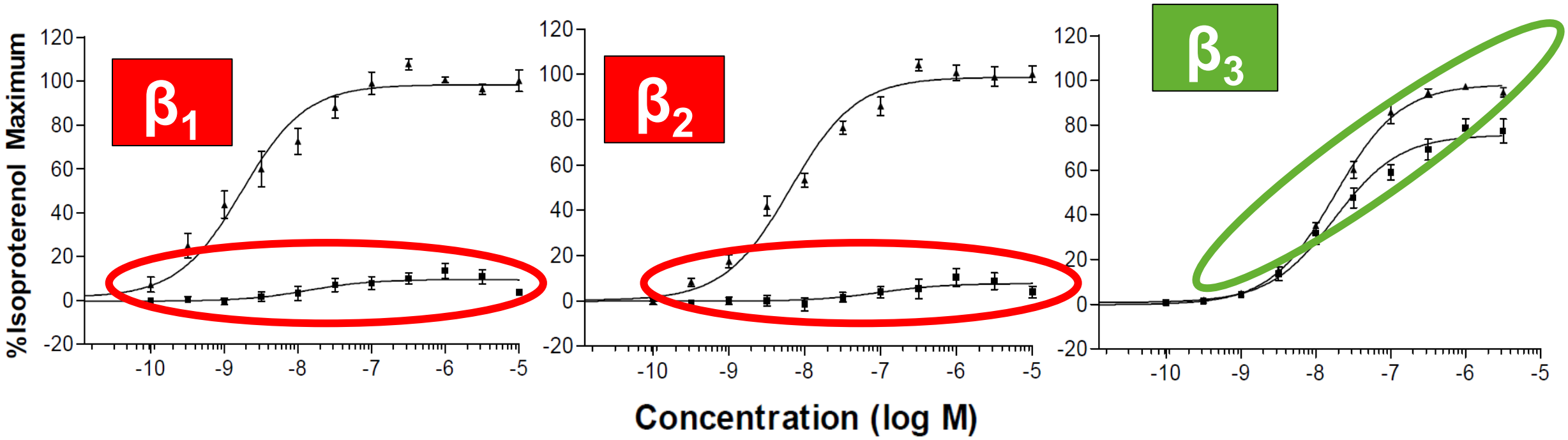
Lubabegron fumarate[9]

- Active pharmaceutical ingredient in Experior™
  - Phen-oxy-ethanolamine core
    - Molecular structure contains an extra oxygen
  - Classified by the CVM as a β-agonist/antagonist
  - $T_{1/2}$ (oral)[10] = 11.75 hours
  - $T_{1/2}$ (IV)[10] = 2.12 hours
  - Plasma steady-state = 3 to 7 days



[9] Elanco Animal Health. Data on file.
[10] Elanco Animal Health. Data on file.

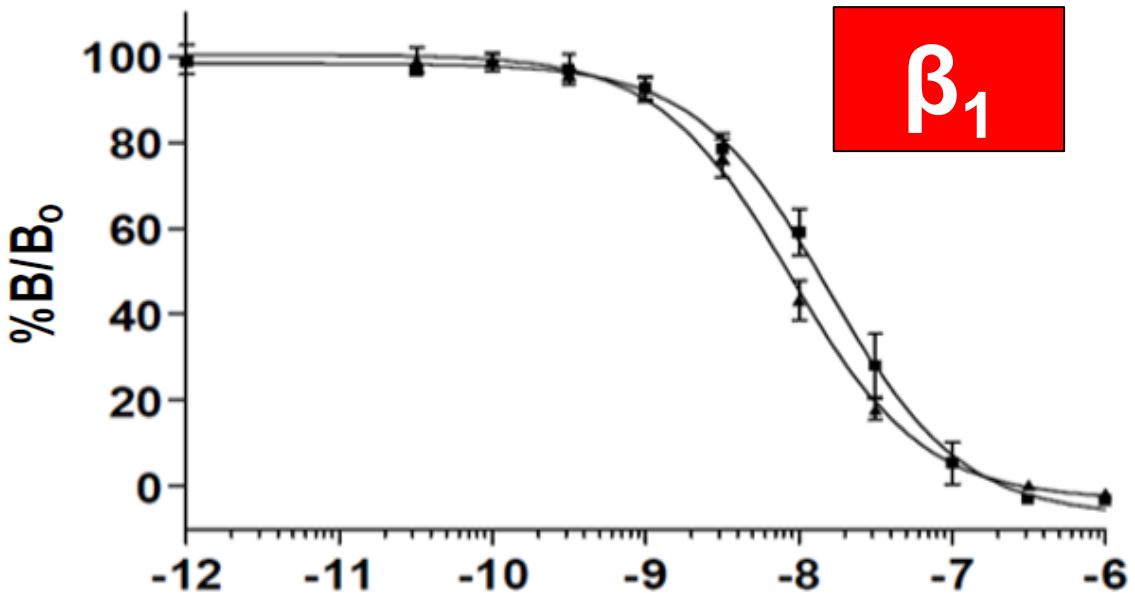
Agonistic behavior[9†]

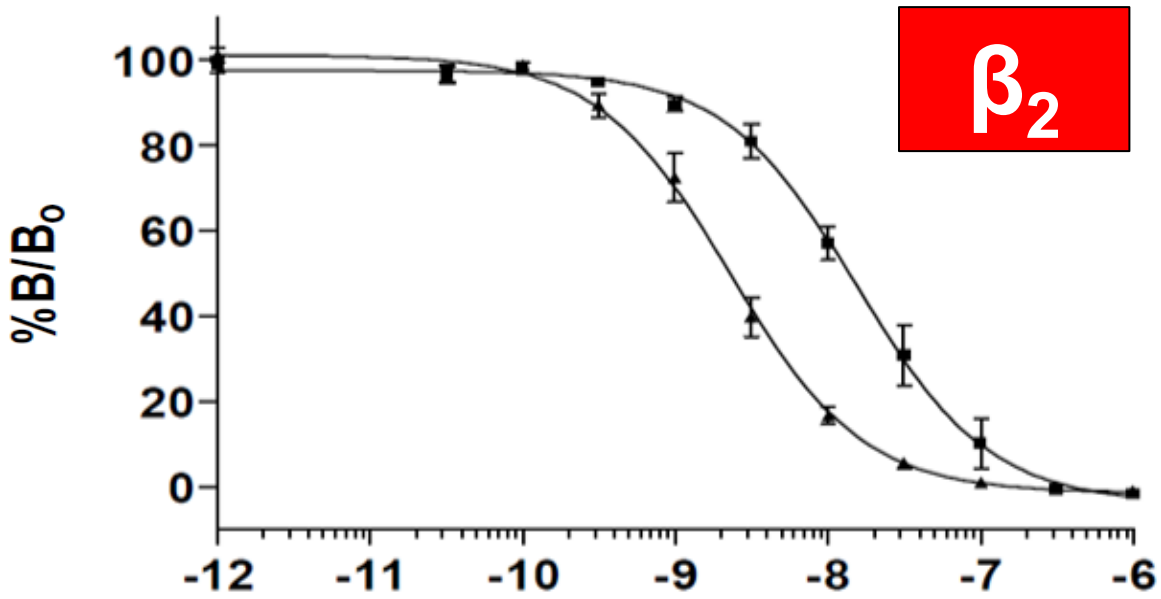


[9] Elanco Animal Health. Data on file.
†Tissue model was Chinese hamster ovary cell line expressing cloned human βreceptors.

■ Lubabegron
▲ Isoproterenol

Antagonistic behavior[9†]



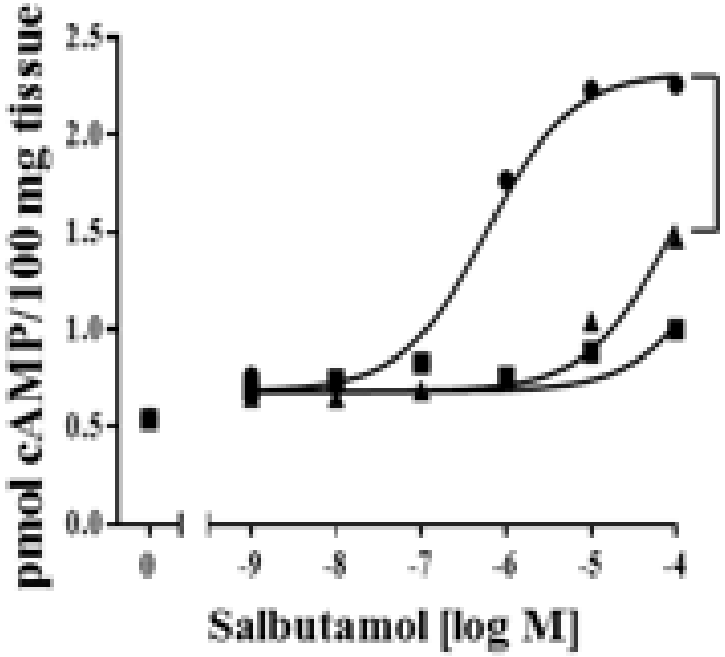


[9] Elanco Animal Health. Data on file.
†Tissue model was Chinese hamster ovary cell line expressing cloned human βreceptors.

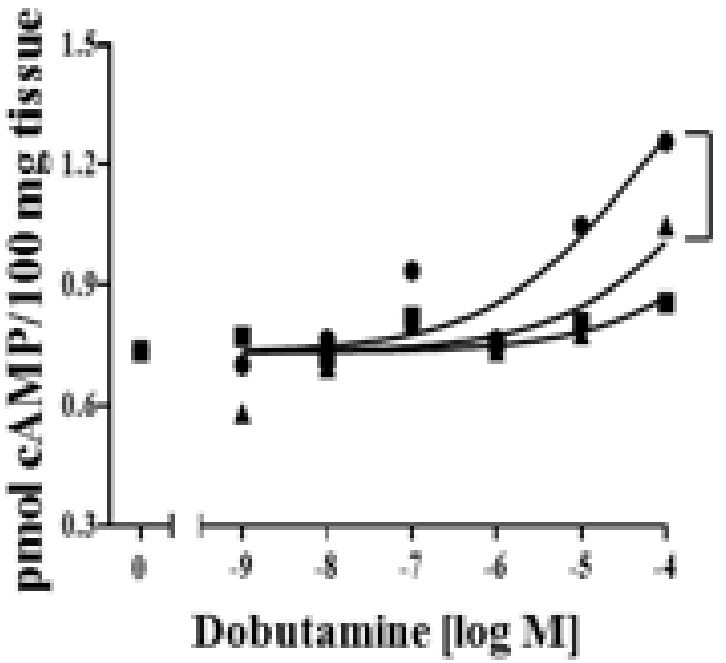
■ Lubabegron
▲ Isoproterenol

Lubabegron blocks cyclic AMP response in cattle subcutaneous adipose explants[11]

Salbutamol (β_2 agonist; ●)
Salbutamol + Experior (■)
Salbutamol + Experior + β3 antagonist L-748,337 (▲)



Dobutamine (β_1 agonist; ●)
Dobutamine + Experior (■)
Dobutamine + Experior + β3 antagonist L-748,337 (▲)



[11]Elanco Animal Health. Data on file.

Receptor behavior

	Approved β-ligand		
Subtype	**Lubabegron**	**Ractopamine**	**Zilpaterol**
β_1	-	+	+
β_2	-	+	+
β_3	+	?	?
+ = agonistic behavior		**- = antagonistic behavior**	

Cardiovascular effects

- The significance of the lubabegron's subtype-specific behavior is evident when comparing the "no observable effect level" (NOEL) determinant of the β ligands currently approved for use in livestock
  - Lubabegron (Experior™; selective β modulator): decrease in heart rate
    - Single-dose human study[12]
  - Ractopamine (Optaflexx™; β_1 agonist): increase in heart rate
    - 1 year monkey study[13]
  - Zilpaterol (Zilmax®; β_2 agonist): increased bronchodilation
    - Asthmatic human study[14]

[12] Experior Freedom of information summary. Available at https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/141-508.
[13] Paylean (1999) Freedom of Information summary. Available at https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/140-863.
[14] Zilmax (2006) Freedom of Information summary. Available at https://animaldrugsatfda.fda.gov/adafda/views/#/home/previewsearch/141-258.

Lubabegron characteristics summary

- Takes up to 7 days to reach steady-state in vivo, driven by the short half-life (12 h)
- Activates β_3 and inhibits β_1 and β_2 receptors
- The cardiovascular effect is a slight slowing of heart rate, in contrast to other approved β-agonists

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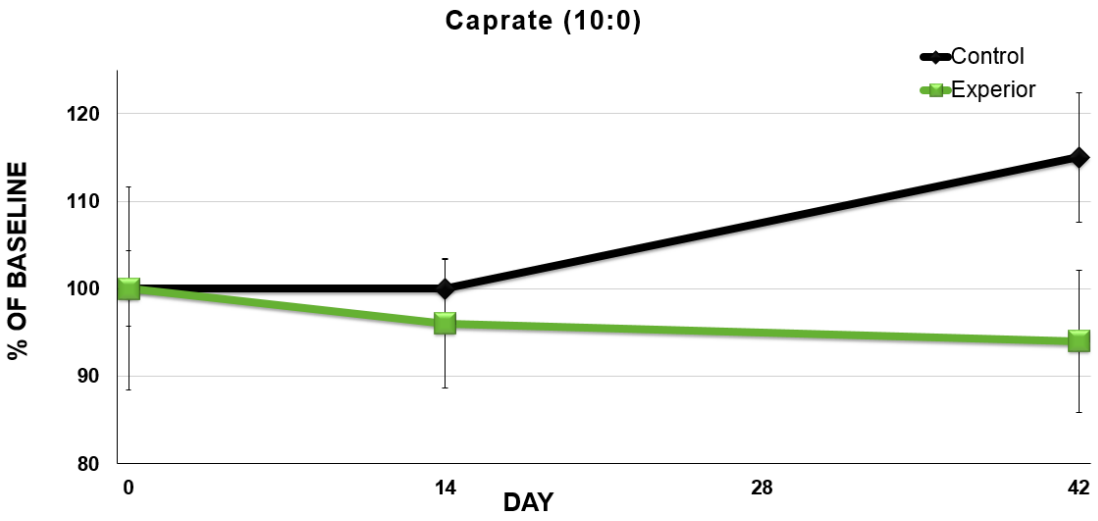
Lubabegron increases protein synthesis

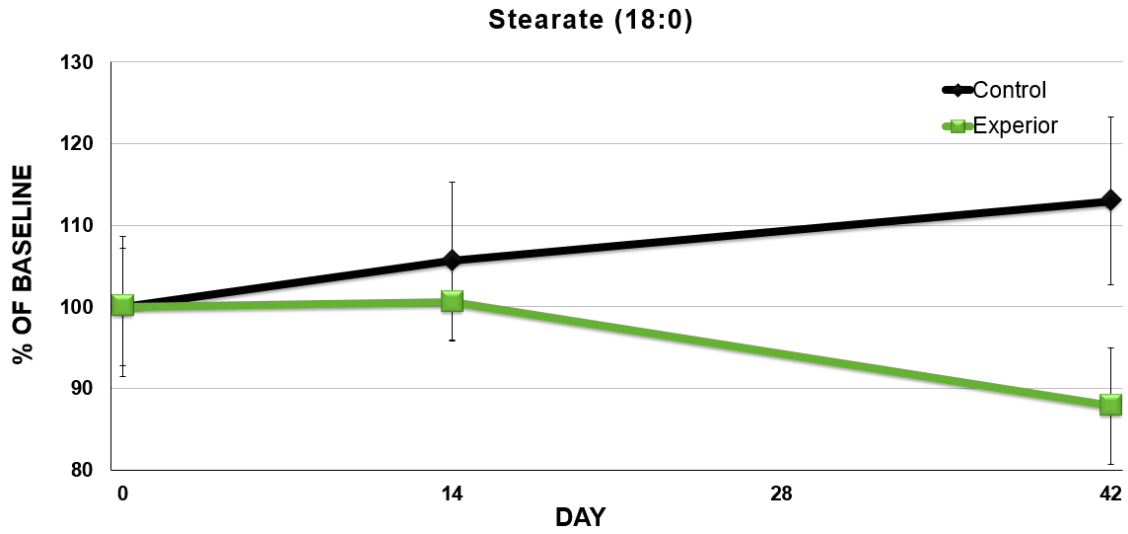
- A quadratic reduction (P = 0.01; reduced above 0 g/ton) in plasma urea N of steers and heifers fed 5, 10, and 20 g/ton of lubabegron on day 14 and over the entire 42-day duration of lubabegron feeding[15]

- Cattle fed 20 g/ton lubabegron for 42 days –
  - Hot carcass weight 23 pounds greater than the control[16]
  - Reduced serum branched-chain amino acids and their catabolites, indicative of increased use for skeletal and/or smooth muscle protein synthesis
  - Concentrations of 3-*n*-methylhistidine (3-MH) remained unchanged; 3-MH is a marker of protein degradation[7]

[15]Elanco Animal Health. Data on file.
[16]Elanco Animal Health. Data on file.
[7] Elanco Animal Health. Data on file.

Effects on fatty acid metabolism[11]

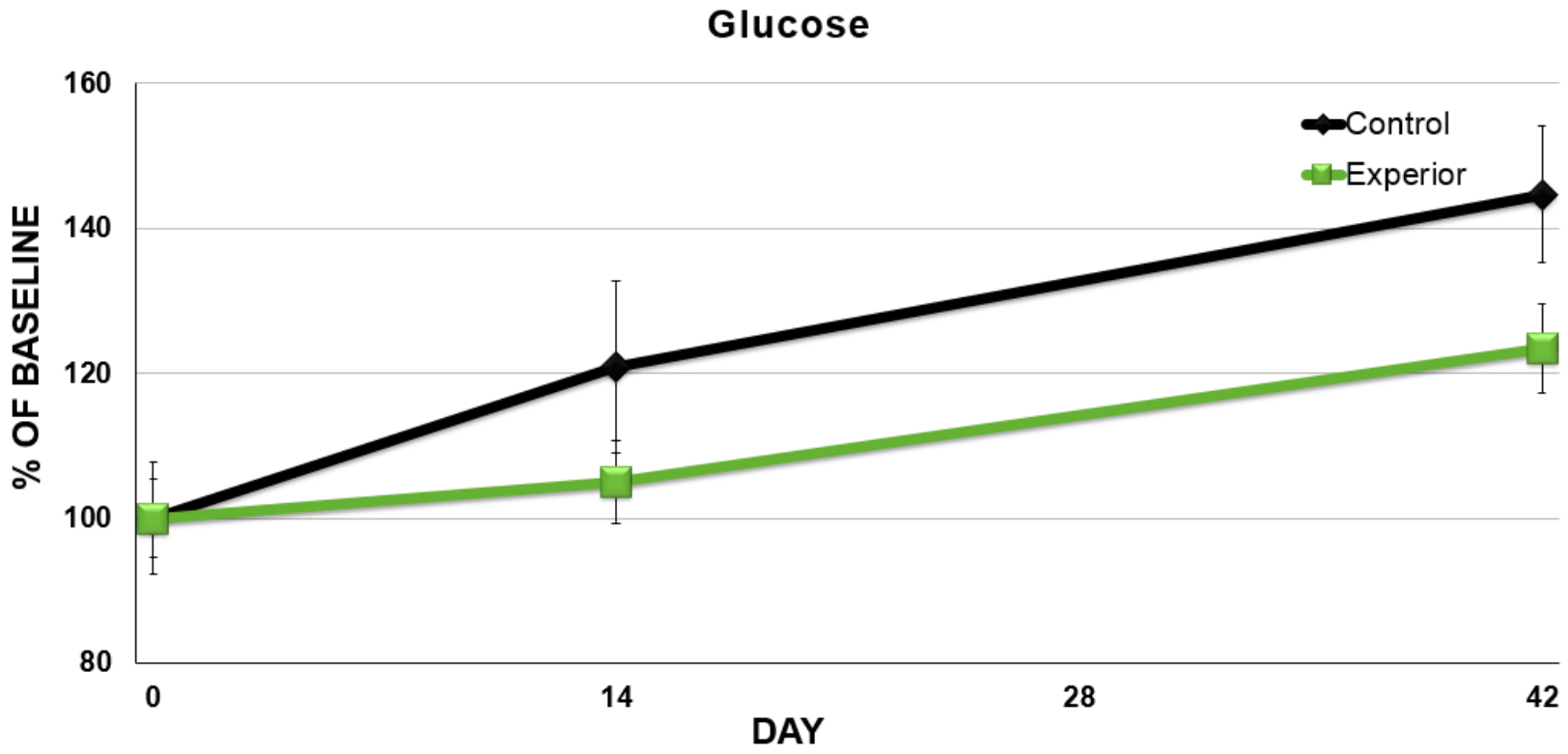




- The reduction in circulating medium and long-chain fatty acids suggests increased use for energy or reduced adipogenesis
- The absence of an increase in tissue cAMP from subcutaneous explants from cattle suggests Experior is not lipolytic

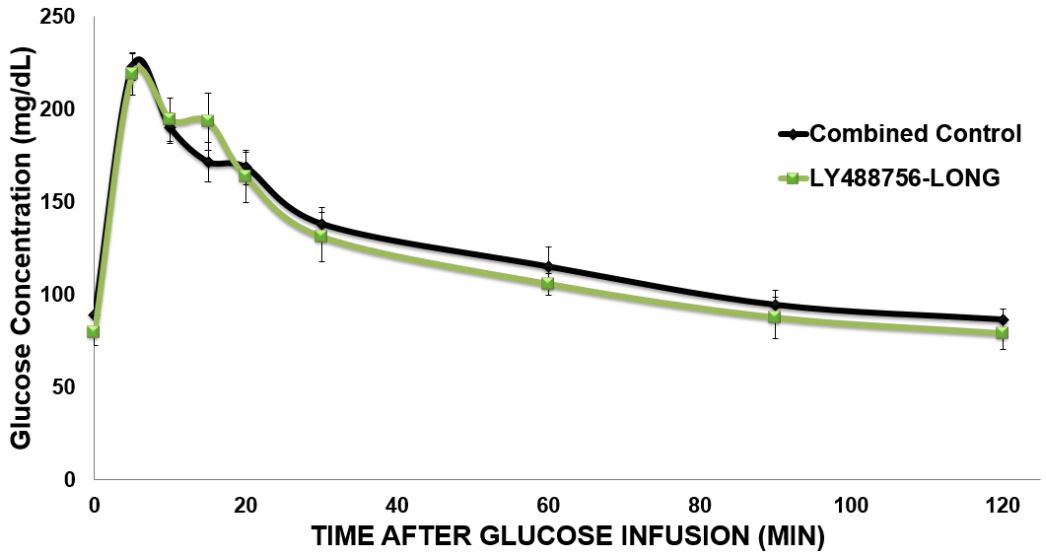
[11] Elanco Animal Health. Data on file.

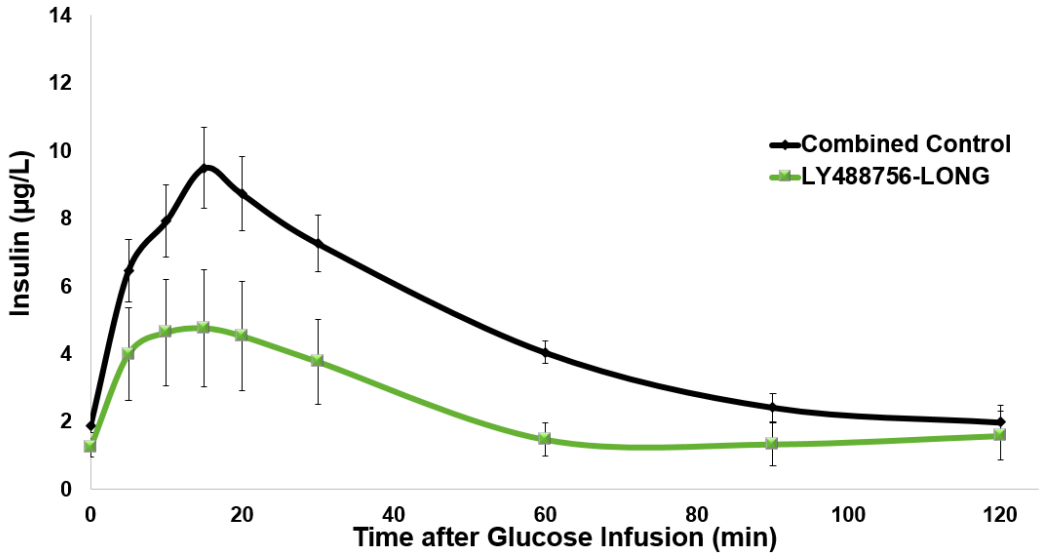
Effects on blood glucose regulation[17]



[16] Elanco Animal Health. Data on file.

Effects on insulin sensitivity[18]





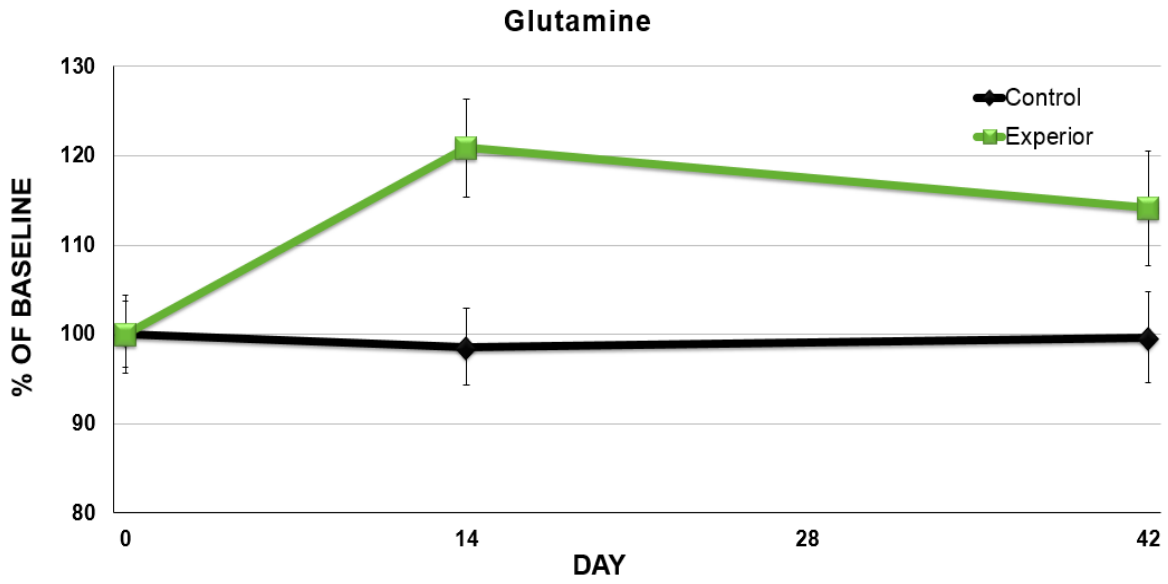
[7]Elanco Animal Health. Data on file.

Effects on gluconeogenesis[17]

Increased glutamine indicates greater rates of gluconeogenesis

Reflected in reductions in both amino acids and carbohydrates

- Histidine
- Methionine
- Proline
- Valine
- Lactate
- Pyruvate
- Pyridoxate
- N-acetylalanine



[16]Elanco Animal Health. Data on file.

Physiology summary

- Lubabegron increases protein synthesis, but did not alter protein degradation
- Lubabegron does not appear to be lipolytic
- Insulin sensitivity was improved in cattle fed lubabegron, suggesting greater potential glucose use by tissues along with increased gluconeogenesis

Overall summary

- Lubabegron's dual mode of action regarding its behavior at the different receptor subtypes distinguishes it from the other β ligands historically fed to cattle

- Evidence suggests it evokes an increase in protein synthesis, no change in protein degradation, is not lipolytic, likely enhances gluconeogenesis, and should promote glucose use by insulin-sensitive tissues

- Lubabegron most likely reduces NH_3 emissions by capturing more nitrogen in the carcass through increased rates of protein accretion

Important Safety Information

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. A decrease in dry matter intake may be noticed in some animals

The label contains complete use information, including cautions And warnings. Always read, understand, and follow the label, and use directions.

Indications for use:
For the reduction of ammonia gas emissions per pound of live weightand hot carcass weight 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 matterbasis) to provide 13-90 mg lubabegron/head/day continuously to beefsteers and heifers fed in confinement for slaughter as sole ration during the Last 14 to 91 days on feed.