Meat and Muscle Biology™

Experior: Development History, Commercial Launch, and Research Plans

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Abstract: Experior® (Elanco Animal Health, Greenfield, IN) with the active ingredient lubabegron fumarate was approved by the US Food and Drug Administration (FDA) in 2018 for the reduction of ammonia gas emissions per kg of live weight and hot carcass weight in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 d on feed. It is labeled to be fed at 1.25 to 4.54 g/t (1.39 to 5 ppm) of complete feed (90% dry matter basis) to provide 13–90 mg lubabegron/head/d continuously to beef steers and heifers fed in confinement for slaughter as the sole ration (FDA, 2018a). Lubabegron is a beta-adrenergic agonist/antagonist with antagonistic activity at the β_1 and β_2 receptors and agonistic activity at the β_3 receptor. After gaining FDA approval following a 10-y clinical research program, Experior was launched following a very disciplined and pragmatic approach to the US beef industry while accounting for the global nature of the US beef trade. This article outlines the history of lubabegron and the practical considerations of launching a novel β-ligand into the US beef industry.

Key words: Experior, lubabegron, Elanco, cattle, beef
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Introduction

Experior® (Elanco Animal Health, Greenfield, IN) with the active ingredient lubabegron fumarate was approved by the FDA in 2018 for the reduction of ammonia gas emissions per kg of live weight and hot carcass weight (HCW) in beef steers and heifers fed in confinement for slaughter during the last 14 to 91 d on feed. It is labeled to be fed at 1.25 to 4.54 g/t (1.39 to 5 ppm) of complete feed (90% dry matter [DM]) basis) to provide 13–90 mg lubabegron/head/d continuously to beef steers and heifers fed in confinement for slaughter as the sole ration (FDA, 2018a). This novel claim was pursued due to anticipated external pressure on animal health products carrying only performance claims and to help bridge the gap between the overarching desire for sustainable agriculture and the use of technologies. As both the global population and the demand for animal protein continue to increase (Calicioglu et al., 2019), achieving increased production while minimizing the impact on natural resources and gas emissions will be paramount. Experior is a beta-adrenergic agonist/antagonist (β-AAA) that binds to and activates the β_3 receptors but acts as an antagonist to β_1 and β_2 receptors (Dilger et al., 2021). This unique mode of action provides several benefits that will be discussed later in this article.

History of Research and Development

Lubabegron was initially developed by Eli Lilly and Company (Indianapolis, IN) as part of a program seeking to create selective adrenergic modulators intended to treat humans suffering from diabetes and/or obesity (Elanco Animal Health, Data on File). The term selective adrenergic modifier refers to the ability of a ligand to either act as an agonist or antagonist to

a specific receptor based on the characteristics of the individual receptor. This research effort continued through phase 2 human clinical studies but was ultimately discontinued, and the molecule was acquired by Elanco. Preliminary research performed by Elanco on lubabegron in cattle commenced in 2006, and the clinical program was initiated in 2008. The decision to pursue a gas emissions claim was made early during the clinical program and studies were designed to find significant reductions in gas emissions while de-emphasizing typical parameters such as average daily gain, feed conversion, and carcass weight. Pivotal studies were conducted in either individual animal or group housing chambers with the ability to monitor all relevant gases on both the intake and exhaust fans allowing changes in gas production to be determined by the difference between these 2 measurements. An example of research conducted in group housing environments can be found in Teeter et al. (2021). The housing for this research was dirt-floored, dome-shaped structures with a steel frame and welded truss arches covered with a Dura-Weave cover (Intertape Polymer Group, Montreal, QC, Canada). The results of this 91-d study indicated reductions ($P < 0.05$) in total ammonia gas emissions ranging from 7% to 20% during all time periods when using an approved label dose. Time periods included days 0 to 7, 14, 28, 56, and 91. Multiple gases (ammonia, methane, carbon dioxide, hydrogen sulfide, and nitrous oxide) were evaluated; however, only significant changes in ammonia gas production were identified ($P < 0.05$) during the clinical research program. Additional observations from this research indicated improvements ($P < 0.05$) in gain:feed, HCW, dressing percentage, and ribeye area. Also noted was a small increase in Warner-Bratzler shear force ($P = 0.017$). More information on the clinical studies is available in the Experior Freedom of Information Summary (FDA, 2018a). The efforts from the clinical program resulted in receiving single approval (approval for Experior to be fed to beef steers and heifers) in November 2018 followed by combination approval (Experior to be fed to beef steers and heifers in combination with Rumensin® or Rumensin and Tylan®) in May 2019. Subsequent approvals including generic versions of monensin and tylosin have also been granted.

Mode of Action

A thorough review of various β-ligands can be found in the publication by Dilger et al. (2021). As previously stated, Experior is a β-AAA. Both β-agonists and β-antagonists are used extensively in human medicine to treat various conditions. β-agonists are commonly used to treat asthma and chronic obstructive pulmonary disease (COPD) and to slow preterm labor (Motazedian et al., 2010; Philipson, 2002). β-antagonists (commonly referred to as β-blockers) are used to treat various conditions such as heart failure, hypertension, migraine headaches, and arrhythmia (Baker et al., 2011). The agonistic activity of Experior on the β_3 receptor activates the G-stimulatory protein, resulting in a cascade of events involving adenylyl cyclase, cyclic adenosine monophosphate, and protein kinase A, ultimately resulting in modification of metabolism in the animal (Dilger et al., 2021; Hwang et al., 2022). The β_3 receptor is thought to lack a key phosphorylation site due to the C-terminal loop being truncated, which is responsible for downregulation in β_1 and β_2 receptors (Hwang et al., 2022). This allows prolonged activation of the receptor by an agonist, which allowed for the feeding duration to be extended to 91 d. Relative to antagonistic activity at the β_1 and β_2 receptors, lubabegron has been shown to decrease heart rate in human clinical studies (FDA, 2018a) and in cattle (Dilger et al., 2021). This is in contrast to β-agonists that activate β_1 and β_2 receptors and typically result in stimulating the cardiac and respiratory systems. Additionally, lubabegron research in cattle has demonstrated increased insulin sensitivity and improved glucose utilization (Elanco Animal Health, Data on File).

Experior Approval and Launch

Following initial approval in 2018, Elanco embarked on a systematic plan to introduce Experior to the marketplace. Several efforts were simultaneously undertaken to further understand the impacts of Experior on cattle and to ensure that the use of Experior did not impede international trade for the beef industry. Relative to international trade, Elanco was able to establish residue limits in several key export markets. International markets follow different processes to establish these levels with some timelines taking a minimum of 2 y to complete. Other geographies tend to either recognize the residue tolerances set by the FDA or remain silent on the topic. Vogel et al. (2023) discuss expected residue levels in a variety of tissues. In general, the gastrointestinal tissues that have direct contact with the feed additive contain the greatest residue levels with other organs or organ systems being very low. Due to the low feeding level and extensive metabolism of lubabegron, residue levels in edible tissues are either low or not detectable

at 0-d withdrawal. Residues also dissipate quickly in all tissues and become nondetectable on or before day 6 of withdrawal (Vogel et al., 2023). The low residue levels and the safety profile of the lubabegron established during the clinical research program allowed for approval with no required withdrawal period when Experior is fed according to label specifications (FDA, 2018a).

While Elanco was seeking to start commercial research trials and gain experience with customers feeding Experior, a couple of unfortunate events impacted the meat industry. First, a fire at a major beef packer in August 2019 temporarily shuttered a plant, causing a 6% decrease in US beef processing capacity and leading to a short-term backlog of cattle ready to be harvested (Dennis, 2020). Shortly following this, a global pandemic caused major disruption. In March 2020, a nationwide emergency was declared in the United States due to the rapid spread of SARS-CoV-2, more commonly known as COVID-19. The spread of this virus and restrictions on traveling or congregating had far-reaching impacts, especially on the meat packing industry. As packing plants were forced to operate with reduced labor forces and slow lines down, throughput dropped to 55% of the levels pre-COVID. This had ripple effects throughout the supply chain resulting in cattle being held at feedlots and adding high levels of uncertainty to marketing dates (Whitehead and Kim, 2022). Unfortunately for the livestock industry, these events would take many months to recover from, which resulted in Elanco pausing research efforts intended to support the launch of Experior.

As part of the stewardship of Experior, Elanco chose to launch in conjunction with a user agreement. The basic tenants of the agreement state that producers wanting to utilize Experior in their operation are required to agree to feed Experior according to a specified dose and duration, provide basic real-time electronic data including feed and health records, and follow a 4-d voluntary removal prior to marketing. The Experior label states to feed 1.25 to 4.54 g/t (1.39 to 5 ppm) of complete feed (90% DM basis) to provide 13–90 mg lubabegron/head/d continuously to beef steers and heifers fed in confinement for slaughter as the sole ration during the last 14 to 91 d on feed (FDA, 2018a). The user agreement at the time of this publication states that producers should feed 36 mg/head/d (about 3.2 g/t on a 100% DM basis) for a duration of 28–63 d. This approach was taken for several reasons. First, with a wide dose range available, Elanco wanted to ensure predictable residue levels in edible products. Second, Experior was the first β-ligand approved with a wide duration of use range, and Elanco would like to ensure that feeding recommendations are based on sound science with predictable outcomes. The feed and health data are captured to ensure that any positive or negative perceptions on animal welfare can be substantiated with data. Performance records are not required as part of the user agreement. Finally, the 4-d voluntary removal ensures that residue levels in all tissues are below the lowest established residue limit anywhere in the world. Note that Experior is approved with a 0-d withdrawal requirement from the FDA, but Elanco requires a 4-d voluntary removal period.

Research

Several studies from the clinical research program have been used to support the launch of Experior. Two studies specifically help potential customers understand the impact that Experior has on ammonia gas emissions. These studies include a 14-d study conducted in individual animal chambers and a 91-d study conducted in group housing cattle pen enclosures. The 91-d study referenced earlier in this article (Teeter et al., 2021) has been published and demonstrates a 16% reduction in ammonia gas emissions per kg of HCW. The 14-d study is currently undergoing review for consideration of publication and demonstrated a reduction of ammonia gas emissions per kg of HCW of 10% ($P = 0.093$) during the 0- to 14-d period and 17% ($P = 0.001$) during the 7- to 14-d period of Experior. These 2 pivotal studies were foundational to achieving approval of the label claim for the reduction of ammonia gas emissions per kg of live weight and HCW. In addition to these efficacy studies, research was conducted to complete all of the technical sections required by the FDA for drug approval, including target animal safety, human food safety, and user safety (FDA, 2018a). Several other studies have been conducted to better understand the commercial aspects of feeding Experior. While some of these are published and many others will be, we will not be summarizing or reviewing these results in the current article. Elanco has a long history of being a science-based organization and will continue to learn more about Experior through the multiyear research program that has been established.

Conclusions

Experior is a β-AAA approved to be fed to beef cattle for the reduction of ammonia gas emissions. It was the first product approved by the FDA to reduce

emissions from an animal or its waste (FDA, 2018b). Elanco has sought to take a pragmatic and science-based approach to commercializing Experior within the US cattle industry. While some research has been conducted, there is much more to learn about this unique molecule.

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