

NUMBER 11

DOSE TITRATION STUDIES SHOW ECONOR® IS EFFECTIVE FOR ILEITIS PREVENTION, TREATMENT

INTRODUCTION Econor® (valnemulin) is a pleuromutilin antimicrobial approved in several countries for preventing and treating swine dysentery. Recently it was approved in Europe for treating ileitis and preventing colitis. Dose titration studies have demonstrated the effectiveness of Econor against *Lawsonia intracellularis*, the organism that causes ileitis in swine.

Ileitis affects pigs in different types of management systems, including high-health herds. The acute form tends to affect finishing pigs and is characterised by bloody diarrhoea and, sometimes, by sudden death. Chronic ileitis tends to affect pigs from about 6 to 20 weeks old and may or may not cause diarrhoea.

Production losses due to ileitis can be staggering. In Western Europe alone, ileitis leads to losses as high as 250 million Euro annually, according to swine ileitis expert Steven McOrist.¹ The global economic toll of ileitis is likely to be much higher since ileitis affects pigs worldwide.

In-Life Studies

Two in-life studies were conducted by McOrist and associates utilizing a challenge exposure model.² For the challenge in both studies, a strain of *L. intracellularis* from the United Kingdom was administered orally to weaned Large White/Landrace cross pigs, which developed typical clinical signs and lesions of chronic ileitis two to three weeks later. The same type of challenge has been used before to validate the efficacy of other antibiotics in growing pigs. To provide controls, some pigs were challenged but not treated.

In the first study, Econor was tested as a preventive in feed before the trial started from days -2 to 21 at a dose of 25 ppm. Econor was then tested as a treatment from days 7 to 21 at a dose of 75 ppm.

In the second study, Econor was tested in feed as a preventive in doses of 25 ppm, 37.5 ppm or 50 ppm. Econor was tested as a treatment in doses of 75 ppm and 125 ppm.

The investigators monitored pigs for diarrhoea, weight gain, feed intake, feed conversion and, on necropsy, for the presence of gross and microscopic lesions characteristic of ileitis.

Two weeks after receiving *L. intracellularis*, untreated pigs developed diarrhoea, demonstrating the validity of the challenge.

Results

> Preclinical *in vitro* tests revealed a higher sensitivity of *L. intracellularis* to valnemulin (MIC 2 mcg/ml) than to tiamulin (MIC 4 mcg/ml).

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KEY POINTS

- > Econor® (valnemulin) reduced the clinical signs of ileitis, such as diarrhoea and anorexia, compared to untreated pigs.
- > Pigs treated with Econor had lower lesion scores than untreated pigs.
- > Compared to tylosin phosphate (110 ppm), Econor administered at 2.6 mg/kg bodyweight (50 ppm) resulted in significantly improved weight gain.

> Treatment of pigs with in-feed Econor at doses of 75 ppm and above was very effective as shown in Table 1.

> There was a dose response with prevention levels; for the dosages tested, 50 ppm yielded the best results for reduced levels of infection and lesions due to *L. intracellularis*.

> Faecal consistency and feed conversion were markedly better in Econor-medicated pigs compared to untreated, challenged pigs.

> Mild gross and histological lesions in pigs that received the lower preventive doses of Econor were substantially less than in challenged, untreated pigs.

Researchers' observations: "The improved performance data suggest that the tolerance of pigs to Econor (valnemulin) at the doses tested was excellent and primarily due to decreased enteric disease."

There were 125 commercial large white cross-bred pigs in the study aged 5 to 6 weeks old. Some pigs were untreated and served as controls. Treatment groups received Econor at a dose of either 1.06 mg/kg bodyweight (25 ppm), 1.87 mg/kg bodyweight (37.5 ppm) or 2.6 mg/kg bodyweight (50 ppm). The tylosin group received 110 ppm.

Test feed and water were provided *ad libitum* to all groups beginning 5 days before the oral challenge and for 21 days after challenge with *L. intracellularis*, which was obtained from the intestines of previously infected pigs.

Pigs were observed clinically on day 0 and then three times weekly for diarrhoea, anorexia and depression. Bodyweight was recorded on days 0, 7, 14 and 21 and feed consumption was monitored throughout the trial.

High mortality in the control group demonstrated the validity of the challenge.

Results

> Average daily gain was significantly higher in pigs receiving 2.6 mg/kg bodyweight (50 ppm) compared to all other treatment groups and controls, as shown in Table 2.

> There was no mortality in any of the treatment groups, compared to a 32% mortality in untreated controls.

> All treatment groups had significantly less diarrhoea and anorexia 14 days after the challenge compared to controls.

> All Econor groups and the tylosin group had better feed efficiency and improved clinical signs compared to unmedicated pigs.

Researchers' observations: "When supplied at 2.6 mg/kg bodyweight (50 ppm), response to

Table 1

In-Life Studies: Weight Gain, Feed Conversion and Lesion Score

Treatment Groups (mg/kg feed)	Weight Gain (kg)	Feed Conversion Efficacy	Histological Lesion Score (%)
Infected, untreated controls	4.1	2.00	100
Econor 25 ppm	6.0	1.47	46
Econor 37.5 ppm	5.4	1.52	22
Econor 50 ppm	5.5	1.56	9
Econor 75 ppm	5.2	1.58	0*
Econor 125 ppm	5.6	1.50	0*

* = p<0.05 compared to infected unmedicated control

Econor and Tylosin Phosphate

To further confirm the effectiveness of Econor for ileitis control and to determine appropriate dosages, Nathan Winkelman and associates administered a mucosal homogenate challenge with *L. intracellularis* as part of a 26-day study.³ To provide a positive control, they also compared Econor to tylosin phosphate.

"Supplied at 50 ppm, response to Econor resulted in significant..."

Econor resulted in significantly improved weight gain compared to tylosin phosphate.”

Econor at Time of Challenge

The therapeutic impact of Econor on the development of ileitis when administered simultaneously was evaluated by Nathan Winkelman and associates.⁴ There were 110 commercially large white crossbreds in the study from 5 to 6 weeks of age. They were challenged with *L. intracellularis*, and received Econor in the feed at the time of challenge and for 21 days thereafter. Untreated pigs served as controls.

The actual doses of Econor administered to treatment groups, based on feed consumption and bodyweight, were 0, 1.45 and 2.55 mg/kg bodyweight/day (0, 25 and 50 ppm).

The pigs were observed for diarrhoea, anorexia and depression. Bodyweights were recorded on days 0, 7, 14 and 21 and feed consumption was monitored throughout the trial. Intestinal samples were taken on necropsy, examined and scored.

Results

> Econor provided in the feed at both 1.45 and 2.55 mg/kg bodyweight/day (25 ppm and 50 ppm) significantly reduced diarrhoea, anorexia and depression scores compared to controls.

> Reduction in diarrhoea scores among treated pigs occurred as early as day 6 of the trial.

> Jejunal and ileal lesion scores on necropsy were significantly lower in the 2.55 mg/kg bodyweight/day (50 ppm) treatment group compared to other groups in the study as shown in Table 3.

> Econor-treated pigs had significantly improved average daily weight gain and better feed efficiency compared to nonmedicated pigs.

Researchers' observations: “Based on the results of this study, Econor supplied at 1.45 and

2.55 mg/kg/day (25 ppm and 50 ppm) in the feed is effective in the therapy of porcine proliferative enteritis.”

Table 2
Econor/Tylosin Challenge Study: Average Daily Gain

Treatment Group	Dosage Administered (mg/kg bodyweight)	Average Daily Gain (kg/hd/day)*
Negative control	no treatment	0.04 ^a
Econor	1.06 (25 ppm)	0.25 ^b
Econor	1.87 (37.5 ppm)	0.27 ^b
Econor	2.6 (50 ppm)	0.33 ^c
Tylosin phosphate	110 ppm	0.25 ^b

^{abc} means with the same letter are not different (p<0.05)

Table 3
Lesion Scores* in Econor Challenge Study

Treatment Group (mg/kg bodyweight/No. of pigs)	Jejunum	Ileum
Control (n = 30)	2.97 ^a	3.10 ^a
Econor 1.45 (25 ppm, n = 40)	2.48 ^a	2.73 ^a
Econor 2.55 (50 ppm, n = 40)	2.13 ^b	2.50 ^b

*Score 1-4, 1 = normal to 4 = severe
^{ab} means with the same letter are not different (p<0.05)

Summary

Dose-titration studies have demonstrated Econor's effectiveness against *L. intracellularis*. Pigs treated with Econor had reduced clinical signs of ileitis and better average daily weight gain compared to untreated pigs with ileitis. When administered at 2.6 mg/kg bodyweight (50 ppm), Econor resulted in significantly improved weight gain compared to tylosin phosphate.

For more information on these studies, please contact your local Novartis Animal Health representative or Dr. Ulrich Klein at Ulrich.klein@ah.novartis.com.

cantly improved weight gain compared to tylosin phosphate.”

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