

NUMBER 5

## IN VITRO STUDIES SHOW *B. HYODYSENTERIAE* ISOLATES HAVE EXCELLENT SUSCEPTIBILITY TO VALNEMULIN (ECONOR<sup>®</sup>)

**INTRODUCTION** Reduced susceptibility of *Brachyspira hyodysenteriae* to different antimicrobials, coupled with a limited number of treatment options, has become an increasing concern to pork producers and swine veterinarians worldwide.

Consequently, isolates of *B. hyodysenteriae* from numerous countries have been tested for *in vitro* sensitivity to various antimicrobials including valnemulin (Econor<sup>®</sup>), the new-generation pleuromutilin.

In all studies, valnemulin proved to be highly active against *B. hyodysenteriae*. In many instances, *B. hyodysenteriae* was more susceptible to valnemulin than to other antimicrobials tested, such as tiamulin, tylosin and lincomycin.

### Denmark

One of the earliest *in vitro* studies on sensitivity to valnemulin was conducted in Denmark. Nine field isolates of *B. hyodysenteriae* obtained during outbreaks of swine dysentery were tested for sensitivity to several antimicrobials, including valnemulin, tiamulin, lincomycin and tylosin.<sup>1</sup> Sensitivity was evaluated by determining the minimal inhibitory concentration (MIC) — the lowest concentration of an antimicrobial needed to inhibit the growth of spirochaetes.

Investigators used the agar dilution method, a commonly used technique for susceptibility testing of *Brachyspira* species.

### Results

> MIC (mcg/ml) values for valnemulin were 0 to 8 times less than those of tiamulin, demonstrating

that all nine *B. hyodysenteriae* isolates were highly susceptible to valnemulin.

> Valnemulin was effective against strains that have been resistant to macrolides, such as tylosin, and lincosamides, such as lincomycin.

**Researchers' observations:** The high susceptibility of valnemulin for *B. hyodysenteriae* makes the compound interesting for use in treatments of clinical cases in infected herds.

### United Kingdom

In this study, 10 strains of *B. hyodysenteriae* were tested for sensitivity to valnemulin, tiamulin, tylosin and lincomycin.<sup>2</sup> The strains were obtained from swine faeces isolated from 1989 to 1990. These investigators also used the agar dilution method.

### Results

> Valnemulin yielded the best MICs 50% (mcg/ml).

## KEY POINTS

> *In vitro* studies testing the sensitivity of *B. hyodysenteriae* to antimicrobials have been conducted in at least seven countries around the world.

> In all studies, *B. hyodysenteriae* isolates were shown to be highly sensitive to valnemulin (Econor).

> In virtually all studies, MICs obtained with valnemulin were lower than those for tiamulin, lincomycin and tylosin.

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> MICs were only 0.1 for valnemulin, compared with 0.3 for tiamulin, 50.0 for lincomycin and 200.0 for tylosin.

**Researchers' observations:** All strains of *B. hyodysenteriae* were susceptible to valnemulin, which was the most active of the agents tested against the pathogen.

### Austria

Austrian researchers tested 102 isolates of weakly and strongly  $\beta$ -haemolytic *Brachyspira* for susceptibility to valnemulin, tiamulin and lincomycin.<sup>3</sup> The isolates were taken from 963 different specimens. The MIC was determined with the trypticase soy agar dilution method. There also were controls for which no antimicrobial was used.

### Results

> Valnemulin was the most effective of the three drugs for controlling *Brachyspira*.

> At a concentration of 0.05 mcg/ml, over 32% of tested *Brachyspira* isolates were susceptible to valnemulin, but at the same concentration, only 2% of the strains were susceptible to tiamulin (see Table 1).

**Table 1**  
Percentage of *Brachyspira* Strains Sensitive at Various MICs (mcg/ml)

	0.01	0.05	0.1	0.5	1.0	5.0	10	20	50	100
Econor	—	32.4	45.1	86.3	91.2	100	—	—	—	—
Tiamulin	—	2.0	21.4	87.7	95.9	100	—	—	—	—
Lincomycin	—	—	—	—	—	—	69.9	69.9	83.3	100

> *Brachyspira* isolates were susceptible to tiamulin once the levels of the antimicrobial reached practical-use dosages. Resistance to tiamulin, which has been reported in other countries, was not found in this particular study.

> From 16.7% to 30.1% of strains were resistant to lincomycin, which required a MIC of 10 mcg/ml before 70% of the strains were inhibited.

**Researchers' observations:** The *in vitro* test results of a high number of *Brachyspira* isolates confirmed the findings of former authors, who found that valnemulin seems to be a very effective drug in controlling *Brachyspira* infections in swine. Lincomycin was of less value for controlling swine dysentery and intestinal spirochaetosis.

### Sweden

Researchers tested the sensitivity of 50 Swedish *B. hyodysenteriae* field isolates using a new broth-dilution method.<sup>4</sup> The isolates were obtained from 46 different farms between 1997 and 2000.

The antimicrobial agents used were the pleuromutilins valnemulin and tiamulin, tylosin, erythromycin, clindamycin and virginiamycin.

### Results

> Testing showed no pleuromutilin resistance for *B. hyodysenteriae* based on the isolates tested.

> The majority of the tested isolates showed resistance to macrolide antimicrobials, such as tylosin and erythromycin.

> Valnemulin was the most active antimicrobial against *B. hyodysenteriae* and was more effective than tiamulin. For different isolates, the MIC of tiamulin was between 0 to 8 times higher than that of valnemulin (see Figure 1).

**Researchers' observations:** "No pleuromutilin resistance has yet been recorded for *B. hyodysenteriae* in Sweden...All isolates resistant to tylosin were cross-resistant to erythromycin and clindamycin."

**"All strains of *B. hyodysenteriae* were susceptible to valne**

## Germany

In Germany, where tiamulin-resistant isolates of *B. hyodysenteriae* have increasingly been identified, investigators MIC-tested the reaction of isolates to antimicrobials including tiamulin, valnemulin and lincomycin.<sup>5</sup>

### Results

> Sensitivity of isolates to valnemulin started at 0.039 mcg/ml.

> Lincomycin (MIC 50.0 mcg/ml) was about 1,000 times less effective than valnemulin, and could no longer be considered effective against the *B. hyodysenteriae* isolates.

> Sensitivity to tiamulin was similar to valnemulin with some isolates, but with other strains, was up to 3.8 times less sensitive than valnemulin.

**Researchers' observations:** As shown in other studies, valnemulin proved to be highly effective against *B. hyodysenteriae*.

## Czech Republic

Antimicrobial susceptibility of *B. hyodysenteriae* strains isolated in the Czech Republic was tested with the agar dilution method. The isolates consisted of 100 field strains obtained from 63 pig farms between 1996 and 2001.<sup>6</sup>

Researchers evaluated several antimicrobials, including the pleuromutilins valnemulin and tiamulin as well as lincomycin and tylosin.

### Results

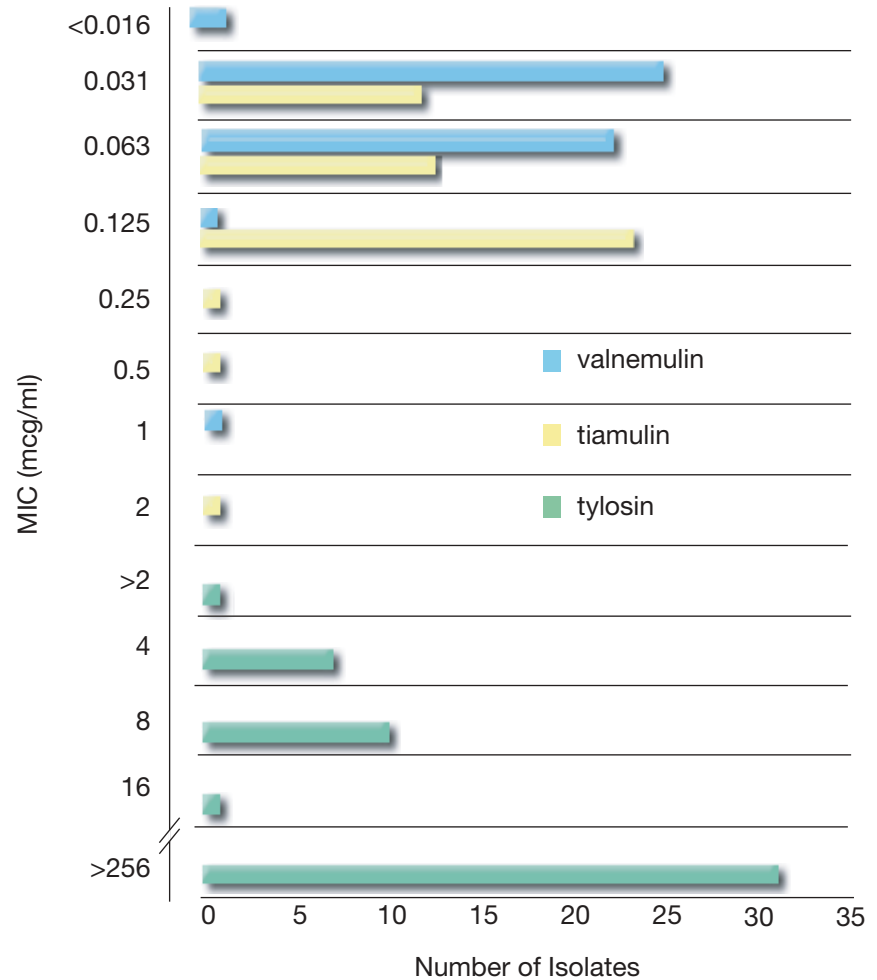
> The pleuromutilins had the lowest MIC values of all the drugs tested.

> MICs for most drugs except tiamulin and valnemulin were high during the years studied.

> About 80% of the strains tested were resistant to lincomycin and tylosin.

**Researchers' observations:** "Based on our results, pleuromutilins should be the first choice of drugs for early treatment of swine dysentery in the Czech Republic."

Figure 1  
Antimicrobial Susceptibility to Valnemulin vs. Tiamulin and Tylosin



## Australia

The susceptibility of 76 *B. hyodysenteriae* field isolates to several antimicrobials was tested.<sup>7</sup>

The isolates were obtained from various states in Australia between 1986 and 2000. They were tested using a new broth-dilution procedure first described in Sweden and determined to be comparable yet easier to use than the more standard trypticase soy agar dilution method.

The antimicrobials tested included valnemulin, tiamulin, tylosin and lincomycin.

emulin, which was the most active of the agents tested..."

## Results

- > Most of the isolates tested had high susceptibility to the pleuromutilins valnemulin and tiamulin, but MIC values were the lowest for valnemulin (see Table 2).
- > Many of the isolates showed poor susceptibility to tylosin and a number also had reduced susceptibility to lincomycin.
- > Higher MICs for lincosamide antimicrobials such as lincomycin are due to the same point mutation that causes tylosin resistance.

**Researchers' observations:** To avoid the development of resistance and ensure their long-term efficacy, pleuromutilins should only be used when clearly indicated, after proper field and lab diagnosis.

## Summary

*In vitro* testing shows that field isolates of *B. hyodysenteriae* from several countries around the globe are highly susceptible to valnemulin, the new-generation pleuromutilin. *B. hyodysenteriae* in most cases was more susceptible to valnemulin than to any other antimicrobial tested.

For more information on this study, please contact your local Novartis Animal Health representative or Dr. Ulrich Klein at [ulrich.klein@ah.novartis.com](mailto:ulrich.klein@ah.novartis.com)

## References

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Table 2  
Results of MIC<sub>90</sub> (mcg/ml) for 76 Isolates Tested in Australia

Antimicrobial	MIC <sub>90</sub> (mcg/ml)
Valnemulin	0.5
Tiamulin	1
Tylosin	>256
Erythromycin	>256
Lincomycin	64
Clindamycin	16

