

Sound science wins

Suspected adverse drug reactions, principally in Scandinavia, prompted the EU to suspend marketing authorisation for Econor in October 2000. A series of extensive investigations were immediately launched by Novartis Animal Health, which have helped to explain the mysterious findings and has led to the successful licence reinstatement of the swine antibiotic.

By Anabel Evans

Novartis Animal Health, has relaunched its swine antibiotic Econor (valnemulin) in the EU following a decision by the European Commission (EC) to lift the 19-month marketing suspension on the new-generation pleuromutilin.

Econor made its debut in 1998, when it was successfully launched in Vietnam, Malaysia and Peru. One year later, it became the first antibiotic feed premix to be approved through the centralised registration procedure in all member states of the EU. It has since been launched in the Philippines - its largest market in terms of volume - and several countries in the Pacific Rim and Latin America. The product is now approved for use in more than 25 countries worldwide.

Econor treats and prevents swine dysentery, which is caused by the pathogen *Brachyspira hyodysenteriae*. It is even effective against strains of *Brachyspira hyodysenteriae* that have

demonstrated resistance to tylosin and lincomycin. It is also used to treat and prevent enzootic pneumonia. In addition, research indicates that it is highly active against spirochaetal colitis and ileitis.

Dr Ulrich Klein, a professional services veterinarian for the company comments, "Unlike most other antibiotics used for enteric and respiratory disease control in animals, Econor is unique in that it was developed specifically for use in food animals. It is not related to any antibiotic used in human medicine."

Isolated reactions

Despite its early success throughout the EU, including Scandinavia, problems arose for Econor in October 2000 when the EC suspended the product's license following a series of adverse drug reactions (ADRs) in four EU countries.

Of the 36 cases reported, 34 of them occurred in Denmark and Sweden. One was reported in Finland and another in Ireland. Overall incidence of ADRs in the affected countries ranged from 0.03% to 1.76% of all pigs treated. Mortality rate in affected herds ranged from 0.7% to 1.2%.

Clinical signs occurred from 2-6 days after treatment, and most affected animals were from 6-7 weeks of age. Common clinical signs included pyrexia and anorexia, stiffness and lethargy. Other less com-



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mon signs reported included erythema and oedema. Pigs recovered after 3-4 days even when medication was continued. There was a high rate of concurrent infections.

"The ADRs in Denmark and Sweden were really puzzling," Klein says. "With the exception of two isolated cases, we had not seen these types of reactions - fever, lack of coordination, depression, oedema, to name a few - anywhere else in the EU, nor had any been reported in Eastern Europe, Latin America or the Pacific Rim. Furthermore, while the ADRs in the affected countries seemed to be associated in some way with the use of Econor, the product alone could not have accounted for all the observed effects we were seeing in Scandinavia."

Following the EU suspension, Novartis Animal Health, which had been reporting all the suspected ADRs to the European Medicine Evaluation Agency (EMA) and the authorities of all EU member states, collaborated with various specialists to investigate the cause of the problem. This effort involved an epidemiological survey, tolerability studies and a review of feed ingredients used in the rations of affected pigs.

Tracing the source

Initially, Klein says, many thought the ADRs in Scandinavia might be linked to vitamin E deficiency or

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possibly interaction with high concentrations of zinc oxide, which is commonly used to control *E. coli* after the removal of antibiotic growth promoters. Since then, however, investigators have trained their sights on the unique breeding programmes used in Denmark and Sweden and, more specifically, a deficiency in the liver enzyme CYP2A P450. This deficiency can slow the metabolic processes of the liver in swine and, in turn, make pigs more susceptible to ADRs.

One of the first studies launched by Novartis sought to identify risk factors that might account for the occurrence of ADRs. Nearly 200 farms were evaluated in seven countries: Belgium, Denmark, Germany, Ireland, Spain, Sweden and the UK. The study involved farms that had ADRs and compared them with two control groups; one comprised Econor-treated herds without ADRs and another consisted of non-treated herds.

"This study showed that breed structure is distinct from country to country and that certain breeds have an increased risk for ADRs if treated with Econor," Klein says. "Specifically, the Danish and Swedish Landrace breeds and their cross-breeds showed an increased predisposition to the occurrence of ADRs."

In a toxicity/tolerance study, the product was found to have no effect on a wide range of physiological, biochemical, haematological and clinical parameters, even when administered at three times the dose involved in ADRs. Pharmacokinetic studies showed that the product's active ingredient, valnemulin, is rapidly metabolised within 24 hours, but that clearance is significantly slower in 5-week old pigs than in 7- or 9-week olds. Higher bioavailability in younger pigs, however, was not accompanied by signs of enhanced toxicity.

The interaction of valnemulin with deficiencies and excesses of zinc, vitamin E and selenium plus the

effects of degradants in feed, the pigs' sex and the source and type of feed were also studied, but the trials yielded no significant findings.

When ADRs were reproduced on a number of farms in Denmark, they were not found to be strongly dose-related. Econor-treated pigs affected by ADRs recovered despite continued medication, and mortality was less than 1%.

Metabolic deficiency key

One of the more telling studies sought to identify the characteristics of valnemulin metabolism in ADR pigs. Independent investigator Dr Christian Friis of the Royal Veterinary and Agricultural University, Copenhagen, considered the possibility that ADRs associated with Econor might be related to a known metabolic deficiency of the enzyme CYP2A P450 that exists in a subpopulation of Danish pigs.

Pigs in the study included those treated that did and did not have

ADRs, as well as non-medicated controls. Indeed, the investigators found that ADR pigs had a slightly reduced ability to metabolise valnemulin, but that they were almost completely deficient in CYP2A P450. In fact, the absence of CYP2A P450 can be considered a marker for ADRs.

Concurrent infections a factor

Another suspected culprit that might help explain the ADR mystery in treated pigs was the standard of hygiene and the presence of concurrent infections, which were extremely widespread on ADR farms. Counts of faecal gram-negative bacteria were found to be significantly higher in medicated pigs with ADRs than in medicated non-susceptible pigs, but were similar to those in non-medicated non-susceptible pigs.

Consequently, the response of pigs from a Danish ADR-susceptible herd to artificial challenge with endotoxins was studied and compared to

that of pigs from France. These findings indicate that a susceptibility to ADR in Econor-treated pigs might be associated with an exaggerated response to gram-negative bacterial toxins such as the endotoxin of *Escherichia coli*.

New territory for everyone involved

Overall, the studies indicate that ADRs are strikingly restricted in geographical occurrence. They appear to be linked to pigs of the Danish and Swedish breeds and their cross-breeds and a deficiency in CYP2A P450 may be involved. "Scientists are still conducting studies to identify the exact cause of the problem in Scandinavia," Klein says. To make sure veterinarians and producers are aware of the risks associated with these specific breeding lines.

Novartis has reintroduced Econor with a new label advising "extreme care" with the product's use in "pigs of Scandinavian origin" especially Danish and Swedish Landrace

breeds and their crossbreeds. The presence of poor hygiene and concurrent gram-negative infections may also increase the risk for ADRs in these breeds.

Reflecting on the re-licencing process Dr Bernhard Putz, head of the company's Farm Animal Business Unit, says, "While challenging at times, this exhaustive and thorough process has helped to validate the safety of Econor, further strengthen user confidence in the product and, in our view, make the unique antibiotic even more valuable to the worldwide pork industry."

"The relaunch of the product is a good example of what can happen when everyone in the industry - pharmaceutical companies, regulatory authorities, veterinarians, nutritionists, epidemiologists - pools their expertise, objectively evaluates the facts and ultimately does what is best for the EU pig industry. We are pleased that sound science had the final word." **PP**